

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 May 2006 (18.05.2006)

PCT

(10) International Publication Number
WO 2006/052962 A2

(51) International Patent Classification:

A61K 31/4745 (2006.01) C07D 487/02 (2006.01)
A61K 31/4196 (2006.01) C07D 471/02 (2006.01)

(21) International Application Number:

PCT/US2005/040419

(22) International Filing Date:

8 November 2005 (08.11.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/626,806 10 November 2004 (10.11.2004) US

(71) Applicant (for all designated States except US):
JANSSEN PHARMACEUTICA, N.V. [BE/US];
Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LAWSON, Edward, C.** [US/US]; 82 Ervin Road, Pipersville, Pennsylvania 18947 (US). **MARYANOFF, Bruce, E.** [US/US]; P.O. Box 239, New Hope, Pennsylvania 18938 (US).

(74) Agent: **STERCHO, Yuriy; JOHNSON & JOHNSON**,
145 King Of Prussia Road, Radnor, Pennsylvania 19087 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BICYCLIC TRIAZOLE A4 INTEGRIN INHIBITORS

(57) Abstract: The compounds of the present invention are novel bicyclic triazole amino acid-derivatives useful as a4 integrin receptor antagonists. The invention is further directed to methods for treating integrin mediated disorders including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders, methods for preparing the compounds and methods for preparing the intermediates, derivatives and pharmaceutical compositions thereof.



WO 2006/052962 A2

BICYCLIC TRIAZOLE α_4 INTEGRIN INHIBITORSCROSS-REFERENCE TO RELATED APPLICATIONS

5

This Application claims priority to United States Provisional Patent Application No. 60/ 626,806, filed November 10, 2004, which is hereby incorporated by reference in its entirety.

10

FIELD OF THE INVENTION

This invention relates to novel compounds and methods for use in treating integrin mediated disorders. More particularly, this invention relates to novel bicyclic triazole amino acid-derived compounds useful as α_4 integrin
15 receptor antagonists, methods for treating integrin mediated disorders including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders. This invention also relates to methods for preparing the instant compounds and methods for preparing intermediates, derivatives and pharmaceutical compositions thereof.

20

BACKGROUND OF THE INVENTION

Integrin receptors are transmembrane, non-covalently linked heterodimers consisting of one α -chain and one β -chain. In addition to
25 performing a structural adhesive function, integrin receptors transmit extracellular signals across the plasma membrane. The integrin receptor $\alpha_4\beta_1$ (also referred to as VLA-4) mediates cell adhesion by binding with either of two protein ligands: vascular cell adhesion molecule-1 (VCAM-1) (Osborn, L.; et al., *Cell*, **1989**, 59, 1203), or the alternatively-spliced fibronectin variant containing
30 the type III connecting segment (CS-1) (Wayner, E. A.; et al., *Cell Biol.*, **1989**, 109, 1321). In contrast to the prototypical integrin receptors $\alpha_5\beta_1$, GPIIb/IIIa and $\alpha_v\beta_3$ that recognize the Arg-Gly-Asp (RGD) tripeptide sequence in their respective ligands, $\alpha_4\beta_1$ binds to other primary protein sequences. The $\alpha_4\beta_1$ integrin receptor recognizes Gln-Ile-Asp-Ser (QIDS) in VCAM-1 and Ile-Leu-
35 Asp-Val (ILDV) in fibronectin. Although these sequences share a conserved

Asp residue with RGD, they are otherwise unrelated. Additionally, recent studies have found that $\alpha_4\beta_1$ binds the matrix ligand osteopontin (Bayless, K. J.; et al., *J. Cell Sci.*, **1998**, *111*, 1165). The osteopontin ligand interaction with the $\alpha_4\beta_1$ receptor may be very important as osteopontin is strongly up-regulated in inflammatory settings, including the inflamed lung.

The $\alpha_4\beta_1$ integrin receptor is expressed at high levels on mast cells, mononuclear leukocytes, eosinophils, macrophages, and basophils (Adams, S. P.; et al., *Ann. Rep. Med. Chem.*, **1999**, *34*, 179). The binding of $\alpha_4\beta_1$ to cytokine-induced VCAM-1 on high-endothelial venules at sites of inflammation results in leukocyte/endothelium adhesion followed by extravasation into the inflamed tissue (Chuluyan, H. E.; et al., *Springer Semin. Immunopathol.*, **1995**, *16*, 391). The role of mast cells and eosinophils in lung inflammation is well established. Induction of VCAM-1 expression on airway endothelial cells seems to play a central role in lung inflammation. The $\alpha_4\beta_1$ receptor interaction with VCAM-1 also exerts an important effect in stem cell adhesion to bone marrow stromal cells (Simmons, P. J.; et al., *Blood*, **1992**, *80*, 388).

The $\alpha_4\beta_7$ integrin is expressed at high levels on lymphocytes and T cells. The trafficking of lymphocytes from the vasculature to normal mucosa and lymphoid tissues is mediated by adhesion of mucosal addressing cell adhesion molecule-1 (MAdCAM-1) with the integrin receptor $\alpha_4\beta_7$. In an inflammatory setting, MAdCAM-1, an immunoglobulin superfamily adhesion molecule, specifically binds $\alpha_4\beta_7$ -expressing lymphocytes and participates in the homing of these cells to the mucosal endothelium. Cloning studies of human MAdCAM-1 have shown that the Leu-Asp-Thr-Ser-Leu (LDTSL) sequence of the CD loop is conserved. In fact, LDT-based peptides bind to $\alpha_4\beta_7$ in a MAdCAM-1/RPMI-8866 cell adhesion assay with IC_{50} values in the 1-10 μ M range (Shroff, H. N.; et al., *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1601).

30

The extensive biology mediated by integrins in general and compelling data for the pathophysiological role of the leukocyte cell adhesion receptor $\alpha 4 \beta 1$ have spurred interest in the study of $\alpha 4 \beta 1$ antagonists in vivo. Cellular adhesion and migration mediated through the $\beta 1$ integrins are critical components of cellular recruitment processes. The integrin $\alpha 4 \beta 1$ provides a key co-stimulatory signal supporting cell activation leading to growth factor and cytokine production and mediator release. Through recognition of the extracellular matrix, $\alpha 4 \beta 1$ increases the survival of activated cells by inhibiting apoptosis (Yoshikawa, H.; et al., *J. Immunol.*, **1996**, 156, 1832).

Monoclonal antibodies directed against $\alpha 4 \beta 1$ or VCAM-1 have been shown to be effective modulators in animal models of chronic inflammatory diseases such as asthma (Laberge, S.; et al., *Am. J. Respir. Crit. Care Med.*, **1995**, 151, 822), rheumatoid arthritis (Barbadillo, C.; et al., *Springer Semin. Immunopathol.*, **1995**, 16, 375) and inflammatory bowel disease (Powrie, F.; et al., *Ther. Immunol.*, **1995**, 2, 115). The initial research in the low molecular weight $\alpha 4 \beta 1$ antagonist arena has focused on simple linear analogues of the prototype Leu-Asp-Val sequence. Phenylacetyl-Leu-Asp-Phe-D-Pro-NH₂ (having an $\alpha 4 \beta 1$ IC₅₀ value of 2 μ M) exhibited efficacy similar to the antibody PS/2 in a mouse model of oxazolone-induced contact hypersensitivity when administered at 6 mg/kg, sc (Tamraz, S.; et al., *Springer Semin. Immunopathol.* **1995**, 16, 437). This tetrapeptide was also effective in a hyperlipidemic rabbit heterotopic heart allograft model (Molossi, S.; et al., *J. Clin. Invest.* **1995**, 95, 2601).

Animal models of asthma have shown that the peptide antagonist BIO-1211 inhibits eosinophilia and airway hyperresponsiveness (Lin, K-C.; et al., *J. Med. Chem.* **1999**, 42, 920). Pre-treatment of allergic sheep with a 3 mg nebulized dose of BIO-1211 (having an $\alpha 4 \beta 1$ IC₅₀ value of 1 nM; 1000-fold selective over $\alpha 4 \beta 7$) inhibited early and late airway responses following antigen challenge and prevented development of nonspecific airway

hyperresponsiveness to carbachol. These results suggest that compounds like BIO-1211 can effect broad pleiotropic activities by acting at $\alpha 4\beta 1$ to achieve pronounced efficacy similar to corticosteroids.

- 5 VLA-4 antagonism may also be effective in reducing restenosis following percutaneous coronary interventions. Administration of an anti- $\alpha 4$ antibody attenuated smooth muscle cell migration associated with electrical injury of rabbit carotid arteries (Kling D, Fingerle J, Harlan JM, Lobb, RR and Lang, F, Mononuclear leukocytes invade rabbit arterial intima during thickening
- 10 formation via CD-18 and VLA-4-dependent mechanisms and stimulate smooth muscle migration, *Circ. Res.*, **1995**, 77, 1121-1128) and was shown to reduce neointimal formation in baboon carotid arteries following endarterectomy (Lumsden AB, Chen C, Hughes JD, Kelly AB, Hanson S and Harker L, Anti-VLA-4 antibody reduces intimal hyperplasia in the endarterectomized carotid
- 15 artery in non-human primates, *J. Vasc. Surg.*, **1997**, 26, 87-93). Furthermore, treatment with z anti- $\alpha 4$ antibody was associated with less neoadventitia formation and less luminal narrowing 14 days after balloon injury of porcine
- coronary arteries (Labinez M, Hoffert C, pels K, Aggarawal S, Pepinsky RB, Leonw D, Koteliensky V, Lobb, RR and O'Brien EO, Infusion on and anti-
- 20 alpha4 integrin antibody is associated with less adventitial formation after balloon injury of porcine coronary arteries, *Can. J. Cardiol.*, **2000**, 16, 187-196).

- The recruitment of leukocytes, particularly monocytes to the vessel wall is a key component in the development of atherosclerotic lesions. VCAM-1
- 25 expression has been reported on endothelial cells in atherosclerotic lesions in humans (O'Brien KD, Allen MD, McDonald TO, Chait A, Harlan JM, Fishbein D, McCarty J, Ferguson M, Hudkins K, Benjamin CD, et al., Vascular cell adhesion molecule-1 is expressed in human atherosclerotic plaques: implications for the mode of progression of advanced atherosclerosis, *J. Clin*
- 30 *Invest.*, **1993**, 92, 945-951), mice (Nakahima Y, Raines EW, Plump AS, Breslow JL and Ross R, Upregulation of VCAM-1 and ICAM-1 at atherosclerotic-prone sites on the endothelium of ApoE-deficient mouse,

Arterioscler. Thromb. Vasc. Biol., **1998**, 18, 842-851) and rabbits (Iiyama K, Hajra L, Iiyama M, Li H, DiChura M, Medoff BD and Cybulsky MI, Patterns of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression in rabbit and mouse atherosclerotic lesion and at sites predisposed to lesion formation, *Circ. Res.*, **1999**, 85, 199-207). Furthermore, a synthetic peptidomimetic of the connecting segment-1 (CS-1) which blocks $\alpha_4\beta_1$ on the leukocyte demonstrated reduced leukocyte homing and lipid accumulation in the aortic sinus in both wild type mice and mice with a low density lipoprotein null mutation (LDLR $-/-$) maintained on a high fat diet (Shih PT, Brennan M-L, Vora DK, Territo MC, Strahl D, Ellices MJ, Aldons J and Berliner JA, Blocking very late antigen-4 integrin decreases leukocyte entry and fatty streak formation in mice fed an atherogenic diet, *Circ. Res.*, **1999**, 84, 345-351). In studies using isolated carotid arteries from ApoE $-/-$ mice (these mice develop spontaneous arterial atherosclerotic lesions with advanced lesions similar to those observed in humans), administration on blocking antibodies to VCAM-1 inhibited the majority of adhesion of monocytes or U937 cells on early atherosclerotic endothelia. In addition, a peptide which inhibits binding of $\alpha_4\beta_1$ to both VCAM-1 and fibronectin was also effective in this model (Huo Y, Hafez-Moghadem A and Ley K, Role of vascular cell adhesion molecule-1 and fibronectin connecting segment-1 in monocyte rolling and adhesion on early atherosclerotic lesions, *Circ. Res.*, **2000**, 87, 153-159). These data support the role of $\alpha_4\beta_1$ in regulating leukocyte recruitment in early and advanced atherosclerotic lesions.

Antibodies to MAdCAM-1 or integrin $\alpha_4\beta_7$ inhibit lymphocyte binding to affinity-purified MAdCAM-1 or MAdCAM-1 transfectants in vitro (Hamann, A.; et al., *J. Immunol.* **1994**, 152, 3282). The antibodies also block localization of lymphocytes to Peyer's patches. Murine MAdCAM-1 recognizes only $\alpha_4\beta_7$ positive human lymphocyte cell lines and $\alpha_4\beta_7$ -high memory T cells. An in vivo role of $\alpha_4\beta_7$ in inflammation has been suggested by increased expression of MAdCAM-1 on HEV-type vessels in the chronically inflamed pancreas of the

non-obese mouse (Hanninen, A.C.; et al., *J. Clin. Invest.* **1993**, 92, 2509). In fact, animal models underscore a significant function of $\alpha_4\beta_7$ in both colitis (Fong, S.; et al., *Immunol. Res.* **1997**, 16, 299) and lymphocytic inflammation of pancreatic islets or development of diabetes (Yang, X.; et al., *Diabetes* **1997**, 46, 1542).

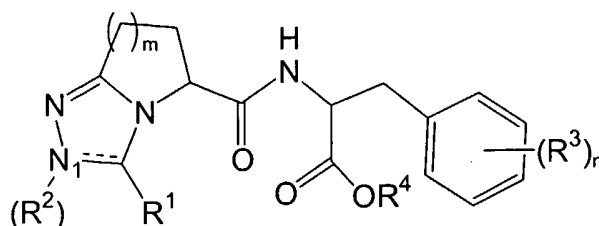
Accordingly, it is an object of the present invention to provide bicyclic triazole compounds that are α_4 integrin receptor antagonists. More particularly, it is an object of the present invention to provide bicyclic triazole compounds that are $\alpha_4\beta_1$ and the $\alpha_4\beta_7$ integrin receptor antagonists. It is also an object of the present invention to provide a process for preparing derivatives of bicyclic triazole amino acid compounds, compositions, intermediates and derivatives thereof. It is a further object of the invention to provide methods for the treatment of integrin mediated disorders that are ameliorated by inhibition of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptors including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders.

It is an object of the present invention to provide methods for producing the instant compounds of Formula (I) and pharmaceutical compositions and medicaments thereof.

