Title: N,N-DISUBSTITUTED AMIDES THAT INHIBIT THE BINDING OF INTEGRINS TO THEIR RECEPTORS

Abstract

A method for the inhibition of the binding of α₄β₁ integrin to its receptors, for example VCAM-1 (vascular cell adhesion molecule-1) and fibronectin; compounds that inhibit this binding; pharmaceutically active compositions comprising such compounds; and the use of such compounds either as above, or in formulations for the control or prevention of diseases states in which α₄β₁ is involved.
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N, N-DISUBSTITUTED AMIDES THAT INHIBIT THE BINDING OF INTEGRINS TO THEIR RECEPTORS

Cross-Reference to Related Application

This application is a continuation-in-part of co-pending U.S. Provisional Application No. 60/082019, filed April 16, 1998.

Field of the Invention

This invention is directed generally to the inhibition of the binding of $\alpha_4\beta_1$ integrin to its receptors, for example VCAM-1 (vascular cell adhesion molecule-1) and fibronectin. The invention also relates to compounds that inhibit this binding; to pharmaceutically active compositions comprising such compounds; and the use of such compounds either as above, or in formulations for the control or prevention of disease states in which $\alpha_4\beta_1$ is involved.

Background of the Invention

When a tissue has been invaded by a microorganism or has been damaged, white blood cells, also called leukocytes, play a major role in the inflammatory response. One of the most important aspects of the inflammatory response involves the cell adhesion event. Generally, white blood cells are found circulating through the bloodstream. However, when a tissue is infected or becomes damaged, the white blood cells recognize the invaded or damaged tissue, bind to the wall of the capillary and migrate through the capillary into the affected tissue. These events are mediated by a family of proteins called cell adhesion molecules.

There are three main types of white blood cells: granulocytes, monocytes and lymphocytes. The integrin $\alpha_4\beta_1$ (also called VLA-4 for very late antigen-4) is a heterodimeric protein expressed on the surface of monocytes, lymphocytes and two subclasses of granulocytes: eosinophils and basophils.
This protein plays a key role in cell adhesion through its ability to recognize and bind VCAM-1 and fibronectin, proteins associated with the endothelial cells that line the interior wall of capillaries.

Following infection or damage of tissue surrounding a capillary, endothelial cells express a series of adhesion molecules, including VCAM-1, that are critical for binding the white blood cells that are necessary for fighting infection. Prior to binding to VCAM-1 or fibronectin, the white blood cells initially bind to certain adhesion molecules to slow their flow and allow the cells to “roll” along the activated endothelium. Monocytes, lymphocytes, basophils and eosinophils are then able to firmly bind to VCAM-1 or fibronectin on the blood vessel wall via the $\alpha_4\beta_1$ integrin. There is evidence that such interactions are also involved in transmigration of these white blood cells into the damaged tissue, as well as the initial rolling event itself.

Although white blood cell migration to the site of injury helps fight infection and destroy foreign material, in many instances this migration can become uncontrolled, with white blood cells flooding to the scene, causing widespread tissue damage. Compounds capable of blocking this process, therefore, may be beneficial as therapeutic agents. Thus, it would be useful to develop inhibitors that would prevent the binding of white blood cells to VCAM-1 and fibronectin.

Some of the diseases that might be treated by the inhibition of $\alpha_4\beta_1$ binding include, but are not limited to, atherosclerosis, rheumatoid arthritis, asthma, allergy, multiple sclerosis, lupus, inflammatory bowel disease, graft rejection, contact hypersensitivity, and type I diabetes. In addition to being found on some white blood cells, $\alpha_4\beta_1$ is also found on various cancer cells, including leukemia, melanoma, lymphoma and sarcoma cells. It has been suggested that cell adhesion involving $\alpha_4\beta_1$ may be involved in the metastasis of certain cancers. Inhibitors of $\alpha_4\beta_1$ binding may, therefore, also be useful in the treatment of some forms of cancer.

The isolation and purification of a peptide which inhibits the binding of $\alpha_4\beta_1$ to a protein is disclosed in U.S. Patent No. 5,510,332. Peptides
which inhibit binding are disclosed in WO 95/15973, EP 0 341 915, EP 0 422
which are useful for inhibition and prevention of cell adhesion and cell
adhesion-mediated pathologies are disclosed in WO 96/22966, WO 98/04247
and WO 98/04913.

It is therefore an object of the invention to provide novel
compounds which are inhibitors of \( \alpha_4 \beta_1 \) binding, and pharmaceutical
compositions including such novel compounds.

Brief Summary of the Invention

The invention is directed to novel compounds of Formula I as follows:

\[
\begin{align*}
\text{formula image}
\end{align*}
\]

Formula I

wherein A is selected from the group consisting of O, S, and NR^6;
E is selected from the group consisting of CH\_2, O, S, and
NR^7;
each J is independently selected from the group consisting of
O, S and NR^8;
s and t are each integers independently of 0 to 3;
T is selected from the group consisting of C(O) and (CH\_2)\_v
wherein v is an integer of 0 to 3;
L is selected from the group consisting of O, NR^9, S, and (CH\_2)\_w
wherein w is an integer of 0 or 1;
M is selected from the group consisting of C(R^{10})(R^{11}) and (CH\_2)\_v
wherein \( v \) is an integer of 0 to 3;

\( X \) is selected from the group consisting of \( \text{CO}_2\text{B}, \text{PO}_3\text{H}, \text{SO}_3\text{H}, \text{OPPO}_3\text{H}, \text{C(O)NH}_2\text{C(O)}\text{R}^{12}, \text{C(O)NSO}_3\text{R}^{13} \), tetrazolyl and hydrogen;

\[ B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} \text{ and } R^{13} \]

are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkoxy, cycloalkylalkyl, alkylamino, haloalkyl, alkylaryl, arylalkyl, heterocyclyl, heterocyclylalkyl and alkylheterocyclyl groups;

\[ \text{wherein } R^1 \text{ and } R^2 \text{ taken together may form a ring; } \]
\[ R^3 \text{ and } R^4 \text{ taken together may form a ring; } \]
\[ R^5 \text{ and } R^9 \text{ taken together may form a ring; } \]
\[ R^{10} \text{ and } R^{11} \text{ taken together may form a ring; } \]

and salts thereof.

Preferably, for formula I, \( M \) is \( \text{C(R}^{10})(\text{R}^{11}) \);
\[ X \text{ is } \text{CO}_2\text{B}; \]
\[ A \text{ is } \text{NR}^6; \]
\[ E \text{ is } \text{NR}^7; \]
\[ \text{each } J \text{ is } \text{O}; \]

\[ s \text{ and } t \text{ each are } 1; \]
\[ R^1, R^2 \text{ and } R^3 \text{ are aryl, alkylaryl, arylalkyl, heterocyclyl alkylheterocyclyl, heterocyclylalkyl or alkyl; } \]
\[ R^3 \text{ and } R^4 \text{ are hydrogen, alkoxy, alkoxyalkyl, aryl, alkylaryl, arylalkyl, heterocyclyl or alkyl; and, } \]
\[ R^6 \text{ and } R^7 \text{ are hydrogen and lower alkyl. } \]

Presently preferred compounds are those of Formula II below.
wherein A is selected from the group consisting of O, S, and NR$_5$;
E is selected from the group consisting of CH$_2$, O, S, and NR$_7$;
each J is independently selected from the group consisting of O, S and NR$_8$;
T is selected from the group consisting of C(O) and (CH$_2$)$_v$, wherein v is an integer of 0 or 1;
L is selected from the group consisting of O, NR$_5$, S, and (CH$_2$)$_w$, wherein w is an integer of 0 or 1;
s and t are each integers independently of 0 to 3;
B, R$_1$, R$_2$, R$_3$, R$_4$, R$_5$, R$_6$, R$_7$, R$_8$, R$_9$, R$_{10}$ and R$_{11}$ are independently selected from the group consisting of hydrogen, alkyl,
cycloalkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkoxy,
cycloalkylalkyl, alkylamino, haloalkyl, alkylaryl, arylalkyl,
heterocyclyl, heterocyclylalkyl and alkylheterocyclyl groups;
wherein R$_1$ and R$_2$ can be linked to form a ring;
R$_3$ and R$_4$ taken together may form a ring;
R$_5$ and R$_9$ taken together may form a ring;
R\textsuperscript{10} and R\textsuperscript{11} taken together may form a ring; and salts thereof.

Preferably, for formula II above,

A is NR\textsuperscript{6};

E is NR\textsuperscript{7};

each J is O;

s and t are 1;

R\textsuperscript{1} and R\textsuperscript{2} are aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl or alkyl;

R\textsuperscript{3} and R\textsuperscript{4} are hydrogen, alkoxy, alkoxalkyl, aryl, alkylaryl, arylalkyl, heterocyclyl or alkyl;

R\textsuperscript{6}, R\textsuperscript{7}, R\textsuperscript{10}, R\textsuperscript{11} and B are hydrogen or lower alkyl; and

R\textsuperscript{5} is aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl or alkyl.

More preferably, the compounds have the structure:

![formula III](image)

wherein substituents, as well as preferred compounds are as defined above for formula II.

