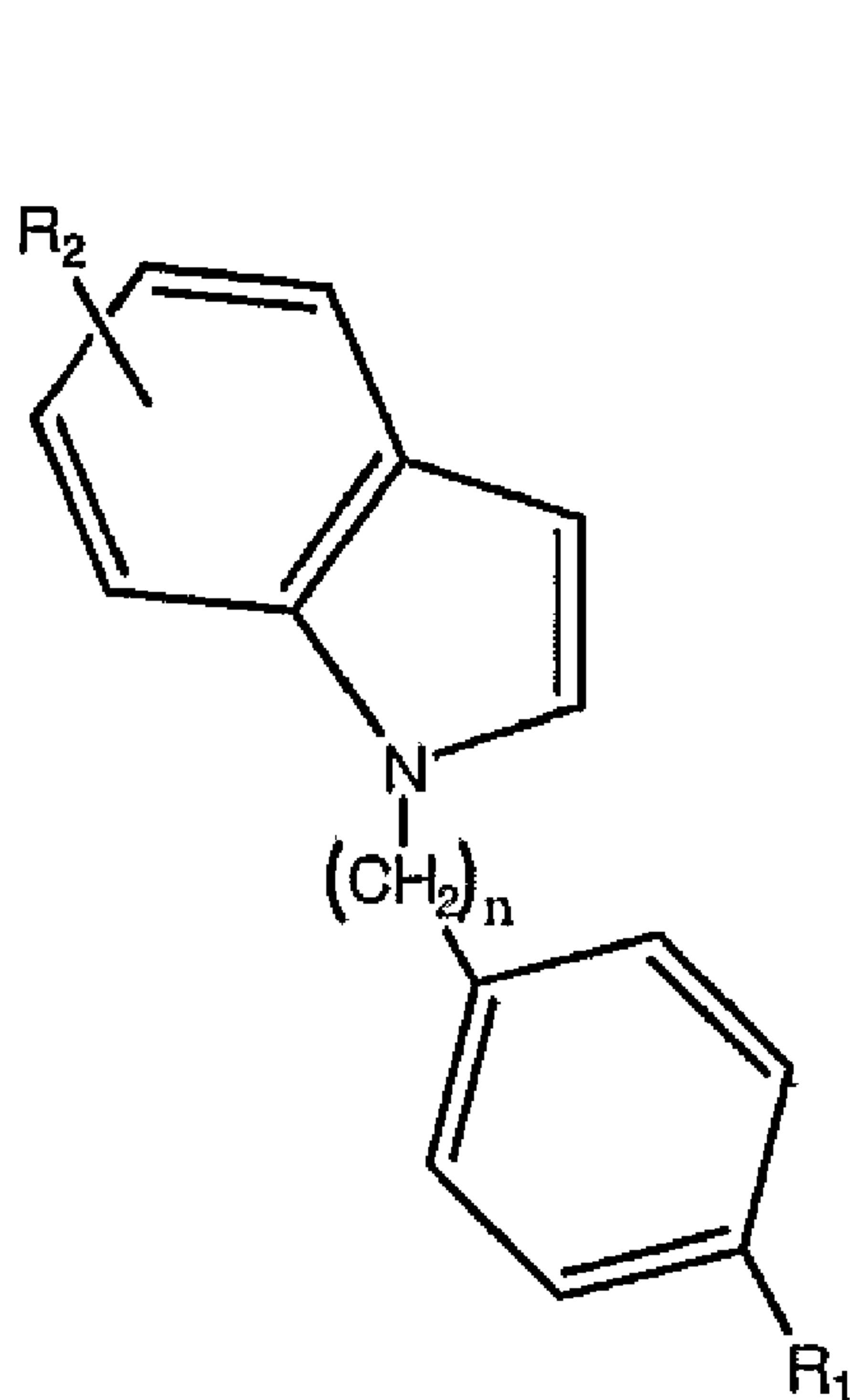




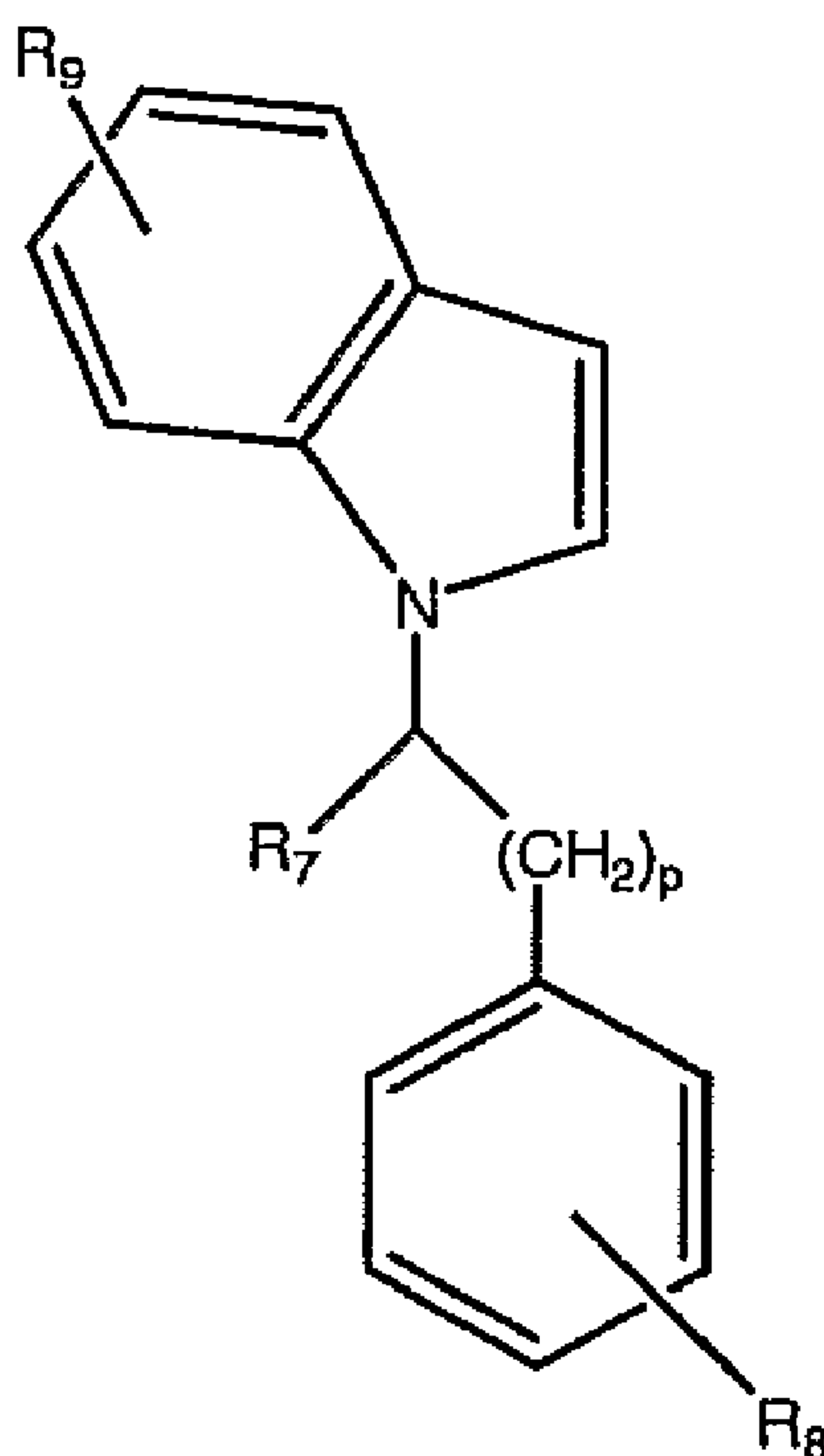
(86) Date de dépôt PCT/PCT Filing Date: 2006/08/16
(87) Date publication PCT/PCT Publication Date: 2007/02/22
(85) Entrée phase nationale/National Entry: 2008/01/30
(86) N° demande PCT/PCT Application No.: US 2006/032066
(87) N° publication PCT/PCT Publication No.: 2007/022321
(30) Priorité/Priority: 2005/08/17 (US60/708,834)

(51) Cl.Int./Int.Cl. *C07D 209/08* (2006.01),
A61K 31/404 (2006.01), *A61P 7/02* (2006.01)
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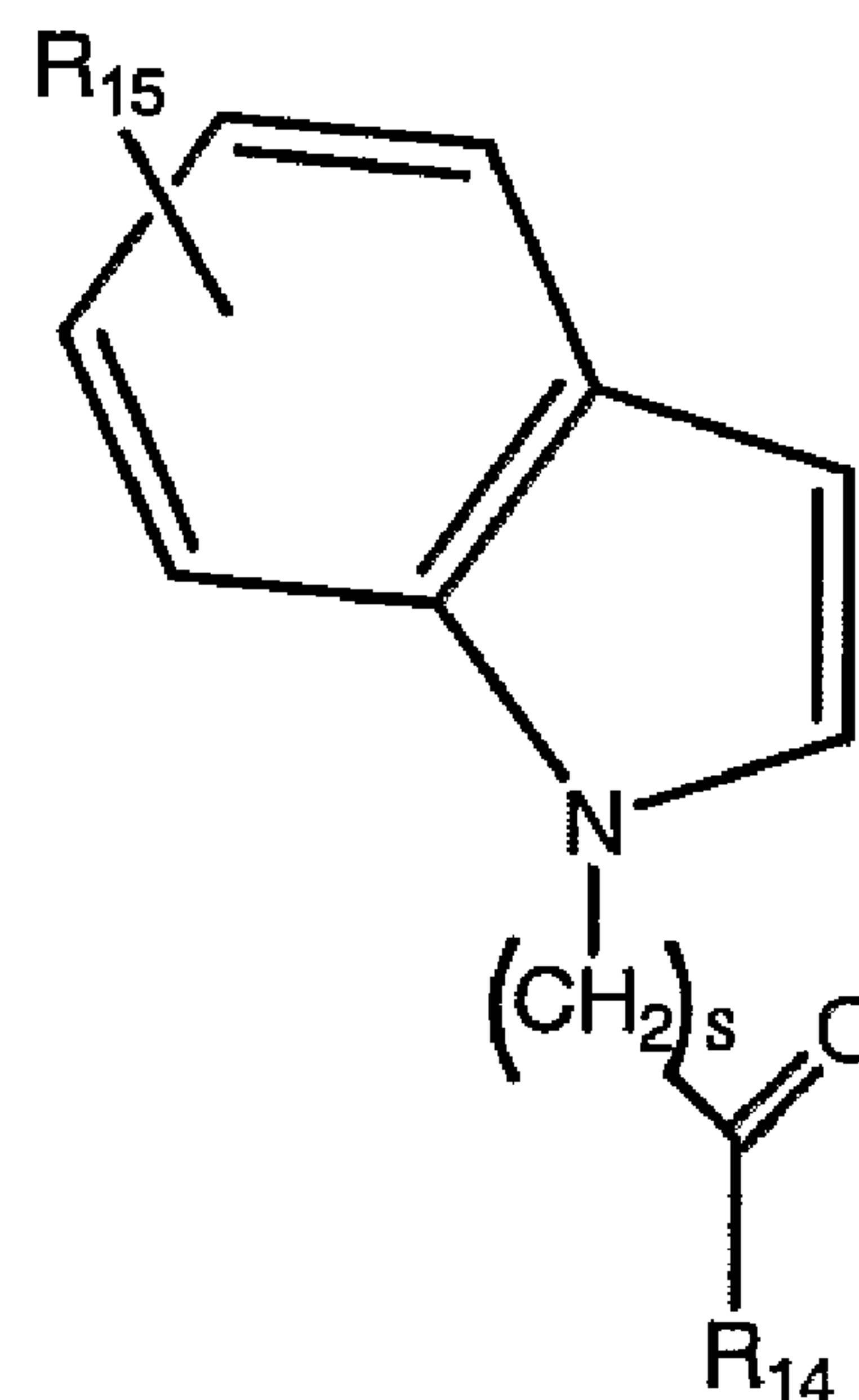
(54) Titre : INDOLES SUBSTITUES ET PROCEDES D'UTILISATION DE CEUX-CI
(54) Title: SUBSTITUTED INDOLES AND USE THEREOF



Formula 1



Formula 2



Formula 3

(57) Abrégé/Abstract:

The present invention relates generally to substituted indoles of formulas (1) (2) (3) and use thereof .



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
22 February 2007 (22.02.2007)

PCT

(10) International Publication Number
WO 2007/022321 A3

(51) International Patent Classification:

C07D 209/08 (2006.01) **A61P 7/02** (2006.01)
A61K 31/404 (2006.01)

(21) International Application Number:

PCT/US2006/032066

(22) International Filing Date: 16 August 2006 (16.08.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/708,834 17 August 2005 (17.08.2005) US

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2891 (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, HN, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT,
LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ,
NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU,
SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, 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:

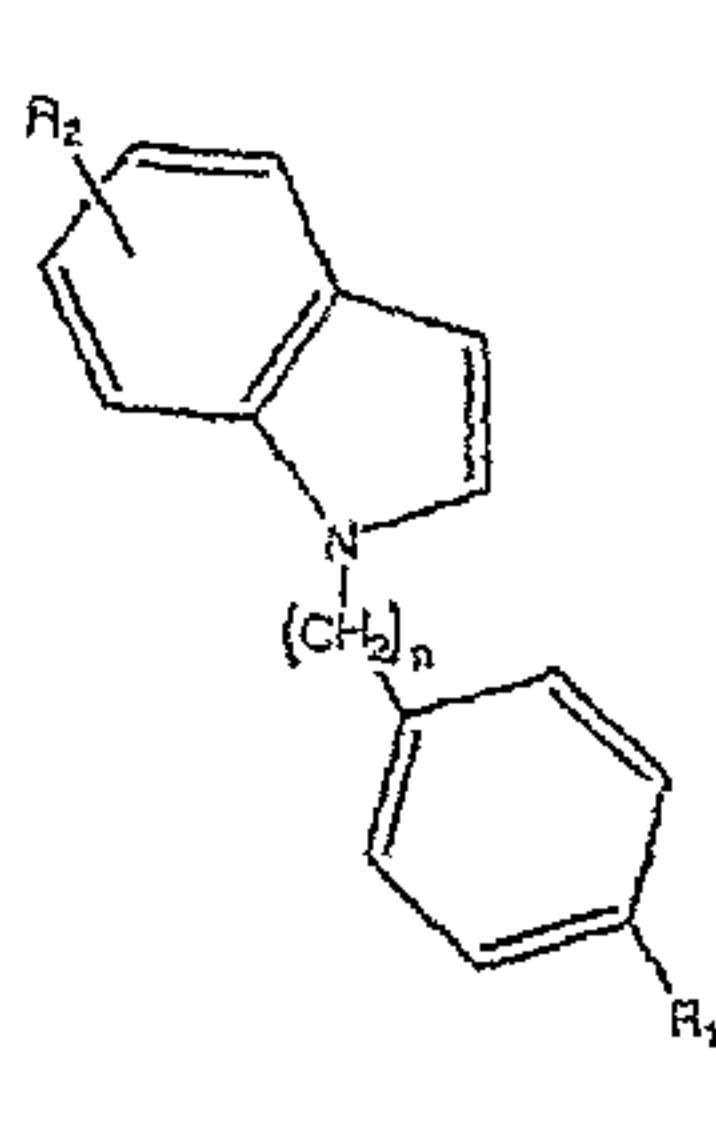
— with international search report

(88) Date of publication of the international search report:

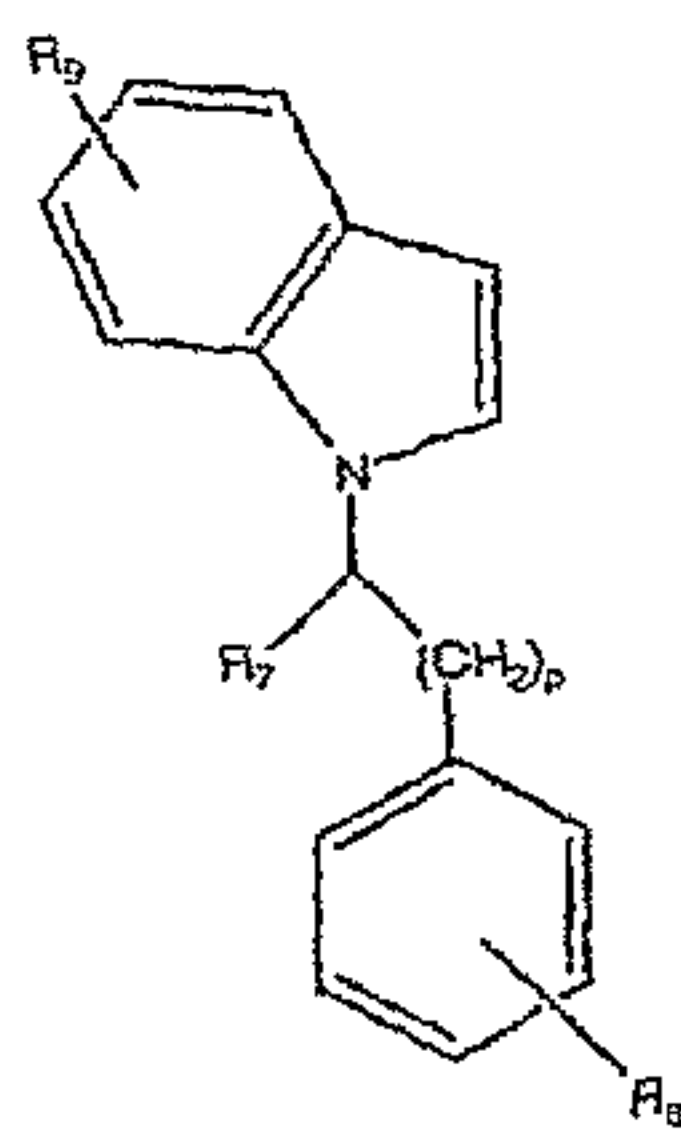
10 May 2007

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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

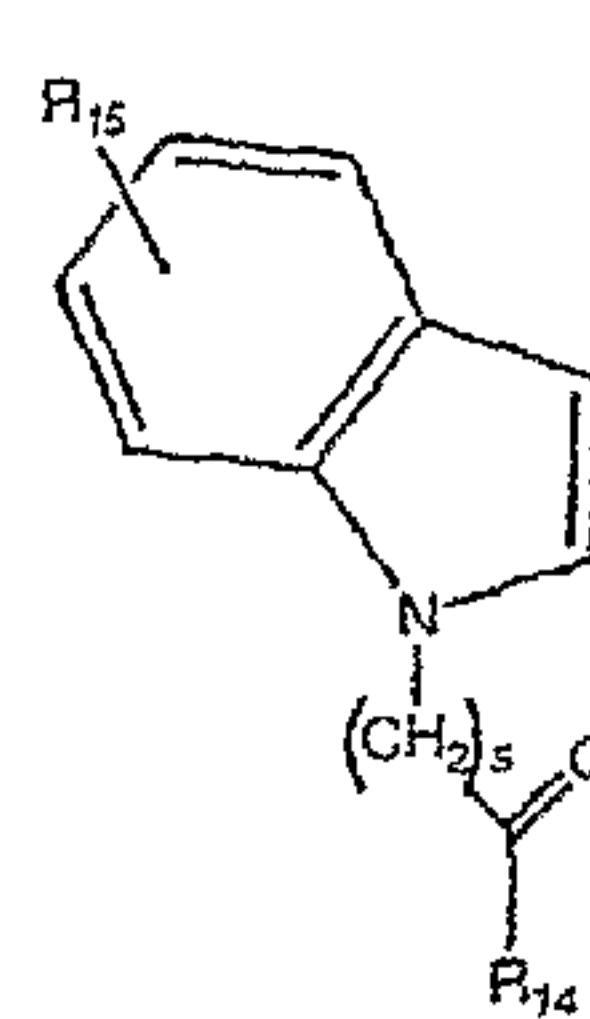
(54) Title: SUBSTITUTED INDOLES AND USE THEREOF



(1)



(2)



(3)

(57) Abstract: The present invention relates generally to substituted indoles of formulas (1) (2) (3) and use thereof .