It is an object of the present invention to provide methods for the use of bicyclic triazole amino acid compounds in the preparation of a medicament for the treatment of an integrin mediated disorder in a subject in need thereof.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I)



Formula (I)

wherein:

- 5 R^1 is a substituent selected from the group consisting of hydrogen, C_{1-4} alkyl, aryl(C_{1-8})alkyl, heteroaryl(C_{1-8})alkyl, aryl, amino(C_{1-4})alkyl, (C_{1-4})alkylamino(C_{1-4})alkyl, di(C_{1-4})alkylamino(C_{1-4})alkyl, aryl(C_{1-4})alkoxycarbonylamino(C_{1-4})alkyl, heteroaryl(C_{1-4})alkoxycarbonylamino(C_{1-4})alkyl, C_{1-4} alkoxycarbonylamino(C_{1-4})alkyl, aryloxycarbonylamino(C_{1-4})alkyl, and oxo; wherein the C_{1-4} alkyl substituents of di(C_{1-4})alkylamino(C_{1-4})alkyl are optionally taken together with nitrogen atom to which they are both attached to form a 5 to 8 membered monocyclic ring;

- 10 provided that when R^1 is a substituent other than oxo, a double bond exists between N_1 and the carbon bearing R^1 ; alternatively, when R^1 is oxo, then R^2 is present;

R^2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, aryl(C_{1-4})alkyl, and heteroaryl(C_{1-4})alkyl;

- 20 m is an integer of 1 or 2;

- R^3 is a substituent independently selected from the group consisting of C_{1-8} alkoxy, heterocyclyl, aryl, heteroaryl, benzo-fused heterocyclyl, $-C(=O)NR^A R^B$, $-NR^A C(=O)$ aryl, $-NR^A C(=O)$ heteroaryl, $-NR^A C(=O)$ heterocyclyl, $-NR^A C(=O)C_{1-8}$ alkyl, $-NR^A C(=O)C_{2-8}$ alkenyl, $-NR^A C(=O)C_{2-8}$ alkynyl, $-NR^A C(=O)C_{1-8}$ alkoxy, $-NR^A C(=O)C_{1-8}$ alkoxyaryl, $-NR^A C(=O)C_{1-8}$ alkoxyheteroaryl, $-NR^A SO_2$ -aryl, $-NR^A SO_2$ -heteroaryl, $-NR^A SO_2(C_{1-8})$ alkyl, $-NR^A C(=O)NR^A R^B$, $-NR^A C(=O)NR^A$ aryl, $-NR^A C(=O)NR^A$ heteroaryl, $-OC(=O)NR^A R^B$, and halogen;

- wherein heterocyclyl and the heterocyclyl-containing substituents of R^3 , aryl and the aryl-containing substituents of R^3 , benzo-fused heterocyclyl, and heteroaryl and the heteroaryl-containing substituents of R^3 are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, aryloxy, heteroaryloxy, cycloalkyloxy, heterocyclyloxy, benzyloxycarbonyl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, C_{1-8} alkylamino, C_{1-8} dialkylamino, $-CF_3$ and $-OCF_3$; provided that no more than one substituent is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, cycloalkyloxy, heterocyclyloxy, benzyloxycarbonyl, arylcarbonyl, heteroarylcarbonyl, and arylsulfonyl;
- and, wherein heterocyclyl of the heterocyclyl-containing substituents of R^3 is optionally further substituted with one to three oxo substituents;

R^A is independently selected from the group consisting of hydrogen and C_{1-8} alkyl;

R^B is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and $(halo)_{1-3}(C_{1-8})alkyl$; wherein C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl are optionally substituted with one to three substituents independently selected from the group consisting of heterocyclyl, aryl, and heteroaryl; wherein the heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with benzyloxycarbonyl, arylcarbonyl, or heteroarylcarbonyl, and optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, $-CF_3$ and $-OCF_3$;

n is an integer from 0 to 3;

R⁴ is a substituent independently selected from the group consisting of hydrogen and C₁₋₄alkyl;

- 5 and pharmaceutically acceptable enantiomers, diastereomers, racemates, solvates, hydrates, polymorphs, and salts thereof.

An embodiment of the present invention is also directed to a process for preparing the instant bicyclic triazole compounds, compositions, intermediates
10 and derivatives thereof.

Another embodiment of the present invention is directed to pharmaceutical compositions comprising the compounds of the present invention.

15

Another embodiment of the present invention is directed to the use of bicyclic triazole amino acid compounds of the present invention in the preparation of a medicament for the treatment of an integrin mediated disorder in a subject in need thereof.

20

The bicyclic triazole derivatives of the present invention are useful α_4 integrin receptor antagonists and, more particularly, $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonists. A further embodiment of the present invention is directed to a method for the treatment of integrin mediated disorders that are
25 ameliorated by inhibition of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders. In an illustration of the invention, the inflammatory, autoimmune and cell-proliferative disorders include, but are not limited to, inflammation and autoimmunity, asthma and bronchoconstriction, restenosis, atherosclerosis, psoriasis, rheumatoid
30 arthritis, inflammatory bowel disease, transplant rejection and multiple sclerosis.

DETAILED DESCRIPTION OF THE INVENTION

Aspects of the present invention include compounds of Formula (I)
5 wherein R¹ is independently selected from the group consisting of hydrogen, C₁₋₈alkyl, aryl(C₁₋₈)alkyl, heteroaryl(C₁₋₈)alkyl, aryl, and oxo; provided that when R¹ is a substituent other than oxo, a double bond exists between N₁ and the carbon bearing R¹; alternatively, when R¹ is oxo, then R² is present.

10 Aspects of the present invention include compounds of Formula (I) wherein R¹ is independently selected from the group consisting of C₁₋₄alkyl, aryl(C₁₋₄)alkyl, heteroaryl(C₁₋₄)alkyl, phenyl, and oxo, provided that when R¹ is a substituent other than oxo, a double bond exists between N₁ and the carbon bearing R¹; alternatively, when R¹ is oxo, then R² is present.

15 Aspects of the present invention include compounds of Formula (I) wherein R¹ is independently selected from the group consisting of propyl, benzyl, thiophen-3-ylmethyl, indol-3-ylmethyl, phenyl, and oxo; provided that when R¹ is a substituent other than oxo, a double bond exists between N₁ and
20 the carbon bearing R¹; alternatively, when R¹ is oxo, then R² is present.

Aspects of the present invention include compounds of Formula (I) wherein R² is independently selected from the group consisting of hydrogen, C₁₋₄alkyl, and aryl(C₁₋₄)alkyl.

25 Aspects of the present invention include compounds of Formula (I) wherein R² is independently selected from the group consisting of hydrogen and benzyl.

30 Aspects of the present invention include compounds of Formula (I) wherein m is the integer 1.

Aspects of the present invention include compounds of Formula (I) wherein R^3 is a substituent independently selected from the group consisting of C_{1-6} alkoxy, $-C(=O)NR^A R^B$, $-NR^A C(=O)aryl$, $-NR^A C(=O)heteroaryl$, $-NR^A C(=O)heterocyclyl$, $-NR^A C(=O)C_{1-8}alkyl$, $-NR^A SO_2-aryl$, $-NR^A SO_2-$ heteroaryl, $-NR^A SO_2(C_{1-8})alkyl$, $-NR^A C(=O)NR^A R^B$, $-NR^A C(=O)NR^A aryl$, $-NR^A C(=O)NR^A heteroaryl$, $-OC(=O)NR^A R^B$, and halogen; wherein the heterocyclyl portion of $-NR^A C(=O)heterocyclyl$, the aryl portion of the aryl-containing substituents of R^3 , and the heteroaryl portion of the heteroaryl-containing substituents of R^3 are optionally substituted with one to three substituents independently selected from the group consisting of halogen, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkylcarbonyl$, $C_{1-4}alkoxycarbonyl$, amino, $C_{1-8}alkylamino$, $C_{1-8}dialkylamino$, $-CF_3$ and $-OCF_3$; and, wherein heterocyclyl of $-NR^A C(=O)heterocyclyl$ is optionally further substituted with one to two oxo substituents.

15

Aspects of the present invention include compounds of Formula (I) wherein R^3 is a substituent independently selected from the group consisting of $C_{1-3}alkoxy$, $-C(=O)NR^A R^B$, $-NR^A C(=O)aryl$, $-NR^A C(=O)heteroaryl$, $-NR^A C(=O)C_{1-4}alkyl$, $-NR^A SO_2-aryl$, $-NR^A SO_2-heteroaryl$, $-NR^A SO_2(C_{1-4})alkyl$, $-OC(=O)NR^A R^B$, and halogen; wherein the aryl portion of the aryl-containing substituents of R^3 , and the heteroaryl portion of the heteroaryl-containing substituents of R^3 are optionally substituted with one to three substituents independently selected from the group consisting of halogen, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, and $C_{1-4}alkoxycarbonyl$.

25

Aspects of the present invention include compounds of Formula (I) wherein R^3 is a substituent independently selected from the group consisting of $-NR^A C(=O)phenyl$, $-NR^A C(=O)naphthalenyl$, $-NR^A C(=O)pyridin-4-yl$, $-NR^A C(=O)C_{1-4}alkyl$, and $-OC(=O)NMe_2$; wherein phenyl, naphthalenyl, and pyridin-4-yl are optionally substituted with one to three substituents independently selected from the group consisting of chloro, methyl, methoxy, ethoxy, and methoxycarbonyl.

30

Aspects of the present invention include compounds of Formula (I) wherein R³ is a substituent independently selected from the group consisting of -NHC(=O)2,6-dichlorophenyl, -NHC(=O)2,6-dimethoxyphenyl,
5 -NHC(=O)naphthalen-1-yl, -NHC(=O)2-ethoxy-naphthalen-1-yl, -NHC(=O)naphthalen-2-yl, and -NHC(=O)3,5-dichloro-pyridin-4-yl.

Aspects of the present invention include compounds of Formula (I) wherein R³ is attached at the 4-position of the phenyl ring of Formula (I) and n
10 is 1.

Aspects of the present invention include compounds of Formula (I) wherein R^A is independently selected from the group consisting of hydrogen and methyl.
15

Aspects of the present invention include compounds of Formula (I) wherein R^B is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, and (halo)₁₋₃(C₁₋₆)alkyl; wherein C₁₋₆alkyl is optionally substituted with one to three substituents independently selected from the group consisting of
20 heterocyclyl, aryl, and heteroaryl; wherein the heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with benzyloxycarbonyl, arylcarbonyl, heteroarylcarbonyl, and optionally further substituted with one to three substituents independently selected from the group consisting of halogen, C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkylcarbonyl, C₁₋₈alkoxycarbonyl, carboxyl, -CF₃ and
25 -OCF₃.

Aspects of the present invention include compounds of Formula (I) wherein R^B is independently selected from the group consisting of hydrogen and C₁₋₄alkyl, wherein C₁₋₄alkyl is optionally substituted with one to three
30 substituents independently selected from the group consisting of heterocyclyl, aryl, and heteroaryl.

Aspects of the present invention include compounds of Formula (I) wherein R^B is independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

5 Aspects of the present invention include compounds of Formula (I) wherein n is an integer from 0 to 2.

Aspects of the present invention include compounds of Formula (I) wherein n is an integer of 1.

10

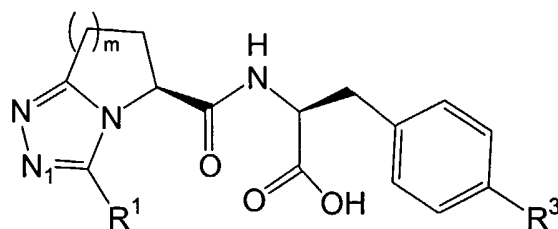
Aspects of the present invention include compounds of Formula (I) wherein R^4 is a substituent independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

15 Aspects of the present invention include compounds of Formula (I) wherein R^4 is a substituent independently selected from the group consisting of hydrogen and methyl.

20 The present invention includes pharmaceutically acceptable enantiomers, diastereomers, racemates, solvates, hydrates, polymorphs, and salts of the compounds described in any one of the embodiments herein.

Aspects of the present invention include compounds of Formula (Ia)

25



Formula (Ia)

selected from the group consisting of:

- a compound of Formula (Ia) wherein R^1 is phenyl, m is 2, and R^3 is -
O(C=O)NMe₂;
- a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 2, and R^3 is
-O(C=O)NMe₂;
- 5 a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is
-O(C=O)NMe₂;
- a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is
-NH(C=O)2,6-dichlorophenyl;
- a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is
10 -NH(C=O)naphthalen-1-yl;
- a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is
-NH(C=O)naphthalen-2-yl;
- a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is
-NH(C=O)(2-ethoxy)-naphthalen-1-yl;
- 15 a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is
-NH(C=O)fluoren-9-on-4-yl;
- a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is
-NHC(=O)(3,5-dichloro)-pyridin-4-yl;
- a compound of Formula (Ia) wherein R^1 is *n*-propyl, m is 1, and R^3 is
20 -NH(C=O)2,6-dichlorophenyl;
- a compound of Formula (Ia) wherein R^1 is -CH₂NH(C=O)OCH₂Ph, m is 1, and
 R^3 is -NH(C=O)2,6-dichlorophenyl;
- a compound of Formula (Ia) wherein R^1 is -CH₂-thiophen-3-yl, m is 1, and R^3 is
-NH(C=O)2,6-dichlorophenyl;
- 25 a compound of Formula (Ia) wherein R^1 is -CH₂Ph, m is 1, and R^3 is 2,6-
dimethoxy-phenyl;
- a compound of Formula (Ia) wherein R^1 is -CH₂NH₂, m is 1, and R^3 is
-NH(C=O)2,6-dichlorophenyl;
- a compound of Formula (Ia) wherein R^1 is -CH₂-thiophen-3-yl, m is 1, and R^3 is
30 2,6-dimethoxy-phenyl;
- a compound of Formula (Ia) wherein R^1 is -CH₂-indol-3-yl, m is 1, and R^3 is 2,6-
dimethoxy-phenyl;

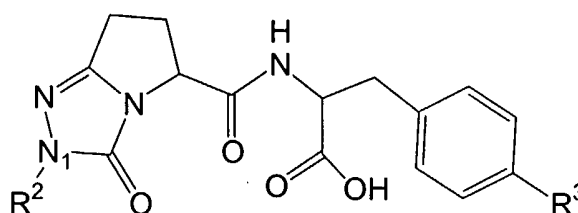
and

a compound of Formula (Ia) wherein R^1 is $-\text{CH}_2\text{Ph}$, m is 1, and R^3 is
5-methoxy-2-methyl-2*H*-pyridazin-3-on-4-yl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates,

5 solvates, hydrates, polymorphs, and salts thereof.