Particularly preferred compounds have the following substituents: R\textsuperscript{1} and R\textsuperscript{2} are independently selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl and alkyl; R\textsuperscript{5} is selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl and alkyl; R\textsuperscript{6} and R\textsuperscript{7} are independently selected from the group consisting of
hydrogen and lower alkyl; B, R^{10} and R^{11} are independently selected from
the group consisting of hydrogen and lower alkyl; and R^{3} and R^{4} are selected from
the group consisting of hydrogen, alkoxy, alkoxyalkoxy, aryl, alkylaryl,
arylalkyl, heterocyclyl and alkyl.

Presently preferred compounds are: (3S)-3-(1,3-benzodioxol-5-yl)-3-
((((1S)-1-((bis(2-thienylmethyl)amino)carbonylpentyl)amino)carbonyl)
amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(1,3-
thiazol-2-ylmethyl)(2-thienylmethyl)amino]carbonylpentyl)amino)carbonyl)
amino)propanoic acid, (3S)-3-(((1S)-1-((bis(2-thienylmethyl)
amino)carbonylpentyl)amino)carbonyl)amino)-4-morpholino-4-oxobutanoic acid, (3R)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((bis(2-
thienylmethyl)amino)carbonylpentyl)amino)carbonyl)amino)-2,2-
dimethylpropanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-
[(diallylamino)carbonylpentyl]amino)carbonyl)amino)propanoic acid, (3S)-3-
((1,3-benzodioxol-5-yl))-3-(((1S)-1-[(diisobutylamino)carbonyl]
pentyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-
3-(((1S)-1-[(bis(3-methoxybenzyl)amino)carbonylpentyl]amino)
carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-
((bis(2-thienylmethyl)amino)carbonylpentyl)amino)carbonyl)

(methyl)amino)propanoic acid,

(3S)-3-(((1S)-1-((bis(2-thienylmethyl)amino)carbonylpentyl)amino)
carbonyl)amino)-3-(2-thienyl)propanoic acid, (3S)-3-(((1S)-1-((bis(2-
thienylmethyl)amino)carbonylpentyl)amino)carbonyl)amino)-3-(3-
methoxyphenyl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3- (((1S)-1-4-
(2-thienylsulfonyl)piperazino)carbonylpentyl)amino)carbonyl)amino)propanoic
acid, and pharmaceutically acceptable salts, optical isomers and pro-drugs
thereof.

The present invention also relates to pharmaceutical compositions
comprising a physiologically acceptable diluent and at least one compound of
the present invention.
The present invention further relates to a process of inhibiting the binding of $\alpha_4\beta_1$ integrin to VCAM-1 comprising exposure of a cell expressing $\alpha_4\beta_1$ integrin to a cell expressing VCAM-1 in the presence of an effective inhibiting amount of a compound of the present invention. The VCAM-1 may be on the surface of a vascular endothelial cell, an antigen presenting cell, or other cell type. The $\alpha_4\beta_1$ may be on a white blood cell such as a monocyte, lymphocyte, granulocyte; a stem cell; or any other cell that naturally expresses $\alpha_4\beta_1$.

The invention also provides a method for treating disease states mediated by $\alpha_4\beta_1$ binding which comprises administration of an effective amount of a compound of the present invention, either alone or in formulation, to an afflicted patient.

**Detailed Description of the Invention**

**Definitions of Terms**

As used herein, the term “alkyl” means straight or branched, saturated or unsaturated carbon chains having up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. This term is also meant to encompass alkenyl and alkynyl groups. “Lower alkyl” refers to C$_1$-C$_6$ alkyl.

The term “cycloalkyl” as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings, including, but not limited to cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, and adamantyl among others. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxy carbonyl and carboxamide. This term is also meant to encompass cycloalkenyl and cycloalkynyl groups.

The term “cycloalkylalkyl” as used herein refers to a cycloalkyl group appended to a lower alkyl radical, including, but not limited to cyclohexylmethyl.
The term “halo” or “halogen” as used herein refers to I, Br, Cl or F.

The term “haloalkyl” as used herein refers to a lower alkyl radical, to which is appended at least one halogen substituent, for example chloromethyl, fluoroethyl, trifluoromethyl and pentafluoroethyl among others.

The term "alkoxy" as used herein refers to RₙO- wherein Rₙ is a lower alkyl group. Examples of alkoxy include, but are not limited to, ethoxy, tert-butoxy, among others.

The term "alkoxyalkoxy" as used herein refers to RₙO-RCₖO- wherein Rₙ is lower alkyl as defined above and Rₖ is alkylene wherein alkylene is -(CH₂)ₙ- wherein n' is an integer from 1 to 6. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy among others.

The term "alkylamino" as used herein refers to RₙNH- wherein Rₙ is a lower alkyl group, for example, ethylamino, butylamino, among others.

The term "carboxy" as used herein refers to a carboxylic acid radical, -(CO)OH.

The term "amino" as used herein refers to H₂N-.

As used herein, the term “aryl” means a carbocyclic aromatic group, as for example phenyl, naphthyl, indenyl, indanyl, anthracenyl, among others.

The term “heterocyclic” refers to an aromatic or non-aromatic cyclic group having one or more oxygen, nitrogen or sulfur atoms in the ring, as for example, furyl, thiienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, indolinyln, benzo[b]furanyl, 2,3-dihydrobenzofuranyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzothiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, quinolinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl, tetrahydrofuranosyl, tetrahydropranosyl, piperidinyl, piperazinyl, among others.
The term "heterocyclylalkyl" as used herein refers to a heterocyclyl group appended to a lower alkyl radical, including but not limited to 2-thienylmethyl, 2-pyridinylmethyl and 2-(1-piperidinyl) ethyl.

The term "alkylheterocyclyl" as used herein refers to an alkyl group appended to a heterocyclyl radical, including but not limited to 2-methyl-5-thiazolyl, 2-methyl-1-pyrrolyl and 5-ethyl-2-thiophenyl.

Suitable substituents for the aryl, alkyl, cycloalkyl, or heterocyclyl groups, when present, include alcohols, amines, heteroatoms, or any combination of aryl, alkyl, cycloalkyl or heterocyclyl groups either attached directly, or via suitable linkers. The linkers are typically short chains of 1-3 atoms containing any combination of C, C=O, CO₂, O, N, or S, S=O, SO₂, as for example ethers, amides, amines, ureas, sulfamides, sulfonamides, and the like.

For example, R¹ and R² in Formulas I, II and III above may independently be, but are not limited to, phenyl, isobutyl, n-butyl, 2-thienylmethyl, 1,3-thiazol-2-yl-methyl, benzyl, thienyl, 3-pyridinylmethyl, 3-methyl-1-benzothiophen-2-yl, allyl, isobutyl, 3-methoxybenzyl, propyl, 2-ethoxyethyl, cyclopropylmethyl, 4-((2-toluidinocarbonyl)amino)benzyl, 2-pyridinylethyl, 2-(1H-indol-3-yl)ethyl, 1H-benzimidazol-2-yl, 4-piperidinylmethyl, 3-hydroxy-4-methoxybenzyl, 4-hydroxyphenethyl, 4-aminobenzyl, phenylsulfonylmethyl, isopropyl or 2-oxo-1-pyrrolidinyl.

R¹ and R² may be linked to form a ring such as 4-(2-thienylmethyl)piperazino, 4-(3-thienylmethyl)piperazino, 4-(2-methoxyphenyl)piperazino, 4-(2-thienylcarbonyl)piperazino, 4-(2-thienylsulfonyl)piperazino, or 4-((benzyloxy)carbonyl)piperazino.

R³ and R⁴ may be linked to form a ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-piperidinyl, and 4-tetrahydropyranyl among others.

R⁵ and R⁶ may be linked to form a ring such as pyrrolidino, 1-piperidino, 4-methyl-1-piperazino, 4-aceto-1-piperazino, and 4-morpholino among others.
R^{10} and R^{11} may be linked to form a ring such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl among others.

The R^3 substituent for Formulas I, II and III above may be, but is not limited to, 1,3-benzodioxol-5-yl, 1-naphthyl, thienyl, 4-isobutoxyphenyl, 2,6-dimethylphenyl, allyloxyphenyl, 3-bromo-4-methoxyphenyl, 4-butoxyphenyl, 1-benzofuran-2-yl, 2-thienylmethyl, phenyl, methysulfanyl, phenylsulfanyl, phenethylsulfanyl, 4-bromo-2-thienyl, 3-methyl-2-thienyl, or 4,5-dihydro-1,3-oxazol-2-yl.

The R^3 and R^4 substituent for Formulas I, II and III above may be, but are not limited to hydrogen, butyl, benzyl, benzylxymethyl, benzylthiomethyl, phenylsulfanyl methyl, benzylsulfanyl methyl, ethylthiomethyl, methylsulfanylethyl, ethylsulfanylmethyl, methyl, or carboxyethyl.

Abbreviations

Abbreviations which have been used in the schemes and the examples which follow are: BOC for t-butyloxycarbonyl; EtOAc for ethyl acetate; DMF for dimethylformamide; THF for tetrahydrofuran; Tos for p-toluenesulfonyl; DCC for dicyclohexylcarbodiimide; HOBT for 1-hydroxybenzotriazole; TFAA for trifluoroacetic anhydride; NMM for N-methyl morpholine; DIPEA for diisopropylethylamine; DCM for methylene dichloride; LHMDS for lithium hexamethyl disilazide; NaHMDS for sodium hexamethyl disilazide; CDI for 1,1'-carbonyldimidazole and TBS for TRIS-buffered saline.