SUBSTITUTED INDOLES AND METHODS OF THEIR USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Application No. 60/708,834 filed August 17, 2005, the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates generally to substituted indoles and methods of using them.

BACKGROUND OF THE INVENTION

[0003] The serine protease inhibitor PAI-1 is one of the primary inhibitors of the fibrinolytic system. The fibrinolytic system includes the proenzyme plasminogen, which is converted to the active enzyme, plasmin, by one of two tissue type plasminogen activators, *t*-PA or *u*-PA. PAI-1 is the principal physiological inhibitor of *t*-PA and *u*-PA. One of plasmin's main responsibilities in the fibrinolytic system is to digest fibrin at the site of vascular injury. The fibrinolytic system, however, is not only responsible for the removal of fibrin from circulation but is also involved in several other biological processes including ovulation, embryogenesis, intima proliferation, angiogenesis, tumorigenesis, and atherosclerosis.

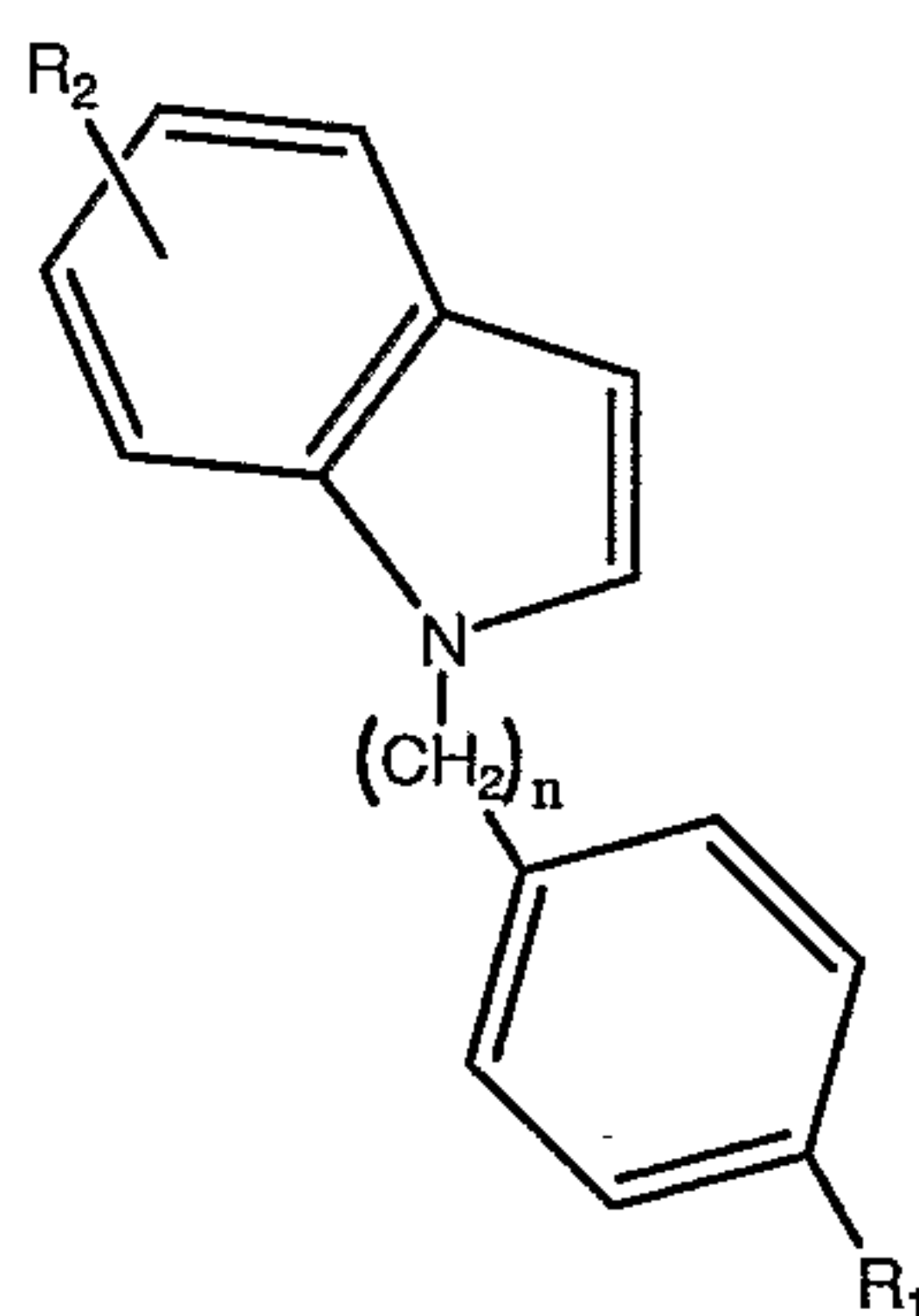
[0004] Elevated levels of PAI-1 have been associated with a variety of diseases and conditions including those associated with impairment of the fibrinolytic system. For example, elevated levels of PAI-1 have been implicated in thrombotic diseases, *e.g.*, diseases characterized by formation of a thrombus that obstructs vascular blood flow locally or detaches and embolizes to occlude blood flow downstream. (Krishnamurti, *Blood*, 69, 798 (1987); Reilly, *Arteriosclerosis and Thrombosis*, 11, 1276 (1991); Carmeliet, *Journal of Clinical Investigation*, 92, 2756 (1993), Rocha, *Fibrinolysis*, 8, 294, 1994; Aznar, *Haemostasis* 24, 243 (1994)). Antibody neutralization of PAI-1 activity resulted in promotion of endogenous thrombolysis and reperfusion (Biemond, *Circulation*, 91, 1175 (1995); Levi, *Circulation* 85, 305, (1992)). Elevated levels of PAI-1 have also been

implicated in diseases such as polycystic ovary syndrome (Nordt, *Journal of clinical Endocrinology and Metabolism*, 85, 4, 1563 (2000)), bone loss induced by estrogen deficiency (Daci, *Journal of Bone and Mineral Research*, 15, 8, 1510 (2000)), cystic fibrosis, diabetes, chronic periodontitis, lymphomas, diseases associated with extracellular matrix accumulation, malignancies and diseases associated with neoangiogenesis, inflammatory diseases, vascular damage associated with infections, and diseases associated with increased μ PA levels such as breast and ovarian cancer.

[0005] In view of the foregoing, there exists a need for the identification of inhibitors of PAI-1 activity and for methods of using the identified inhibitors to modulate PAI-1 expression or activity in a subject in order to treat disorders associated with elevated PAI-1 levels.

SUMMARY OF THE INVENTION

[0006] The present invention provides substituted indoles and methods of using them. In certain embodiments, substituted indoles are provided, including those of Formula 1:



Formula 1

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_1 is C_{1-6} alkyl;

R_2 is $NR_3SO_2R_4$ or $NHC(=O)NHR_5$;

R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

R_4 is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

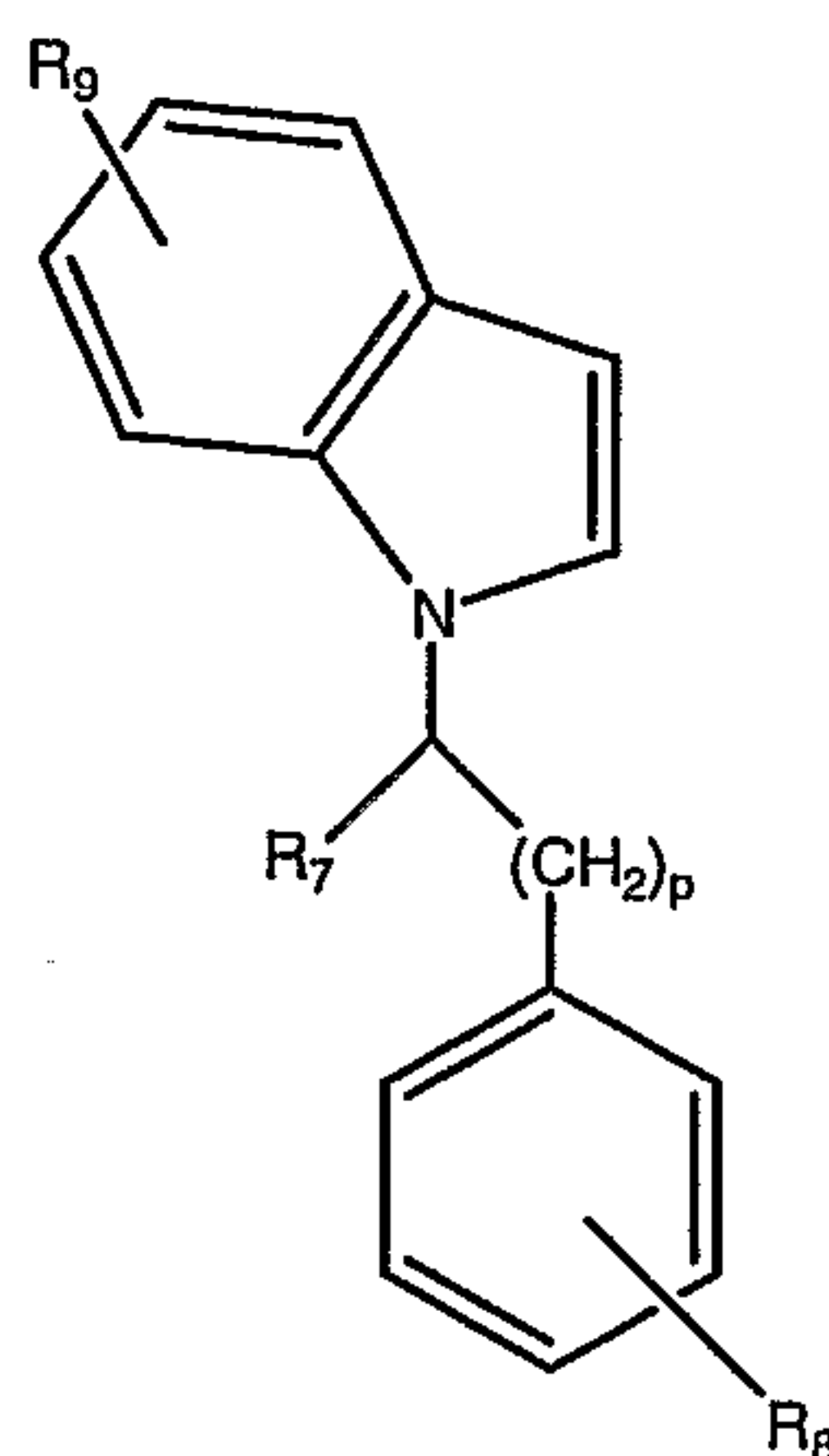
with the proviso that at least one of R_3 or R_4 is substituted by $COOR_6$;

R_5 is phenyl(CO_2H) or $-C_{1-6}$ alkyl(CO_2H) wherein the alkyl group is optionally substituted with phenyl or benzyl;

R_6 is hydrogen, or C_{1-6} alkyl; and

n is from 1 to 4.

[0007] Substituted indoles of the present invention also include those of Formula 2:



Formula 2

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_7 is hydrogen, CO_2H , or $CONHNH_2$;

p is from 0 to 4;

R_8 is hydrogen, $-C_{1-6}alkoxy(CO_2H)$, $C(=O)NR_{10}R_{11}$ or $C(=O)amino$ acid;

R_{10} and R_{11} are joined together with the nitrogen to which they are attached to form a 3 to 9 membered saturated ring comprising 2 to 8 carbon ring atoms;

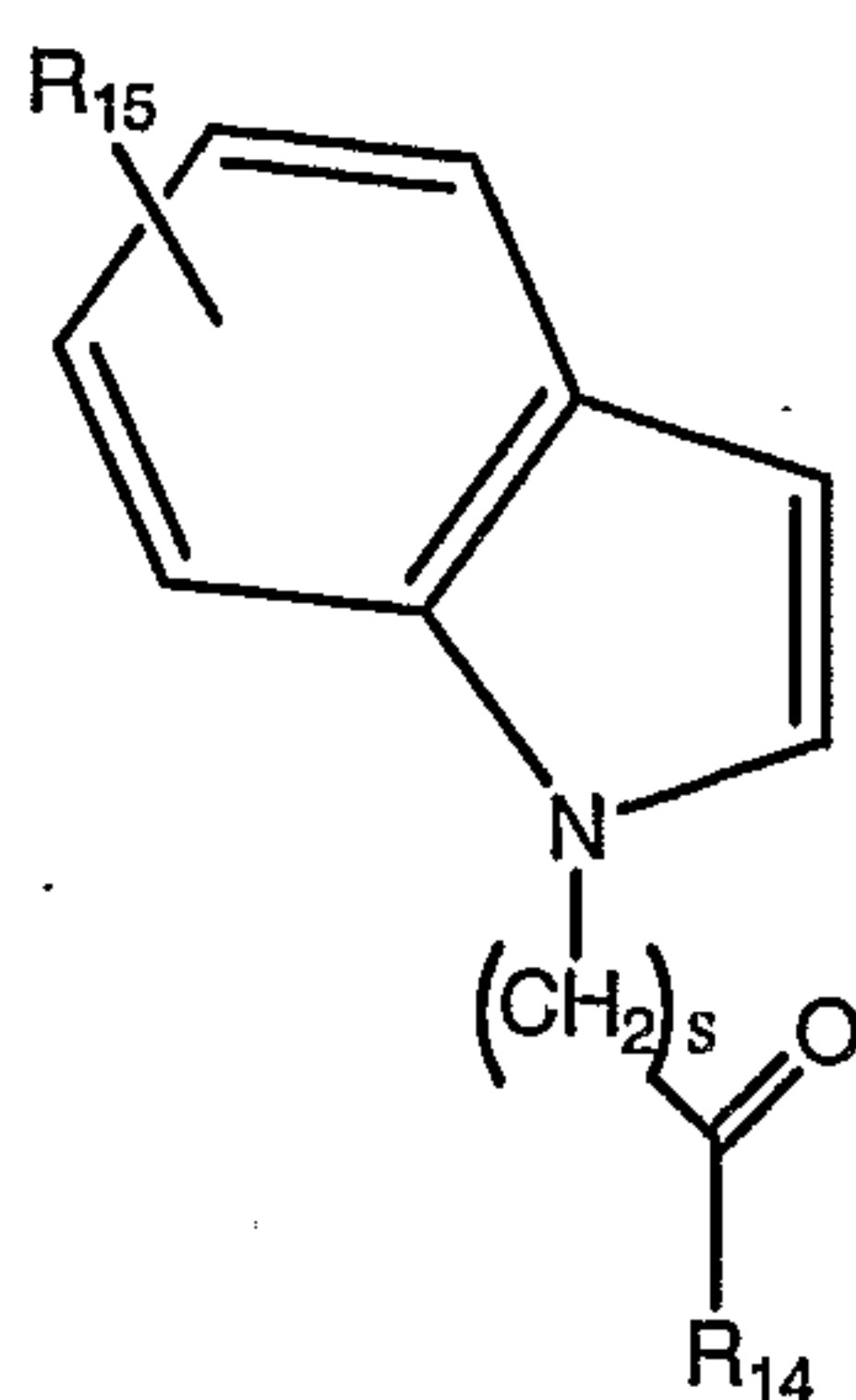
with the proviso that when R_8 is hydrogen, R_7 is CO_2H or $CONHNH_2$;

R_9 is $NR_{12}SO_2R_{13}$;

R_{12} is H, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl; and

R_{13} is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl.

[0008] Also included in the present invention are substituted indoles of Formula 3:



Formula 3

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_{14} is $-OH$, C_{1-6} alkoxy, or amino acid;

R_{15} is $NR_{16}SO_2R_{17}$;

R_{16} is H or a C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

R_{17} is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl; and

s is from 1 to 4.

[0009] The present invention further provides, *inter alia*, methods of using substituted indoles. In one aspect of the present invention, a therapeutically effective amount of one or more substituted indole is administered to a subject in order to treat a PAI-1 related disorder, *e.g.*, by inhibiting PAI-1 activity in the subject. For example, in one embodiment of the present invention, one or more substituted indoles of the present invention is administered to a subject in order to treat impairment of the fibrinolytic system. In other embodiments, one or more substituted indoles of the present invention is administered to a subject in order to treat thrombosis, *e.g.*, venous thrombosis, arterial thrombosis, cerebral thrombosis, and deep vein thrombosis, atrial fibrillation, pulmonary fibrosis, thromboembolic complications of surgery, cardiovascular disease, *e.g.*, myocardial ischemia, atherosclerotic plaque formation, chronic obstructive pulmonary disease, renal fibrosis, polycystic ovary syndrome, Alzheimer's disease, or cancer.

DETAILED DESCRIPTION OF THE INVENTION

GENERAL OVERVIEW

[0010] The present invention provides compounds that, for example, inhibit PAI-1 activity, processes for preparing such compounds, pharmaceutical compositions containing such compounds, and methods for using such compounds in medical therapies. The compounds have properties that are useful for the treatment, including the prevention and inhibition, of a wide variety of diseases and disorders involving the production and/or action of PAI-1. These include disorders resulting from impairment of the fibrinolytic system including, but not limited to, thrombosis, coronary heart disease, renal fibrosis, atherosclerotic plaque formation, pulmonary disease, myocardial ischemia, atrial fibrillation, coagulation syndromes, thromboembolic complications of surgery, peripheral arterial occlusion and pulmonary fibrosis. Other disorders include, but are not limited to, polycystic ovary syndrome, Alzheimer's disease, and cancer.

[0011] Where a functional moiety herein is optionally substituted herein, it may be by one or more substituents dependent on the positions available, *e.g.*, 1 to 2, 1 to 3, 1 to 4, or 1 to 5, as in the case of substituted phenyl or benzyl groups.

[0012] The terms "alkyl" and "alkylene," as used herein, whether used alone or as part of another group, refer to substituted or unsubstituted aliphatic hydrocarbon chains, the difference being that alkyl groups are monovalent (*i.e.*, terminal) in nature whereas alkylene groups are divalent and typically serve as linkers. Both include, but are not limited to, straight and branched chains containing from 1 to about 12 carbon atoms, preferably 1 to about 6 carbon atoms, unless explicitly specified otherwise. For example, methyl, ethyl, propyl, isopropyl, butyl, *i*-butyl and *t*-butyl are encompassed by the term "alkyl." Unless otherwise indicated, specifically included within the definition of "alkyl" are those aliphatic hydrocarbon chains that are optionally substituted, *e.g.*, by one or more substituents, such 1 to 3 substituents. Optional substituents include, for example, OCF₃, halogen, C₁₋₆ alkyl, C₁₋₆ perfluoroalkyl, benzyl, phenyl, heterocyclyl, and CO₂H.

[0013] The carbon number as used in the definitions herein refers to carbon backbone and carbon branching, but does not include carbon atoms of the substituents, such as alkoxy substitutions and the like.

[0014] The rings of the “phenyl” and “benzyl” groups described herein can be optionally substituted. The methylene linkage of the benzyl group can also be optionally substituted. Optional substituents include, for example, OCF₃, halogen, C₁₋₆ alkyl, C₁₋₆ perfluoroalkyl, benzyl, phenyl, heterocyclyl, and CO₂H.

[0015] The term “alkoxy,” as used herein, refers to the group –O-R_a wherein R_a is an alkyl group as defined above. Specifically included within the definition of “alkoxy” are those alkoxy groups that are optionally substituted. Optional substituents include, for example, OCF₃, halogen, C₁₋₆ alkyl, C₁₋₆ perfluoroalkyl, benzyl, phenyl, heterocyclyl, and CO₂H.