Aspects of the present invention include compounds of Formula (Ib)



10

Formula (Ib)

selected from the group consisting of

a compound of Formula (Ib) wherein R^2 is H and R^3 is $-\text{NH}(\text{C}=\text{O})$ 2,6-dichloro-phenyl;

15 a compound of Formula (Ib) wherein R^2 is $-\text{CH}_2\text{Ph}$ and R^3 is $-\text{NH}(\text{C}=\text{O})$ 2,6-dichlorophenyl;

a compound of Formula (Ib) wherein R^2 is H and R^3 is $-\text{NHC}(=\text{O})$ 3,5-dichloro-pyridin-4-yl;

and

20 a compound of Formula (Ib) wherein R^2 is $-\text{CH}_2\text{Ph}$ and R^3 is $-\text{NHC}(=\text{O})$ 3,5-dichloro-pyridin-4-yl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates,
solvates, hydrates, polymorphs, and salts thereof.

25

Additional embodiments of the present invention include those wherein the substituents selected for one or more of the variables defined herein (i.e. R^1 , R^2 , m , R^3 , n , R^4 , R^A , and R^B) are independently selected to be any

individual substituent or any subset of substituents selected from the description provided herein.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts" (*Ref. International J. Pharm.*, **1986**, 33, 201-217; *J. Pharm.Sci.*, **1997** (Jan), 66, 1, 1). Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds, which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. Where the processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form or as individual enantiomers or diastereomers by either stereospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers or diastereomers by standard techniques, such as the formation of stereoisomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of stereoisomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column. It is to be understood that all stereoisomers, racemic mixtures, diastereomers and enantiomers thereof are encompassed within the scope of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water

(i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

5 As used herein, unless otherwise noted, "alkyl" whether used alone or as part of a substituent group refers to straight and branched carbon chains having 1 to 8 carbon atoms or any number within this range. Therefore, designated numbers of carbon atoms (e.g. C₁₋₈) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

10

As used herein, unless otherwise noted, the term "alkoxy" refers to an -Oalkyl substituent group, wherein alkyl is as defined supra. Similarly, the terms "alkenyl" and "alkynyl" refer to straight and branched carbon chains having 2 to 8 carbon atoms or any number within this range, wherein an alkenyl
15 chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. An alkyl and alkoxy chain may be substituted on a carbon atom. In substituent groups with multiple alkyl groups such as (C₁₋₆alkyl)₂amino- the C₁₋₆alkyl groups of the dialkylamino may be the same or different.

20

As used herein, unless otherwise noted "oxo" whether used alone or as part of a substituent group refers to an O= to either a carbon or a sulfur atom. For example, phthalimide and saccharin are examples of compounds with oxo substituents.

25

The term "heterocyclyl" as used herein refers to an optionally substituted, stable, saturated or partially saturated 5 or 7 membered monocyclic ring which consists of carbon atoms and from one to three heteroatoms selected from N, O or S. Examples of heterocyclyl groups include, but are not limited to, pyrrolinyl
30 (including 2*H*-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl, dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl or piperazinyl. The heterocyclyl group may

be attached at any heteroatom or carbon atom that results in the creation of a stable structure.

5 The term "aryl" refers to an unsaturated, aromatic monocyclic ring of 6 carbon members or to an unsaturated, aromatic polycyclic ring of from 10 to 14 carbon members. Examples of such aryl rings include, and are not limited to, phenyl, naphthalenyl or anthracenyl. Preferred aryl groups for the practice of this invention are phenyl and naphthalenyl.

10 The term "heteroaryl" as used herein represents a stable five or six membered monocyclic aromatic ring system or a nine or ten membered benzo-fused heteroaromatic ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S. The heteroaryl group may be attached at any heteroatom or carbon atom which results in the creation
15 of a stable structure. Examples of heteroaryl groups include, and are not limited to, furyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyridazinonyl, pyrimidinyl or pyrazinyl; fused heteroaryl groups include indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl,
20 benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, quinoliziny, quinolinyl, isoquinolinyl or quinazolinyl. Preferred examples in the practice of this invention include pyridinyl, thiophenyl, indolyl, and pyridazinonyl.

25 The term "arylalkyl" means an alkyl group substituted with an aryl group (e.g., benzyl, phenethyl). The term "arylalkoxy" indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy, phenethoxy, etc.). Similarly, the term "aryloxy" indicates an oxy group substituted with an aryl group (e.g., phenoxy).

30 The term "halogen" refers to fluorine, chlorine, bromine and iodine. Substituents that are substituted with multiple halogens are substituted in a manner that provides compounds which are stable. Chlorine is a preferred

halogen in the present invention.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkyl, alkylamino) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₆) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root. For alkyl and alkoxy substituents, the designated number of carbon atoms includes all of the independent members included in the range specified individually and all the combination of ranges within in the range specified. For example C₁₋₆ alkyl includes, but is not limited to, methyl, ethyl, propyl, butyl, pentyl and hexyl individually as well as sub-combinations thereof (e.g. C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₂₋₆, C₃₋₆, C₄₋₆, C₅₋₆, C₂₋₅, etc.).

15

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The bicyclic triazole amino acid compounds of the present invention are useful $\alpha 4$ integrin receptor antagonists and, more particularly, $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor antagonists for treating a variety of integrin mediated disorders that are ameliorated by inhibition of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders.

30

Illustrative of the invention is a pharmaceutical composition comprising a

pharmaceutically acceptable carrier and any of the compounds described above. Also illustrative of the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. A further illustration of the invention is a process for making a

5 pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier.

10 An example of the invention is a method for the treatment of integrin mediated disorders in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. Also included in the invention is the use of a compound of Formula (I) for the preparation of a medicament for
15 treating an integrin mediated disorder in a subject in need thereof.

Further exemplifying the invention is the method for the treatment of integrin mediated disorders, wherein the therapeutically effective amount of the compound is from about 0.01 mg/kg/day to about 30 mg/kg/day.

20

In accordance with the methods of the present invention, the individual components of the pharmaceutical compositions described herein can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is
25 therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment,
30 observation or experiment.

The term "therapeutically effective amount" as used herein, means that

amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal, or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

5

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

10

The utility of the compounds to treat integrin mediated disorders can be determined according to the procedures herein. The present invention therefore provides a method for the treatment of integrin mediated disorders in a subject in need thereof which comprises administering any of the compounds as defined herein in a quantity effective to inhibit the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders. Accordingly, a compound of the present invention may be administered by any conventional route of administration including, but not limited to oral, nasal, pulmonary, sublingual, ocular, transdermal, rectal, vaginal and parenteral (i.e. subcutaneous, intramuscular, intradermal, intravenous etc.).

20

To prepare the pharmaceutical compositions of this invention, one or more compounds of Formula (I) or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in The Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

30

Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1-3, edited by
5 Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1-2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

10 In preparing a pharmaceutical composition of the present invention in liquid dosage form for oral, topical and parenteral administration, any of the usual pharmaceutical media or excipients may be employed. Thus, for liquid dosage forms, such as suspensions (i.e. colloids, emulsions and dispersions) and solutions, suitable carriers and additives include but are not limited to
15 pharmaceutically acceptable wetting agents, dispersants, flocculation agents, thickeners, pH control agents (i.e. buffers), osmotic agents, coloring agents, flavors, fragrances, preservatives (i.e. to control microbial growth, etc.) and a liquid vehicle may be employed. Not all of the components listed above will be required for each liquid dosage form.

20 In solid oral preparations such as, for example, dry powders for reconstitution or inhalation, granules, capsules, caplets, gelcaps, pills and tablets (each including immediate release, timed release and sustained release formulations), suitable carriers and additives include but are not limited to
25 diluents, granulating agents, lubricants, binders, glidants, disintegrating agents and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated, gelatin coated, film coated or enteric coated by standard
30 techniques.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

The therapeutically effective amount of the compounds of Formula (I)

5 exemplified in such a method is from about 0.01 mg/kg/day to about 300 mg/kg/day. Particularly, the range is from about 0.5 to about 5.0 mg/kg of body weight per day; and more particularly, from about 1.0 to about 3.0 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

10

Preferably, for the method of treating integrin mediated disorders described in the present invention using any of the compounds as defined herein, the dosage form will contain a pharmaceutically acceptable carrier containing between about 0.01 mg and 100 mg, more preferably about 5 to 50 mg, of the
15 compound, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

20

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, dry powders for reconstitution or inhalation, granules, lozenges, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories for
25 administration by oral, intranasal, sublingual, intraocular, transdermal, parenteral, rectal, vaginal, dry powder inhaler or other inhalation or insufflation means. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a
30 depot preparation for intramuscular injection.

For preparing solid pharmaceutical compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as diluents, binders, adhesives, disintegrants, lubricants, antiadherents and gildants. Suitable diluents include, but are not limited to, starch (i.e. corn, wheat, or potato starch, which may be hydrolyzed), lactose (granulated, spray dried or anhydrous), sucrose, sucrose-based diluents (confectioner's sugar; sucrose plus about 7 to 10 weight percent invert sugar; sucrose plus about 3 weight percent modified dextrans; sucrose plus invert sugar, about 4 weight percent invert sugar, about 0.1 to 0.2 weight percent cornstarch and magnesium stearate), dextrose, inositol, mannitol, sorbitol, microcrystalline cellulose (i.e. AVICEL[™] microcrystalline cellulose available from FMC Corp.), dicalcium phosphate, calcium sulfate dihydrate, calcium lactate trihydrate and the like. Suitable binders and adhesives include, but are not limited to acacia gum, guar gum, tragacanth gum, sucrose, gelatin, glucose, starch, and cellulose (i.e. methylcellulose, sodium carboxymethylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and the like), water soluble or dispersible binders (i.e. alginic acid and salts thereof, magnesium aluminum silicate, hydroxyethylcellulose [i.e. TYLOSE[™] available from SE TYLOSE GmbH & Co. KG], polyethylene glycol, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates and pregelatinized starch) and the like. Suitable disintegrants include, but are not limited to, starches (corn, potato, etc.), sodium starch glycolates, pregelatinized starches, clays (magnesium aluminum silicate), celluloses (such as crosslinked sodium carboxymethylcellulose and microcrystalline cellulose), alginates, pregelatinized starches (i.e. corn starch, etc.), gums (i.e. agar, guar, locust bean, karaya, pectin, and tragacanth gum), cross-linked polyvinylpyrrolidone and the like. Suitable lubricants and antiadherents include, but are not limited to, stearates (magnesium, calcium and sodium), stearic acid, talc waxes, stearowet, boric acid, sodium chloride, DL-leucine, carbowax 4000, carbowax 6000, sodium oleate, sodium benzoate, sodium acetate, sodium lauryl sulfate, magnesium lauryl sulfate and the like. Suitable gildants include, but are not

limited to, talc, cornstarch, silica (i.e. CAB-O-SIL[™] silica available from Cabot, SYLOID[™] silica available from W.R. Grace/Davison, and AEROSIL[™] silica available from Degussa) and the like. Sweeteners and flavorants may be added to chewable solid dosage forms to improve the palatability of the oral dosage form. Additionally, colorants and coatings may be added or applied to the solid dosage form for ease of identification of the drug or for aesthetic purposes. These carriers are formulated with the pharmaceutical active to provide an accurate, appropriate dose of the pharmaceutical active with a therapeutic release profile.

10

Generally these carriers are mixed with the pharmaceutical active to form a solid preformulation composition containing a homogeneous mixture of the pharmaceutical active of the present invention, or a pharmaceutically acceptable salt thereof. Generally the preformulation will be formed by one of three common methods: (a) wet granulation, (b) dry granulation and (c) dry blending. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from about 0.1 mg to about 500 mg of the active ingredient of the present invention. The tablets or pills containing the novel compositions may also be formulated in multilayer tablets or pills to provide a sustained or provide dual-release products. For example, a dual release tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric materials such as shellac, cellulose acetate (i.e. cellulose acetate phthalate, cellulose acetate trimellitate), polyvinyl acetate phthalate,

30

hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, methacrylate and ethylacrylate copolymers, methacrylate and methyl methacrylate copolymers and the like. Sustained release tablets may also be made by film coating or wet granulation using slightly soluble or insoluble substances in solution (which for a wet granulation acts as the binding agents) or low melting solids a molten form (which in a wet granulation may incorporate the active ingredient). These materials include natural and synthetic polymers waxes, hydrogenated oils, fatty acids and alcohols (i.e. beeswax, carnauba wax, cetyl alcohol, cetylstearyl alcohol, and the like), esters of fatty acids metallic soaps, and other acceptable materials that can be used to granulate, coat, entrap or otherwise limit the solubility of an active ingredient to achieve a prolonged or sustained release product.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, but are not limited to aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable suspending agents for aqueous suspensions, include synthetic and natural gums such as, acacia, agar, alginate (i.e. propylene alginate, sodium alginate and the like), guar, karaya, locust bean, pectin, tragacanth, and xanthan gum, cellulose such as sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose, and combinations thereof, synthetic polymers such as polyvinyl pyrrolidone, carbomer (i.e. carboxypolymethylene), and polyethylene glycol; clays such as bentonite, hectorite, attapulgite or sepiolite; and other pharmaceutically acceptable suspending agents such as lecithin, gelatin or the like. Suitable surfactants include but are not limited to sodium docusate, sodium lauryl sulfate, polysorbate, octoxynol-9, nonoxynol-10, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polyoxamer 188, polyoxamer 235 and combinations thereof. Suitable deflocculating or dispersing agent

include pharmaceutical grade lecithins. Suitable flocculating agent include but are not limited to simple neutral electrolytes (i.e. sodium chloride, potassium, chloride, and the like), highly charged insoluble polymers and polyelectrolyte species, water soluble divalent or trivalent ions (i.e. calcium salts, alums or sulfates, citrates and phosphates (which can be used jointly in formulations as pH buffers and flocculating agents). Suitable preservatives include but are not limited to parabens (i.e. methyl, ethyl, *n*-propyl and *n*-butyl), sorbic acid, thimerosal, quaternary ammonium salts, benzyl alcohol, benzoic acid, chlorhexidine gluconate, phenylethanol and the like. There are many liquid vehicles that may be used in liquid pharmaceutical dosage forms, however, the liquid vehicle that is used in a particular dosage form must be compatible with the suspending agent(s). For example, nonpolar liquid vehicles such as fatty esters and oils liquid vehicles are best used with suspending agents such as low HLB (Hydrophile-Lipophile Balance) surfactants, stearylalkonium hectorite, water insoluble resins, water insoluble film forming polymers and the like. Conversely, polar liquids such as water, alcohols, polyols and glycols are best used with suspending agents such as higher HLB surfactants, clays silicates, gums, water soluble cellulose, water soluble polymers and the like. For parenteral administration, sterile suspensions and solutions are desired. Liquid forms useful for parenteral administration include sterile solutions, emulsions and suspensions. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Furthermore, compounds of the present invention can be administered in an intranasal dosage form via topical use of suitable intranasal vehicles or via transdermal skin patches, the composition of which are well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the administration of a therapeutic dose will, of course, be continuous rather than intermittent throughout the dosage regimen.