Amino acids are abbreviated as follows: C for L-cysteine; D for L-aspartic acid; E for L-glutamic acid; G for glycine; H for L-histidine; I for L-isoleucine; L for L-leucine; N for L-asparagine; P for L-proline; Q for L-glutamine; S for L-serine; T for L-threonine; V for L-valine, and W for L-tryptophan.

Examples of procedures that may be used to synthesize compounds of the formulae shown above are presented in Schemes 1-6.
Scheme 1
Scheme 2 is shown above.
Scheme 5 is shown above.
Scheme 6 is shown above.

A detailed description of the preparation of representative compounds of the present invention is set forth in the Examples.

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salt" means those salts which are, within
the scope of sound medical judgement, suitable for use in contact with the
tissues of humans and lower animals without undue toxicity, irritation, allergic
response and the like and are commensurate with a reasonable benefit/risk ratio.
Pharmaceutically acceptable salts are well-known in the art. For example, S.
M. Berge et al. describe pharmaceutically acceptable salts in detail in 1.
Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts can be prepared in situ
during the final isolation and purification of the compounds of the invention or
separately by reacting a free base function with a suitable organic acid.
Representative acid addition salts include, but are not limited to acetate, adipate,
alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate,
camphorate, camphor sulfonate, digluconate, glycerophosphate, hemisulfate,
heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-
hydroxymethanesulfonate (isothionate), lactate, maleate, methane sulfonate,
nicotinate, 2-naphthalene sulfonate, oxalate, palmitoate, pectinate, persulfate, 3-
phenylpropionate, picate, pivalate, propionate, succinate, tartrate, thiocyanate,
phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also,
the basic nitrogen-containing groups can be quaternized with such agents as
lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides
and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates;
long chain halides such as decyl, lauryl, myristyl and stearyl chlorides,
bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and
others. Water or oil-soluble or dispersible products are thereby obtained.
Examples of acids which can be employed to form pharmaceutically acceptable
acid addition salts include such inorganic acids as hydrochloric acid,
hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as
oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared in situ during the final isolation and
purification of compounds of this invention by reacting a carboxylic acid-
containing moiety with a suitable base such as the hydroxide, carbonate or
bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or
an organic primary, secondary or tertiary amine. Pharmaceutically acceptable
salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium among others. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) which is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The
phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.0001 to about 1000 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.001 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The present invention also provides pharmaceutical compositions that comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be specially formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracranially, intravaginally, intraperitoneally, topically (as by powders, ointments or drops),
bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

In another aspect, the present invention provides a pharmaceutical composition comprising a component of the present invention and a physiologically tolerable diluent. The present invention includes one or more compounds as described above formulated into compositions together with one or more non-toxic physiologically tolerable or acceptable diluents, carriers, adjuvants or vehicles that are collectively referred to herein as diluents, for parenteral injection, for intranasal delivery, for oral administration in solid or liquid form, for rectal or topical administration, or the like.

The compositions can also be delivered through a catheter for local delivery at a target site, via an intracoronary stent (a tubular device composed of a fine wire mesh), or via a biodegradable polymer. The compounds may also be complexed to ligands, such as antibodies, for targeted delivery.

Compositions suitable for parenteral injection may comprise physiologically acceptable, sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), vegetable oils (such as olive oil), injectable organic esters such as ethyl oleate, and suitable mixtures thereof.

These compositions can also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical
form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulate matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound
may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene
glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are natural and synthetic phospholipids and phosphatidyl cholines (lecithins) used separately or together.


The term "pharmacologically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk
ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. Prodrugs of the present invention may be rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987), hereby incorporated by reference.

Compounds of the present invention that are formed by in vivo conversion of a different compound that was administered to a mammal are intended to be included within the scope of the present invention.

Compounds of the present invention may exist as stereoisomers wherein asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom.

The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol among others are equivalent to the unsolvated forms for the purposes of the invention. In another aspect, the present invention contemplates a process of inhibiting the binding of α4β1 integrin to VCAM-1. A process of the present
invention can be used either in vitro or in vivo. In accordance with a process of
the present invention, a cell expressing $\alpha_4\beta_1$ integrin is exposed to a cell
expressing VCAM-1 in the presence of an effective inhibiting amount of a
compound of the present invention.

A cell expressing $\alpha_4\beta_1$ integrin can be a naturally occurring white blood
cell, mast cell or other cell type that naturally expresses $\alpha_4\beta_1$ on the cell surface,
or a cell transfected with an expression vector that contains a poly-nucleotide
(e.g., genomic DNA or cDNA) that encodes $\alpha_4\beta_1$ integrin. In an especially
preferred embodiment, $\alpha_4\beta_1$ integrin is present on the surface of a white blood
cell such as a monocyte, a lymphocyte or a granulocyte (e.g., an eosinophil or a
basophil).

A cell that expresses VCAM-1 can be a naturally occurring cell (e.g. an
endothelial cell) or a cell transfected with an expression vector containing a
polynucleotide that encodes VCAM-1. Methods for producing transfected cells
that express VCAM-1 are well known in the art.

Where VCAM-1 exists on the surface of cell, the expression of that
VCAM-1 is preferably induced by inflammatory cytokines such as tumor
necrosis factor-$\alpha$, interleukin-4 and interleukin-1$\beta$.

Where the cells expressing $\alpha_4\beta_1$ integrin and VCAM-1 are in a living
organism, a compound of the present invention is administered in an effective
amount to the living organism. Preferably, the compound is in a pharmaceutical
composition of this invention. A process of the present invention is especially
useful in treating diseases associated with uncontrolled migration of white blood
cells to damaged tissue. Such diseases include, but are not limited to, asthma,
atherosclerosis, rheumatoid arthritis, allergy, multiple sclerosis, lupus,
inflammatory bowel disease, graft rejection, contact hypersensitivity, type I
diabetes, leukemia, and brain cancer. Administration is preferably
accomplished via intravascular, subcutaneous, intranasal, transdermal or oral
delivery.

The present invention also provides a process of selectively inhibiting
the binding of $\alpha_4\beta_1$ integrin to a protein comprising exposing the integrin to the
protein in the presence of an effective inhibiting amount of a compound of the present invention. In a preferred embodiment, the \(\alpha_4\beta_1\) integrin is expressed on the surface of a cell, either naturally occurring or a cell transformed to express \(\alpha_4\beta_1\) integrin.

The protein to which the \(\alpha_4\beta_1\) integrin binds can be expressed either on a cell surface or be part of the extracellular matrix. Especially preferred proteins are fibronectin or invasin.

The ability of compounds of the present invention to inhibit binding is described in detail hereinafter in the Examples. These Examples are presented to describe preferred embodiments and utilities of the invention and are not meant to limit the invention unless otherwise stated in the claims appended hereto.

Example 1

Synthesis of (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[[benzyl(2-thienylmethyl)amino]carbonyl]-3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid (6).

**Step One:** Thiophene 2-methylamine (1.36 ml, 13.26 mmol) was dissolved in methanol (20 ml). To this solution was added benzaldehyde (1.34 ml, 13.26 mmol), sodium cyanoborohydride (832 mg, 13.26 mmol) and 2 drops of acetic acid. The reaction was stirred at room temperature for 24 hours. The mixture was concentrated under reduced pressure and then taken up in ethyl acetate (500 ml). The organic layer was washed with water (200 ml), saturated NaHCO\(_3\) (200 ml) and brine (200 ml). The organic solution was dried over MgSO\(_4\) and then concentrated under reduced pressure. The residue was flushed through silica gel with ethyl acetate:hexane (1:3) which yielded 1 (1.305 g, 48%).
**Step Two:** Compound 1 (50 mg, 0.246 mmol) and Nα-t-BOC-Nε-Cbz-L-lysine (94 mg, 0.246 mmol) were dissolved in DMF (3 ml), 1,3-dicyclohexylcarbodiimide (61 mg, 0.295 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (100 ml), and the solution washed with water (2 x 100 ml), dried over MgSO₄, and concentrated under reduced pressure. The residue was flushed through silica gel with ethyl acetate:hexane (1:3) which yielded 2 (127 mg, 91%).

**Step Three:** Compound 2 (120 mg, 0.212 mmol) was dissolved 2N HCl in dioxane (4 ml) and stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (150 ml) and washed with saturated NaHCO₃ (150 ml). The organic layer was dried over MgSO₄, and concentrated under reduced pressure to yield 3 (90 mg, 92%).

**Step Four:** Compound 3 (85 mg, 0.18 mmol) and 4 (71 mg, 0.18 mmol) were dissolved in a mixture of THF (2 ml) and CH₂Cl₂ (2 ml). Triethylamine (0.03ml, 0.18 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (100 ml), the solution was washed with 0.5N aqueous NaOH (5 x 25 ml) and dried over MgSO₄. Concentration under reduced pressure gave 5 (119 mg, 92%).