[0016] The term “cycloalkyl,” as used herein, refers to an optionally substituted alkyl group having one or more rings in their structures and having from about 3 to about 20 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 3 to about 10 carbon atoms being preferred. Multi-ring structures may be bridged or fused ring structures. Cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, 2-[4-isopropyl-1-methyl-7-oxa-bicyclo[2.2.1]heptanyl], 2-[1,2,3,4-tetrahydro-naphthalenyl], and adamantyl.

[0017] The term “aryl,” as used herein, refers to an optionally substituted, mono-, di-, tri-, or other polycyclic aromatic ring system having from about 5 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 6 to about 10 carbons being preferred. Non-limiting examples include, for example, phenyl, naphthyl, anthracenyl, and phenanthrenyl.

[0018] The term “alkylaryl,” as used herein, refers to an optionally substituted ring system composed of an aryl radical bearing an alkyl substituent, wherein alkyl and aryl are as previously defined. Exemplary alkylaryl groups include, but are not limited to, methylphenyl (tolulyl), dimethyl phenyl (xylyl), ethylphenyl and methylnaphthyl.

[0019] The term “heteroaryl,” as used herein, refers to an optionally substituted aryl ring system wherein in at least one of the rings, one or more of the carbon atom ring members is independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH, wherein aryl is as previously defined. Heteroaryl groups having a total of from about 5 to about 14 carbon atom ring members and heteroatom ring members (and all combinations and subcombinations of ranges and specific numbers of carbon and heteroatom ring members) are preferred. Exemplary heteroaryl groups include, but are not limited to, pyrrolyl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, thiophenyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl. Heteroaryl may be attached via a carbon or a heteroatom to the rest of the molecule.

[0020] The term “alkylheteroaryl,” as used herein, refers to an optionally substituted ring system composed of a heteroaryl radical bearing an alkyl substituent, wherein alkyl and heteroaryl are as previously defined. Exemplary alkylheteroaryl groups include, but are not limited to, alkyl substituted pyrrolyl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, thiophenyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl.

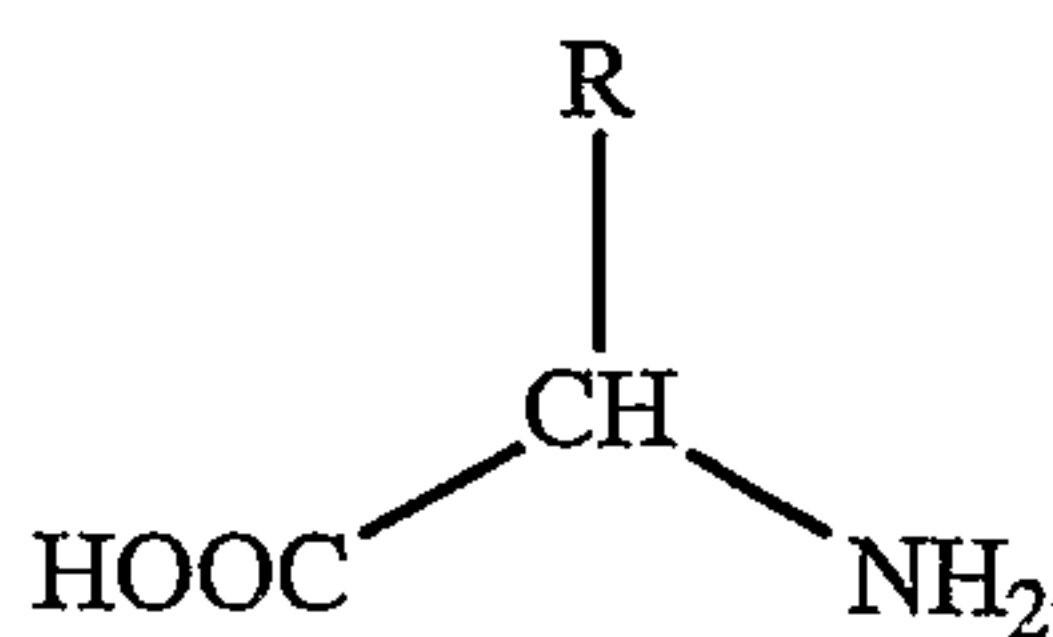
[0021] The term “heterocyclyl” or “Het,” as used herein, whether used alone or as part of another group, refers to a stable 3 to about 10-member ring, preferably 5 to 10-member ring containing carbons atoms and from 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. A heterocyclyl of this invention can be either a monocyclic or bicyclic ring system, and can be either saturated, unsaturated, or partially saturated. A heterocyclyl can be optionally fused to a phenyl ring. Heterocyclyl groups include, but are not limited to, aziridinyl, azetidiny, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, dihydro-1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinolyl, and

tetrahydroisoquinoliny. Preferred heterocyclyl moieties include: (a) 6-membered saturated, partially unsaturated, or unsaturated heterocycles containing 1-2 nitrogens, optionally fused to a phenyl ring; (b) 5-membered saturated, partially saturated, or unsaturated heterocycles containing 1-3 nitrogen, oxygen, or sulfur atoms, optionally fused to a phenyl ring; (c) saturated, partially unsaturated, or unsaturated bicyclic heterocycles containing 1-4 nitrogen, oxygen, or sulfur atoms; (d) carbazole, dibenzofuran, and dibenzothiophene. Unless otherwise indicated, specifically included in the definition of "heterocyclyl" are those heterocycles that are optionally substituted. Optional substituents include, for example, OCF₃, halogen, C₁₋₆ alkyl, C₁₋₆ perfluoroalkyl, benzyl, phenyl, heterocyclyl and CO₂H.

[0022] The term "perfluoroalkyl", as used herein, whether used alone or as part of another group, refers to a saturated aliphatic hydrocarbon having 1 to 6 carbon atoms and two or more fluorine atoms and includes, but is not limited to, straight or branched chains, such as -CF₃, -CH₂CF₃, -CF₂CF₃ and -CH(CF₃)₂. Optional substituents include, for example, OCF₃, halogen, C₁₋₆ alkyl, C₁₋₆ perfluoroalkyl, benzyl, phenyl, heterocyclyl, and CO₂H.

[0023] The term "halogen" or "halo" refers to chlorine, bromine, fluorine, and iodine.

[0024] The term "amino acid" refers to any molecule that contains both amino and carboxylic acid functional groups, including both naturally-occurring amino acids and non-naturally-occurring amino acids and including both alpha amino acids, beta amino acids, and amino acid derivatives. Preferably, the amino acid has a molecular weight of between 50 and 400 Daltons. Preferably, the amino acid is linked via the nitrogen atom to the balance of the molecule in compounds of Formula 2 and Formula 3. The term "alpha amino acid" refers to those amino acids in which the amino and carboxylate functionalities are attached to the same carbon, including both naturally-occurring alpha amino acids and non-naturally-occurring alpha amino acids of the general formula:



wherein R is H, C₁₋₆ alkyl optionally substituted with hydroxy, carboxy, amino, amido, amidino, thio, alkylthio, heterocycle, aryl, or heteroaryl; optionally substituted heterocycle, optionally substituted aryl; and optionally substituted heteroaryl or where the R and the nitrogen of the amino group form a ring.

Suitable naturally-occurring alpha amino acids include alanine, valine, leucine, isoleucine, methionine, phenylalanine, glycine, tryptophan, proline, serine, threonine, cysteine, asparagine, glutamine, tyrosine, lysine, arginine, histidine, aspartate, and glutamate. Suitable non-naturally-occurring alpha amino acids include D-alanine and D-glutamic acid, L-homoserine and L-ornithine, L-thyroxine, Fmoc-(Boc-4-aminomethyl)-L-phenylalanine, Boc-(Fmoc-4-aminomethyl)-L-phenylalanine, Fmoc-(Boc-4-aminomethyl)-D-phenylalanine, Boc-(Fmoc-4-aminomethyl)-D-phenylalanine, Fmoc-4-amino-L-phenylalanine, Boc-4-amino-L-phenylalanine, Fmoc-4-amino-D-phenylalanine, Boc-4-amino-D-phenylalanine, Fmoc-(Boc-4-amino)-L-phenylalanine, Fmoc-(Boc-4-amino)-D-phenylalanine, Fmoc-4-bromo-L-phenylalanine, Boc-4-bromo-L-phenylalanine, Fmoc-4-bromo-D-phenylalanine, Boc-4-bromo-D-phenylalanine, Fmoc-4-bis(2-chloroethyl)amino-L-phenylalanine, Boc-4-bis(2-chloroethyl)amino-L-phenylalanine, Fmoc-2-chloro-L-phenylalanine, Boc-2-chloro-L-phenylalanine, Fmoc-4,5-dehydro-L-leucine and Boc-4,5-dehydro-L-leucine; Fmoc-L-allylglycine, Boc-L-allylglycine dicyclohexylammonium salt, Fmoc-D-allylglycine, Boc-D-allylglycine dicyclohexylammonium salt, Fmoc-DL-methionine methylsulfonium chloride, Boc-DL-methionine methylsulfonium chloride, Fmoc-a-methyl-DL-methionine, Boc-a-methyl-DL-methionine, Fmoc-L-selenomethionine, Boc-L-selenomethionine, Fmoc-DL-selenomethionine and Boc-DL-selenomethionine). Other suitable non-naturally occurring amino acids are known in the art. The exemplary non-naturally occurring amino acids given above have protecting groups, but also exist without the protecting groups and are specifically included herein. Exemplary amino acid derivatives include 4-hydroxyproline and 5-hydroxylysine. Preferred amino acids include alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, β -alanine and esters thereof. Preferred amino acids also include those represented by the formula $-NR_{18}R_{19}$ wherein R_{18} and R_{19} are joined together with the nitrogen to which they are attached to form a 3 to 9 membered saturated ring comprising 2 to 8 carbon ring atoms and substituted with CO_2H or $C(O)C_{1-6}$ alkoxy including, for example, cyclopropane amino acids (such as 1-aminocyclopropane-1-carboxylic acid, allo-coronamic acid and 2,3-methanohomoserine), 1-aminocyclohexane-1-carboxylic acid, isonipecotic acid, 2-azetidinecarboxylic acid, and esters thereof. Preferred amino acids also include alpha amino acids and those amino acids represented by the formula $C(=O)NH(CH_2)_mCO_2H$, wherein m is from 1 to 4.

[0025] The term “treating” or “treatment” refers to any indicia of success in amelioration of an injury, pathology, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology, or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; or improving a subject’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neurological examination, and/or psychiatric evaluation. “Treating” or “treatment of a PAI-1 related disorder” includes preventing the onset of symptoms in a subject that may be predisposed to a PAI-1 related disorder but does not yet experience or exhibit symptoms of the disorder (prophylactic treatment), inhibiting the symptoms of the disorder (slowing or arresting its development), providing relief from the symptoms or side-effects of the disorder (including palliative treatment), and/or relieving the symptoms of the disorder (causing regression). Accordingly, the term “treating” includes the administration of the compounds or agents of the present invention to a subject to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with PAI-1 related disorders, *e.g.*, tumor growth associated with cancer. A skilled medical practitioner will know how to use standard methods to determine whether a patient is suffering from a disease associated with enhanced levels and/or activity of PAI-1, *e.g.*, by examining the patient and determining whether the patient is suffering from a disease known to be associated with elevated PAI-1 levels or activity or by assaying for PAI-1 levels in blood plasma or tissue of the individual suspected of suffering from a PAI-1 related disease and comparing PAI-1 levels in the blood plasma or tissue of the individual suspected of suffering from a PAI-1 related disease to PAI-1 levels in the blood plasma or tissue of a healthy individual. Increased PAI-1 levels are indicative of disease. Accordingly, the present invention provides, *inter alia*, methods of administering a compound of the present invention to a subject and determining levels of PAI-1 in the subject. The level of PAI-1 in the subject can be determined before and/or after administration of the compound.

[0026] In healthy individuals, PAI-1 is found at low levels in the plasma (from about 5-26 ng/mL), but it is elevated in many PAI-1 related disorders, including, for example, atherosclerosis (Schneiderman J. *et. al*, *Proc Natl Acad Sci* 89: 6998-7002, 1992) deep vein thrombosis (Juhan-Vague I, *et. al*, *Thromb Haemost* 57: 67-72, 1987), and non-insulin dependent diabetes mellitus (Juhan-Vague I, *et. al*, *Thromb Haemost* 78: 565-660, 1997).

PAI-1 stabilizes both arterial and venous thrombi, contributing respectively to coronary arterial occlusion in post-myocardial infarction (Hamsten A, *et. al. Lancet* 2:3-9, 1987), and venous thrombosis following post-operative recovery from orthopedic surgery. (Siemens HJ, *et. al, J Clin Anesthesia* 11: 622-629, 1999). Plasma PAI-1 is also elevated, for example, in postmenopausal women, and has been proposed to contribute to the increased incidence of cardiovascular disease in this population (Koh K *et. al, N Engl J Med* 336: 683-690, 1997).

[0027] The term “PAI-1 related disorder or disease” refers to any disease or condition that is associated with increased or enhanced expression or activity of PAI-1 or increased or enhanced expression or activity of a gene encoding PAI-1. Examples of such increased activity or expression can include one or more of the following: activity of the protein or expression of the gene encoding the protein is increased above the level of that in normal subjects; activity of the protein or expression of the gene encoding the protein is in an organ, tissue or cell where it is not normally detected in normal subjects (*i.e.* spatial distribution of the protein or expression of the gene encoding the protein is altered); activity of the protein or expression of the gene encoding the protein is increased when activity of the protein or expression of the gene encoding the protein is present in an organ, tissue or cell for a longer period than in a normal subjects (*i.e.*, duration of activity of the protein or expression of the gene encoding the protein is increased). A normal or healthy subject is a subject not suffering from a PAI-1 related disease or condition.

[0028] The term “pharmaceutically acceptable excipient “ means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous.

[0029] “Pharmaceutically acceptable salts and esters” refers to salts and esters that are pharmaceutically acceptable and have the desired pharmacological properties. Such salts include, for example, salts that can be formed where acidic protons present in the compounds are capable of reacting with inorganic or organic bases. Suitable inorganic salts include, for example, those formed with the alkali metals or alkaline earth metals, *e.g.* sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include, for example, those formed with organic bases such as the amine bases, *e.g.* ethanolamine, diethanolamine,

triethanolamine, tromethamine, N methylglucamine, and the like. Pharmaceutically acceptable salts can also include acid addition salts formed from the reaction of basic moieties, such as amines, in the parent compound with inorganic acids (*e.g.* hydrochloric and hydrobromic acids) and organic acids (*e.g.* acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). Pharmaceutically acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the compounds, *e.g.* C₁₋₆ alkyl esters. When there are two acidic groups present, a pharmaceutically acceptable salt or ester can be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly where there are more than two acidic groups present, some or all of such groups can be salified or esterified. Compounds named in this invention can be present in unsalified or unesterified form, or in salified and/or esterified form, and the naming of such compounds is intended to include both the original (unsalified and unesterified) compound and its pharmaceutically acceptable salts and esters. Also, certain compounds named in this invention can be present in more than one stereoisomeric form, and the naming of such compounds is intended to include all single stereoisomers and all mixtures (whether racemic or otherwise) of such stereoisomers.

[0030] “Inhibitors,” “activators,” and “modulators” of expression or of activity are used to refer to inhibitory, activating, or modulating molecules, respectively, identified using *in vitro* and *in vivo* assays for expression or activity. Inhibitors of the present invention are compositions that, inhibit expression of PAI-1 or bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate the activity of PAI-1. Samples or assays comprising PAI-1 can be treated with a composition of the present invention and compared to control samples without a composition of the present invention. Control samples (untreated with compositions of the present invention) can be assigned a relative activity value of 100%. In certain embodiments, inhibition of PAI-1 is achieved when the activity value relative to the control is about 80% or less, optionally 50% or 25, 10%, 5% or 1%.

[0031] The terms “pharmaceutically acceptable”, “physiologically tolerable” and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to or upon a human without the production of undesirable physiological effects such as nausea,

dizziness, gastric upset and the like which would be to a degree that would prohibit administration of the compound.

[0032] A “therapeutically effective amount” or “pharmaceutically effective amount” means the amount that, when administered to a subject, produces effects for which it is administered. For example, a “therapeutically effective amount,” when administered to a subject to inhibit PAI-1 activity, is sufficient to inhibit PAI-1 activity. A “therapeutically effective amount,” when administered to a subject for treating a disease, is sufficient to effect treatment for that disease.

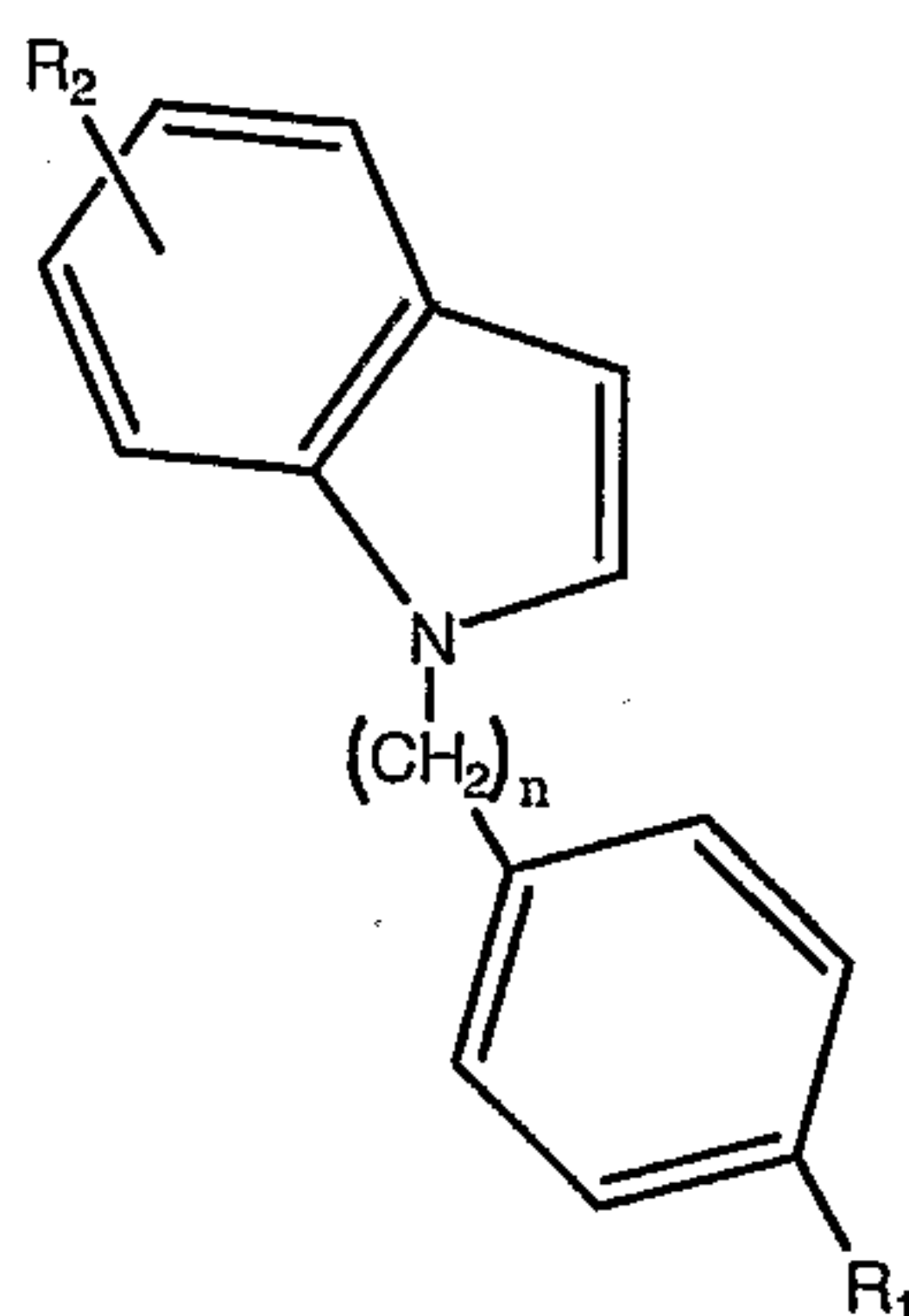
[0033] Except when noted, the terms “subject” or “patient” are used interchangeably and refer to mammals such as human patients and non-human primates, as well as experimental animals such as rabbits, rats, and mice, and other animals. Accordingly, the term “subject” or “patient” as used herein means any mammalian patient or subject to which the compounds of the invention can be administered. In an exemplary embodiment of the present invention, to identify subject patients for treatment according to the methods of the invention, accepted screening methods are employed to determine risk factors associated with a targeted or suspected disease or condition or to determine the status of an existing disease or condition in a subject. These screening methods include, for example, conventional work-ups to determine risk factors that may be associated with the targeted or suspected disease or condition. These and other routine methods allow the clinician to select patients in need of therapy using the methods and formulations of the present invention.