30

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules

are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include, but are not limited to polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, to homopolymers and copolymers (which means polymers containing two or more chemically distinguishable repeating units) of lactide (which includes lactic acid d-, l- and meso lactide), glycolide (including glycolic acid), ϵ -caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, δ -valerolactone, β -butyrolactone, γ -butyrolactone, ϵ -decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels and blends thereof.

Compounds of this invention may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever treatment of integrin mediated disorders is required for a subject in need thereof.

The daily dose of a pharmaceutical composition of the present invention may be varied over a wide range from about 0.1 to 20,000 mg per adult human per day, however the dose will preferably be in the range of from about 1 to about 1,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about

0.01 mg/kg/day to about 300 mg/kg/day. Particularly, the range is from about 0.5 to about 5.0 mg/kg of body weight per day; and more particularly, from about 1.0 to about 3.0 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

5

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject
 10 being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

15	Bn or Bzl	benzyl
	Boc	<i>tert</i> -butoxycarbonyl
	BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
	BSA	bovine serum albumin
	CBZ	benzyloxycarbonyl
20	d	day(s)
	DBC	2,6-Dichlorobenzoylchloride
	DMAP	4-dimethylaminopyridine
	DMF	N, N-dimethylformamide
	DMSO	dimethylsulfoxide
25	DIPEA	Diisopropylethylamine
	DMAP	Dimethylaminopyridine
	EDC	ethyl dimethylaminopropyl-carbodiimide
	EDTA	ethylenediaminetetraacetic acid
	Et ₃ N	triethylamine

	EDAC	N-ethyl-N'-dimethylaminopropylcarbodiimide hydrochloride
	Et ₂ O	Diethyl ether
	EtOAc	Ethyl acetate
	EtOH	Ethanol
5	h	hour
	HBTU	O-Benzotiazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HOBt	hydroxybenzotriazole hydrate
10	HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
	HPLC	High Performance Liquid Chromatography
	HEPES	4-(2-hydroxyethyl)-1- piperazine-ethanesulfonic acid
15	Me	methyl
	MeOH	methanol
	MeCN	acetonitrile
	min	Minutes
	MPK	milligrams per kilogram
20	NMM	N-methyl-morpholine
	NT	not tested
	PBS	Phosphate Buffer Solution
	Ph	Phenyl
	(<i>o</i> -tolyl) ₃ P	tri- <i>o</i> -tolylphosphine
25	Pd/C	palladium on activated carbon
	Pd(OAc) ₂	palladium(II) acetate
	Ph ₃ P	triphenylphosphine
	PPT	precipitate
	psi	pounds per square inch
30	rt	Room temperature

	SDS	Sodium Dodecasulfate
	TEA	Triethylamine
	THF	Tetrahydrofuran
	Thi	Thienyl
5	TMS	Tetramethylsilane
	TFA	Trifluoroacetic acid
	Tol	Toluene

GENERAL SYNTHETIC METHODS

10

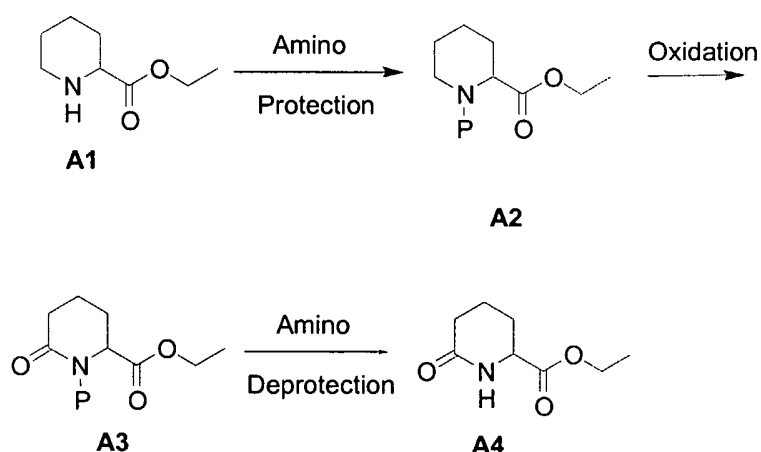
Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

15

20

Scheme A describes the preparation of a lactam intermediate (**A4**) which may be used to prepare compounds of the present invention.

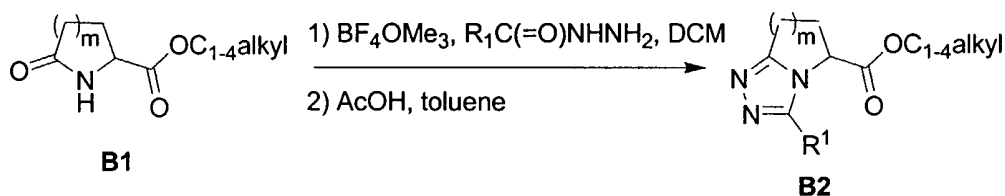
Scheme A



A cyclic amine of the formula **A1** may be protected with a conventional amino protecting group (P) to give a compound of the formula **A2**, which may be oxidized with an oxidizing agent such as ruthenium oxide in the presence of a perchlorate salt or to give a protected lactam of the formula **A3**. The amino-protecting group may then be removed using conventional deprotective methods appropriate for a given P-group to give compounds of formula **A4**.

Scheme B describes the preparation of bicyclic triazole intermediates, which may be used to prepare compounds of the present invention.

Scheme B

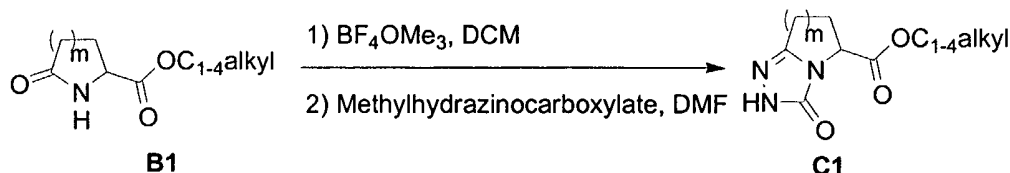


A lower alkyl ester of formula **B1** may be converted to an iminoether.

Subsequent reaction of the iminoether with an appropriately substituted hydrazide followed by treatment with acetic acid in toluene provides bicyclic triazole compounds of formula **B2**.

Scheme C describes the preparation of oxobicyclic triazole intermediates which may be used to prepare compounds of the present invention.

Scheme C

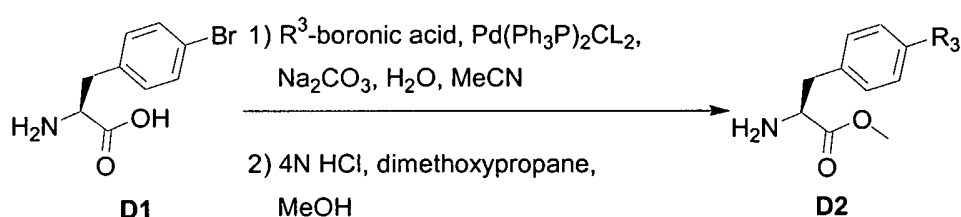


A compound of the formula **B1** may be converted to an imino ether, and subsequently may be reacted with methylhydrazinocarboxylate in a solvent such as DMF to give an oxobicyclic triazole of formula **C1**.

- 5 Scheme D describes the synthesis of amino ester intermediates wherein R^3 is an aryl or heteroaryl substituent as defined herein.

Scheme D

10



R^3 = aryl or heteroaryl

Commercially available compounds of formula **D1** may be coupled with an R^3 -substituted boronic acid in the presence of a palladium catalyst, followed conversion to its methyl ester to yield compounds of formula **D2**.

15

Scheme E describes the synthesis of compounds of the formula **E2**.

Scheme E



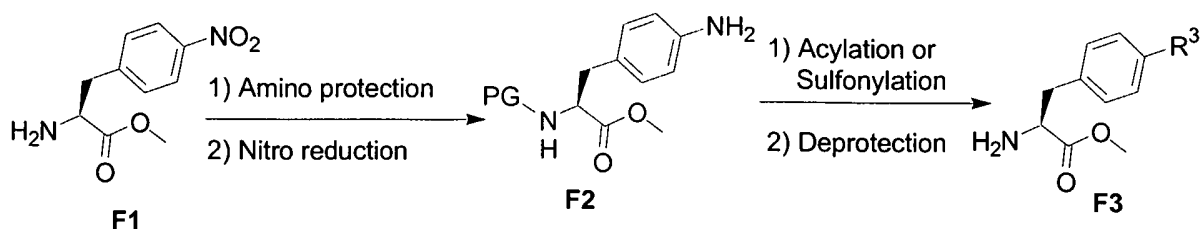
20

The hydroxyl functionality of compounds of the formula **E1** may be acylated with an appropriately substituted isocyanate, carbamoyl chloride or the like to give carbamates of formula **E2**.

Scheme F describes the synthesis of compounds of the formula **F3**, which are used to prepare certain compounds of the present invention.

Scheme F

5



PG= protecting group

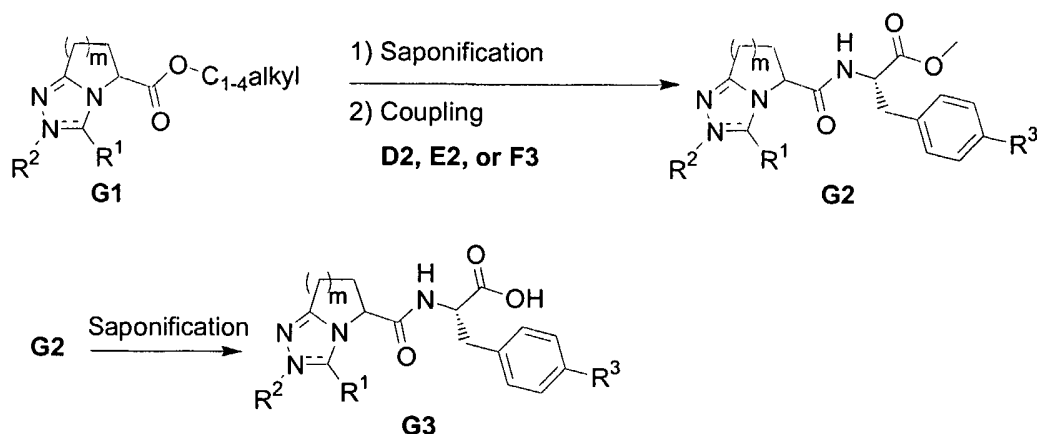
The amino functionality of compounds of formula **F1** may be protected with a conventional amino protecting group (PG). The nitro group may be converted to its corresponding amine under reducing conditions such as in a hydrogen atmosphere in the presence of an appropriate transition metal catalyst, like palladium on carbon. Other suitable reaction conditions for the conversion of nitro groups to amines include subjection of a compound of formula **F1** to zinc powder or tin chloride under basic conditions to yield compounds of formula **F2**. Compounds of formula **F2** may be further derivatized via acylation or sulfonylation of the amino group using an appropriately substituted acid chloride, sulfonyl chloride or the like to give compounds wherein R^3 may be an amide, sulfonamide, carbamate, or urea as defined herein. Deprotection of the amino group using conventional chemistry yields compounds of formula **F3**.

20

Scheme G describes the synthesis of certain compounds of the present invention.

Scheme G

25



The ester of compounds of formula **G1** may be converted to its corresponding carboxylic acid upon treatment with hydroxide. The carboxylic acid may then be coupled with the amine of a compound of the formula **D2**, **E2**, or **F3** under standard coupling conditions to yield a compound of formula **G2**. Standard coupling conditions include a coupling agent such as HBTU, an activating agent such as HOBt, an appropriate base, and solvent. Saponification of compounds of formula **G2** under basic conditions provides compounds of formula **G3**.

10

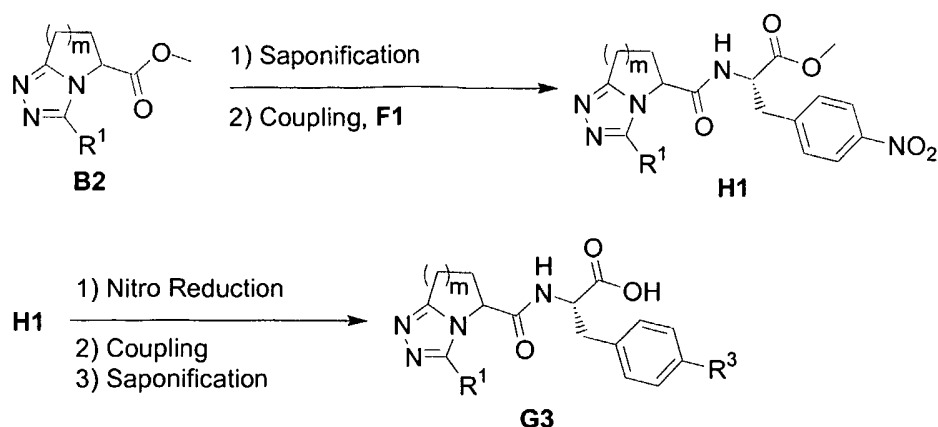
Compounds of formula **G2** wherein R¹ is oxo and R² is hydrogen may be further elaborated by the alkylation of the N₁ nitrogen to yield additional compounds of the present invention where the R² substituents are as defined herein. Standard amine alkylation conditions involve the displacement of a leaving group (iodide, bromide, sulfonate, chloride) from a functionalized precursor of R² under basic conditions. The resulting compounds are those of formula **G3** wherein R² is a substituent other than hydrogen as previously defined.

15

Scheme H describes the synthesis of certain compounds of the present invention.

20

Scheme H



Compound **B2** may be saponified by treatment with hydroxide anion to afford the corresponding carboxylic acid. The carboxylic acid may then be coupled using standard coupling conditions with an appropriate amine, such as compound **F1**, to afford an amide of formula **H1**. Compounds of the formula **H1** may be used to prepare compounds of the present invention as described in the previous schemes described herein. Reduction of the aryl nitro group using conventional methods known to one versed in the art, followed by acylation of the resulting amine as described above. Saponification of the ester of compounds of formula **H1** provide compounds of formula **G3**.