**Step Five:** Compound 5 (110 mg, 0.154 mmol) was dissolved in a mixture of methanol (2 ml), water (2 ml), and THF (1 ml). Lithium hydroxide (13 mg, 0.31 mmol) was added and the reaction mixture was heated at 50 °C overnight. After cooling, the reaction mixture was diluted with ethyl acetate (100 ml), washed with 0.5N aqueous HCl (50 ml), dried over MgSO₄, and concentrated under reduced pressure. Purification by reversed-phase HPLC (C₁₈, water:acetonitrile plus 0.1% TFA, gradient 20-60% acetonitrile over 30 minutes, detection at 254 nm) yielded 6 (10 mg, 9%). ¹HNMR (400 MHz, methanol-d₄):
δ 7.25-7.35 (m, 10 H), 6.7-7.0 (m, 6 H), 5.9 (m, 2 H), 5.0-5.1 (m, 4 H), 4.4-4.7 (m, 4 H), 2.9-3.0 (m, 2 H), 2.6-2.8 (m, 2 H), 1.1-1.6 (m, 6 H).

Example 2

Synthesis of 3-((1S)-1-{{benzyl(2-thienylmethyl)amino}carbonyl}
pentyl)amino}carbonyl}amino)-3-(4-butoxyphenyl) propanoic acid (12).

Step One: (1S, 2R, 5S)-(−)-Menthyl (R)-p-toluenesulfonate (0.59 g, 2.0 mmol) was dissolved in THF (5 mL) and chilled to -78 °C under nitrogen. The mixture was treated with lithium N, N-bis(trimethylsilyl)amide (3.0 mL, 1.0 M in THF) via dropwise addition. Upon completion, the cold bath was removed and the mixture was stirred at room temperature for 5 hours. The solution was chilled to 0 °C and thiophene-2-carboxaldehyde (0.37 mL, 4.0 mmol) was added, via syringe followed immediately with powdered cesium fluoride (0.61 g, 4.0 mmol). The resulting suspension was stirred at room temperature for 18 hours. The reaction was quenched with saturated, aqueous ammonium chloride and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na₂SO₄. The organic solution was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 14:1 hexanes:ethyl acetate) to give compound 7 (0.30 g, 67%).

Step Two: Sodium N, N-bis(trimethylsilyl)amide (1.4 mL, 1.0M in THF) was chilled to -78 °C and treated dropwise with ethyl acetate (0.14 mL, 1.4 mmol). After 15 minutes, diethyl ether (4.2 mL) was added slowly down the side of the flask followed by a solution of compound 7 in diethyl ether (3.6 mL). The mixture was maintained at -78 °C for 5 hours, then quenched with saturated, aqueous ammonium chloride and warmed to room temperature. The mixture was extracted with ethyl acetate (three times). The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under
reduced pressure. The residue was purified by flash chromatography (silica gel, gradient elution 6:1 to 3:1 to 2:1 hexanes:ethyl acetate) to give compound 8 (0.259 g, 80% yield at 78% conversion).

5 Step Three: Compound 8 (0.259 g, 0.827 mmol) dissolved in dry methanol (3.3 mL) was chilled to 0 °C and trifluoroacetic acid (0.127 mL, 1.65 mmol) was added dropwise. The mixture was stirred for 2.5 hours at 0 °C, then concentrated under reduced pressure. The residue was partitioned between diethyl ether and 2N HCl. The aqueous layer was poured into dichloromethane and saturated aqueous sodium bicarbonate and washed with dichloromethane (2x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Compound 9 (0.119 g, 72%) was recovered as a clear oil and was used without further purification.

10 Step Four: Compound 9 (0.119 g, 0.598 mmol) dissolved in dichloromethane was treated with 1,1'-carbonyldiimidazole (0.097 g, 0.60 mmol). After stirring 30 minutes at room temperature, compound 10 (0.19 g, 0.60 mmol) was added and the solution was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed sequentially with 2N HCl, water, saturated sodium bicarbonate solution, and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, gradient elution 3:1 to 2:1 hexanes:ethyl acetate) to give compound 11 (0.26 g, 79%).

15 Step Five: Compound 11 (0.26 g, 0.48 mmol) was dissolved in 3:1 THF:water (1.9 mL) and methanol (0.5 mL). Lithium hydroxide monohydrate (0.030 g, 0.72 mmol) was added as a solid at room temperature. After 4 hours, the mixture was diluted with water and extracted with diethyl ether. The ether layer was discarded, and the aqueous layer was acidified with excess 2N HCl. The acidic aqueous layer was extracted with ethyl acetate (2x) and combined. The organic layer was washed with water and brine and dried over Na₂SO₄. The
organic solution was filtered and concentrated under reduced pressure to give compound 12 (0.23 g, 92%). 1H NMR (400 MHz, DMSO-d6): δ 12.25 (br. S, 1H), 7.47 (dd, J = 1.1, 5.1 Hz, 1H), 7.42 (dd, J = 1.1, 5.1 Hz, 1H), 7.35 (dd, J = 1.4, 5.1 Hz, 1H), 7.07 (d, J = 3.3 Hz, 1H), 7.00 (m, 2H), 6.93 (m 3H), 6.65 (d, J = 8.8 Hz, 1H), 6.43 (d, J = 8.8 Hz, 1H), 5.29 (dd, J = 7.1, 15.4 Hz, 1H), 4.92 (d, J = 16.5 Hz, 1H), 6.68 (m, 3H), 4.56 (d, J = 15.0 Hz, 1H), 2.75 (d, J = 7.0 Hz, 2H), 1.46 (m, 2H), 1.18 (m, 4H), 0.78 (t, J = 7.0 Hz, 3H).

Example 3

Synthesis of (3S)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pentyl)amino]-carbonyl]amino)-3-(2-methyl-1,3-thiazol-4-yl)propanoic acid, sodium salt (19).

Step One: To a solution of N-t-Boc-aspartic acid β-methyl ester (6.0 g, 24.2 mmol) in dry THF (30 mL) was added triethylamine (5.2 mL, 36.4 mmol). The reaction mixture was cooled to 0 °C, treated with isobutylchloroformate (3.6 g, 26.2 mmol), and then stirred at 0 °C for 1 hour. The ice-cold solution was filtered and then treated with a solution of diazomethane (100 mmol) in ether (75 mL). After stirring at low temperature for 1 hour, nitrogen gas was bubbled into the reaction to remove the excess diazomethane. Concentration gave 13 (4.5 g), which was used without further purification.

Step Two: Diazoketone 13 (4 g, 14.7 mmol) was dissolved in ether (20 mL). The reaction mixture was cooled to −30 °C, and then treated with 48% HBr in H2O (5 mL). When a persistent yellow color formed the mixture was diluted with EtOAc and washed with water. The organic solution was dried over MgSO4 and concentrated. Purification by chromatography (silica gel, 3:1 hexanes:EtOAc) gave 14 (3.5 g, 74%).
Step Three: To a solution of 14 (1 g, 3.0 mmol) in dry THF (7 mL) was added triethylamine (0.45 g, 4.5 mmol) and thioacetamide (0.23 g, 3.3 mmol). The reaction mixture was stirred at 50 °C for 30 minutes and then concentrated under reduced pressure. Purification of the crude product by chromatography (silica, 35% EtOAc in hexanes) gave 15 (0.92 g, 60%).

Step Four: Compound 15 (800 mg, 2.5 mmol) was dissolved in dioxane (3 mL) and 4.0M HCl in dioxane (3 mL) was added. The reaction mixture was stirred at room temperature for 1 hour, and then concentrated under reduced pressure. This gave 16 (580 mg, 78%), which was used without further purification.

Step Five: Compound 16 (300 mg, 1.40 mmol) was suspended in dry THF (5 ml) and then diisopropylethylamine (0.40 mL, 2.8 mmol) was added. The reaction mixture was treated with carbamate 17 (700 mg, 1.6 mmol), and the reaction was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate, extracted with 5% solution of NaOH, and then the organic layer was dried over MgSO₄. Concentration and purification by chromatography (silica gel, 1:1 Hexane:EtOAc) gave 18 (175 mg, 65%).

Step Six: Compound 18 (100 mg, 0.18 mmol) was dissolved in THF (2 mL), and then a solution of NaOH (7.0 mg, 0.18 mmol) in water (1 ml) was added. The reaction mixture was stirred at 45 °C for 2 hours. The crude reaction was lyophilized to give 19 as a yellow solid. ¹H NMR (400 MHz, MeOH-d₄): δ 0.85 (m, 3H), 1.42 (m, 4H), 1.48 (m, 2H), 2.65 (s, 3H), 2.80 (m, 1H), 3.05 (m, 1H), 3.65 (s, 3H), 4.95 (m, 1H), 5.30 (m, 1H), 5.63(m, 1H), 5.85 (m, 1H), 6.90 (s, 1H), 7.25 (m, 4H), 7.30 (m, 2H).
Example 4

Synthesis of 5-[(1S)-1-{{[(bis(2-thienylmethyl)amino)carbonyl]penty}l}amino]-5-oxo-3-phenylpentanoic acid (20).

To a solution of 10 (0.30 g, 1.0 mmol) and 3-phenylglutamic acid (214 mg, 1.1 mmol) in dry DMF (8 mL), DCC (225 mg, 1.2 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between EtOAc and 5% HCl. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by chromatography (silica gel, 2% MeOH in EtOAc) gave 20 (80 mg, 52%). ¹H NMR (400 MHz, MeOH-d₄): δ 0.89 (m, 3 H), 0.95 (m, 4 H), 1.30 (m, 2 H), 2.85 (m, 1 H), 2.95 (m, 2 H), 3.83 (m, 1 H), 4.6-4.8 (m, 4 H), 5.00 (m, 1 H), 6.95 (m, 4 H), 7.22 (m, 5 H).