[0034] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

SUBSTITUTED INDOLES

[0035] The present invention provides substituted indoles. The substituted indoles are preferably administered to inhibit PAI-1 expression or activity in a subject and, ultimately, to treat diseases or conditions associated with increased PAI-1 activity in a subject, *e.g.*, a PAI-1 related disorder.

[0036] Substituted indoles include those of the Formula 1:



Formula 1

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_1 is C_{1-6} alkyl;

R_2 is $NR_3SO_2R_4$ or $NHC(=O)NHR_5$;

R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

R_4 is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

with the proviso that either R_3 or R_4 is substituted by $COOR_6$;

R_5 is phenyl(CO_2H) or $-C_{1-6}$ alkyl(CO_2H) wherein the alkyl group is optionally substituted with phenyl or benzyl;

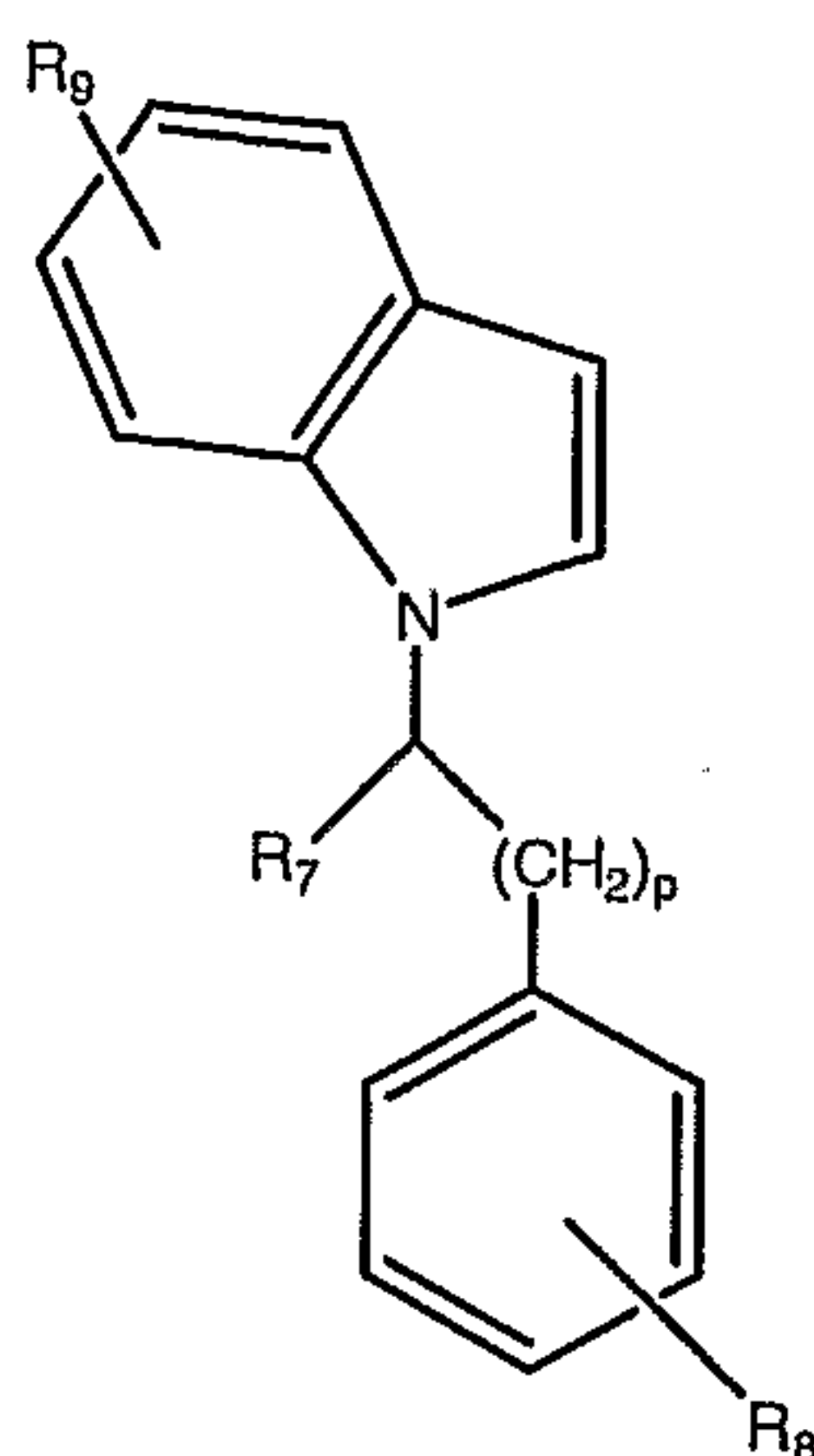
R_6 is hydrogen or C_{1-6} alkyl; and

n is from 1 to 4.

[0037] Exemplary compounds of Formula 1 include those wherein R_1 is branched butyl (*e.g.*, iso-butyl and tert-butyl). Examples of R_3 are CH_2CO_2H , hydrogen or benzyl wherein the ring of the benzyl group is substituted with CO_2H . Examples of R_4 are phenyl substituted by $COOR_6$. R_5 may be, for example, $-C_{1-6}$ alkyl(CO_2H) wherein the alkyl group is substituted with phenyl or benzyl. An example of n is 1.

[0038] Exemplary compounds include those wherein the alkyl and perfluoroalkyl groups of R_3 and R_4 are unsubstituted or substituted with COOR_6 and the rings of the phenyl, benzyl or heterocyclyl groups of R_3 and R_4 are unsubstituted or substituted with COOR_6 .

[0039] Substituted indoles include those of Formula 2:



Formula 2

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_7 is hydrogen, CO_2H , or CONHNH_2 ;

p is from 0 to 4;

R_8 is hydrogen, $-\text{C}_{1-6}\text{alkoxy}(\text{CO}_2\text{H})$, $\text{C}(=\text{O})\text{NR}_{10}\text{R}_{11}$ or $\text{C}(=\text{O})\text{amino acid}$;

R_{10} and R_{11} are joined together with the nitrogen to which they are attached to form a 3 to 9 membered saturated ring comprising 2 to 8 carbon ring atoms;

with the proviso that when R_8 is hydrogen, R_7 is CO_2H or CONHNH_2 ;

R_9 is $\text{NR}_{12}\text{SO}_2\text{R}_{13}$;

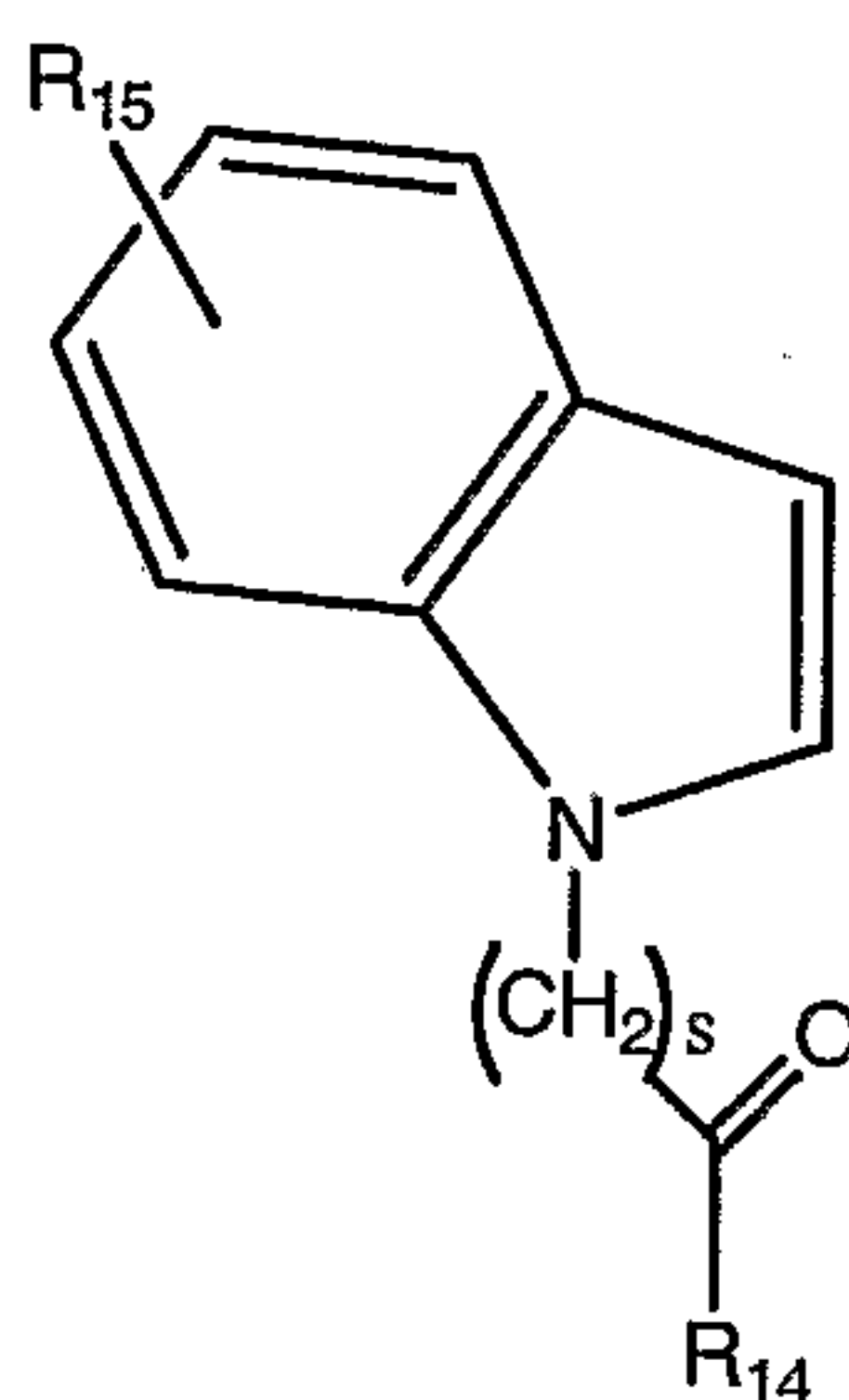
R_{12} is H, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl; and

R_{13} is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl.

[0040] Exemplary compounds of Formula 2 include those wherein p is from 1 to 4. Examples of R_8 are hydrogen, $\text{OCH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})$ -phenylalanine, $-\text{C}(=\text{O})$ - β -alanine or $-\text{C}(=\text{O})$ -piperidinyl substituted with carboxylic acid. An example of R_{12} is H. Examples of R_{13} are unsubstituted phenyl and phenyl substituted with OCF_3 , phenyl, C_{1-6} alkyl or halogen.

[0041] Exemplary compounds include those wherein the alkyl and perfluoroalkyl groups of R_{12} and R_{13} are unsubstituted or substituted with OCF_3 , C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl and the rings of the rings of the phenyl, benzyl or heterocyclyl groups of R_{12} and R_{13} are unsubstituted or substituted with OCF_3 , C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, or phenyl.

[0042] Substituted indoles include those of Formula 3



Formula 3

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_{14} is $-OH$, C_{1-6} alkoxy, or amino acid;

R_{15} is $NR_{16}SO_2R_{17}$;

R_{16} is H or a C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

R_{17} is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl; and

s is from 1 to 4.

[0043] In some embodiments, when R_{14} is $-OH$ or C_{1-6} alkoxy, R_{16} or R_{17} is substituted with OCF_3 , benzyl, phenyl, or heterocyclyl.

[0044] Preferred compounds of Formula 3 include those wherein R_{14} is $-OH$, phenylalanine or leucine. Preferably, R_{16} is hydrogen. Preferably, R_{17} is unsubstituted phenyl; phenyl substituted with OCF_3 , halogen, C_{1-6} alkyl, or phenyl; or heterocyclyl. Preferably, s is 1.

[0045] Exemplary substituted indoles of the present invention include, but are not limited to:

3-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)sulfonylbenzoic acid;
 {benzenesulfonyl-[1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]-amino}-acetic acid;
 4-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl](phenylsulfonyl)amino)methylbenzoic acid;
 4-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)sulfonylbenzoic acid;
N-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)carbonyl-L-phenylalanine;
 3-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)carbonylamino]benzoic acid;
 [4-([5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl)methyl]phenoxy]acetic acid;
 3-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)carbonylamino]benzoic acid;
 {4-([5-[(4-*tert*-butylphenyl)sulfonyl]amino]-1*H*-indol-1-yl)methyl]phenoxy}acetic acid;
 3-phenyl-2-[5-([4-(trifluoromethoxy)phenyl]sulfonyl)amino]-1*H*-indol-1-yl]propanoic acid;
 1-[4-([5-[(3,4-dichlorophenyl)sulfonyl]amino]-1*H*-indol-1-yl)methyl]benzoyl]piperidine-4-carboxylic acid;
 1-[4-([5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl)methyl]benzoyl]piperidine-4-carboxylic acid;
 1-[4-([5-[(4-*tert*-butylphenyl)sulfonyl]amino]-1*H*-indol-1-yl)methyl]benzoyl]piperidine-4-carboxylic acid;
N-(4-([5-([4-(trifluoromethoxy)phenyl]sulfonyl)amino]-1*H*-indol-1-yl)methyl]benzoyl)- β -alanine;
N-[4-([5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl)methyl]benzoyl]- β -alanine;
N-[4-([5-[(4-*tert*-butylphenyl)sulfonyl]amino]-1*H*-indol-1-yl)methyl]benzoyl]- β -alanine;
N-[4-([5-[(phenylsulfonyl)amino]-1*H*-indol-1-yl)methyl]benzoyl]-L-phenylalanine;
N-(4-([5-([4-(trifluoromethoxy)phenyl]sulfonyl)amino]-1*H*-indol-1-yl)methyl]benzoyl)-L-phenylalanine;
N-[4-([5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl)methyl]benzoyl]-L-phenylalanine;
N-[4-([5-[(4-*tert*-butylphenyl)sulfonyl]amino]-1*H*-indol-1-yl)methyl]benzoyl]-L-phenylalanine;

N-[1-(1-Benzyl-2-hydrazino-2-oxoethyl)-1H-indol-5-yl]-4-(trifluoromethoxy)benzenesulfonamide;

{5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}acetic acid;

N-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)-L-phenylalanine;

N-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1H-indol-1-yl)acetyl]-L-phenylalanine;

N-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)-L-leucine;

N-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1H-indol-1-yl)acetyl]-L-leucine;

N-{{5-([4-(trifluoromethoxy)phenyl]sulfonyl)amino}-1H-indol-1-yl}acetyl}-L-phenylalanine;

N-({5-[(quinolin-8-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)-L-phenylalanine;

N-{{5-([4-(trifluoromethoxy)phenyl]sulfonyl)amino}-1H-indol-1-yl}acetyl}-L-leucine;

1-{{5-([4-(trifluoromethoxy)phenyl]sulfonyl)amino}-1H-indol-1-yl}acetyl}piperidine-4-carboxylic acid;

1-({5-[(quinolin-8-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)piperidine-4-carboxylic acid;

1-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)piperidine-4-carboxylic acid;

1-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1H-indol-1-yl)acetyl]piperidine-4-carboxylic acid;

N-({5-[(quinolin-8-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)-L-leucine;

or a pharmaceutically acceptable salt or ester form thereof.

[0046] The present invention also provides compositions comprising substituted indoles, including those compounds of Formulae 1 to 3 or a stereoisomer or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such compositions include pharmaceutical compositions for treating or controlling disease states or conditions associated with increased PAI-1 activity. In certain embodiments, the compositions comprise mixtures of one or more substituted indoles.

[0047] Certain of the compounds of Formulae 1 to 3 contain stereogenic carbon atoms or other chiral elements and thus give rise to stereoisomers, including enantiomers and diastereomers. The present invention includes all of the stereoisomers of Formulas 1-3, as well as mixtures of the stereoisomers. Throughout this application, the name of the product,

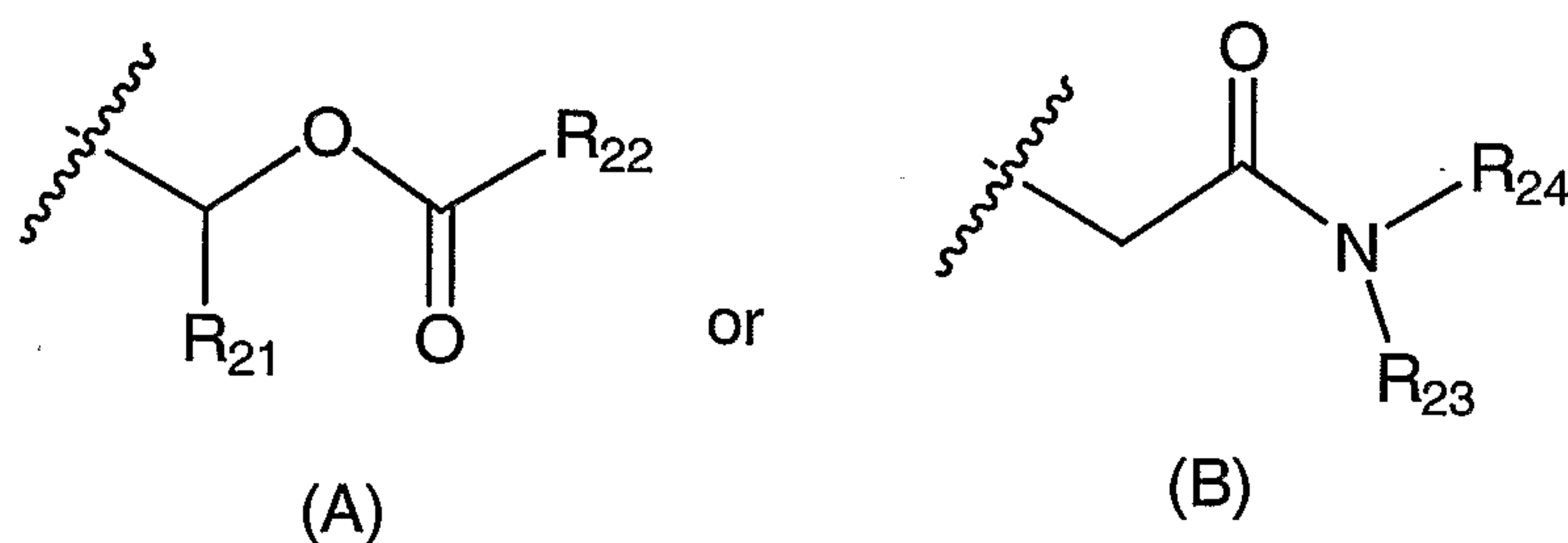
where the absolute configuration of an asymmetric center is not indicated, is intended to embrace the individual stereoisomers as well as mixtures of stereoisomers.