SPECIFIC EXAMPLES

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The instant compounds may also be used as intermediates in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine

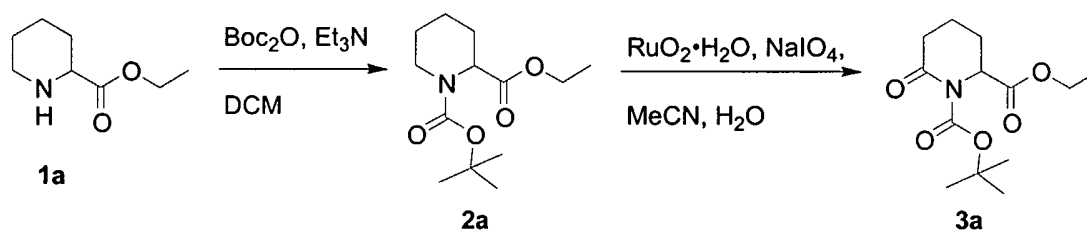
variations in reaction times, temperatures, solvents and/or reagents.

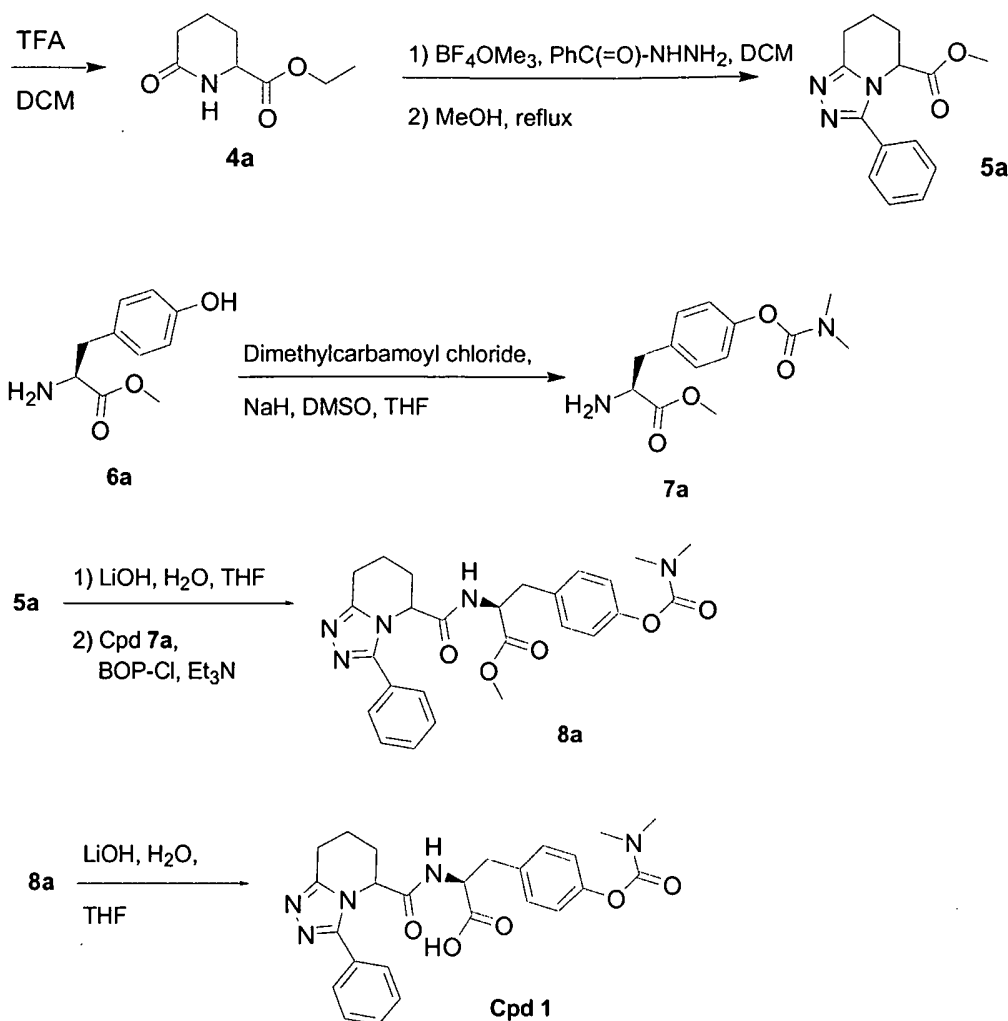
Reagents were purchased from commercial sources. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with (TMS) as the internal standard on a Bruker AM-360 (360 MHz) spectrometer. The values are expressed in parts per million down field from TMS. The mass spectra (MS) were determined on a Micromass Platform LC spectrometer or an Agilent LC spectrometer using electrospray techniques. Microwave accelerated reactions were performed using either a CEM Discover or a Personal Chemistry Smith Synthesizer microwave instrument. Stereoisomeric compounds may be characterized as racemic mixtures or as separate diastereomers and enantiomers thereof using X-ray crystallography and other methods known to one skilled in the art. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis. The substituent groups, which vary between examples, are hydrogen unless otherwise noted.

Example 1

3-(4-Dimethylcarbamoyloxy-phenyl)-2-(S)-[(3-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-5-carbonyl)-amino]-propionic acid (Cpd 1)

25





5

Procedure 1

Compound **1a** (5.00 g, 0.032 mol) was dissolved in dry DCM (160 mL) containing TEA (6.0 mL, 0.043 mol) and di-*tert*-butyl dicarbonate (6.90 g, 0.032 mol) was added in 3 portions. The reaction was stirred for 18 h at room temperature. The reaction mixture was diluted with DCM (200 mL) and washed with 1.0 N HCl. The organic layers were combined and dried over MgSO_4 , filtered through CELITE[®], and concentrated in vacuo to give Compound **2a** as a viscous oil. ^1H NMR (300 MHz, CDCl_3) δ 4.70-4.86 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.94-3.99 (m, 1H), 2.87-2.97 (m, 1H), 2.19-2.22 (m, 1H), 1.70-1.72 (m, 3H), 1.67-1.69 (m, 2H), 1.45 (s, 9H), and 1.27 (t, J = 7.2 Hz, 3H); MS (ES^+) 258.

Procedure 2

Compound **2a** (8.20 g, 0.032 mol) was dissolved in MeCN (20 mL) and H₂O (92 mL). Sodium periodate (19.8 g, 0.093 mol) was added followed by ruthenium (IV) oxide hydrate (0.13 g, 0.001 mol). The mixture was stirred at room temperature for 24 h followed by extraction with EtOAc (500 mL). The organic layer was then treated with isopropanol (100 mL) at room temperature for 2 h. The mixture was then filtered through CELITE[®] and the filtrate washed with saturated aqueous NaCl. The organic layer was dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo to give Compound **3a** as a viscous oil. The oil was dissolved in TFA (14.0 mL), DCM (56.0 mL), and stirred at room temperature for 1 h. The mixture was concentrated in vacuo to give Compound **4a** as a viscous oil. ¹H NMR (300 MHz, CDCl₃) δ 8.32 (br s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.15-4.19 (m, 1H), 2.47-2.52 (m, 2H), 2.20-2.27 (m, 1H), 1.82-1.96 (m, 3H), and 1.31 (t, *J* = 7.1 Hz, 3H); MS (ES⁺) 172.

Procedure 3

Compound **4a** (0.64 g, 0.004 mol) was dissolved in DCM (12.5 mL) and treated with trimethyloxonium tetrafluoroborate (0.64 g, 0.004 mol). The mixture was stirred at room temperature for 24 h. Benzoic hydrazide (0.58 g, 0.004 mol) was added and the mixture was stirred at room temperature for 24 h. The mixture was concentrated in vacuo and dissolved in MeOH (16.0 mL). The solution was heated to reflux using a Dean-Stark trap for 24 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography (silica gel, using a gradient of DCM:MeOH 98:2 to 92:8) to provide Compound **5a**. ¹H NMR (300 MHz, CDCl₃) δ 8.32 (br s, 1H), 7.81 (d, *J* = 1.8 Hz, 2H), 7.39-7.50 (m, 3H), 4.22 (q, *J* = 6.6 Hz, 2H), 4.13-4.20 (m, 1H), 2.33-2.39 (m, 2H), 2.13-2.21 (m, 1H), 1.78-1.88 (m, 3H), and 1.29 (t, *J* = 7.1 Hz, 3H); MS (ES⁺) 272.

Procedure 4

L-Tyrosine methyl ester (compound **6a**, 35.0 g, 0.179 mol) was dissolved in THF (900 mL) and DMSO (70 mL). The mixture was cooled using

an acetone/dry ice bath to 0°C. Sodium hydride (5.0 g, 0.198 mol) was added in three portions. The mixture was stirred for 30 min in the acetone/dry ice bath and then cooled to

–10°C. Dimethylcarbamoyl chloride (16.5 mL, 0.179 mol) was added dropwise and stirred at 0°C for 1 h. The reaction was quenched with 1N NaOH and extracted with EtOAc. The organic layers were dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo to give Compound **7a**. MS (ES⁺) 267.

10 Procedure 6

Compound **5a** (0.22 g, 0.0008 mol) was dissolved in THF (4.0 mL). LiOH (0.06 g, 0.001 mol) was dissolved in water (8.0 mL) and added to the THF mixture. After stirring at room temperature for 30 min the mixture was acidified with 1N HCl and extracted with DCM. The organic layers were dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude oil (0.13 g) was dissolved in DCM (1.0 mL). BOP-Cl (0.20 g, 0.0008 mol) and Et₃N (0.14 mL, 0.001 mol) were added and the mixture stirred at room temperature for 15 min. Compound **7a** (0.16 g, 0.0006 mol) was added and the mixture stirred for 18 h. The mixture was diluted with DCM and washed with 1N HCl. The organic layers were dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude oil was dissolved in THF (0.2 mL) and stirred at room temperature. LiOH (5.0 mg, 0.12 mmol) was dissolved in H₂O (0.4 mL) and added to the THF solution. After stirring for 1 h at room temperature the mixture was acidified with 1N HCl and extracted with DCM. The organic layers were dried using MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude oil was purified using a Gilson HPLC containing a Kromasil column (10 μ , 100Å C18, column length 250x50 mm, gradient 90:10 H₂O:MeCN) to give the title compound (**1**). ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.62 (m, 5H), 7.02-7.22 (m, 4H), 5.10-5.21 (m, 1H), 4.53-4.65 (m, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 2.98-3.15 (m, 4H), and 2.03-2.34 (m, 4H); MS (ES⁺) 478.

Example 2

**2-(S)-[(3-Benzyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-5-carbonyl)-amino]-3-(4-dimethylcarbamoyloxy-phenyl)-propionic acid
(Cpd 2)**

5

Compound 2 was prepared using the method provided in Example 1, substituting phenylacetic hydrazide (0.54 g) for benzoic hydrazide in Procedure 3. Compound 2: ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.32 (m, 7H), 7.00-7.12 (m, 2H), 4.98-5.02 (m, 1H), 4.05-4.13 (m, 1H), 3.32 (s, 3H), 3.30 (s, 3H), 3.10 (2Hs, 10), 2.95-3.00 (m, 2H), 2.30-2.35 (m, 2H), and 1.81-2.12 (m, 4H); MS (ES⁺) 492.

Example 3

**2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-(4-dimethylcarbamoyloxy-phenyl)-propionic acid
(Cpd 3)**

15

Compound 3 was prepared was prepared using the method provided in Example 1, substituting (S)-ethyl 2-pyrrolidone-5-carboxylate (2.05 g) for Compound 4a and phenylacetic hydrazide (2.17 g) for benzoic hydrazide in 20 Procedure 3. Compound 3: ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.34 (m, 5H), 6.95-7.12 (m, 4H), 4.77-4.89 (m, 1H), 4.36-4.44 (m, 1H), 3.76 (s, 2H), 3.06-3.18 (m, 2H), 3.02 (s, 3H), 2.99 (s, 3H), and 2.69-2.88 (m, 4H); MS (ES⁺) 478.

Example 4

**2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid
(Cpd 4)**

25

Compound 4 was prepared was prepared using the method provided in 30 Example 1, substituting (S)-ethyl 2-pyrrolidone-5-carboxylate (2.05 g) for Compound 4a and phenylacetic hydrazide (2.17 g) for benzoic hydrazide in Procedure 3; and substituting 2-amino-3-(4-nitro-phenyl)-propionic acid methyl

ester (1.95 g) for Compound **7a** in Procedure 6 to give 2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-(4-nitro-phenyl)-propionic acid.

5 Procedure 7

2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-(4-nitro-phenyl)-propionic acid (2.8 g, 0.006 mol) was dissolved in EtOAc (30 mL) and treated with 10% Pd/C (0.28 g) and hydrogen (50 psi) for 24 h. The mixture was filtered through CELITE[®] and purified by
10 flash chromatography (98:2 – 92:8 DCM:MeOH gradient). The solid (100.0 mg, 0.239 mmol) was dissolved in DCM (1.2 mL) and treated with Et₃N (0.1 mL, 0.717 mmol). A portion of 2,6-dichlorobenzoyl chloride (0.04 mL, 0.272 mmol) was added and the mixture was stirred at room temperature for 24 h. The mixture was diluted with DCM and washed with 1N NaOH. The organic layers
15 were combined, dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude solid was dissolved in THF (1.2 mL), treated with a solution of LiOH (15.0 mg, 0.358 mmol) in H₂O (2.4 mL), and stirred at room temperature for 1 h. The mixture was treated with 1N HCl and extracted with DCM. The organic layers were combined, dried over MgSO₄, filtered through
20 CELITE[®], and concentrated in vacuo. The crude oil was purified using a reversed phase Gilson containing a Kromasil column (10 μ , 100Å C18, column length 250x50 mm, gradient 90:10 to 0:100 H₂O:MeCN) to give the title compound **4**. ¹H NMR (300 MHz, CDCl₃) δ 7.09-7.68 (1m, 2H), 4.60-4.78 (m, 1H), 4.14-4.19 (m, 1H), 3.79 (s, 2H), 3.22-3.34 (m, 2H), 3.19 (s, 3H), 3.07 (s, 3H), and 2.74-2.96 (m, 4H): MS (ES⁺) 579.
25

Example 5

2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-{4-[(naphthalene-1-carbonyl)-amino]-phenyl}-
30 propionic acid (Cpd 5)

Compound **5** was prepared using the method provided in Example 4, substituting 1-naphthoyl chloride (0.04 mL) for 2,6-dichlorobenzoyl chloride in Procedure 7. Compound **5**: ^1H NMR (300 MHz, CDCl_3) δ 9.09 (m, 1H), 7.82-8.21 (m, 6H) 7.08-7.75 (m, 9H), 4.74-4.83 (m, 1H), 4.04-4.14 (m, 1H), 3.85 (s, 2H), 3.32-3.43 (m, 2H), and 2.81-3.13 (m, 4H): MS (ES^+) 560.