Example 5

Synthesis of (3R)-3-(1,3-benzodioxol-5-yl)-3-{{[(1S)-1-{{[(bis(2-thienylmethyl)amino)carbonyl]penty}l}amino}carbonyl}amino}-2,2-dimethylpropanoic acid (25).

Step One: To a solution of isobutyryl chloride (47 g, 0.44 mol) in CH₂Cl₂ (75 ml) and tert-butanol (75 ml) at 0 °C, pyridine (39.3 ml, 486 mmol) was added slowly by syringe. The mixture was allowed to warm to room temperature, stirred overnight, diluted with CH₂Cl₂ (400 ml) and washed with H₂O, HCl (2N, two times), H₂O (two times) and saturated NaHCO₃. The organic phase was dried over MgSO₄ and filtered. The filtrate was then concentrated under reduced pressure without heat. The resulting oil was simply distilled, collecting the fraction boiling at 128-129 °C to give tert-butyl isobutyrate, 21 (35.9 g, 56%).
Step Two: To a solution of piperonal (751 mg, 5.0 mmol) in THF (5.0 ml) cooled to 0 °C under a dry nitrogen atmosphere, lithium bistrimethylsilylamide (5.0 ml of a 1.0 M solution in THF, 5.0 mmol) was added by syringe. The resulting mixture was stirred at 0 °C for 15 minutes and then was allowed to warm to room temperature. This solution of the TMS-aldimine was used directly as described below.

Step Three: To a solution of diisopropylamine (0.84 ml, 6.0 mmol) in THF (10 ml) cooled to -78 °C under a dry nitrogen atmosphere, butyllithium (3.75 ml of a 1.6 M solution in hexanes, 6.0 mmol) was added by syringe. The mixture was stirred at -78 °C for 15 minutes, then a solution of 21 (721 mg, 5.0 mmol) in THF (10 ml) was added by cannula dropwise along the side of the flask over the course of 20 minutes along with a THF (1 ml) rinse. The mixture was stirred at -78 °C for 15 minutes, then the TMS-aldimine solution prepared in step two was added dropwise by cannula along the side of the flask over the course of 15 minutes along with a THF (1 ml) rinse. The resulting mixture was allowed to gradually warm to room temperature over the course of 24 hours, then was quenched with HCl (20 ml, 2N) followed immediately by the addition of ethyl acetate. The mixture was washed with H₂O (two times), saturated NaHCO₃ and brine and the organic phase was dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 3:2 hexanes:ethyl acetate increasing to 1:1 hexanes:ethyl acetate and finally 1:3 hexanes:ethyl acetate to yield β-lactam 22 (226 mg, 21%) as a white solid.

Step Four: To a solution of amine 10 (770 mg, 2.39 mmol) in CH₂Cl₂ (12 ml) cooled to 0 °C under a dry nitrogen atmosphere, triethylamine (0.50 ml, 3.6 mmol) and phenyl chloroformate (0.37 ml, 3.0 mmol) were added by syringe. The resulting mixture was stirred at 0 °C for 1 hour, then was diluted with 7:3 hexanes:ethyl acetate and washed with H₂O (twice) and brine. The organic phase was dried over MgSO₄ and filtered and the filtrate was concentrated under
reduced pressure. The residue was purified by silica gel chromatography, eluting with 4:1 hexanes:ethyl acetate to yield carbamate 23 (907 mg, 86%) as a colorless oil.

Step Five: To a solution of β-lactam 22 (117 mg, 0.53 mmol) in THF (5.3 ml) cooled to -45 °C under a dry nitrogen atmosphere, butyllithium (0.33 ml of a 1.6 M solution in hexanes, 0.53 mmol) was added by syringe. The resulting mixture was stirred for 15 minutes at -45 °C then was added rapidly to a solution of carbamate 23 (293 mg, 0.66 mmol) in THF (1.3 ml) cooled to -45 °C under a dry nitrogen atmosphere by cannula along with a THF (1 ml) rinse. The resulting mixture was allowed to warm to 0 °C over the course of 1 hour, then was quenched with a solution of glacial acetic acid (0.5 ml) in H₂O (5 ml) and immediately diluted with a 1:1 mixture of hexanes:ethyl acetate and H₂O. The organic phase was washed with H₂O (twice), saturated NaHCO₃, H₂O and brine. The organic phase was dried over MgSO₄ and filtered. Then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 4:1 hexanes:ethyl acetate increasing to 3:1 hexanes:ethyl acetate and finally 13:7 hexanes:ethyl acetate to yield β-lactam 24 (most polar diastereomer, 106 mg, 35%) as a colorless oil.

Step Six: To a solution of β-lactam 24 (73 mg, 0.13 mmol) in THF (1.5 ml) at room temperature, a solution of lithium hydroxide (27 mg, 0.65 mmol) in H₂O (0.75 ml) was added. The mixture was stirred at room temperature for 24 hours, then was acidified with HCl and extracted with ethyl acetate. The organic phase was washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give 25 (78 mg, 100%) as a light yellow powder. ¹H NMR (400 MHz, CD₃SOCD₃) δ 0.73 (t, J = 6.8 Hz, 3H), 1.01 (s, 3H), 1.02 (s, 3H), 1.05-1.53 (m, 6H), 4.63 (m, 4H), 4.86 (d, J = 10.2 Hz, 1H), 4.94 (d, J = 16.9 Hz, 1H), 5.96 (s, 1H), 5.97 (s, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.66 (dd, J = 8.1, 1.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.95 (dd, J = 5.1, 3.3 Hz, 1H), 7.01 (m, 2H), 7.05 (d, J
= 2.9 Hz, 1H), 7.43 (m, 1H), 7.47 (m, 1H).

Example 6

Synthesis of (3S)-3-[(1,3-benzodioxol-5-yl)-3-[[((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pentyl)amino]carbonyl] (methyl)amino] propanoic acid (30).

Step One: To a solution of 26 (513 mg, 1.93 mmol) in CH₂Cl₂ (4 ml) at room temperature under a dry nitrogen atmosphere, triethylamine (0.32 ml, 2.3 mmol) and di-tert-butyl dicarbonate (443 mg, 2.03 mmol) were added. The resulting mixture was stirred at room temperature overnight, then was diluted with a 7:3 mixture of hexanes:ethyl acetate and washed with HCl (2N), H₂O, saturated NaHCO₃ and brine. The organic phase was dried over MgSO₄ and filtered. Next, the filtrate was concentrated under reduced pressure to give the N-tert-butoxycarbonyl-β-aminoester 27 (743 mg) as a pale yellow oil. This material contained 4-5% of di-tert-butyl dicarbonate but was used without purification.

Step Two: To a solution of 27 (370 mg, 1.01 mmol) in THF (10 ml) at room temperature under a dry nitrogen atmosphere, potassium bis(trimethylsilyl)amide (4.04 ml of a 0.50 M solution in toluene, 2.02 mmol) was added by syringe. The resulting mixture was stirred at room temperature for 15 minutes, then iodomethane (0.25 ml, 4.04 mmol) was added rapidly by syringe. The mixture was stirred at room temperature for 30 minutes, quenched with HCl (2N) and immediately diluted with 3:2 hexanes:ethyl acetate. The organic phase was washed with H₂O, saturated NaHCO₃ and brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 17:3 hexanes:ethyl acetate to yield N-methyl-N-tert-butoxycarbonyl-β-aminoester 28 (238 mg, 62%, [87% based on consumed 27]) as a colorless oil along with N-
tert-butoxycarbonyl-β-aminoester 27 (106 mg, 29%).

**Step Three:** To a flask containing 28 (405 mg, 1.07 mmol) sealed with a rubber septum at room temperature under a dry nitrogen atmosphere, HCl (5.3 ml, 4.0M in dioxane, 21 mmol) was added by syringe. The nitrogen needle was removed and the mixture in the sealed flask was stirred overnight. The resulting suspension was diluted with diethyl ether, the excess HCl was removed under a stream of nitrogen. The mixture was then concentrated under reduced pressure and the residue was taken up in H₂O (40 ml) and lyophilized to give 29 (251 mg, 95%) as a tan solid.

**Step Four:** To a solution of 10 (110 mg, 0.34 mmol) in 1,2-dichloroethane (1 ml) at room temperature under a dry nitrogen atmosphere, N, N-diisopropylethylamine (0.13 ml, 0.75 mmol) and phosgene (0.18 ml of a 1.9 M solution in toluene, 0.34 mmol) were added by syringe. The mixture was stirred for 30 minutes, then added to a solution of 29 (88 mg, 0.34 mmol) in 1,2-dichloroethane (1 ml) and N, N-diisopropylethylamine (0.066 ml, 0.38 mmol) by cannula. The resulting mixture was heated to 40 °C overnight, then was cooled to room temperature, diluted with ethyl acetate and washed with HCl (2N, twice) and brine. The organic phase was dried over MgSO₄ and filtered. Next, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 19:1 chloroform:methanol increasing to 9:1 chloroform:methanol to yield 30 (129 mg, 66%). ¹H NMR (400 MHz, CD₂SOCD₂) : δ 0.80 (m, 3H), 1.20 (m, 4H), 1.59 (m, 2H), 2.60 (dd, J = 15.4, 7.3 Hz, 1H), 2.82 (m, 1H), 4.57-4.75 (m, 4H), 5.61 (t, J = 7.3 Hz, 1H), 5.98 (s, 1H), 5.99 (s, 1H), 6.72 (dd, J = 8.1, 1.5 Hz, 1H), 6.80 (d, J = 1.5 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.95 (dd, J = 5.1, 3.3 Hz, 1H), 7.02 (m, 2H), 7.10 (d, J = 3.3 Hz, 1H), 7.42 (m, 1H), 7.48 (m, 1H).