[0048] Where an enantiomer is preferred, it can, in some embodiments, be provided substantially free of the corresponding enantiomer. Thus, an enantiomer substantially free of the corresponding enantiomer refers to a compound that is isolated or separated via separation techniques or prepared free of the corresponding enantiomer. "Substantially free," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In preferred embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments of the invention, the compound is made up of at least about 99% by weight of a preferred enantiomer. Preferred enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts, or preferred enantiomers can be prepared by methods described herein. Methods for the preparation of preferred enantiomers are described, for example, in Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0049] Exemplary salt forms of the compounds herein include, but are not limited to, sodium salts and potassium salts. Other exemplary salt forms of these compounds include, but are not limited to, those formed with pharmaceutically acceptable inorganic and organic bases or acids known in the art. The acids include, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety. Salt forms prepared using inorganic bases include hydroxides, carbonates or bicarbonates of the therapeutically acceptable alkali metals or alkaline earth metals, such as sodium potassium, magnesium, calcium and the like. Acceptable organic bases include amines, such as benzylamine, mono-, di- and trialkylamines, preferably those having alkyl groups of from 1 to 6 carbon atoms, more preferably 1 to 3 carbon atoms, such as methylamine, dimethylamine, trimethylamine,

ethylamine, diethylamine, triethylamine, mono-, di-, and triethanolamine. Exemplary salts also include alkylene diamines containing up to 6 carbon atoms, such as hexamethylenediamine; cyclic saturated or unsaturated bases containing up to 6 carbon atoms, including pyrrolidine, piperidine, morpholine, piperazine and their N-alkyl and N-hydroxyalkyl derivatives, such as N-methyl-morpholine and N-(2-hydroxyethyl)-piperidine, or pyridine. Quaternary salts can also be formed, such as tetralkyl forms, such as tetramethyl forms, alkyl-alkanol forms, such as methyl-triethanol or trimethyl-monoethanol forms, and cyclic ammonium salt forms, such as N-methylpyridinium, N-methyl-N-(2-hydroxyethyl)-morpholinium, N,N-di-methylmorpholinium, N-methyl-N-(2-hydroxyethyl)-morpholinium, or N,N-dimethyl-piperidinium salt forms. These salt forms can be prepared using the acidic compound(s) of Formulas 1-3 and procedures known in the art.

[0050] Exemplary ester forms of the compounds of this invention include, but are not limited to, straight chain alkyl esters having from 1 to 6 carbon atoms or branched chain alkyl groups containing 1 to 6 carbon atoms (such as methyl, ethyl, propyl, butyl, 2-methylpropyl and 1,1-dimethylethyl esters), cycloalkyl esters (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, 2-[4-isopropyl-1-methyl-7-oxa-bicyclo[2.2.1]heptanyl], 2-[1,2,3,4-tetrahydro-naphthalenyl], and adamantyl esters), alkylaryl esters (such as methylphenyl, dimethylphenyl, ethylphenyl, and methylnaphthyl esters), benzyl esters, and the like. Other exemplary esters include, but are not limited to, those of the formula $-\text{COOR}_{20}$ wherein R_{20} is selected from the formula:



wherein R_{21} , R_{22} , R_{23} , and R_{24} are independently selected from hydrogen, alkyl of from 1 to 10 carbon atoms (such as methyl, ethyl, propyl, isopropyl, butyl, *i*-butyl and *t*-butyl), aryl of 6 to 12 carbon atoms (such as phenyl, naphthyl, anthracenyl, and phenanthrenyl), arylalkyl of from 6 to 12 carbon atoms (such as phenyl, naphthyl, anthracenyl, and phenanthrenyl); heteroaryl (such as pyrrolyl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, thiophenyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl) or

alkylheteroaryl wherein the heteroaryl ring is bound by an alkyl chain of from 1 to 6 carbon atoms (such as alkyl substituted pyrrolyl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, thiophenyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl).

[0051] Preferred compounds of the present invention inhibit PAI-1 activity. Accordingly, the compounds can be used for the treatment, including prevention, inhibition, and/or amelioration of PAI-1 related disorders in a subject, including, for example, in the treatment of noninsulin dependent diabetes mellitus, in the treatment of cardiovascular disease, and in the treatment of thrombotic events associated with coronary artery and cerebrovascular disease. Using the methods of the present invention, a skilled medical practitioner will know how to administer substituted indoles, including those represented by Formulas 1-3, to a subject suffering from any of the diseases associated with increased PAI-1 activity or expression, *e.g.*, diabetes or cardiovascular disease, in order to effect treatment for that disease.

[0052] In one exemplary embodiment, substituted indoles are administered to a subject in order to treat disease processes involving thrombotic and prothrombotic states which include, but are not limited to, formation of atherosclerotic plaques, venous and arterial thrombosis, myocardial ischemia, atrial fibrillation, deep vein thrombosis, coagulation syndromes, pulmonary thrombosis, cerebral thrombosis, thromboembolic complications of surgery (such as joint or hip replacement), and peripheral arterial occlusion.

[0053] Any disease or condition that is associated with increased PAI-1 activity or expression in a subject can be treated using substituted indoles. Exemplary diseases and conditions include stroke, *e.g.*, stroke associated with or resulting from atrial fibrillation; diseases associated with extracellular matrix accumulation including, but not limited to, renal fibrosis, chronic obstructive pulmonary disease, polycystic ovary syndrome, restenosis, renovascular disease, and organ transplant rejection; diseases associated with neoangiogenesis, including, but not limited to, diabetic retinopathy; Alzheimer's disease, *e.g.*, by increasing or normalizing levels of plasmin concentration in a subject; myelofibrosis with myeloid metaplasia, *e.g.*, by regulating stromal cell hyperplasia and increases in extracellular matrix proteins; diabetic nephropathy and renal dialysis associated with nephropathy;

malignancies or cancers, including, but not limited to, leukemia, breast cancer and ovarian cancer; tumors, including, but not limited to, liposarcomas and epithelial tumors; septicemia; obesity; insulin resistance; proliferative diseases, including, but not limited to, psoriasis; conditions associated with abnormal coagulation homeostasis; low grade vascular inflammation; cerebrovascular diseases; hypertension; dementia; osteoporosis; arthritis; respiratory diseases, such as asthma; heart failure; arrhythmia; angina, including, but not limited to, angina pectoris; atherosclerosis and sequelae; kidney failure; multiple sclerosis; osteoporosis; osteopenia; dementia; peripheral vascular disease; peripheral arterial disease; acute vascular syndromes; microvascular diseases including, but not limited to, nephropathy, neuropathy, retinopathy and nephrotic syndrome; hypertension; Type I and II diabetes and related diseases; hyperglycemia; hyperinsulinemia; malignant lesions; premalignant lesions; gastrointestinal malignancies; coronary heart disease, including, but not limited to, primary and secondary prevention of myocardial infarction, stable and unstable angina, primary prevention of coronary events, and secondary prevention of cardiovascular events; and inflammatory diseases, including, but not limited to, septic shock and the vascular damage associated with infections.

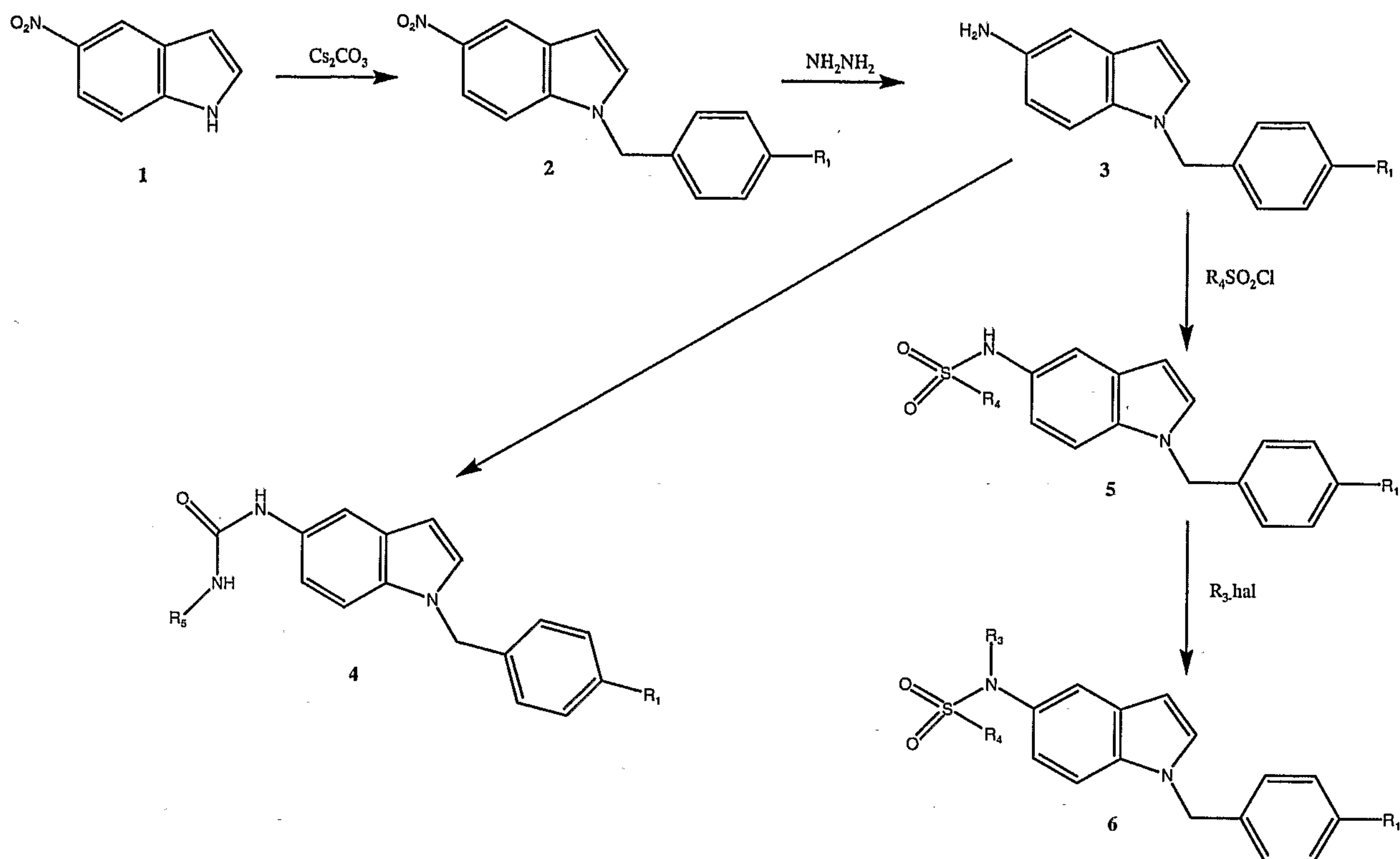
[0054] The compounds of the present invention can also be administered to a subject in combination with a second therapeutic agent, including, but not limited to, prothrombolytic, fibrinolytic, and anticoagulant agents, or in conjunction with other therapies, for example, protease inhibitor-containing highly active antiretroviral therapy (HAART) for the treatment of diseases which originate from fibrinolytic impairment and hyper-coagulability of HIV-1 infected patients. In certain embodiments, the compounds of the present invention can be administered in conjunction with and/or following processes or procedures involving maintaining blood vessel patency, including, but not limited to, vascular surgery, vascular graft and stent patency, organ, tissue and cell implantation and transplantation. The compounds of the present invention can also be used for the treatment of blood and blood products used in dialysis, blood storage in the fluid phase, especially *ex vivo* platelet aggregation. The compounds of the present invention can also be administered to a subject as a hormone replacement agent or to reduce inflammatory markers or C-reactive protein. The compounds can be administered to improve coagulation homeostasis, to improve endothelial function, or as a topical application for wound healing, *e.g.*, the prevention of scarring. The compounds of the present invention can be administered to a subject in order to reduce the risk of undergoing a myocardial revascularization procedure. The present compounds can

also be added to human plasma during the analysis of blood chemistry in hospital settings to determine the fibrinolytic capacity thereof. In certain embodiments, the compounds of the present invention can be used as imaging agents for the identification of metastatic cancers.

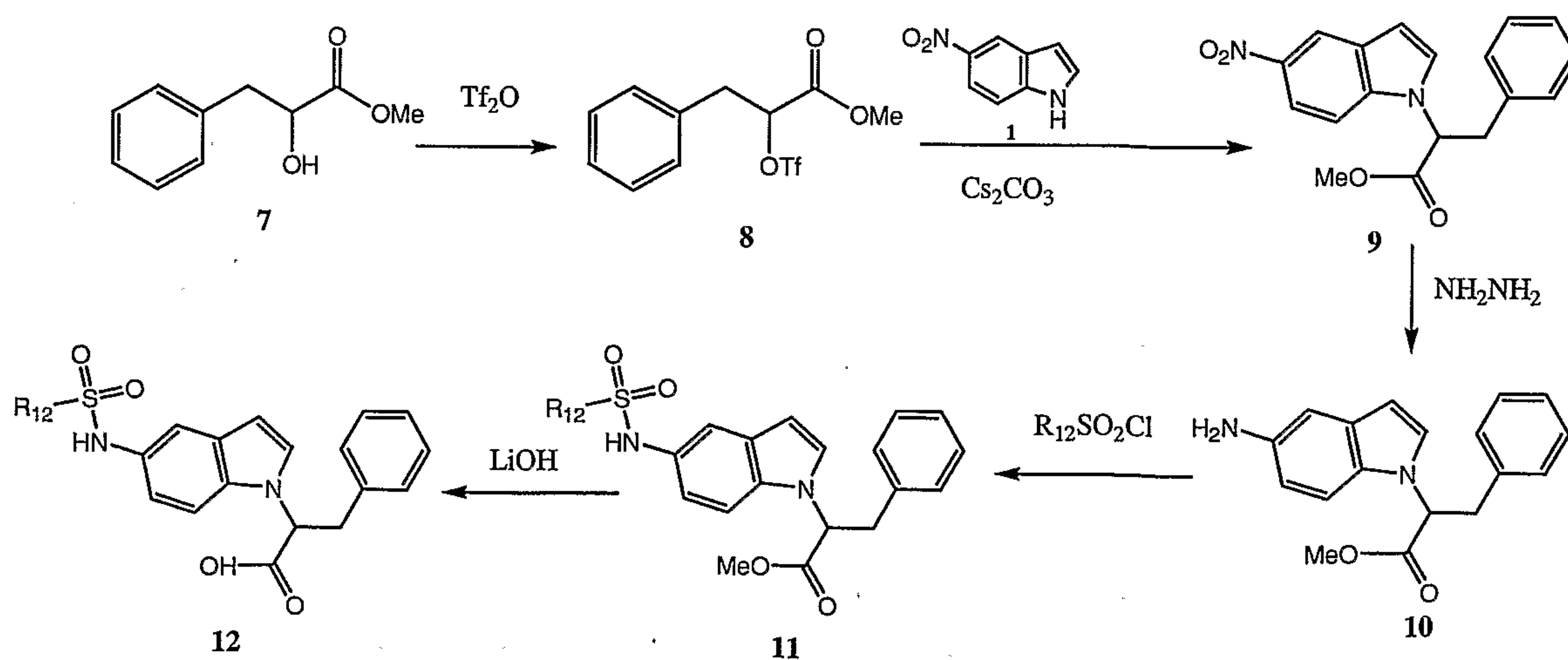
SYNTHESIS OF SUBSTITUTED INDOLES

[0055] Compounds of the present invention can be prepared by those skilled in the art of organic synthesis employing conventional methods that utilize readily available reagents and starting materials. Representative compounds of the present invention can be prepared using the following synthetic schemes. The skilled practitioner will know how to make use of variants of these process steps, which in themselves are well known in the art. In the following reaction schemes, R_1 to R_{17} are selected from the groups defined above.

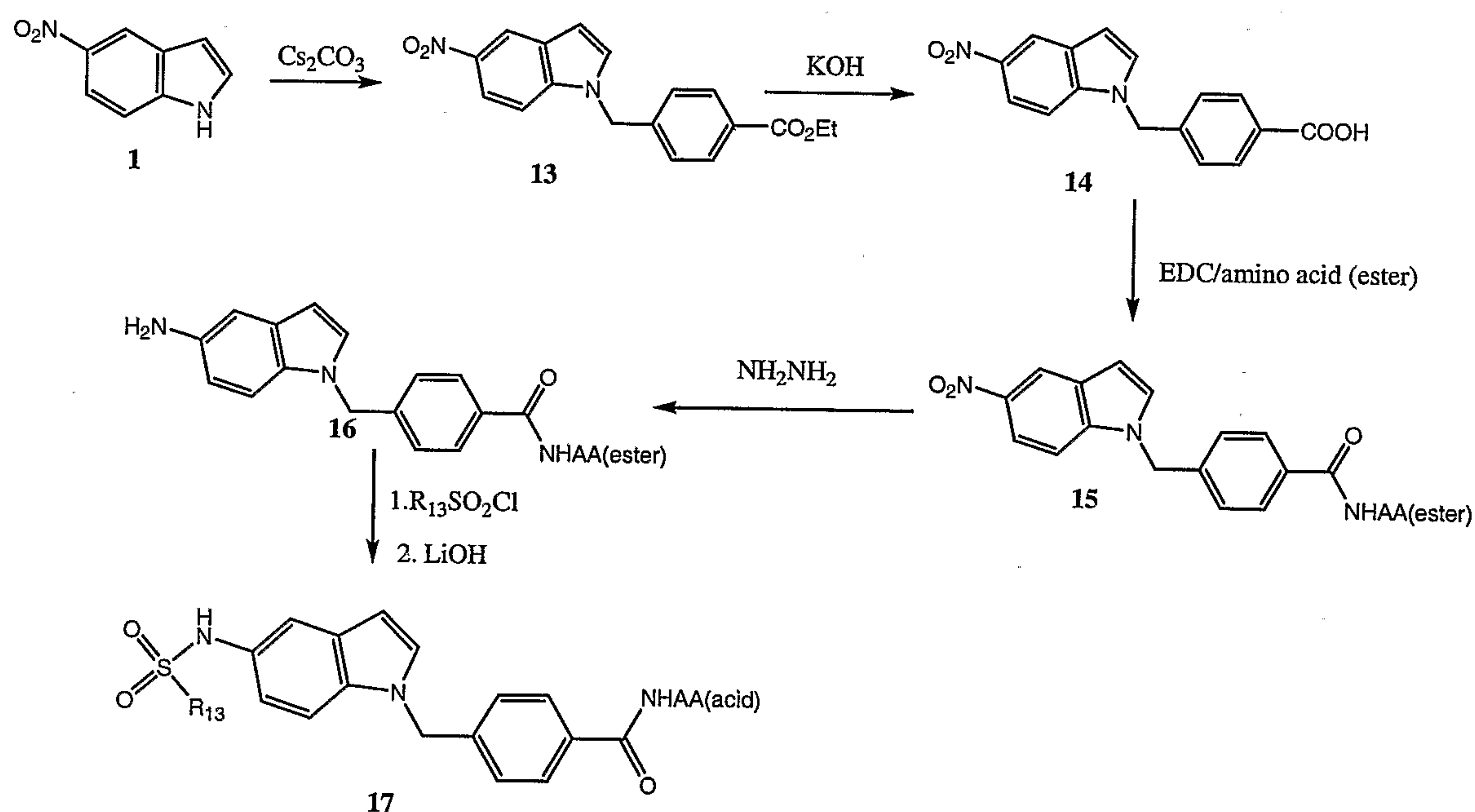
[0056] The *1H*-indole 1 can be alkylated with substituted benzyl halides in the presence of a base, such as K_2CO_3 , CS_2CO_3 , KOH or NaH, in an inert solvent, such as THF, dioxane, pyridine, DMF, NMP, or DMSO, at -40 to 100 °C. The resulting nitro intermediate 2 can be reduced to the aniline 3 upon treatment with Raney® nickel in a mixture of hydrazine and ethanol at temperature of 0 to 40 °C. Treatment of the free NH_2 of compound 3 with an isocyanate of formula R_5-NCO provides the urea 4. Compound 3 can also be converted to sulfonamide 5, wherein R_4 is alkyl, phenyl, or Het, upon treatment with a sulfonyl halide, preferably alkyl, aryl, or Het sulfonyl chloride, and a base such as *N,N*-diisopropylethylamine in an anhydrous solvent such as dichloromethane for 0.5 to 24 hours at temperature of 0 to 40 °C. Alkylation of the N-H of sulfonamide 4 with an alkylating agent R_3 -halo using sodium hydride as the base provides the alkylated compound 6. The carboxylic acid ester moiety of R_3 , R_4 , and R_5 group of the compound of formula (I) can be transformed to the carboxylic acid upon treatment with aqueous lithium, sodium or potassium hydroxide in a suitable organic solvent such as methanol, ethanol, dioxane and the like. The final products can be purified by recrystallization, trituration, preparative thin layer chromatography, flash column chromatography on silica gel, or high performance liquid chromatography. Purification of intermediates can be achieved in the same manner. A salt is optionally produced by the addition of an acid or base, such as hydrogen chloride gas or hydrochloric acid.