Example 6

2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-{4-[(naphthalene-2-carbonyl)-amino]-phenyl}-propionic acid (Cpd 6)

Compound **6** was prepared using the method provided in Example 4, substituting 2-naphthoyl chloride (0.04 mL) for 2,6-dichlorobenzoyl chloride in Procedure 7. Compound **6**: ^1H NMR (300 MHz, CDCl_3) δ 8.35 (s, 1H), 7.87-8.02 (m, 5H) 7.60-7.75 (m, 4H), 7.08-7.37 (m, 6H), 4.82-4.90 (m, 2H), 3.70-3.93 (m, 2H), and 2.84-3.33 (m, 6H): MS (ES^+) 560.

Example 7

2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-{4-[(2-ethoxy-naphthalene-1-carbonyl)-amino]-phenyl}-propionic acid (Cpd 7)

Compound **7** was prepared using the method provided in Example 4, substituting 2-ethoxy-1-naphthoyl chloride (0.062 g) for 2,6-dichlorobenzoyl chloride in Procedure 7. Compound **7**: ^1H NMR (300 MHz, CDCl_3) δ 9.02 (m, 1H), 7.69-7.99 (m, 6H) 7.29-7.47 (m, 6H), 7.05-7.17 (m, 2H), 4.75-4.83 (m, 2H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.92-3.98 (m, 2H), 2.83-3.43 (m, 6H), and 1.34 (t, $J = 7.0$ Hz, 3H): MS (ES^+) 604.

Example 8

2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-{4-[(9-oxo-9H-fluorene-4-carbonyl)-amino]-phenyl}-propionic acid (Cpd 8)

5

Compound **8** was prepared using the method provided in Example 4, substituting 9-fluorenone-4-carbonyl chloride (0.064 g) for 2,6-dichlorobenzoyl chloride in Procedure 7. Compound **8**: ¹H NMR (300 MHz, CDCl₃) δ 7.67-7.76 (m, 6H) 7.29-7.50 (m, 8H), 7.09-7.20 (m, 2H), 4.73-4.83 (m, 2H), 3.91-4.08 (m, 10 2H), and 2.98-3.37 (m, 6H): MS (ES⁺) 612.

Example 9

2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-{4-[(3,5-dichloro-pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Cpd 9)

15

Compound **9** was prepared using the method provided in Example 4, substituting 3,5-dichloroisonicotinic chloride (0.055 g) for 2,6-dichlorobenzoyl chloride. Compound **9**: ¹H NMR (300 MHz, CDCl₃) δ 8.65 (s, 2H), 7.68 (d, *J* = 8.48 Hz, 2H), 7.37 (d, *J* = 8.49 Hz, 2H), 7.27-7.29 (m, 3H), 7.05-7.07 (m, 2H), 20 4.69-4.87 (m, 2H), 3.87-4.00 (m, 2H), and 2.94-3.33 (m, 6H): MS (ES⁺) 580.

Example 10

2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-[4-(5-methoxy-2-methyl-3-oxo-2,3-dihydro-pyridazin-4-yl)-phenyl]-propionic acid (Cpd 17)

25

3-Phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid methyl ester was prepared using the method provided in Procedure 3, substituting (S)-ethyl 2-pyrrolidone-5-carboxylate (2.05 g) for Compound **4a** 30 and substituting phenylacetic hydrazide (2.17 g) for benzoic hydrazide.

Procedure 8

4-Borono-L-phenylalanine (0.30 g, 1.0 mmol), 4-Bromo-5-methoxy-2-methyl-2H-pyridazin-3-one (0.35 g, 1.0 mmol), tetrakis(triphenylphosphine) palladium(0) (0.09 g), and 2.0 M aqueous sodium carbonate (3.0 mL) were
5 refluxed in MeCN (900 mL) for 4 d. The mixture was acidified with 2.0 N HCl and treated with MeOH. The solid was filtered off and the mixture was concentrated in vacuo. The crude solid was purified using a Gilson HPLC containing a Kromasil column (10 μ , 100Å C18, column length 250x50 mm, gradient 100:0 to 10:90 H₂O:MeCN) to give 2-(S)-Amino-3-[4-(5-methoxy-2-methyl-3-oxo-2,3-dihydro-pyridazin-4-yl)-phenyl]-propionic acid. MS (ES⁺) 304.
10

Procedure 9

2-(S)-Amino-3-[4-(5-methoxy-2-methyl-3-oxo-2,3-dihydro-pyridazin-4-yl)-phenyl]-propionic acid (0.40 g, 1.0 mmol) was dissolved in MeOH (2.6 mL).
15 Dimethoxypropane (0.26 mL) and 1N HCl in dioxane (0.33 mL) were added and stirred at room temperature for 24 h. The mixture was concentrated in vacuo to give 2-Amino-3-[4-(5-methoxy-2-methyl-3-oxo-2,3-dihydro-pyridazin-4-yl)-phenyl]-propionic acid methyl ester. MS (ES⁺) 318.

20 Using the method described in Procedure 6, substituting 2-(S)-Amino-3-[4-(5-methoxy-2-methyl-3-oxo-2,3-dihydro-pyridazin-4-yl)-phenyl]-propionic acid methyl ester (0.57 g) for Compound 7a, 2(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-[4-(5-methoxy-2-methyl-3-oxo-2,3-dihydro-pyridazin-4-yl)-phenyl]-propionic acid methyl ester was
25 prepared in crude form.

The crude solid was dissolved in THF, treated with a solution of LiOH in H₂O, and stirred at room temperature for 1 h. The mixture was treated with 1N HCl and extracted with DCM. The organic layers were combined, dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude oil
30 was purified using a Gilson HPLC containing a Kromasil column (10 μ , 100Å C18, column length 250x50 mm, gradient 90:10 to 10:90 H₂O:MeCN) to

give the title compound 17. ¹H NMR (300 MHz, CD₃OD) δ 8.12 (s, 1H), 7.23-7.45 (m, 7H), 7.06-7.12 (m, 2H), 4.86-4.95 (m, 2H), 3.84 (s, 3H), 3.76 (s, 2H), 3.31 (s, 3H), and 2.82-3.23 (m, 6H); MS (ES⁺) 529.

5

Example 11

**3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-(S)-[(3-oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid
(Cpd 18)**

Procedure 10

10 A portion of (S)-methyl 2-pyrrolidone-5-carboxylate (3.00 g, 0.021 mol) was dissolved in DCM (105 mL) and treated with trimethyloxonium tetrafluoroborate (3.10 g, 0.021 mol). The mixture was stirred at room temperature for 24 h. The mixture was concentrated in vacuo. The oil was dissolved in DMF (100 mL). Methyl hydrazinocarboxylate (2.00 g, 0.022 mol)
15 was added and the solution was heated to reflux using a Dean-Stark trap for 24 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography (silica gel, using a gradient of DCM:MeOH 95:5 to 90:10) to provide 3-Oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid methyl ester. ¹H NMR (300 MHz,
20 CDCl₃) δ 4.68-4.72 (m, 1H), 3.82 (s, 3H), 2.75-2.99 (m, 4H); MS (ES⁺) 184.

Procedure 11

3-Oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid methyl ester (0.50 g, 2.7 mmol) was dissolved in THF (3.0 mL). LiOH
25 (0.14 g, 3.3 mmol) was dissolved in water (3.0 mL), which was added to the THF mixture and stirred at room temperature for 30 min. The mixture was acidified with 1N HCl and extracted with DCM. The organic layers were dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo to give 3-Oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid.

30

Procedure 12

The crude oil of 3-Oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid (0.46 g, 2.7 mmol) was dissolved in MeCN (27.0 mL) and HOBt (0.406 g, 3.0 mmol), HBTU (2.1 g, 6.0 mmol), and Et₃N (0.84 mL, 6.0 mmol) were added and the mixture stirred at room temperature for 15 min. 2-(S)-Amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester (1.6 g, 3.3 mmol) and the mixture stirred at room temperature for 18 h. The mixture was diluted with DCM and washed with 1N HCl. The organic layers were dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude oil was dissolved in THF (1.5 mL) and stirred at room temperature. LiOH (20.0 mg, 0.48 mmol) was dissolved in H₂O (3.0 mL) and added to the THF solution. After stirring for 1 h at room temperature the mixture was acidified with 1N HCl and extracted with DCM. The organic layers were dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude oil was purified using a reversed phase Gilson containing a Kromasil column (10 μ , 100Å C18, column length 250x50 mm, gradient 90:10 H₂O:MeCN) to give the title compound (**18**). ¹H NMR (300 MHz, CDCl₃) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.36-7.49 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.66-4.73 (m, 2H), 3.24-3.31 (m, 1H), 3.00-3.24 (m, 1H), 2.72-2.86 (m, 3H), and 2.55-2.61 (m, 1H); MS (ES⁺) 505.

Example 12

3-{4-[(3,5-Dichloro-pyridine-4-carbonyl)-amino]-phenyl}-2-(S)-[(3-oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid (Cpd 20)

Using the method described in Example 11, substituting 2-amino-3-{4-[(3,5-dichloro-pyridine-4-carbonyl)-amino]-phenyl}-propionic acid methyl ester (0.15 g) for 2-amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester in Procedure 12. Compound **20**: ¹H NMR (300 MHz, CDCl₃) δ 8.67 (s, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.68-4.75 (m,

2H), 3.27-3.33 (m, 1H), 3.03-3.25 (m, 1H), 2.75-2.92 (m, 3H), and 2.57-2.65 (m, 1H): MS (ES⁺) 506.

Example 13

5 **2-(S)-[(2-Benzyl-3-oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Cpd 19)**

Procedure 13

10 3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-(S)-[(3-oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid methyl ester (0.12 g, 0.2 mmol) was dissolved in MeCN (1.2 mL). Potassium carbonate (0.05 g, 0.4 mmol) and benzyl bromide (0.03 mL, 0.3 mmol) were added to the solution. The mixture was refluxed for 24 h, then cooled to room
15 temperature and filtered through CELITE[®]. The filtrate was concentrated in vacuo. The crude oil was dissolved in THF (1.3 mL) and stirred at room temperature. LiOH (20.0 mg, 0.48 mmol) was dissolved in H₂O (2.6 mL) and added to the THF solution. After stirring for 1 h at room temperature the mixture was acidified with 1N HCl and extracted with DCM. The organic layers
20 were dried over MgSO₄, filtered through CELITE[®], and concentrated in vacuo. The crude oil was purified using a Gilson HPLC containing a Kromasil column (10 μ , 100Å C18, column length 250x50 mm, gradient 90:10 H₂O:MeCN) to give Compound 18. ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.60 (m, 12H), 5.10-5.38 (m, 2H), 4.70-4.82 (m, 2H), and 2.73-3.27 (m, 6H): MS (ES⁺) 595.

25

Example 14

2-(S)-[(2-Benzyl-3-oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-[4-[(3,5-dichloro-pyridine-4-carbonyl)-amino]-phenyl]-propionic acid (Cpd 21)

30

Using the method described in Procedure 13, substituting 3-[4-[(3,5-Dichloro-pyridine-4-carbonyl)-amino]-phenyl]-2-(S)-[(3-oxo-2,5,6,7-tetrahydro-3H-

pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid methyl ester(0.08 g) for 3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-(S)-[(3-oxo-2,5,6,7-tetrahydro-3H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid methyl ester, the title compound **21** was prepared. ¹H NMR (300 MHz, CDCl₃) δ 8.61 (s, 2H), 7.16-7.63 (m, 9H), 5.11-5.48 (m, 2H), 4.56-4.87 (m, 2H), 3.30-3.34 (m, 1H), 2.88-3.08 (m, 4H), and 2.73-2.76 (m, 1H): MS (ES⁺) 596.

Example 15

10 **3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-(S)-[(3-propyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid (Cpd 10)**

Using the method described in Example 1, substituting (S)-methyl 2-pyrrolidone-5-carboxylate (1.0 g) for Compound **4a**, butyric acid hydrazide (0.76 g) for benzoic hydrazide in Procedure 3 and substituting 2-(S)-amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester (0.50 g) for Compound **7a** in Procedure 6, Compound **10** was prepared. ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.68 (m, 2H), 7.43-7.52 (m, 3H), 7.29-7.35 (m, 2H), 4.80-4.85 (m, 2H), 2.95-3.26 (m, 6H), 2.84 (t, *J* = 7.7 Hz, 1H), 2.54 (t, *J* = 7.2 Hz, 1H), 1.58-1.78 (m, 2H), and 1.02 (t, *J* = 7.3 Hz, 3H): MS (ES⁺) 531.

Example 16

25 **2-(S)-{[3-(Benzyloxycarbonylamino-methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Cpd 11)**

Using the method described in Example 1, substituting (S)-methyl 2-pyrrolidone-5-carboxylate (0.64 g) for Compound **4a**, hydrazinocarbonylmethyl-carbamic acid benzyl ester (1.0 g) for benzoic hydrazide in Procedure 3 and substituting 2-(S)-amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester (0.50 g) for Compound **7a** in Procedure 6, Compound **11** was

prepared. ^1H NMR (300 MHz, CDCl_3) δ 7.29-7.63 (m, 12H), 5.11 (s, 2H), 4.73-4.89 (m, 2H), 4.33 (s, 1H), and 2.95-3.41 (m, 6H): MS (ES^+) 652.

Example 17

5 **3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-(S)-[(3-thiophen-3-ylmethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid (Cpd 12)**

Using the method described in Example 1, substituting (S)-methyl 2-pyrrolidone-5-carboxylate (1.09 g) for Compound **4a**, thiophen-3-yl-acetic acid hydrazide (1.19 g) for benzoic hydrazide in Procedure 3 and substituting 2-(S)-amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester (0.50 g) for Compound **7a** in Procedure 6, Compound **12** was prepared. ^1H NMR (300 MHz, CDCl_3) δ 7.61 (d, J = 8.4 Hz, 2H), 7.47-7.56 (m, 4H), 7.45 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 4.9 Hz, 1H), 4.81-4.86 (m, 1H), 4.72-4.76 (m, 1H), 4.81-4.86 (m, 1H), 3.33-3.41 (m, 2H), 4.81-4.86 (m, 1H), 2.93-3.05 (m, 4H), and 2.05 (s, 2H): MS (ES^+) 585.

Example 18

20 **2-(S)-[(3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-3-(2',6'-dimethoxy-biphenyl-4-yl)-propionic acid (Cpd 13)**

3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid methyl ester was prepared using the method provided in Procedure 3, substituting (S)-methyl 2-pyrrolidone-5-carboxylate (3.0 g) for Compound **4a** and substituting phenylacetic hydrazide (2.17 g) for benzoic hydrazide.