The procedures described above may also be utilized to synthesize the following compounds: (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[[benzyl(2-
thienylmethyl)amino[carbonyl]-3,11-dioxo-1-phenyl-2-oxa-4,10,12-
triazapentadecan-15-oic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-
{[benzyl(2-thienylmethyl)amino[carbonyl]pentyl}amino[carbonyl] amino)
propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((2-[benzyl(2-
thienylmethyl)amino]-2-oxoethyl}amino)[carbonyl]amino)propanoic acid,
3-(((1S)-1-[[benzyl(2-thienylmethyl)amino[carbonyl]pentyl]
amino[carbonyl]amino)-3-(1-naphthyl) propanoic acid, 3-(((1S)-1-
{[benzyl(2-thienylmethyl)amino[carbonyl]pentyl}amino[carbonyl] amino)-3-
(2-thienyl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((bis(2-
thienylmethyl)amino)[carbonyl]pentyl)amino)[carbonyl]amino)propanoic acid, 3-
(((1S)-1-[[benzyl(2-thienylmethyl)amino[carbonyl]pentyl]amino]
carbonyl)amino)-3-(4-isobutoxyphenyl)propanoic acid, 3-(((1S)-1-
{[benzyl(2-thienylmethyl)amino[carbonyl]pentyl}amino[carbonyl] amino)-3-
(2,6-dimethylphenyl)propanoic acid, 3-[4-(allyloxy)phenyl]-3-(((1S)-1-
{[benzyl(2-thienylmethyl)amino[carbonyl]pentyl}amino[carbonyl] amino)
propanoic acid, 3-[4-(benzyloxy)phenyl]-3-(((1S)-1-[[benzyl(2-
thienylmethyl)amino[carbonyl]pentyl]amino][carbonyl]amino)propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-
{[dibenzylamino[carbonyl]pentyl}amino[carbonyl]amino)propanoic acid, 3-
(((1S)-1-[[benzyl(2-thienylmethyl)amino]
carbonyl]pentyl)amino[carbonyl]amino)-3-(3-bromo-4-methoxyphenyl)
propanoic acid, 3-(((1S)-1-[[benzyl(2-thienylmethyl)amino[carbonyl]
pentyl]amino[carbonyl]amino)-3-(2-naphthyl)propanoic acid, 3-(((1S)-1-
{[benzyl(2-thienylmethyl)amino[carbonyl]pentyl}amino[carbonyl] amino)-3-(4-
butoxyphenyl)propanoic acid, 3-(((1S)-1-[[bis(2-thienylmethyl)amino]
carbonyl]pentyl)amino[carbonyl]amino)-3-(2-thienyl)propanoic acid,
3-(((1S)-1-[[bis(2-thienylmethyl)amino[carbonyl]pentyl]amino[carbonyl]
amino)-3-(3-thienyl)propanoic acid, 3-(1-benzofuran-2-yl)-3-(((1S)-1-[[bis(2-
thienylmethyl)amino[carbonyl]pentyl]amino[carbonyl]amino)propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[[bis(2-thienylmethyl)amino]
carbonyl]pentyl)oxy[carbonyl]amino)propanoic acid, (3S)-3-(1,3-benzodioxol-
5-yl)-3-({[(1S)-1-{[bis(3-pyridinylmethyl)amino]carbonyl}pentyl]amino} carbonyl) amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-({[(1S)-1- [bis(2-thienylmethyl)amino]carbonyl}morpholino-3-oxopropyl]amino} carbonyl) amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(1S)-1- benzyl}-2-[bis(2-thienylmethyl)amino]-2-oxoethyl] amino} carbonyl]amino} propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(1R)-1- [benzylthio)methyl]-2-[bis(2-thienylmethyl)amino]-2-oxoethyl] amino} carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(1S)-1- [benzyloxy)methyl]-2-[bis(2-thienylmethyl)amino]-2-oxoethyl] amino} carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(1R)-2- [bis(2-thienylmethyl)amino]-1-[(ethylthio)methyl]-2-oxoethyl] amino}carbonyl] amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(3S)-1-{[3- methyl-1-benzothiophen-2-yl)methyl][2-thienylmethyl]amino[carbonyl} pentyl]amino[carbonyl] amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(1S)-1-{[3-(pyridinylmethyl)(2-thienylmethyl)amino]carbonyl}pentyl] amino[carbonyl] amino}propanoic acid, ethyl (3S)-3-(1,3-benzodioxol-5-yl)-3- {{[(1S)-1-{[bis(2-thienylmethyl)amino]carbonyl}pentyl]amino[carbonyl} amino]propanoate, 3-{{[(1S)-1-{[bis(2-thienylmethyl)amino] carbonyl}pentyl] amino} carbonyl] amino}-3-(5-methyl-2-thienyl)propanoic acid, (3S)-3- {{[(1S)-1-{[bis(2-thienylmethyl)amino]carbonyl}pentyl] amino} carbonyl] amino}-3-(2-methyl-1,3-thiazol-4-yl)propanoic acid, (3S)-3-(1,3- benzodioxol-5-yl)-3-{{[(1S)-1-{[(1,3-thiazol-2-ylmethyl)(2- thiencylmethyl)amino]carbonyl}pentyl]amino[carbonyl] amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(1S)-2-[bis(2-thienylmethyl)amino]-1- methyl-2-oxoethyl] amino}carbonyl]amino}propanoic acid, (3S)-3-(1,3- benzodioxol-5-yl)-3-{{[2-[bis(2-thienylmethyl)amino]-2- oxoethyl] amino}carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5- yl)-3-{{[(1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]-3-methylbutyl]amino} carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{{[(1S)-1- [bis(2-thienylmethyl)amino]carbonyl]-2-methylpropyl]amino[carbonyl} amino]propanoic acid, (4S)-4-{{[(1S)-1-(1,3-benzodioxol-5-yl)-2-
(((1S)-1-[(dipropylamino)carbonyl]pentyl|amino)carbonyl|amino)propanoic acid, (3S)-3-(((1S)-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino)carbonyl)amino)-3-(2-thienyl)propanoic acid, (8S,12S)-12-(1,3-benzodioxol-5-yl)-8-butyl-6-(2-ethoxyethyl)-7,10-dioxo-3-oxa-6,9,11-triazatetradecan-14-oic acid, (3S)-3-(((1S)-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino)carbonyl)amino)-3-(4,5-dihydro-1,3-oxazol-2-yl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(bis(cyclopropylmethyl)amino)carbonyl]pentyl)amino)carbonyl)amino)propanoic acid, 3-(1,3-benzodioxol-5-yl)-5-(((1S)-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino)-5-oxopentanoic acid, (3S)-3-(((1S)-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino)carbonyl)amino)-3-(3-methoxyphenyl)propanoic acid, (10S,14S)-14-(1,3-benzodioxol-5-yl)-10-[(bis(2-thienylmethyl)amino)carbonyl]-2,2-dimethyl-4,12-dioxo-3-oxa-5,11,13-triazahexadecan-16-oic acid, (3S)-3-[((1S)-5-amino-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino]carbonyl)amino)-3-(1,3-benzodioxol-5-yl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(4-(2-thienylmethyl)piperazino)carbonyl]pentyl)amino)carbonyl)amino)propanoic acid, 3-(((1S)-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino)carbonyl)amino)-5-hexenoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(4-[(3-thienylmethyl)piperazino]carbonyl]pentyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(4-(2-methoxyphenyl)piperazino]carbonyl]pentyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(4-(2-thienyl)carbonyl)piperazino]carbonyl]pentyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(4-(2-thienyl)sulfonfyl)piperazino]carbonyl]pentyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(4-[(benzyloxy)carbonyl]piperazino]carbonyl]pentyl)amino)carbonyl)amino)propanoic acid, ethyl (3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino)carbonyl)amino)propanoate, methyl 3-(((1S)-1-[(bis(2-thienylmethyl)amino)carbonyl]pentyl)amino)carbonyl)amino)propanoate,
carbonyl)penty|amino|carbonyl)amino)-3-(3-thienyl)propanoate and pharmaceutically acceptable salts thereof.