Scheme 1

[0057] N-propanoic acid indole derivative **12** is also readily prepared by methods described in the literature or known to those skilled in the art. The ester **7** is converted to the triflate **8** using standard literature procedures. Reaction of **8** with indole **1** in the presence of a base, such as Cs_2CO_3 , in an inert solvent, such as DMF, at 0 to 40°C provides the alkylated indole **9**. The resulting nitro intermediate **9** can be reduced to the desired aniline **10** upon treatment with Raney® nickel in a mixture of hydrazine and ethanol at temperature of 0 to 40 °C. The aniline **10** can be converted to indole sulfonamide derivatives **12**, as described in *Scheme 1*.

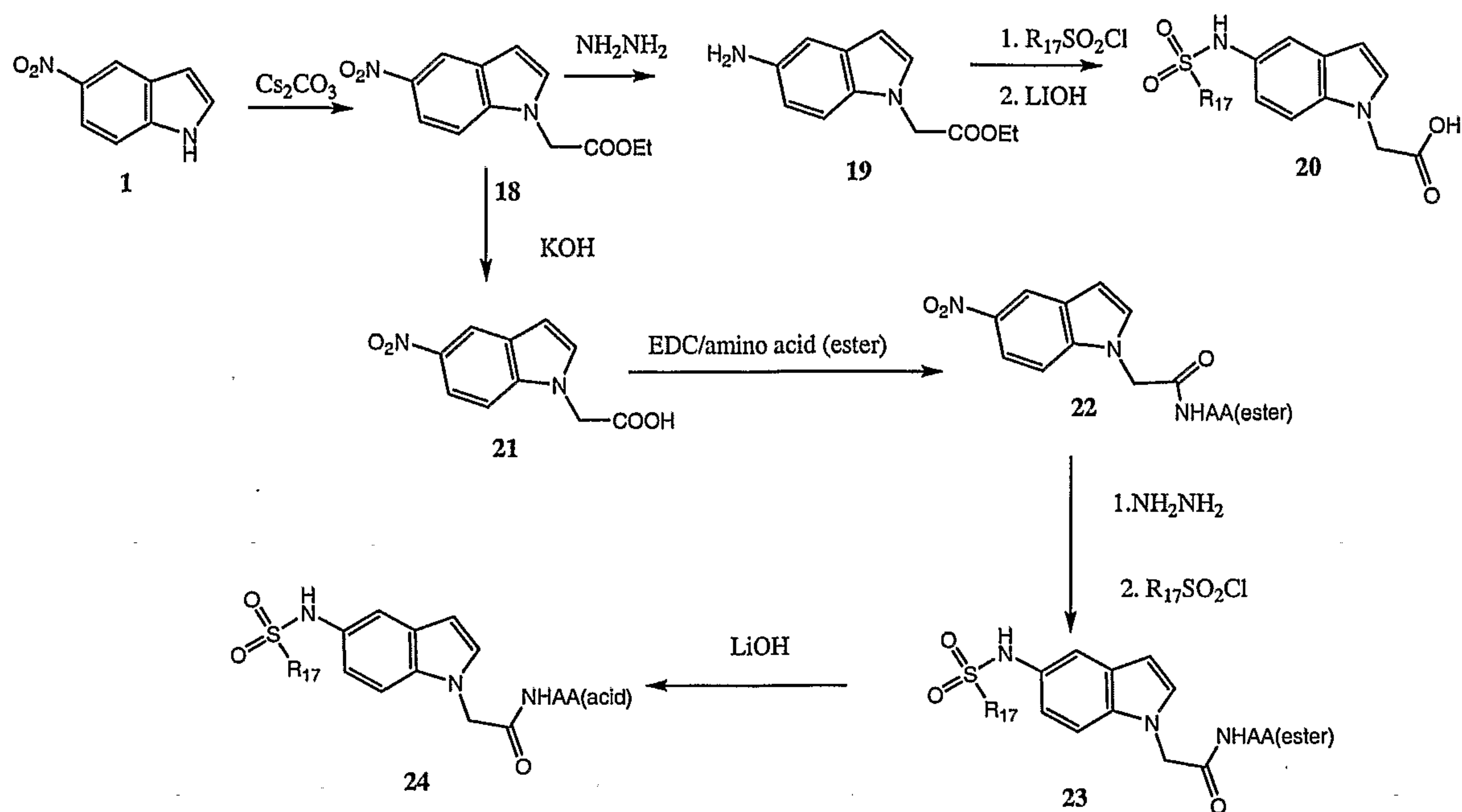
Scheme 2

[0058] Mono peptide derived from the acid **14** and amino acid and its ester thereof, can be prepared by, for example, the following synthetic scheme (*Scheme 3*). The carboxylic acid **14**, which is prepared by alkylation and basic hydrolysis from **1**, is coupled to the amine nitrogen of amino acid (ester), wherein the amino acid (ester) means the carboxylic acid functionality of the amino acid was protected as an ester. In this amide bond formation process 1,3-dicyclohexylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, diisopropyl carbodiimide, 1,1'-carbonyldiimidazole, 6-chloro-2,4-dimethoxy-1,3,5-triazine and the like can be used as a coupling agent and triethylamine, diisopropylethyl amine, N-methyl morpholine and the like can be used as a base. At this time, as a solvent, methylene chloride, diethyl ether, tetrahydrofuran, dioxane and the like is used. Nitro reduction, sulfonylation, and ester hydrolysis, as previously described in *Scheme 1*, furnishes the desired final product **17**, wherein R_{13} is as defined above and AA is amino acid.

Scheme 3

[0059] According to Scheme 4, certain N-acetic acid indole compounds of formula (III) can be readily prepared. N-Alkylation of indole **1** with ethyl bromoacetate using cesium carbonate as the base provides the alkylated compound **18**. The alkylated indole **18** can be converted to carboxylic acid derivate **20** or amino acid derivative **24** as described in *Scheme 1-3*.

Scheme 4



PHARMACEUTICAL COMPOSITIONS

[0060] The present invention provides substituted indoles as pharmaceuticals. In a preferred embodiment, the substituted indoles are formulated as pharmaceuticals to treat diseases associated with increased PAI-1 activity, *e.g.*, by inhibiting PAI-1 activity in a subject.

[0061] In general, substituted indoles can be administered as pharmaceutical compositions by any method known in the art for administering therapeutic drugs including oral, buccal, topical, systemic (*e.g.*, transdermal, intranasal, or by suppository), or parenteral (*e.g.*, intramuscular, subcutaneous, or intravenous injection). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, emulsions, syrups, elixirs, aerosols, or any other appropriate compositions; and comprise at least one compound of this invention in combination with at least one pharmaceutically acceptable excipient. Suitable excipients are well known to persons of ordinary skill in the art, and they, and the methods of formulating the compositions, can be found in such standard references as Alfonso AR: *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton PA, 1985. Suitable liquid carriers, especially for injectable solutions, include water, aqueous saline solution, aqueous dextrose solution,

and glycols. In some embodiments of the present invention, substituted indoles suitable for use in the practice of this invention can be administered either singly or in combination with at least one other compound of this invention. Substituted indoles suitable for use in the practice of the present invention can also be administered with at least one other conventional therapeutic agent for the disease being treated.

[0062] Aqueous suspensions of the invention can contain a substituted indole in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients can include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (*e.g.*, polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[0063] Oil suspensions can be formulated by suspending a substituted indole in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as

polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

[0064] The compound of choice, alone or in combination with other suitable components, can be made into aerosol formulations (*i.e.*, they can be “nebulized”) to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

[0065] Formulations suitable for parenteral administration, such as, for example, by intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Among the acceptable vehicles and solvents that can be employed are water and Ringer’s solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. Where the compounds are sufficiently soluble they can be dissolved directly in normal saline with or without the use of suitable organic solvents, such as propylene glycol or polyethylene glycol. Dispersions of the finely divided compounds can be made-up in aqueous starch or sodium carboxymethyl cellulose solution, or in suitable oil, such as arachis oil. These formulations can be sterilized by conventional, well known sterilization techniques. The formulations can contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, *e.g.*, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of substituted indoles in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient’s needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to

the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol. The formulations of commends can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials.

[0066] Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0067] Substituted indoles suitable for use in the practice of this invention can be administered orally. The amount of a compound of the present invention in the composition can vary widely depending on the type of composition, size of a unit dosage, kind of excipients, and other factors well known to those of ordinary skill in the art. In general, the final composition can comprise, for example, from 0.000001 percent by weight (% w) to 10 % w of the substituted indole, preferably 0.00001 % w to 1 % w, with the remainder being the excipient or excipients.

[0068] Pharmaceutical formulations for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical formulations to be formulated in unit dosage forms as tablets, pills, powder, dragees, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, *etc.* suitable for ingestion by the patient. Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the packaged nucleic acid suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions.

[0069] Pharmaceutical preparations for oral use can be obtained, for example, through combination of the compounds of the present invention with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or dragee cores. Suitable solid excipients are carbohydrate or protein fillers and include, but are not limited to sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxymethyl cellulose, hydroxypropylmethyl-cellulose or sodium

carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, *e.g.*, sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

[0070] The substituted indoles of the present invention can also be administered in the form of suppositories for rectal administration of the drug. These formulations can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperatures and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0071] The compounds of the present invention can also be administered by intranasal, intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, *J. Clin. Pharmacol.* 35:1187-1193, 1995; Tjwa, *Ann. Allergy Asthma Immunol.* 75:107-111, 1995).

[0072] The substituted indoles of the present invention can be delivered transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0073] Encapsulating materials can also be employed with the compounds of the present invention and the term "composition" can include the active ingredient in combination with an encapsulating material as a formulation, with or without other carriers. For example, the compounds of the present invention can also be delivered as microspheres for slow release in the body. In one embodiment, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater.*

Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, *e.g.*, Gao, *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, *e.g.*, Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months. Cachets can also be used in the delivery of the compounds of the present invention, *e.g.*, anti-atherosclerotic medicaments.

[0074] In another embodiment, the compounds of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compound into the target cells *in vivo*. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

[0075] In other cases, the preferred preparation can be a lyophilized powder which may contain, for example, any or all of the following: 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

[0076] A pharmaceutical composition of the invention can optionally contain, in addition to a substituted indole, at least one other therapeutic agent useful in the treatment of a disease or condition associated with increased PAI-1 activity.

[0077] The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

DOSAGE REGIMENS

[0078] The present invention provides methods of inhibiting PAI-1 activity in a subject for the treatment of diseases and conditions associated with increased PAI-1 activity using substituted indoles. In an exemplary embodiment of the present invention, a skilled

practitioner will treat a subject having a disease associated with elevated PAI-1 levels and/or activity with the compounds of the present invention.

[0079] For treatment purposes, the compositions or compounds disclosed herein can be administered to the subject in a single bolus delivery, via continuous delivery (*e.g.*, continuous transdermal, mucosal, or intravenous delivery) over an extended time period, or in a repeated administration protocol (*e.g.*, by an hourly, daily or weekly, repeated administration protocol). The pharmaceutical formulations of the present invention can be administered, for example, one or more times daily, 3 times per week, or weekly. In an exemplary embodiment of the present invention, the pharmaceutical formulations of the present invention are orally administered once or twice daily.

[0080] In this context, a therapeutically effective dosage of the biologically active agent(s) can include repeated doses within a prolonged treatment regimen that will yield clinically significant results to alleviate one or more symptoms or detectable conditions associated with increased PAI-1 activity. Determination of effective dosages in this context is typically based on animal model studies followed up by human clinical trials and is guided by determining effective dosages and administration protocols that significantly reduce the occurrence or severity of targeted exposure symptoms or conditions in the subject. Suitable models in this regard include, for example, murine, rat, porcine, feline, non-human primate, and other accepted animal model subjects known in the art. Alternatively, effective dosages can be determined using *in vitro* models (*e.g.*, immunologic and histopathologic assays). Using such models, only ordinary calculations and adjustments are typically required to determine an appropriate concentration and dose to administer a therapeutically effective amount of the biologically active agent(s) (*e.g.*, amounts that are intranasally effective, transdermally effective, intravenously effective, or intramuscularly effective to elicit a desired response). In alternative embodiments, an “effective amount” or “therapeutically effective dose” of the biologically active agent(s) will simply inhibit or enhance one or more selected biological activity(ies) correlated with a disease or condition, as set forth above, for either therapeutic or diagnostic purposes.

[0081] The actual dosage of biologically active agents will of course vary according to factors such as the extent of exposure and particular status of the subject (*e.g.*, the subject's age, size, fitness, extent of symptoms, susceptibility factors, etc), time and route of

administration, as well as other drugs or treatments being administered concurrently. Dosage regimens can be adjusted to provide an optimum prophylactic or therapeutic response. By “therapeutically effective dose” herein is meant a dose that produces effects for which it is administered. More specifically, a therapeutically effective dose of the compound(s) of the invention preferably alleviates symptoms, complications, or biochemical indicia of diseases associated with increased PAI-1 activity. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (Vols. 1-3, 1992); Lloyd, 1999, *The Art, Science, and Technology of Pharmaceutical Compounding*; and Pickar, 1999, *Dosage Calculations*). A therapeutically effective dose is also one in which any toxic or detrimental side effects of the active agent is outweighed in clinical terms by therapeutically beneficial effects. It is to be further noted that for each particular subject, specific dosage regimens should be evaluated and adjusted over time according to the individual need and professional judgment of the person administering or supervising the administration of the compounds.

[0082] In an exemplary embodiment of the present invention, unit dosage forms of the compounds are prepared for standard administration regimens. In this way, the composition can be subdivided readily into smaller doses at the physician’s direction. For example, unit dosages can be made up in packeted powders, vials or ampoules and preferably in capsule or tablet form. The active compound present in these unit dosage forms of the composition can be present in an amount, for example, of from about one gram to about fifteen grams or more, for single or multiple daily administration, according to the particular need of the patient. By initiating the treatment regimen with a minimal daily dose of about one gram, the blood levels of PAI-1 and the patient’s symptomatic relief analysis can be used to determine whether a larger or smaller dose is indicated. Effective administration of the compounds of this invention can be given at an oral dose of, for example, from about 0.1 mg/kg/day to about 1,000 mg/kg/day. Preferably, administration will be from about 10/mg/kg/day to about 600 mg/kg/day, more preferably from about 25 to about 200 mg/kg/day, and even more preferably from about 50 mg/kg/day to about 100 mg/kg /day.

[0083] In certain embodiments, the present invention is directed to prodrugs of compounds of Formulas 1-3. The term “prodrug,” as used herein, means a compound that is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of Formulas 1-3. Various forms of prodrugs are known in the art such as those discussed in, for example, Bundgaard,

(ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991), Bundgaard, *et al.*, *Journal of Drug Delivery Reviews*, 8:1-38(1992), Bundgaard, *J. of Pharmaceutical Sciences*, 77:285 et seq. (1988); and Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society (1975).

KITS

[0084] After a pharmaceutical comprising a substituted indole has been formulated in a suitable carrier, it can be placed in an appropriate container and labeled for treatment of a PAI-1 related disorder, *e.g.*, leukemia. Additionally, another pharmaceutical comprising at least one other therapeutic agent useful in the treatment of the PAI-1 related disorder can be placed in the container as well and labeled for treatment of the indicated disease. Alternatively, a single pharmaceutical comprising a substituted indole and at least one other therapeutic agent useful in the treatment of a PAI-1 related disorder can be placed in an appropriate container and labeled for treatment. For administration of pharmaceuticals comprising substituted indoles and of pharmaceuticals comprising, in a single pharmaceutical, substituted indoles and at least one other therapeutic agent useful in the treatment of a PAI-1 related disorder, such labeling would include, for example, instructions concerning the amount, frequency, and method of administration. Similarly, for administration of multiple pharmaceuticals provided in the container, such labeling would include, for example, instructions concerning the amount, frequency and method of administration of each pharmaceutical.

EXAMPLES

Example 1

3-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)sulfonyl)benzoic acid

[0085] Step 1: To 5-nitro-1*H*-indole (1.50 g, 9.26 mmol) in DMF (15 ml) at 0°C under a nitrogen atmosphere sodium hydride (60% dispersion in mineral oil, 0.43 g, 10.3 mmol) was added in 4 equal portions over 10 minutes.

[0086] The resulting dark red mixture was stirred at 0°C for 20 minutes upon which 4-*tert*-butylbenzyl bromide (2.55 g, 13.88 mmol) was added in one portion. The resulting yellow mixture was allowed to warm to room temperature and stirred a total reaction time of 90 minutes. The reaction was quenched with H₂O (5 ml) and then partitioned between brine (50 ml) and EtOAc (50 ml). The layers were separated. The organic layer was extracted with brine (4 X 15ml), dried with MgSO₄, filtered, and concentrated *in vacuo* to give 1-(4-*tert*-butylbenzyl)-5-nitro-1*H*-indole as a yellow powder (2.59 g, 91% yield): MS (ESI) *m/z* 309.

[0087] Step 2: To 1-(4-*tert*-butylbenzyl)-5-nitro-1*H*-indole (1.00 g, 3.24 mmol) in EtOH (35 ml) at ambient temperature under a nitrogen atmosphere was added hydrazine (2.0g, 62.5 mmol) and Raney-Ni (0.20 g of a 50% slurry in H₂O). The yellow mixture was stirred at 45°C for 1 hr. The mixture was cooled to room temperature and filtered through a celite pad (1 X 4.25cm). The pad was washed with EtOH (10 ml) and concentrated *in vacuo* to afford a dark yellow powder. Gradient SiO₂ chromatography (Hex : EtOAc) afforded 1-(4-*tert*-butylbenzyl)-5-amino-1*H*-indole as a yellow powder (0.87 g, 96% yield): MS (ESI) *m/z* 279.

[0088] Step 3: 3-chlorosulfonyl-benzoic acid (0.80 g, 0.36 mmol) was added in one portion to 1-(4-*tert*-butylbenzyl)-5-amino-1*H*-indole (0.30 g, 1.08 mmol) and diisopropylethylamine (0.25 g, 0.90 mmol) in acetone (25 ml) at 0 °C under a nitrogen atmosphere. The resulting yellow solution was stirred at 0 °C for 5 minutes and then stirred for 3 hours at room temperature. The reaction was quenched with water (2 ml) and concentrated *in vacuo* to a brown powder. The powder was partitioned between EtOAc (15 ml) and std NaHCO₃ (10 ml). All organics were combined, extracted with water (10 ml) and brine (10 ml), dried with MgSO₄, filtered and concentrated *in vacuo* to afford a brown powder. This brown powder was subjected to gradient RP-HPLC (H₂O : CH₃CN) and the title compound was isolated as a brown powder (0.36 g, 8.6% yield): MS (ESI) *m/z* 463, MS (ESI) *m/z* 461.