Using the method described in Example 10, substituting 4-Bromo-L-phenylalanine (5.0 g) for 4-Borono-L-phenylalanine, and substituting 2,6-dimethoxyphenylboronic acid (4.1 g) for 4-Bromo-5-methoxy-2-methyl-2H-pyridazin-3-one in Procedure 8, 3-Benzyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid methyl ester was converted to Compound **13**. ^1H NMR (300 MHz, CDCl_3) δ 7.09-7.32 (m, 10 H), 6.67-6.72 (m, 2H), 4.70-4.77

(m, 2H), 3.66 (s, 2H), 3.61 (s, 6H), 4.81-4.86 (m, 1H), and 2.82-3.40 (m, 6H): MS (ES⁺) 527.

Example 19

5 **2-(S)-[(3-Aminomethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-**
 carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid
 (Cpd 14)

Compound **11** was dissolved in EtOAc (1.0 mL). 1N HCl (1.0 mL) and
10 10% Pd/C (5.0 mg) were added and the mixture was hydrogenated at 50 psi H₂
for 24 h. The mixture was filtered through CELITE® and concentrated in vacuo.
Compound **14** was isolated. ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.61 (m, 7 H),
4.78-4.89 (m, 2H), 3.32 (s, 2H), and 2.98-3.30 (m, 6H): MS (ES⁺) 518.

15 Example 20

**3-(2',6'-Dimethoxy-biphenyl-4-yl)-2-(S)-[(3-thiophen-3-ylmethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-(S)-carbonyl)-amino]-propionic acid
(Cpd 15)**

20 3-Thiophen-3-ylmethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-
carboxylic acid methyl ester was prepared using the method provided in
Procedure 3, substituting (S)-methyl 2-pyrrolidone-5-carboxylate (2.0 g) for
Compound **4a** and substituting thiophen-3-yl-acetic acid hydrazide (2.29 g) for
25 benzoic hydrazide.

Using the method described in Example 10, substituting 4-Bromo-L-phenylalanine (5.0 g) for 4-Borono-L-phenylalanine, and substituting 2,6-dimethoxyphenylboronic acid (4.1 g) for 4-Bromo-5-methoxy-2-methyl-2H-pyridazin-3-one in Procedure 8, 3-Thiophen-3-ylmethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-carboxylic acid methyl ester was converted to the title compound **15**. ¹H NMR (300 MHz, CDCl₃) δ 7.19-7.33 (m, 6 H), 6.70-6.76 (m, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 4.64-4.69 (m, 1H), 4.31-4.36 (m, 1H), 3.94-

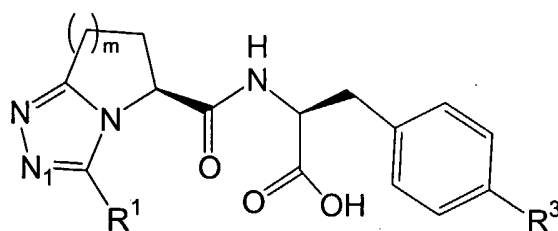
4.00 (m, 1H), 3.65-3.71 (m, 1H), 3.61 (s, 6H), 3.37 (s, 2H), and 2.74-3.01 (m, 4H): MS (ES⁺) 533.

Example 21

5 3-(2',6'-Dimethoxy-biphenyl-4-yl)-2-{[3-(1H-indol-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-5-carbonyl]-amino}-propionic acid (Cpd 16)

Using the method described in Example 20, substituting (1H-Indol-3-yl)-
 10 acetic acid hydrazide (2.79 g) for thiophen-3-yl-acetic acid hydrazide in Procedure 3, the title compound **16** was prepared. ¹H NMR (300 MHz, CDCl₃) δ 7.11-7.35 (m, 8 H), 7.02-7.07 (m, 1H), 6.69-6.93 (m, 2H), 4.71-4.84 (m, 1H), 4.15-4.20 (m, 1H), 4.00-4.03 (m, 1H), 3.84-3.94 (m, 1H), 3.61 (s, 6H), 3.36 (s, 2H), 2.90-2.98 (m, 1H), 2.54-2.69 (m, 2H), and 2.08-2.19 (m, 1H): MS (ES⁺)
 15 566.

Compounds 1 to 17 of Formula (Ia) were prepared by the methods described in the schemes and specific examples described herein.



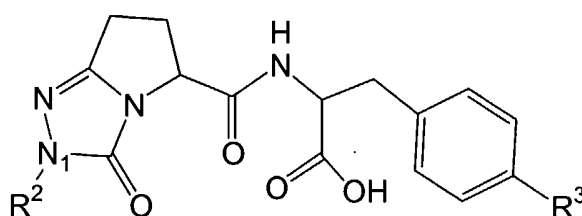
Formula (Ia)

Table 1

Cpd	R ¹	m	R ³
1	Phenyl	2	-O(C=O)NMe ₂
2	-CH ₂ Ph	2	-O(C=O)NMe ₂
3	-CH ₂ Ph	1	-O(C=O)NMe ₂
4	-CH ₂ Ph	1	-NH(C=O)2,6-dichlorophenyl

Cpd	R ¹	m	R ³
5	-CH ₂ Ph	1	-NH(C=O)naphthalen-1-yl
6	-CH ₂ Ph	1	-NH(C=O)naphthalen-2-yl
7	-CH ₂ Ph	1	-NH(C=O)(2-ethoxy-naphthalen-1-yl)
8	-CH ₂ Ph	1	-NH(C=O)fluoren-9-on-4-yl
9	-CH ₂ Ph	1	-NHC(=O)3,5-dichloro pyridin-4yl
10	n-Propyl	1	-NH(C=O)2,6-dichlorophenyl
11	-CH ₂ NH(C=O)Obenzyl	1	-NH(C=O)2,6-dichlorophenyl
12	-CH ₂ -thiophen-3-yl	1	-NH(C=O)2,6-dichlorophenyl
13	-CH ₂ Ph	1	2,6-methoxyphenyl
14	-CH ₂ NH ₂	1	-NH(C=O)2,6-dichlorophenyl
15	-CH ₂ -thiophen-3-yl	1	2,6-methoxyphenyl
16	-CH ₂ -indol-3-yl	1	2,6-methoxyphenyl
17	-CH ₂ Ph	1	5-methoxy-2-methyl-2H- pyridazin-3-on-4-yl

Compounds 18 to 21 of Formula (Ib) were prepared by the methods
5 described in the schemes and specific examples described herein.



Formula (Ib)

Table 2

Cpd	R ²	R ³
18	H	-NH(C=O)2,6-dichlorophenyl
19	-CH ₂ Ph	-NH(C=O)2,6-dichlorophenyl
20	H	-NHC(=O)3,5-dichloropyridin-4yl
21	-CH ₂ Ph	-NHC(=O)3,5-dichloropyridin-4yl

5

Biological Examples

As demonstrated by the biological studies described hereinafter, and shown in Table 3, the compounds of the present invention are $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor antagonists useful in treating integrin mediated disorders including, but not limited to, inflammatory, autoimmune and cell-proliferative disorders.

10

Example 1

15

Ramos Cell Adhesion Assay ($\alpha 4\beta 1$ Mediated Adhesion / VCAM-1)

Immulon 96 well plates (Dynex) were coated with 100 μ L recombinant hVCAM-1 at 4.0 μ g/mL in 0.05 M NaCO₃ buffer pH 9.0 overnight at 4°C (R&D Systems). Plates were washed 3 times in PBS with 1 % BSA and blocked for 1 h @ room temperature in this buffer. PBS was removed and compounds to be tested (50 μ L) were added at 2X concentration. Ramos cells, (50 μ L at 2 X 10⁶/mL) labeled with 5 μ M Calcein AM (Molecular Probes) for 1 h at 37 °C, were added to each well and allowed to adhere for 1 h at room temperature. Plates were washed 3 X in PBS + 1 % BSA and cells were lysed for 15 minutes in 100 μ L of

20

1 M Tris pH 8.0 with 1 % SDS. The plate was read at 485 nm excitation and 530 nm emission. The resultant data is shown in Table 1.

Example 2

5 *$\alpha_4\beta_7$ -K562 Cell Adhesion Assay ($\alpha_4\beta_7$ Mediated Adhesion / MAdCAM-1)*

M2 anti-FLAG antibody coated 96-well plates (Sigma) were coated for 1 hour at 4 °C with 2-8 μ L / well recombinant FLAG-hMAdCAM-1 contained in 100 μ L of Dulbecco's PBS, pH 7.4, with 1% BSA and 1 mM Mn^{2+} (PBS-BSA-Mn).

Plates were washed once with PBS-BSA-Mn. Buffer was removed and

10 compounds to be tested (50 μ L) were added at 2 times concentration. Stably transfected K562 cells expressing human $\alpha_4\beta_7$ integrin, (50 μ L at 2×10^6 /mL) that had been labeled with 100 μ g/mL carboxymethyl fluorescein diacetate succinimidyl ester (CFDA-SE; Molecular Probes) for 15 min at 37 °C were added to each well and allowed to adhere for 1 h at room temperature. Plates
15 were washed 4 times in PBS-BSA-Mn and then cells were lysed for 2 minutes by addition of 100 μ L of PBS without Ca, Mg supplemented with 0.1 M NaOH. The plate was read on a 96-well fluorescent plate reader at 485 nm excitation and 530 nm emission. The resultant data is shown in Table 3.

20 Table 3

Cpd	$\alpha_4\beta_7$, Madcam	
	$\alpha_4\beta_1$ IC50 (μ M)	IC50 (μ M)
1	3.30	1.22
2	5.09	1.66
3	4.15	>5
4	0.62	0.29
5	>5	>5
6	>5	>5
7	>5	>5
8	1.56	0.35

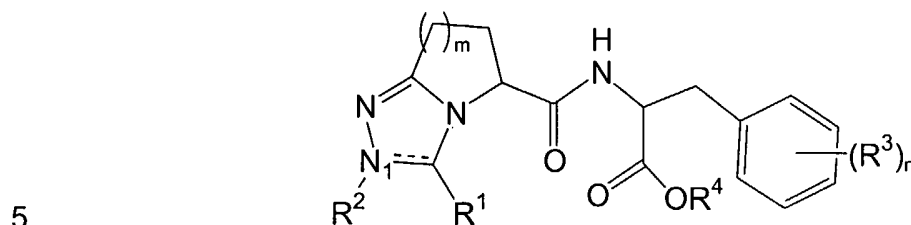
Cpd	$\alpha 4\beta 7$, Madcam	
	$\alpha 4\beta 1$ IC50 (μ M)	IC50 (μ M)
9	0.08	0.02
10	1.04	0.08
11	>5	0.55
12	0.38	0.12
13	1.19	0.32
14	>5	0.00
15	0.71	0.09
16	>5	0.04
17	0.64	0.40
18	0.85	0.09
19	>5	0.20
20	0.45	0.05
21	>5	0.78

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

All publications disclosed in the above specification are hereby incorporated by reference in full.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

- 10 R^1 is a substituent selected from the group consisting of hydrogen, C_{1-4} alkyl, aryl(C_{1-8})alkyl, heteroaryl(C_{1-8})alkyl, aryl, amino(C_{1-4})alkyl, (C_{1-4})alkylamino(C_{1-4})alkyl, di(C_{1-4})alkylamino(C_{1-4})alkyl, aryl(C_{1-4})alkoxycarbonylamino(C_{1-4})alkyl, heteroaryl(C_{1-4})alkoxycarbonylamino(C_{1-4})alkyl, C_{1-4} alkoxycarbonylamino(C_{1-4})alkyl, aryloxycarbonylamino(C_{1-4})alkyl, and oxo; wherein the C_{1-4} alkyl substituents of di(C_{1-4})alkylamino(C_{1-4})alkyl are optionally taken together with the nitrogen atom to which they are both
- 15 attached to form a 5 to 8 membered monocyclic ring;

provided that when R^1 is a substituent other than oxo, a double bond exists between N_1 and the carbon bearing R^1 ; alternatively, when R^1 is oxo, then R^2 is present;

20

- R^2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, aryl(C_{1-4})alkyl, and heteroaryl(C_{1-4})alkyl;

m is an integer of 1 or 2;

25

- R^3 is a substituent independently selected from the group consisting of C_{1-8} alkoxy, heterocyclyl, aryl, heteroaryl, benzo-fused heterocyclyl, $-C(=O)NR^A R^B$, $-NR^A C(=O)$ aryl, $-NR^A C(=O)$ heteroaryl, $-NR^A C(=O)$ heterocyclyl,
- 30 $-NR^A C(=O)C_{1-8}$ alkyl, $-NR^A C(=O)C_{2-8}$ alkenyl, $-NR^A C(=O)C_{2-8}$ alkynyl,

-NR^A(C=O)C₁₋₈alkoxy, -NR^A(C=O)C₁₋₈alkoxyaryl,
 -NR^A(C=O)C₁₋₈alkoxyheteroaryl, -NR^ASO₂-aryl, -NR^ASO₂-heteroaryl,
 -NR^ASO₂(C₁₋₈)alkyl, -NR^AC(=O)NR^AR^B, -NR^AC(=O)NR^Aaryl,
 -NR^AC(=O)NR^Aheteroaryl, -OC(=O)NR^AR^B, and halogen;

5

wherein heterocyclyl and the heterocyclyl-containing substituents of R³, aryl
 and the aryl-containing substituents of R³, benzo-fused heterocyclyl, and
 heteroaryl and the heteroaryl-containing substituents of R³ are optionally
 substituted with one to five substituents independently selected from the
 10 group consisting of halogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy,
 C₁₋₈alkylcarbonyl, C₁₋₈alkoxycarbonyl, carboxyl, aryl, heteroaryl, aryloxy,
 heteroaryloxy, cycloalkyloxy, heterocycliloxy, benzyloxycarbonyl,
 arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, C₁₋₈alkylamino,
 C₁₋₈dialkylamino, -CF₃ and -OCF₃; provided that no more than one
 15 substituent is selected from the group consisting of aryl, heteroaryl, aryloxy,
 heteroaryloxy, cycloalkyloxy, heterocycliloxy, benzyloxycarbonyl,
 arylcarbonyl, heteroarylcarbonyl, and arylsulfonyl;

and, wherein heterocyclyl of the heterocyclyl-containing substituents of R³ is
 20 optionally further substituted with one to three oxo substituents;

R^A is independently selected from the group consisting of hydrogen and C₁₋₈
 alkyl;

25 R^B is independently selected from the group consisting of hydrogen, C₁₋₈alkyl,
 C₂₋₈alkenyl, C₂₋₈alkynyl, and (halo)₁₋₃(C₁₋₈)alkyl; wherein C₁₋₈alkyl,
 C₂₋₈alkenyl and C₂₋₈alkynyl are optionally substituted with one to three
 substituents independently selected from the group consisting of
 heterocyclyl, aryl, and heteroaryl wherein the heterocyclyl, aryl, and
 30 heteroaryl substituents are optionally substituted with benzyloxycarbonyl,
 arylcarbonyl, or heteroarylcarbonyl, and optionally substituted with one to
 three substituents independently selected from the group consisting of

halogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, C₁₋₈alkylcarbonyl, C₁₋₈alkoxycarbonyl, carboxyl, -CF₃ and -OCF₃;

n is an integer from 0 to 3;

5

R⁴ is a substituent independently selected from the group consisting of hydrogen and C₁₋₄alkyl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates,
10 solvates, hydrates, polymorphs, and salts thereof.