Example 7

The ability of compounds of the present invention to inhibit binding is determined by a procedure in which a 26-amino acid peptide containing the CS1 sequence of fibronectin with an N-terminal Cys (CDELPSVLTPHNLHGEILDVPST) was coupled to maleimide activated ovalbumin. Bovine serum albumin (BSA) and CS1 conjugated ovalbumin were coated onto 96-well polystyrene plates at 0.5 \(\mu\)g/ml in TBS (50 mM Tris, pH 7.5; 150 mM NaCl) at 4°C for 16 hours. The plates were washed three times with TBS and blocked with TBS containing 3% BSA at room temperature for 4 hours. Blocked plates were washed three times in binding buffer (TBS; 1 mM MgCl\(_2\); 1 mM CaCl\(_2\); 1 mM MnCl\(_2\)) prior to assay. Ramos cells fluorescently labeled with calcein AM were resuspended in binding buffer (10\(^7\) cells/ml) and diluted 1:2 with same buffer with or without compound. The cells were added immediately to the wells (2.5 x 10\(^3\) cells/well) and incubated for 30 minutes at 37°C. Following three washes with binding buffer, adherent cells were lysed and quantitated using a fluorometer. The results are shown in Table 1. IC\(_{50}\) is defined as the dose required to give 50% inhibition. A stands for inhibition in Table 1, and the percent inhibition indicates the inhibition of cell adhesion when compound is included in the assay at a concentration of 100 \(\mu\)M. The lower the IC\(_{50}\) value and the greater the percentage of inhibition, the more efficient the compound is at prevention of cell adhesion.
Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>% A</th>
</tr>
</thead>
<tbody>
<tr>
<td>(9S,13S)-13-{(1,3-benzodioxol-5-yl)-9-[(benzyl[(2-thienylmethyl)amino]carbonyl]-3,1-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-ic acid, 6}</td>
<td>0.0008</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl}penty]amino}carbonyl]amino]propanoic acid</td>
<td>0.007</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(2-[benzyl[(2-thienylmethyl)amino]2-oxoethyl]amino]carbonyl]amino]propanoic acid</td>
<td>0.9</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(1-naphthyl)propanoic acid</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(2-thiényl)propanoic acid</td>
<td>0.075</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1S)-1-{(bis(2-thienylmethyl)amino]carbonyl}penty]amino}carbonyl]amino]propanoic acid</td>
<td>0.0004</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-[benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(4-isobutoxyphenyl)propanoic acid</td>
<td>0.2</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(2,6-dimethylphenyl)propanoic acid</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3-[4-(allyloxy)phenyl]-3-{(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino]propanoic acid</td>
<td>0.3</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1S)-1-{(dibenzylamino]carbonyl]penty]amino}carbonyl]amino]propanoic acid</td>
<td>0.2</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(3-bromo-4-methoxyphenyl)propanoic acid</td>
<td>0.2</td>
<td>99</td>
</tr>
<tr>
<td>3-{(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(2-naphthyl)propanoic acid</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{benzyl[(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(4-butoxyphenyl)propanoic acid, 12</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{(bis(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(2-thiényl)propanoic acid</td>
<td>0.017</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(3-thiényl)propanoic acid</td>
<td>0.02</td>
<td>100</td>
</tr>
<tr>
<td>3-{(1S)-1-{(2-thienylmethyl)amino]carbonyl]penty]amino}carbonyl]amino-3-(2-thiényl)propanoic acid</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1S)-1-{(bis(2-thienylmethyl)amino]carbonyl]penty]oxy]carbonyl]amino]propanoic acid</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1S)-1-{(bis(2-thienylmethyl)amino]carbonyl]penty]oxy]carbonyl]amino]propanoic acid</td>
<td>0.3</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1S)-1-{(bis(2-thienylmethyl)amino]carbonyl]penty]oxy]carbonyl]amino]propanoic acid</td>
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<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1S)-1-{benzyl[(2-thienylmethyl)amino]2-oxoethyl]amino}carbonyl]amino]propanoic acid</td>
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<td>(3S)-3-{(1,3-benzodioxol-5-yl)-3-[(1R)-1-{(benzylthio)metal}]-2-[bis(2-thienyl methyl]amino]2-oxoethyl]amino}carbonyl]amino]propanoic acid</td>
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<td>Uniprot ID</td>
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<td>(3S)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]penty1amino]propanoic acid</td>
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<td>(3S)-3-((1,3-benzodioxol-5-yl)-3-((1S)-1-[[bis(2-thienylmethyl)amino]2-methylbutyl]amino)carbonyl]pety1amino]propanoic acid</td>
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<td>(3S)-3-((1,3-benzodioxol-5-yl)-3-((1S)-2-[[bis(2-thienylmethyl)amino]1-methyl2-oxoethyl]amino)carbonyl]pety1amino]propanoic acid</td>
<td>nd</td>
<td>0</td>
</tr>
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<td>(3S)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]penty1amino]propanoic acid, 4-morpholino-4-oxobutanic acid</td>
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<td>(3R)-3-((1,3-benzodioxol-5-yl)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pety1amino]propanoic acid, 25</td>
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<td>(9S,13S)-13-((1,3-benzodioxol-5-yl)-9-[[bis(2-thienylmethyl)amino]carbonyl]-3-11-dioxo-1-phenyl-2-oxa-4,10,12-triazapatadecan-15-oxic acid</td>
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<td>100</td>
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<td>(3S)-3-((1,3-benzodioxol-5-yl)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pety1amino]propanoic acid, 46</td>
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<td>3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pety1amino]propanoic acid, 3-3-[3-methyl-2-thienylpropanoic acid</td>
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<td>0.7</td>
<td>100</td>
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<td>(3S)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pety1amino]propanoic acid, 3-2-[3-thienylmethyl]-1,3-thiazol-4-ypropanoic acid</td>
<td>0.2</td>
<td>100</td>
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<td>(3S)-3-((1,3-benzodioxol-5-yl)-3-((1S)-1-[[dipropylamino]carbonyl]pety1amino]propanoic acid</td>
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<td>(3S)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pety1amino]propanoic acid, 3-2-thienylpropanoic acid</td>
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<td>0.3</td>
<td>100</td>
</tr>
<tr>
<td>(3S)-3-((1S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pety1amino]propanoic acid, 3-4,5-dihydro-1,3-oxazol-2-ypropanoic acid</td>
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<td>nd</td>
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<tr>
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<td>3-(1,3-benzodioxol-5-yl)-5-[[1(S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pentylamino]-5-oxopentanoic acid</td>
<td>0.3</td>
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<td>0.035</td>
<td>(3S)-3-[[1(S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pentylamino]carbonyl]amino]-3-(3-methoxyphenyl)propanoic acid</td>
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<td>(10S,14S)-14-(1,3-benzodioxol-5-yl)-10-[[bis(2-thienylmethyl)amino]carbonyl]-2,2-dimethyl-4,12-dioxo-3-oxa-5,11,13-triazaheptadecan-16-oic acid</td>
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<td>0.1</td>
<td>(3S)-3-[[1(S)-5-amino-1-[[bis(2-thienylmethyl)amino]carbonyl]pentylamino]carbonyl]amino]-3-(1,3-benzodioxol-5-yl)propanoic acid</td>
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<tr>
<td>0.05</td>
<td>(3S)-3-(1,3-benzodioxol-5-yl)-3-[[1(S)-1-[[4-(2-thienylmethyl)piperazino]carbonyl]pentylamino]carbonyl]amino]propanoic acid</td>
<td>0.05</td>
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<td>3-[[1(S)-1-[[bis(2-thienylmethyl)amino]carbonyl]pentylamino]carbonyl]amino]-5-hexenoic acid</td>
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<td>(3S)-3-(1,3-benzodioxol-5-yl)-3-[[1(S)-1-[[4-(3-thienylmethyl)piperazino]carbonyl]pentylamino]carbonyl]amino]propanoic acid</td>
<td>0.7</td>
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<td>0.7</td>
<td>(3S)-3-(1,3-benzodioxol-5-yl)-3-[[1(S)-1-[[4-(2-methoxyphenyl)piperazino]carbonyl]pentylamino]carbonyl]amino]propanoic acid</td>
<td>0.7</td>
</tr>
<tr>
<td>1.5</td>
<td>(3S)-3-(1,3-benzodioxol-5-yl)-3-[[1(S)-1-[[4-(2-thienylcarbonyl)piperazino]carbonyl]pentylamino]carbonyl]amino]propanoic acid</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>(3S)-3-(1,3-benzodioxol-5-yl)-3-[[1(S)-1-[[4-(2-thienylsulfonfyl)piperazino]carbonyl]pentylamino]carbonyl]amino]propanoic acid</td>
<td>2</td>
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<tr>
<td>1</td>
<td>(3S)-3-(1,3-benzodioxol-5-yl)-3-[[1(S)-1-[[4-(benzylxyl)carbonyl)piperazino]carbonyl]pentylamino]carbonyl]amino]propanoic acid</td>
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nd = not determined

All references cited are hereby incorporated by reference.

The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since many variations will become apparent to those skilled in the art in view thereof. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

Changes can be made in the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention as defined in the following claims:
We claim:

1. A compound of the structure

\[
\begin{align*}
&N_0^1\quad R^1\quad R^2 \quad R^3 \quad J \quad R^4 \quad R^5 \quad X
&J \quad A \quad E \quad M
&\quad T
\end{align*}
\]

wherein A is selected from the group consisting of O, S, and NR^6;
E is selected from the group consisting of \(CH_2\), O, S, and NR^7;
each J is independently selected from the group consisting of
O, S and NR^8;
s and t are each integers independently of 0 to 3;
T is selected from the group consisting of C(O) and (CH_2),
wherein v is an integer of 0 to 3;
L is selected from the group consisting of O, NR^9, S, and (CH_2)_w
wherein w is an integer of 0 or 1;
M is selected from the group consisting of C(R^10)(R^11) and (CH_2)_v
wherein v is an integer of 0 to 3;
X is selected from the group consisting of CO_2B, PO_3H, SO_3H,
OPO_3H, C(O)NHCH(O)R^{12}, C(O)NHSO_2R^{13}, tetrazolyl and hydrogen;
B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are
independently selected from the group consisting of hydrogen, alkyl,
cycloalkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkoxy,
cycloalkylalkyl, alkylamino, haloalkyl, alkylaryl, arylalkyl, heterocyclyl, heterocyclylalkyl and alkylheterocyclyl groups;

wherein $R^1$ and $R^2$ taken together may form a ring;
$R^3$ and $R^4$ taken together may form a ring;
$R^5$ and $R^6$ taken together may form a ring;
$R^{10}$ and $R^{11}$ taken together may form a ring;
and salts thereof.