Example 2

{Benzenesulfonyl-[1-(4-*tert*-butyl-benzyl)-1*H*-indol-5-yl]-amino}-acetic acid methyl ester

[0089] Step1: Benzenesulfonyl chloride (0.56 g, 3.12 mmol) was added in one portion to 1-(4-*tert*-butylbenzyl)-5-amino-1*H*-indole (0.84 g, 3.02 mmol) and diisopropylethylamine (0.43

g, 3.17 mmol) in CH₂Cl₂ (20 ml) at 0 °C under a nitrogen atmosphere. The resulting yellow solution was stirred at 0 °C for 5 minutes and then at room temperature for 2 hours. The reaction was quenched with water (2 ml) and then concentrated *in vacuo* to a brown powder. The powder was partitioned between EtOAc (15 ml) and satd NaHCO₃ (10 ml). All organics were combined, extracted with water (10 ml) and brine (10 ml), dried with MgSO₄, filtered and concentrated *in vacuo* to a brown powder. Gradient SiO₂ chromatography (Hexane : EtOAc) afforded N-[1-(4-*tert*-butyl-benzyl)-1H-indol-5-yl]-benzenesulfonamide as a brown powder (1.18 g, 94% yield): MS (ESI) *m/z* 419, MS (ESI) *m/z* 417.

[0090] Step 2: To N-[1-(4-*tert*-butyl-benzyl)-1H-indol-5-yl]-benzenesulfonamide (0.20 g, 0.48 mmol) in DMF (5 ml) at room temperature under a nitrogen atmosphere was added sodium hydride (60% dispersion in mineral oil, 0.03 g, 0.72 mmol) in one portion. The resulting brown mixture was stirred 10 minutes upon which bromo-acetic acid methyl ester was added (0.19 g, 0.96 mmol). After 90 minutes total reaction time, the reaction was quenched with water (2 ml). The brown solution was partitioned between EtOAc (15 ml) and H₂O (10 ml) and the layers were separated. The aqueous layer was extracted with EtOAc (5 ml). All organics were combined, extracted with brine (3 X 10 ml), dried with MgSO₄, filtered and concentrated *in vacuo* to afford a brown powder. Gradient SiO₂ chromatography (Hexane : EtOAc) afforded {benzenesulfonyl-[1-(4-*tert*-butyl-benzyl)-1H-indol-5-yl]-amino}-acetic acid methyl ester as a pale red powder (0.18 g, 72% yield): MS (ESI) *m/z* 533.

[0091] Step 3: To {benzenesulfonyl-[1-(4-*tert*-butyl-benzyl)-1H-indol-5-yl]-amino}-acetic acid methyl ester (0.68 g, 1.39 mmol), in THF (5 ml), H₂O (2.5 ml), MeOH (2.5 ml) at room temperature under a laboratory atmosphere, was added lithium hydroxide (0.3 g, 7.14 mmol, dissolved up in H₂O (1 ml)). The resulting red solution was stirred at 45 °C for 3 hours and subsequently concentrated *in vacuo* to remove the organic solvents upon which a pink precipitate formed. This pink mixture was treated with acetic acid (1 ml, pH > 2), left standing for 10 minutes and filtered resulting in the title compound as a pink powder (0.62 g, 94 % yield). MS (ESI) *m/z* 477, MS (ESI) *m/z* 475.

Example 3

4-[[[1-(4-*tert*-Butylbenzyl)-1H-indol-5-yl](phenylsulfonyl)amino]methyl]benzoic acid

[0092] The title compound was prepared from 4-({benzenesulfonyl-[1-(4-*tert*-butylbenzyl)-1H-indol-5-yl]-amino}-methyl)-benzoic acid methyl ester following the procedure of Example 2 Step 3: MS (ESI) *m/z* 553, MS (ESI) *m/z* 551.

Example 4

4-([1-(4-*tert*-butylbenzyl)-1H-indol-5-yl]amino)sulfonyl)benzoic acid

[0093] The title compound was prepared from 1-(4-*tert*-butylbenzyl)-1H-indol-5-ylamine following the procedure of Example 1 Step 3: MS (ESI) *m/z* 463, MS (ESI) *m/z* 461.

Example 5

N-([1-(4-*tert*-Butylbenzyl)-1H-indol-5-yl]amino)carbonyl)-L-phenylalanine

[0094] A mixture of 1-(4-*tert*-butylbenzyl)-1H-indol-5-amine (0.233 g, 0.84 mmol) and 2-isocyanato-3-phenyl-propionic acid ethyl ester (0.10 g, 0.8 mmol) in 10 mL of dichloromethane was stirred at room temperature overnight. The reaction mixture was concentrated and dissolved in 2:1:1 THF/MeOH/Water (10 mL). Lithium hydroxide monohydrate (0.30 g, 7.1 mmol) was added and the mixture was stirred at room temperature overnight. Most of the organic solvents were removed and the reaction mixture was made acidic (pH 6) with glacial acetic acid. The solid was collected and purified by semi-preparative HPLC (Column: Phenomenex C18 Luna 21.6 mm x 60 mm, 5 μ M; Solvent A: Water (0.1% TFA buffer); Solvent B: Acetonitrile (0.1 % TFA buffer); Solvent Gradient: Time 0: 0% B; 10 minutes: 100% B; Hold 100% B 5 minutes. Flow Rate: 22.5 mL/min) The product was collected based on UV absorption and concentrated to give the title compound as an off-white solid (0.15 g, 40%): MS (ESI) *m/z* 470; MS (ESI) *m/z* 468.

Example 6

3-([1-(4-*tert*-Butylbenzyl)-1H-indol-5-yl]amino)carbonyl)amino]benzoic acid

[0095] The title compound was prepared from 1-(4-*tert*-butylbenzyl)-1H-indol-5-amine and 3-isocyanato-benzoic acid ethyl ester following the procedure of Example 5: MS (ESI) *m/z* 442.

Example 7**[4-({5-[(1,1'-Biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl}methyl)phenoxy]acetic acid**

[0096] Step 1: {4-[5-(Biphenyl-4-sulfonylamino)-indol-1-ylmethyl]-phenoxy}-acetic acid methyl ester was prepared from [4-(5-amino-indol-1-ylmethyl)-phenoxy]-acetic acid methyl ester following the procedure of Example 2 Step 1. The title compound was prepared from {4-[5-(biphenyl-4-sulfonylamino)-indol-1-ylmethyl]-phenoxy}-acetic acid methyl ester following the procedure of Example 2 Step 3: MS (ESI) *m/z* 513, MS (ESI) *m/z* 511.

Example 8**{4-[(5-{[(4-*tert*-Butylphenyl)sulfonyl]amino}-1*H*-indol-1-yl)methyl]phenoxy}acetic acid**

[0097] {4-[5-(4-*tert*-butyl-benzenesulfonylamino)-indol-1-ylmethyl]-phenoxy}-acetic acid methyl ester was prepared from [4-(5-amino-indol-1-ylmethyl)-phenoxy]-acetic acid methyl ester following the procedure of Example 2 Step 1. The title compound was prepared from {4-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1*H*-indol-1-yl)methyl]phenoxy}acetic acid methyl ester following the procedure of Example 2 Step 3: MS (ESI) *m/z* 493, MS (ESI) *m/z* 491.

Example 9**3-Phenyl-2-[5-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)-1*H*-indol-1-yl]propanoic acid**

[0098] Step 1: Hydrochloric acid gas was bubbled into a solution of 2-hydroxy-3-phenyl-propionic acid (6.0 g, 36.10 mmol) in MeOH (250 ml) at room temperature under CaSO₄ tube for 20 minutes. The resulting colorless solution was stirred for 7 hours and concentrated *in vacuo* to afford 2-hydroxy-3-phenyl-propionic acid methyl ester as a brown syrup (6.36 g, 98% yield): MS (ESI) *m/z* 181.

[0099] Step 2: To 2-hydroxy-3-phenyl-propionic acid methyl ester (6.36 g, 35.32 mmol) in anhydrous CHCl₃ (75 ml) at -78 °C under a nitrogen atmosphere was added triethylamine (4.29 g, 42.38 mmol) and trifluoromethanesulfonyl anhydride (10.96 g, 38.85 mmol). The

resulting yellow solution was stirred at -78°C for 5 minutes upon which the cooling bath was removed and allowed to warm to room temperature. After 2.5 hours total reaction time, the reaction was quenched with H_2O (50 ml) followed by 1N HCl (150 ml). Extraction, separation, and further extraction of the organic layer with std NaHCO_3 (100 ml), H_2O (75 ml), brine (50 ml) was performed. The extract was dried with MgSO_4 , filtered and concentrated *in vacuo* to afford 3-phenyl-2-trifluoromethanesulfonyloxy-propionic acid methyl ester as a brown syrup (10.96 g, 98% yield): MS (ESI) m/z 313.

[0100] Step 3: To 5-nitro-1H-indole (5.18 g, 31.93 mmol) in acetone (200 ml) at ambient temperature under a nitrogen atmosphere was added cesium carbonate (21.80 g, 67.06 mmol) followed by 3-phenyl-2-trifluoromethanesulfonyloxy-propionic acid methyl ester (10.96 g, 35.13 mmol). The resulting dark red mixture was stirred for 5 hours, concentrated *in vacuo* to a brown powder which was then partitioned between H_2O (100 ml) and EtOAc (300 ml). All organics were combined, extracted with brine (250 ml), dried with MgSO_4 , filtered, and concentrated *in vacuo*. Gradient SiO_2 chromatography (Hexane : EtOAc) afforded 2-(5-nitro-indol-1-yl)-3-phenyl-propionic acid methyl ester as an opaque syrup (5.91 g, 57% yield): MS (ESI) m/z 325, MS (ESI) m/z 323.

[0101] Step 4: 2-(5-Amino-indol-1-yl)-3-phenyl-propionic acid hydrazide was prepared from 2-(5-nitro-indol-1-yl)-3-phenyl-propionic acid methyl ester following the procedure of Example 1 Step 2: MS (ESI) m/z 295, MS (ESI) m/z 293.

[0102] Step 5: N-[1-(1-Hydrazinocarbonyl-2-phenyl-ethyl)-1H-indol-5-yl]-4-trifluoromethoxy-benzenesulfonamide was prepared from 2-(5-amino-indol-1-yl)-3-phenyl-propionic acid hydrazide following the procedure of Example 2 Step 1 substituting 4-trifluoromethoxy-benzene sulfonyl chloride for benzenesulfonyl chloride: MS (ESI) m/z 519, MS (ESI) m/z 517.

[0103] Step 6: To N-[1-(1-hydrazinocarbonyl-2-phenyl-ethyl)-1H-indol-5-yl]-4-trifluoromethoxy-benzenesulfonamide (0.07 g, 0.13 mmol) in acetic acid at ambient temperature under a laboratory atmosphere was added conc. HCl (1 ml) then the reaction vessel was capped. The dark red mixture was heated at 80°C for 15 hours (the vessel was periodically uncapped then recapped to release pressure build up with in the vessel). The reaction was cooled to ambient temperature and concentrated *in vacuo* to a dark red powder. The crude

product was subjected to gradient RP-HPLC (H₂O : CH₃CN) and the title compound was isolated as a red powder (0.06 g, 91% yield): MS (ESI) *m/z* 505, MS (ESI) *m/z* 503.

Example 10

N-[4-({5-[(Phenylsulfonyl)amino]-1H-indol-1-yl)methyl}benzoyl]-L-phenylalanine

[0104] Step1: 4-(5-Nitro-indol-1-ylmethyl)-benzoic acid methyl ester was prepared from methyl 4-[(5-nitro-1H-indol-1-yl)methyl]benzoate followed by Example 1, Step 1 except substituting cesium carbonate for sodium hydride and 4-bromomethyl-benzoic acid methyl ester for 4-*tert*-butylbenzyl bromide. MS (ESI) *m/z* 311.

[0105] Step 2: 4-[(5-Nitro-1H-indol-1-yl)methyl]benzoic acid was prepared by NaOH hydrolysis of methyl 4-[(5-nitro-1H-indol-1-yl)methyl]benzoate: MS (ESI) *m/z* 295;

[0106] Step 3: A mixture of 4-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid (1.78 g, 6.0 mmol), 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (1.15 g, 6.0 mmol), 1- hydroxybenzotriazole hydrate (0.81 g, 6.0 mmol), and L-phenylalanine ethyl ester hydrochloride (1.38 g, 6.0 mmol) was stirred in CH₂Cl₂ (150 mL). N-methylmorpholine (3.03 g, 30 mmol) was added and the mixture was stirred at room temperature for 15 h. The mixture was then washed with 0.05 N HCl and water. The resulting solution was dried with MgSO₄ and concentrated to give ethyl N-{4-[(5-nitro-1H-indol-1-yl)methyl]benzoyl}-L-phenylalaninate as an off-white solid (2.55 g, 90%): MS (ESI) *m/z* 472; MS (ESI) *m/z* 470.

[0107] Step 4: A large excess of Raney® nickel was added in portions to a stirred solution of ethyl N-{4-[(5-nitro-1H-indol-1-yl)methyl]benzoyl}-L-phenylalaninate (2.36 g, 5 mmol), and hydrazine (1.2 mL, 38 mmol) in 100 mL of ethanol and 15 mL of THF. After stirring at room temperature for 2 h the catalyst was then removed by filtering through a short pad of Celite®521. The filtrate was concentrated to give ethyl N-{4-[(5-amino-1H-indol-1-yl)methyl]benzoyl}phenylalaninate as an off-white solid: MS (ESI) *m/z* 442.

[0108] Step 5: Treatment of ethyl N-{4-[(5-amino-1H-indol-1-yl)methyl]benzoyl}phenylalaninate with benzenesulfonyl chloride followed by LiOH hydrolysis as described in the procedure of Example 1 gave the title compound: MS (ESI) *m/z* 554; MS (ESI) *m/z* 552.

Example 11

N-(4-([5-([4-(Trifluoromethoxy)phenyl]sulfonyl)amino)-1H-indol-1-yl]methyl]benzoyl)-L-phenylalanine

[0109] The title compound was prepared from ethyl N-{4-[(5-amino-1H-indol-1-yl)methyl]benzoyl}phenylalaninate and 4-trifluoromethoxyphenyl sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 638; MS (ESI) m/z 636.

Example 12

N-[4-([5-[(1,1'-Biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl]methyl]benzoyl)-L-phenylalanine

[0110] The title compound was prepared from ethyl N-{4-[(5-amino-1H-indol-1-yl)methyl]benzoyl}phenylalaninate and biphenyl 4-sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 630; MS (ESI) m/z 628.

Example 13

N-{4-[(5-([4-*tert*-Butylphenyl]sulfonyl)amino)-1H-indol-1-yl]methyl]benzoyl)-L-phenylalanine

[0111] The title compound was prepared from ethyl N-{4-[(5-amino-1H-indol-1-yl)methyl]benzoyl}phenylalaninate and 4-*tert*-butylphenyl sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 610; MS (ESI) m/z 608.

Example 14

N-(4-([5-([4-(Trifluoromethoxy)phenyl]sulfonyl)amino)-1H-indol-1-yl]methyl]benzoyl)- β -alanine

[0112] The title compound was prepared from 4-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid, β -alanine ethyl ester hydrochloride, and 4-trifluoromethoxyphenyl sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 562; MS (ESI) m/z 560.

Example 15**N-[4-({5-[(1,1'-Biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl)methyl}benzoyl]- β -alanine**

[0113] The title compound was prepared from 4-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid, β -alanine ethyl ester hydrochloride, and biphenyl 4-sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 554; MS (ESI) m/z 552.

Example 16**N-{4-[(5-{[(4-*tert*-Butylphenyl)sulfonyl]amino}-1H-indol-1-yl)methyl}benzoyl]- β -alanine**

[0114] The title compound was prepared from 4-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid, β -alanine ethyl ester hydrochloride, and 4-*tert*-butylphenyl sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 534; MS (ESI) m/z 532.

Example 17**1-{4-[(5-{[(3,4-Dichlorophenyl)sulfonyl]amino}-1H-indol-1-yl)methyl}benzoyl]piperidine-4-carboxylic acid**

[0115] The title compound was prepared from 4-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid, ethyl nipecotate, and 3,4-dichlorophenyl sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 586; MS (ESI) m/z 584.

Example 18**1-[4-({5-[(1,1'-Biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl)methyl}benzoyl]piperidine-4-carboxylic acid**

[0116] The title compound was prepared from 4-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid, ethyl nipecotate, and biphenyl 4-sulfonyl chloride following the procedure of Example 10: MS (ESI) m/z 594; MS (ESI) m/z 592.

Example 19**1-{4-[(5-{[(4-*tert*-Butylphenyl)sulfonyl]amino}-1H-indol-1-yl)methyl}benzoyl]piperidine-4-carboxylic acid**

[0117] The title compound was prepared from 4-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid, ethyl nipecotate, and 4-*tert*-butylphenyl sulfonyl chloride following the procedure of Example 10: MS (ESI) *m/z* 574; MS (ESI) *m/z* 572.

Example 20

{5-[(1,1'-Biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}acetic acid

MS (ESI) *m/z* 407; MS (ESI) *m/z* 405

[0118] Step 1: A mixture of 5-nitroindole (3.24 g, 20 mmol), methyl bromoacetate (3.36 g, 22 mmol), cesium carbonate (32.58 g, 100 mmol) in 150 mL of DMF was stirred at room temperature for 3 h. The reaction mixture was poured into water and the solid was collected and dried to give methyl (5-nitro-1H-indol-1-yl)acetate as a pale yellow solid: MS (ESI) *m/z* 235.

[0119] Step 2: The title compound was prepared from methyl (5-nitro-1H-indol-1-yl)acetate by the procedures described in Example 1 and Example 3: MS (ESI) *m/z* 407; MS (ESI) *m/z* 405

Example 21

N-({5-[(1,1'-Biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)-L-phenylalanine

[0120] Step 1: (5-Nitro-1H-indol-1-yl)acetic acid was prepared from methyl (5-nitro-1H-indol-1-yl)acetate by KOH hydrolysis: MS (ESI) *m/z* 219.

[0121] Step 2: Ethyl *N*-[(5-nitro-1H-indol-1-yl)acetyl]-L-phenylalaninate was prepared from (5-nitro-1H-indol-1-yl)acetic acid and L-phenylalanine ethyl ester following the procedure of Example 10 Step 3: MS (ESI) *m/z* 396; MS (ESI) *m/z* 394.

[0122] Step 3: The title compound was prepared from ethyl *N*-[(5-nitro-1H-indol-1-yl)acetyl]-L-phenylalaninate and biphenyl-4-sulfonyl chloride following the procedures of Example 10 Step 4 & Step 5: MS (ESI) *m/z* 554; MS (ESI) *m/z* 552

Example 22

***N*-[(5-{[(4-*tert*-Butylphenyl)sulfonyl]amino}-1*H*-indol-1-yl)acetyl]-L-phenylalanine**

[0123] The title compound was prepared from ethyl *N*-[(5-nitro-1*H*-indol-1-yl)acetyl]-L-phenylalaninate and 4-*tert*-butylphenylsulfonyl chloride following the procedures of Example 10 Step 4 & Step 5: MS (ESI) *m/z* 534; MS (ESI) *m/z* 532.

Example 23***N*-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl}acetyl)-L-leucine**

[0124] Step 1: Methyl *N*-[(5-nitro-1*H*-indol-1-yl)acetyl]-L-leucinate was prepared from 5-nitro-1*H*-indol-1-yl)acetic acid and L-leucine ethyl ester following the procedure of Example 10 Step 3: MS (ESI) *m/z* 348; MS (ESI) *m/z* 346.

[0125] Step 2: The title compound was prepared from methyl *N*-[(5-nitro-1*H*-indol-1-yl)acetyl]-L-leucinate and biphenyl-4-sulfonyl chloride following the procedures of Example 10 Step 4 and Step 5: MS (ESI) *m/z* 520; MS (ESI) *m/z* 518.

Example 24***N*-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1*H*-indol-1-yl)acetyl]-L-leucine**

[0126] The title compound was prepared from methyl *N*-[(5-nitro-1*H*-indol-1-yl)acetyl]-L-leucinate and 4-*tert*-butylphenyl sulfonyl chloride following the procedures of Example 10 Step 4 and Step 5: MS (ESI) *m/z* 500; MS (ESI) *m/z* 498.