2. A compound according to claim 1 wherein R¹ is independently selected from the group consisting of hydrogen, C₁₋₄alkyl, aryl(C₁₋₈)alkyl, heteroaryl(C₁₋₈)alkyl, aryl, and oxo; provided that when R¹ is a substituent other than oxo, a
15 double bond exists between N₁ and the carbon bearing R¹; alternatively, when R¹ is oxo, then R² is present.

3. A compound according to claim 2 wherein R¹ is independently selected from the group consisting of C₁₋₄alkyl, aryl(C₁₋₄)alkyl, heteroaryl(C₁₋₄)alkyl, aryl, and oxo;.
20

4. A compound according to claim 3 wherein aryl is phenyl.

5. A compound according to claim 4 wherein C₁₋₄alkyl is propyl, aryl(C₁₋₄)alkyl is benzyl, heteroaryl(C₁₋₄)alkyl is selected from the group consisting of thiophen-3-ylmethyl and indol-3-ylmethyl.
25

6. A compound according to claim 1 wherein R² is independently selected from the group consisting of hydrogen, C₁₋₄alkyl, and aryl(C₁₋₄)alkyl.
30

7. A compound according to claim 6 wherein R² is independently selected from the group consisting of hydrogen and aryl(C₁₋₄)alkyl.

8. A compound according to claim 7 wherein aryl(C₁₋₄)alkyl is benzyl.
9. A compound according to claim 1 wherein m is 1.
- 5 10. A compound according to claim 1 wherein R³ is a substituent independently selected from the group consisting of C₁₋₆alkoxy, -C(=O)NR^AR^B, -NR^AC(=O)aryl, -NR^AC(=O)heteroaryl, -NR^AC(=O)heterocyclyl, -NR^AC(=O)C₁₋₈alkyl, -NR^ASO₂-aryl, -NR^ASO₂-heteroaryl, -NR^ASO₂(C₁₋₈)alkyl, -NR^AC(=O)NR^AR^B, -NR^AC(=O)NR^Aaryl, -NR^AC(=O)NR^Aheteroaryl, 10 -OC(=O)NR^AR^B, and halogen; wherein the heterocyclyl portion of -NR^AC(=O)heterocyclyl, the aryl portion of the aryl-containing substituents of R³, and the heteroaryl portion of the heteroaryl-containing substituents of R³ are optionally substituted with one to three substituents independently selected from the group consisting of halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylcarbonyl, 15 C₁₋₄alkoxycarbonyl, amino, C₁₋₈alkylamino, C₁₋₈dialkylamino, -CF₃ and -OCF₃; and, wherein heterocyclyl of -NR^AC(=O)heterocyclyl is optionally further substituted with one to two oxo substituents.
11. A compound according to claim 10 wherein R³ is a substituent 20 independently selected from the group consisting of C₁₋₃alkoxy, -C(=O)NR^AR^B, -NR^AC(=O)aryl, -NR^AC(=O)heteroaryl, -NR^AC(=O)C₁₋₄alkyl, -NR^ASO₂-aryl, -NR^ASO₂-heteroaryl, -NR^ASO₂(C₁₋₄)alkyl, -OC(=O)NR^AR^B, and halogen; wherein the aryl portion of the aryl-containing substituents of R³, and the heteroaryl portion of the heteroaryl-containing substituents of R³ are optionally 25 substituted with one to three substituents independently selected from the group consisting of halogen, C₁₋₄alkyl, C₁₋₄alkoxy, and C₁₋₄alkoxycarbonyl.
12. A compound according to claim 11 wherein R³ is a substituent independently selected from the group consisting of NR^AC(=O)aryl, - 30 NR^AC(=O)heteroaryl, -NR^AC(=O)C₁₋₄alkyl, and -OC(=O)NR^AR^B.

13. A compound according to claim 12 wherein $\text{NR}^{\text{A}}\text{C}(=\text{O})\text{aryl}$ is selected from the group consisting of $-\text{NR}^{\text{A}}\text{C}(=\text{O})\text{phenyl}$ and $-\text{NR}^{\text{A}}\text{C}(=\text{O})\text{naphthalenyl}$, $-\text{NR}^{\text{A}}\text{C}(=\text{O})\text{heteroaryl}$ is $-\text{NR}^{\text{A}}\text{C}(=\text{O})\text{pyridin-4-yl}$, and $-\text{OC}(=\text{O})\text{NR}^{\text{A}}\text{R}^{\text{B}}$ is $-\text{OC}(=\text{O})\text{NMe}_2$.

5

14. A compound according to Claim 13 wherein in the optional substituents, halogen is chloro, $\text{C}_{1-4}\text{alkyl}$ methyl, $\text{C}_{1-4}\text{alkoxy}$ is methoxy or ethoxy, and $\text{C}_{1-4}\text{alkoxycarbonyl}$ is methoxy carbonyl.

10 15. A compound according to claim 12 wherein R^3 is a substituent independently selected from the group consisting of $\text{NR}^{\text{A}}\text{C}(=\text{O})\text{aryl}$ and $-\text{NR}^{\text{A}}\text{C}(=\text{O})\text{heteroaryl}$.

15 16. A compound according to claim 15 wherein $\text{NR}^{\text{A}}\text{C}(=\text{O})\text{aryl}$ is selected from the group consisting of $-\text{NHC}(=\text{O})2,6\text{-dichloro-phenyl}$, $-\text{NHC}(=\text{O})2,6\text{-dimethoxy-phenyl}$, $-\text{NHC}(=\text{O})\text{naphthalen-1-yl}$, $\text{NHC}(=\text{O})2\text{-ethoxy-naphthalen-1-yl}$, and $-\text{NHC}(=\text{O})\text{naphthalen-2-yl}$, and $\text{NR}^{\text{A}}\text{C}(=\text{O})\text{heteroaryl}$ is $-\text{NHC}(=\text{O})3,5\text{-dichloro-pyridin-4-yl}$.

20 17. A compound according to claim 16 wherein R^3 is attached at the 4-position of the phenyl ring of Formula (I).

18. A compound according to claim 1 wherein R^{A} is independently selected from the group consisting of hydrogen and methyl.

25

19. A compound according to claim 1 wherein R^{B} is independently selected from the group consisting of hydrogen, $\text{C}_{1-6}\text{alkyl}$, and $(\text{halo})_{1-3}(\text{C}_{1-6})\text{alkyl}$; wherein $\text{C}_{1-6}\text{alkyl}$ is optionally substituted with one to three substituents independently selected from the group consisting of heterocyclyl, aryl, and heteroaryl; wherein the heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with benzyloxycarbonyl, arylcarbonyl, heteroarylcarbonyl, and optionally further substituted with one to three substituents independently

30

selected from the group consisting of halogen, C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkylcarbonyl, C₁₋₈alkoxycarbonyl, carboxyl, -CF₃ and -OCF₃.

20. A compound according to claim 19 wherein R^B is independently
5 selected from the group consisting of hydrogen and C₁₋₆alkyl.

21. A compound according to claim 20 wherein C₁₋₆alkyl is C₁₋₄alkyl.

22. A compound according to claim 21 wherein C₁₋₄alkyl is optionally
10 substituted with one to three substituents independently selected from the group consisting of heterocyclyl, aryl, and heteroaryl.

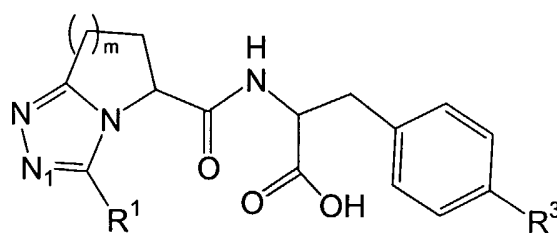
23. A compound according to claim 1 wherein n is an integer from 0 to 2.

15 24. A compound according to claim 23 wherein n is 1.

25. A compound according to claim 1 wherein R⁴ is a substituent independently selected from the group consisting of hydrogen and C₁₋₄alkyl.

20 26. A compound according to claim 25 wherein C₁₋₄alkyl is methyl.

27. A compound of Formula (Ia):



Formula (Ia)

selected from the group consisting of:

- a compound of Formula (Ia) wherein R¹ is phenyl, m is 2, and R³ is -O(C=O)NMe₂;
- a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 2, and R³ is -O(C=O)NMe₂;
- 5 a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is -O(C=O)NMe₂;
- a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is -NH(C=O)2,6-dichlorophenyl;
- 10 a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is -NH(C=O)naphthalen-1-yl;
- a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is -NH(C=O)naphthalen-2-yl;
- a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is -NH(C=O)(2-ethoxy)-naphthalen-1-yl;
- 15 a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is -NH(C=O)fluoren-9-on-4-yl;
- a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is -NHC(=O)(3,5-dichloro)-pyridin-4-yl;
- a compound of Formula (Ia) wherein R¹ is *n*-propyl, m is 1, and R³ is -NH(C=O)2,6-dichlorophenyl;
- 20 a compound of Formula (Ia) wherein R¹ is -CH₂NH(C=O)OCH₂Ph, m is 1, and R³ is -NH(C=O)2,6-dichlorophenyl;
- a compound of Formula (Ia) wherein R¹ is -CH₂-thiophen-3-yl, m is 1, and R³ is -NH(C=O)2,6-dichlorophenyl;
- 25 a compound of Formula (Ia) wherein R¹ is -CH₂Ph, m is 1, and R³ is 2,6-dimethoxy-phenyl;
- a compound of Formula (Ia) wherein R¹ is -CH₂NH₂, m is 1, and R³ is -NH(C=O)2,6-dichlorophenyl;
- a compound of Formula (Ia) wherein R¹ is -CH₂-thiophen-3-yl, m is 1, and R³ is 2,6-dimethoxy-phenyl;
- 30 a compound of Formula (Ia) wherein R¹ is -CH₂-indol-3-yl, m is 1, and R³ is 2,6-dimethoxy-phenyl;

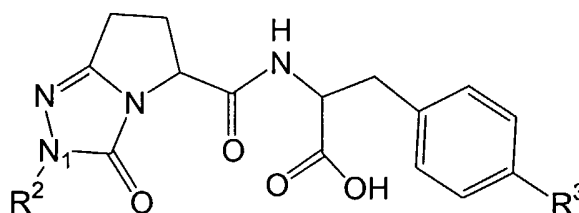
and

a compound of Formula (Ia) wherein R^1 is $-\text{CH}_2\text{Ph}$, m is 1, and R^3 is 5-methoxy-2-methyl-2H-pyridazin-3-on-4-yl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates,

5 solvates, hydrates, polymorphs, and salts thereof.

28. A compound of Formula (Ib):



10 Formula (Ib)

selected from the group consisting of

a compound of Formula (Ib) wherein R^2 is H and R^3 is $-\text{NH}(\text{C}=\text{O})2,6$ -dichloro-phenyl;

a compound of Formula (Ib) wherein R^2 is $-\text{CH}_2\text{Ph}$ and R^3 is -

15 $\text{NH}(\text{C}=\text{O})2,6$ -dichloro-phenyl;

a compound of Formula (Ib) wherein R^2 is H and R^3 is $-\text{NHC}(=\text{O})3,5$ -dichloro-pyridin-4-yl;

and

a compound of Formula (Ib) wherein R^2 is $-\text{CH}_2\text{Ph}$ and R^3 is -

20 $\text{NHC}(=\text{O})3,5$ -dichloro-pyridin-4-yl;

and pharmaceutically acceptable enantiomers, diastereomers,

racemates, solvates, hydrates, polymorphs, and salts thereof.

25 29. A compound of claim 1 wherein the compound is an effective antagonist of an integrin receptor.

30. A compound of claim 29 wherein the compound is a selective antagonist of an $\alpha 4$ integrin receptor.
31. A compound of claim 30 wherein the $\alpha 4$ integrin receptor is selected from the group consisting of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptors.
32. A compound of claim 29 wherein the compound is an antagonist of at least two $\alpha 4$ integrin receptors.
33. A compound of claim 32 wherein the two $\alpha 4$ integrin receptors are selected from the group consisting of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptors.
34. A compound of claim 1 wherein the compound is an effective agent for the treatment of an integrin mediated disorder selected from the group consisting of inflammatory disorders, autoimmune disorders, and cell-proliferative disorders.
35. A compound of claim 1 wherein the the compound is an effective agent for the treatment of an integrin mediated disorder is selected from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, irritable bowel disease, irritable bowel syndrome, transplant rejection and multiple sclerosis.
36. A compound of claim 35 wherein the integrin mediated disorder is selected from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, irritable bowel syndrome, and multiple sclerosis.
37. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

38. A method for the treatment of an integrin mediated disorder ameliorated by inhibition of an $\alpha 4$ integrin receptor comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.
- 5 39. A method for the treatment of claim 38 wherein the integrin mediated disorder is selected from the group consisting of inflammatory disorders, autoimmune disorders, and cell-proliferative disorders.
- 10 40. A method for the treatment of claim 38 wherein the integrin mediated disorder is selected from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, irritable bowel disease, irritable bowel syndrome, transplant rejection and multiple sclerosis.
- 15 41. A method for the treatment of claim 40 wherein the integrin mediated disorder is selected from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, irritable bowel syndrome, and multiple sclerosis.
- 20 42. A method of claim 38 wherein the compound inhibiting the $\alpha 4$ integrin receptor is selected from the group consisting of a selective antagonist of the $\alpha 4\beta 1$ integrin receptor, a selective antagonist of the $\alpha 4\beta 7$ integrin receptor, and an antagonist of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptors.
- 25 43. A method of claim 38 wherein the therapeutically effective amount of the compound of claim 1 is from about 0.01 mg/kg/day to about 300 mg/kg/day.
44. A use of a compound of claim 1 for the preparation of a medicament for the treatment of an integrin mediated disorder in a subject in need thereof.
- 30 45. A use of claim 44 wherein the integrin mediated disorder is selected from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease,

irritable bowel disease, irritable bowel syndrome, transplant rejection or multiple sclerosis.

46. A use of claim 45 wherein the integrin mediated disorder is selected
5 from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, irritable bowel syndrome, and multiple sclerosis.