2. A compound of claim 1 wherein
$M$ is $C(R^{10})(R^{11})$;
$X$ is $CO_2B$;
$A$ is $NR^6$;
$E$ is $NR^7$;
$J$ is $O$;
s and $t$ are each $1$;
$R^1$ and $R^2$ are independently selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl and alkyl;
$R^3$ and $R^4$ are each independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, aryl, alkylaryl, arylalkyl, heterocyclyl and alkyl;
$R^5$ is selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl and alkyl; and,
$R^6$ and $R^7$ are independently selected from the group consisting of hydrogen and lower alkyl.

3. A compound of claim 1 wherein $R^1$ and $R^2$ are linked to form a ring
selected from the group consisting of 4-(2-thienylmethyl)piperazino, 4-(3-thienylmethyl)piperazino, 4-(2-methoxyphenyl)piperazino, 4-(2-
thienylcarbonyl)piperazino, 4-(2-thienylsulfonyl)piperazino, and 4-
((benzyloxy)carbonyl)piperazino.

4. A compound of claim 1 further comprising derivatives of said compound
selected from the group consisting of esters, carbamates, aminals,
amides, and prodrugs thereof.

5. A compound of claim 1 of the structure

![Chemical Structure](attachment:image.png)

wherein A is selected from the group consisting of O, S, and
NR^6;
E is selected from the group consisting of CH₂, O, S, and
NR^3;
each J is independently selected from the group consisting of
O, S and NR^8;
T is selected from the group consisting of C(O) and (CH₂)v wherein v is
an integer of 0 or 1;
L is selected from the group consisting of O, NR^9, S, and
(CH₂)w wherein w is an integer of 0 or 1;
s and t are each integers independently of 0 to 3;
B, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are independently
selected from the group consisting of hydrogen, alkyl,
cycloalkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkoxy, cycloalkylalkyl, alkylamino, haloalkyl, alkylaryl, arylalkyl, heterocyclyl, heterocyclylalkyl and alkylheterocyclyl groups;

wherein R¹ and R² can be linked to form a ring;
5 R³ and R⁴ taken together may form a ring;
R² and R⁹ taken together may form a ring;
R¹⁰ and R¹¹ taken together may form a ring;
and salts thereof.

6. A compound of claim 5 wherein
A is NR⁶;
E is NR⁷;
each J is O;
s and t are each 1;
R¹ and R² are independently selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl and alkyl;
R³ and R⁴ are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, aryl, alkylaryl, arylalkyl,
heterocyclyl and alkyl;
R¹⁰, R¹¹ and B are independently selected from the group consisting of hydrogen and lower alkyl;
R⁵ is selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl and alkyl; and,
R⁶ and R⁷ are independently selected from the group consisting of hydrogen and lower alkyl.

7. A compound of claim 5 wherein R¹ and R² are linked to form a ring
selected from the group consisting of 4-(2-thienylmethyl)piperazino, 4-(3-thienylmethyl)piperazino, 4-(2-methoxyphenyl)piperazino, 4-(2-
thienyl(carbonyl)piperazino, 4-(2-thienylsulfonyl)piperazino, and 4-((benzyloxy)carbonyl)piperazino.

8. A compound of claim 5 further comprising derivatives of said compound
   selected from the group consisting of esters, carbamates, aminals,
   amides, and pro-drugs thereof.

9. A compound of claim 1 of the structure

   wherein A is selected from the group consisting of O, S, and NR\(^6\);
   E is selected from the group consisting of CH\(_2\), O, S, and
   NR\(^7\);
   T is selected from the group consisting of C(O) and (CH\(_2\)), wherein v is
   an integer of 0 or 1;

10. L is selected from the group consisting of O, NR\(^3\), S, and
     (CH\(_2\))\(_w\) wherein w is an integer of 0 or 1;

15. s and t are each integers independently of 0 to 3;

16. B, R\(^1\), R\(^2\), R\(^3\), R\(^4\), R\(^5\), R\(^6\), R\(^7\), R\(^8\), R\(^9\), R\(^10\) and R\(^{11}\) are independently selected
   from the group consisting of hydrogen, alkyl, cycloalkyl, aryl,
   hydroxyalkyl, alkoxy, alkoxyalkoxy, cycloalkylalkyl, alkylamino,
   haloalkyl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl and
   heterocyclylalkyl groups;

20. wherein R\(^1\) and R\(^2\) taken together may form a ring;

21. R\(^3\) and R\(^4\) taken together may form a ring;
R⁵ and R⁹ taken together may form a ring;
R¹⁰ and R¹¹ taken together may form a ring;
and salts thereof.

10. A compound of claim 9 wherein
A is NR⁶;
E is NR⁷;
each J is O;
s and t are each 1;
R¹ and R² are independently selected from the group consisting of aryl,
alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl
and alkyl;
R³ and R⁴ are independently selected from the group consisting of
hydrogen, alkoxy, alkoxyalkyl, aryl, alkylaryl, arylalkyl,
heterocyclyl and alkyl;
R¹⁰, R¹¹ and B are independently selected from the group consisting of
hydrogen and lower alkyl;
R⁵ is selected from the group consisting of aryl, alkylaryl, arylalkyl,
heterocyclyl, alkylheterocyclyl, heterocyclylalkyl and alkyl; and,
R⁶ and R⁷ are independently selected from the group consisting of
hydrogen and lower alkyl.

11. A compound of claim 9 wherein R¹ and R² are linked to form a ring
selected from the group consisting of 4-(2-thienylmethyl)piperazino, 4-
(3-thienylmethyl)piperazino, 4-(2-methoxyphenyl)piperazino, 4-(2-
thienylcarbonyl)piperazino, 4-(2-thiethylsulfonyl)piperazino, and 4-
((benzyloxy)carbonyl)piperazino.

12. A compound of claim 9 further comprising derivatives of said compound
selected from the group consisting of esters, carbamates, aminals, amides, and pro-drugs thereof.

13. A compound of claim 1 selected from the group consisting of:

(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((bis(2-thienylmethyl)amino)carbonyl)pentyl)amino)carbonyl)amino)propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-(((1,3-thiazol-2-ylmethyl)(2-thienylmethyl)amino)carbonyl)pentyl)amino)carbonyl)amino) propanoic acid,
(3S)-3-(((1S)-1-((bis(2-thienylmethyl)amino)carbonyl)pentyl)amino)carbonyl)amino)-4-morpholino-4-oxobutanoic acid,
(3R)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((bis(2-thienylmethyl)amino)carbonyl)pentyl)amino)carbonyl)amino)-2,2-dimethylpropanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((diallylamino)carbonyl)pentyl)amino)carbonyl)amino)propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((diisobutylamino)carbonyl)pentyl)amino)carbonyl)amino) propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((bis(3-methoxybenzyl)amino)carbonyl)pentyl)amino) carbonyl)amino)propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((bis(2-thienylmethyl)amino)carbonyl)pentyl)amino)carbonyl) (methyl)amino)propanoic acid,
(3S)-3-(((1S)-1-((bis(2-thienylmethyl)amino)carbonyl)pentyl)amino)carbonyl)amino)-3-(2-thienyl)propanoic acid,
(3S)-3-(((1S)-1-((bis(2-thienylmethyl)amino)carbonyl)pentyl)amino)carbonyl)amino)-3-(3-methoxyphenyl)propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((1S)-1-((4-(2-thienylsulfonyl)piperazino)carbonyl)pentyl)amino)carbonyl)amino)propanoic acid, and pharmaceutically acceptable salts thereof.

14. A compound of claim 13 further comprising derivatives of said compound selected from the group consisting of esters, carbamates, aminals, amides, optical isomers and pro-drugs thereof.

15. A pharmaceutical composition comprising:
a compound of claim 1
and pharmaceutically acceptable salts thereof,
in a pharmaceutically acceptable carrier.

5 16. A method for selectively inhibiting $\alpha_4\beta_1$, integrin binding in a mammal
comprising administering to said mammal a therapeutic amount of a compound
of claim 1.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5): Please See Extra Sheet.
US CL: Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S.: 544/379; 548/204; 549/60, 69, 441; 546/153; 514/252, 365, 444, 447, 466, 616

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ON LINE: structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>US 5,654,301 A (KOHN et al) 05 AUGUST 1997, see abstract.</td>
<td>1</td>
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</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search
19 JULY 1999

Date of mailing of the international search report
27 AUG 1999

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A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):
C07D 405/00, 277/30, 409/00, 333/36, 317/44; C07C 233/00; A61K 31/495, 31/425, 31/38, 31/36, 31/16

A. CLASSIFICATION OF SUBJECT MATTER:
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544/379; 548/204; 549/60, 69, 441; 546/153; 514/252, 365, 444, 447, 466, 616