Example 25***N*-{[5-({[4-(Trifluoromethoxy)phenyl]sulfonyl}amino)-1*H*-indol-1-yl]acetyl}-L-phenylalanine**

[0127] The title compound was prepared following the procedures of Example 10. MS (ESI) *m/z* 562.

Example 26

N-({5-[(Quinolin-8-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)-L-phenylalanine

[0128] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 529.

Example 27**N-({5-([4-(Trifluoromethoxy)phenyl]sulfonyl)amino)-1H-indol-1-yl}acetyl)-L-leucine**

[0129] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 528.

Example 28**1-({5-([4-(Trifluoromethoxy)phenyl]sulfonyl)amino)-1H-indol-1-yl}acetyl)piperidine-4-carboxylic acid**

[0130] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 526.

Example 29**1-({5-[(Quinolin-8-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)piperidine-4-carboxylic acid**

[0131] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 493.

Example 30**1-({5-[(1,1'-Biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)piperidine-4-carboxylic acid**

[0132] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 518.

Example 31

1-[(5-[[4-*tert*-Butylphenyl)sulfonyl]amino]-1H-indol-1-yl)acetyl]piperidine-4-carboxylic acid

[0133] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 498.

Example 32

N-[1-(1-Benzyl-2-hydrazino-2-oxoethyl)-1H-indol-5-yl]-4-(trifluoromethoxy) benzenesulfonamide

[0134] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 519.

Example 33

N-({5-[(Quinolin-8-ylsulfonyl)amino]-1H-indol-1-yl}acetyl)-L-leucine

[0135] The title compound was prepared following the procedures of Example 10. MS (ESI) m/z 495.

Example 34**Primary Screen for PAI-1 Inhibition**

[0136] The ability of the compounds of this invention to inhibit Plasminogen Activator Inhibitor-1 was established by the following experimental procedure:

[0137] Test compounds were dissolved in DMSO at a final concentration of 10 mM, then diluted 100X in physiologic buffer. The inhibitory assay was initiated by the addition of the

test compound (1 – 100 μ M final concentration, maximum DMSO concentration of 0.2%) in a pH 6.6 buffer containing 140 nM recombinant human plasminogen activator inhibitor-1 (PAI-1; *Molecular Innovations, Royal Oak, MI*). Following a 1 hour incubation at room temperature, 70 nM of recombinant human tissue plasminogen activator (tPA) was added, and the combination of the test compound, PAI-1 and tPA was incubated for an additional 30 minutes. Following the second incubation, Spectrozyme-tPA (*American Diagnostica, Greenwich, CT*), a chromogenic substrate for tPA, was added and absorbance read at 405 nm at 0 and 60 minutes. Relative PAI-1 inhibition is equal to the residual tPA activity in the presence of the test compound and PAI-1. Control treatments include the complete inhibition of tPA by PAI-1 at the molar ratio employed (2:1), and the absence of any effect of the test compound on tPA alone.

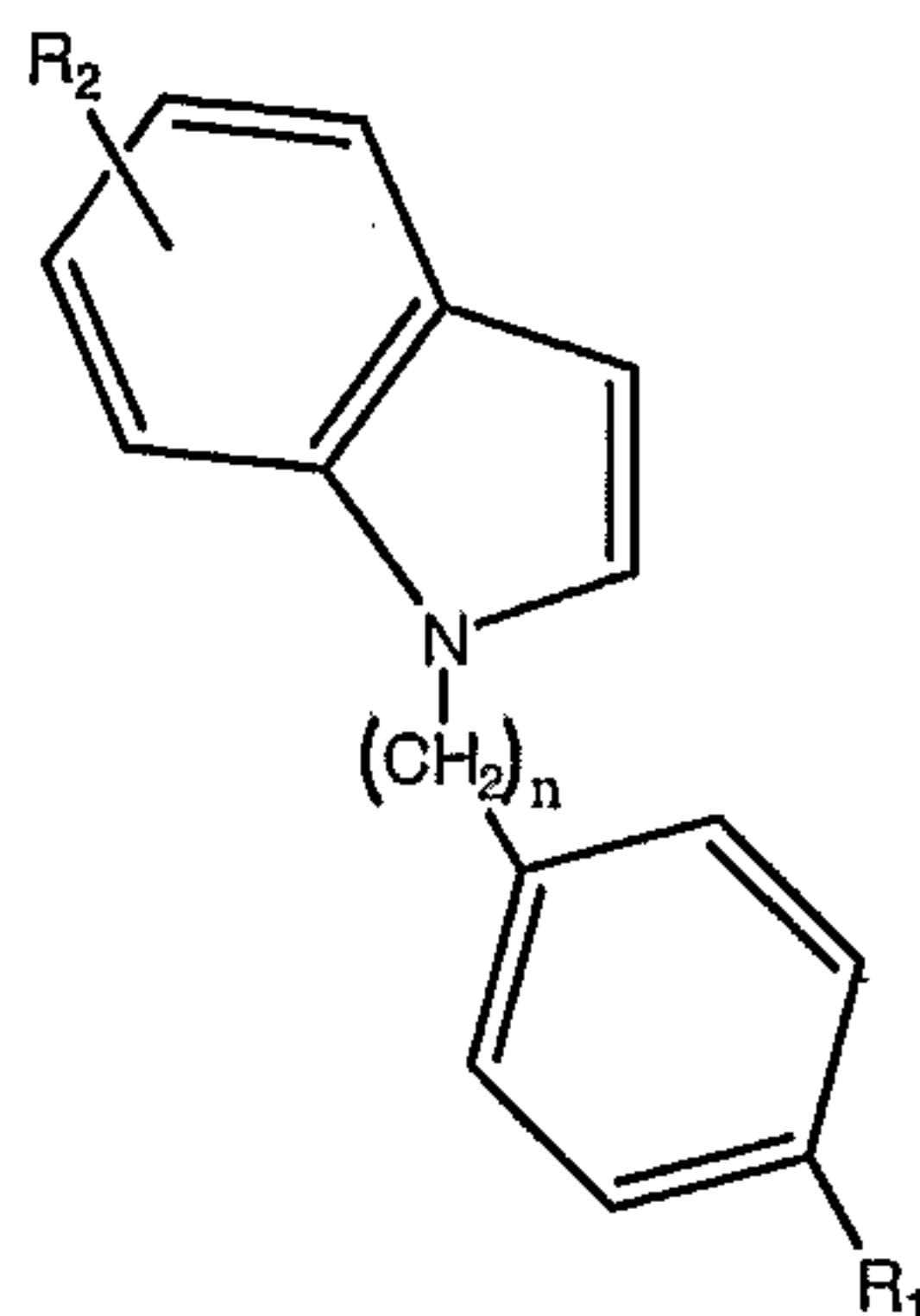
[0138] The inhibition of Plasminogen Activator Inhibitor-1 by the compounds of Example 1 -24 ranged from 6% to 78% inhibition at 25 μ M. Some of the remaining were tested and some showed no inhibitory activity at 25 μ M. However, Examples 25 to 33 are expected to show inhibitory activity when employed at higher levels, such as 100 μ M.

[0139] Although the foregoing invention has been described in detail by way of example for purposes of clarity of understanding, it will be apparent to the artisan that certain changes and modifications are comprehended by the disclosure and can be practiced without undue experimentation within the scope of the appended claims, which are presented by way of illustration not limitation.

[0140] All publications and patent documents cited above are hereby incorporated by reference in their entirety for all purposes to the same extent as if each were so individually denoted.

What is claimed:

1. A compound having Formula 1:



Formula 1

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_1 is C_{1-6} alkyl;

R_2 is $NR_3SO_2R_4$ or $NHC(=O)NHR_5$;

R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

R_4 is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

with the proviso that either R_3 or R_4 is substituted by $COOR_6$;

R_5 is phenyl(CO_2H) or $-C_{1-6}$ alkyl(CO_2H) wherein the alkyl group is optionally substituted with phenyl or benzyl;

R_6 is hydrogen or C_{1-6} alkyl; and

n is from 1 to 4.

2. The compound of claim 1, wherein:

R_5 is $-C_{1-6}$ alkyl(CO_2H) wherein the alkyl group is substituted with phenyl or benzyl.

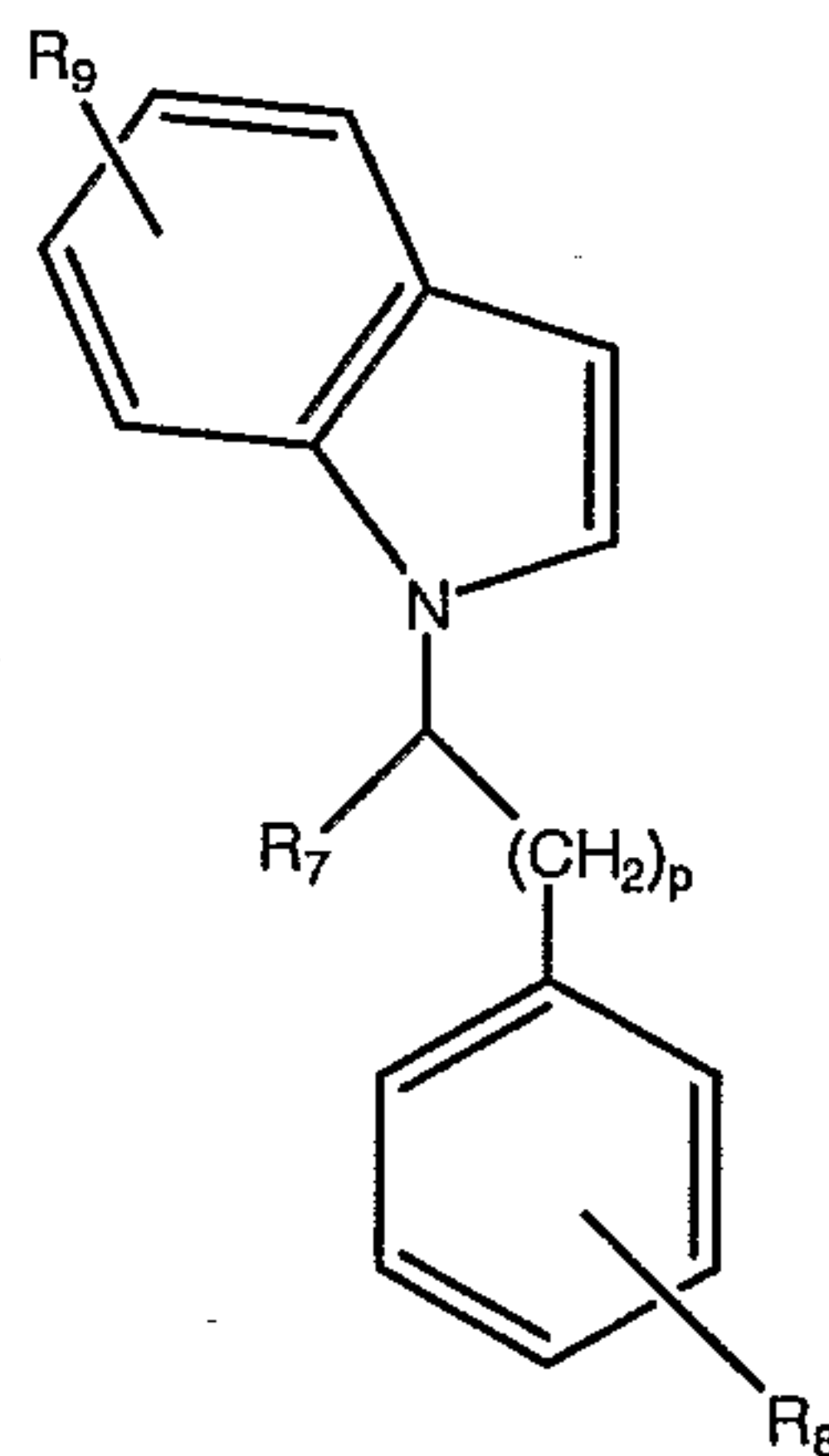
3. The compound of claim 1 or claim 2, wherein:

R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with $COOR_6$.

4. The compound of any one of claims 1 to 3, wherein:

R_4 is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with $COOR_6$.

5. The compound of any one of claims 1 to 4, wherein:
n is 1.
6. The compound of claim 1 that is one of the following:
3-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)carbonyl)amino]benzoic acid;
3-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)sulfonyl)benzoic acid;
{benzenesulfonyl-[1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]-amino}-acetic acid;
4-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl](phenylsulfonyl)amino)methyl)benzoic acid;
4-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)sulfonyl)benzoic acid;
N-([1-(4-*tert*-butylbenzyl)-1*H*-indol-5-yl]amino)carbonyl)-*L*-phenylalanine;
or
a pharmaceutically acceptable salt or ester form thereof.
7. A compound having Formula 2



Formula 2

- or a pharmaceutically acceptable salt or ester form thereof, wherein
R₇ is hydrogen, CO₂H, or CONHNH₂;
p is from 0 to 4;
R₈ is hydrogen, -C₁₋₆alkoxy(CO₂H), C(=O)NR₁₀R₁₁ or C(=O)amino acid;
R₁₀ and R₁₁ are joined together with the nitrogen to which they are attached to form a 3 to 9 membered saturated ring comprising 2 to 8 carbon ring atoms;
with the proviso that when R₈ is hydrogen, R₇ is CO₂H or CONHNH₂;
R₉ is NR₁₂SO₂R₁₃;

R_{12} is H, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl; and

R_{13} is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl.

8. The compound of claim 7, wherein:

said alkyl, perfluoroalkyl, benzyl, phenyl, and heterocyclyl groups are unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl.

9. The compound of claim 7 or claim 8, wherein:

the amino acid is β -alanine, phenylalanine, or $-NR_{18}R_{19}$ wherein R_{18} and R_{19} are joined together with the nitrogen to which they are attached to form a 3 to 9 membered saturated ring comprising 2 to 8 carbon ring atoms and substituted with CO_2H or $C(O)C_{1-6}$ alkoxy.

10. The compound of claim 7 that is one of the following:

[4-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl)methyl}phenoxy]acetic acid;

{4-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1*H*-indol-1-yl)methyl}phenoxy]acetic acid;

3-phenyl-2-[5-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)-1*H*-indol-1-yl]propanoic acid;

1-{4-[(5-{[(3,4-dichlorophenyl)sulfonyl]amino}-1*H*-indol-1-yl)methyl]benzoyl}piperidine-4-carboxylic acid ;

1-[4-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl)methyl}benzoyl]piperidine-4-carboxylic acid;

1-{4-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1*H*-indol-1-yl)methyl]benzoyl}piperidine-4-carboxylic acid;

N-(4-{[5-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)-1*H*-indol-1-yl)methyl}benzoyl)- β -alanine;

N-[4-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}methyl)benzoyl]- β -alanine;

N-{4-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1H-indol-1-yl)methyl]benzoyl}- β -alanine;

N-[4-({5-[(phenylsulfonyl)amino]-1H-indol-1-yl}methyl)benzoyl]-L-phenylalanine;

N-(4-{[5-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)-1H-indol-1-yl]methyl}benzoyl)-L-phenylalanine;

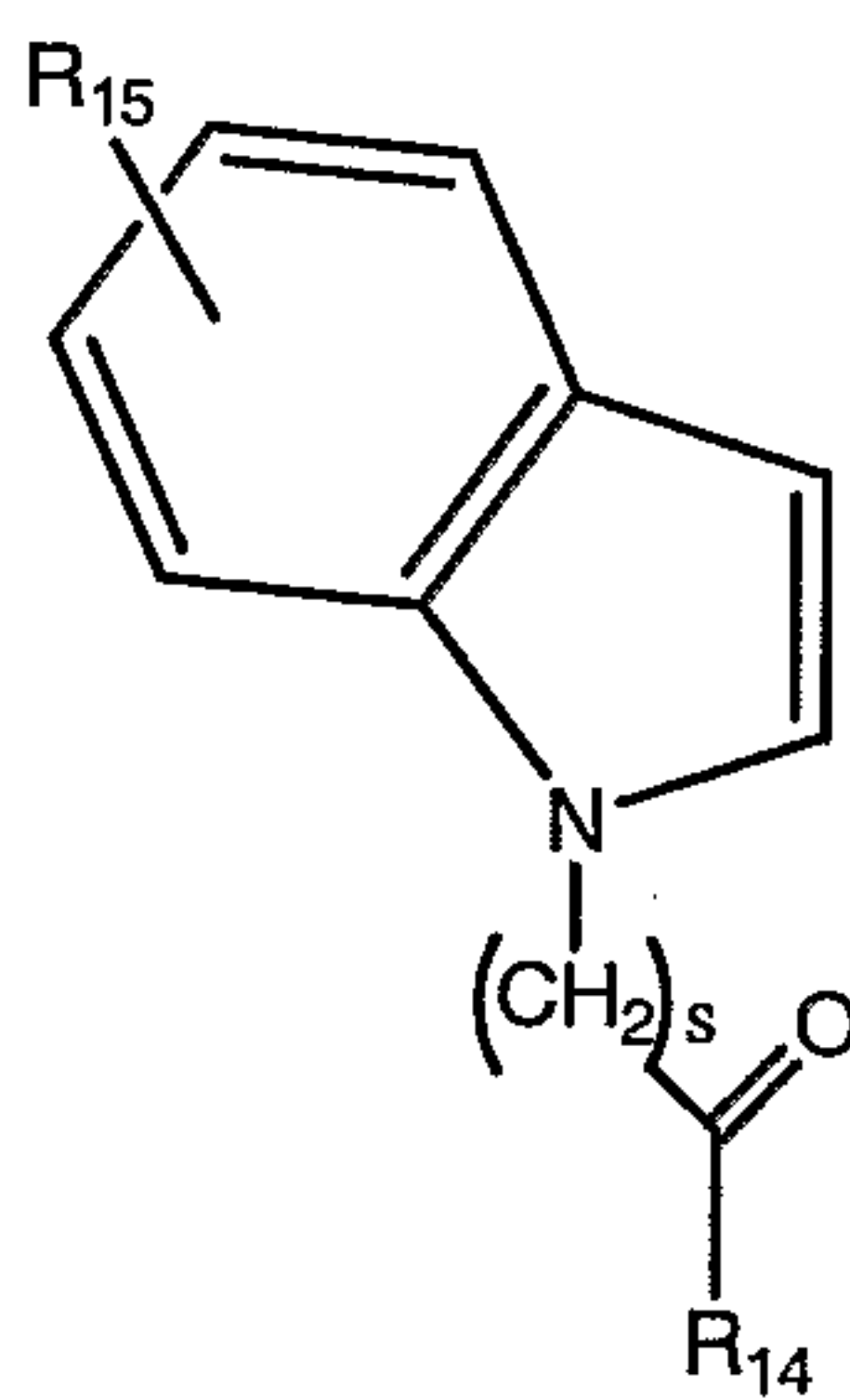
N-[4-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1H-indol-1-yl}methyl)benzoyl]-L-phenylalanine;

N-{4-[(5-{[(4-*tert*-butylphenyl)sulfonyl]amino}-1H-indol-1-yl)methyl]benzoyl}-L-phenylalanine;

N-[1-(1-benzyl-2-hydrazino-2-oxoethyl)-1H-indol-5-yl]-4-(trifluoromethoxy)benzenesulfonamide; or

a pharmaceutically acceptable salt or ester form thereof.

11. A compound having Formula 3



Formula 3

or a pharmaceutically acceptable salt or ester form thereof, wherein

R_{14} is -OH, C_{1-6} alkoxy, or amino acid;

R_{15} is $NR_{16}SO_2R_{17}$;

R_{16} is H or a C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl;

R_{17} is C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl unsubstituted or substituted with OCF_3 , halogen, C_{1-6} alkyl, C_{1-6} perfluoroalkyl, benzyl, phenyl, or heterocyclyl; and

s is from 1 to 4.

12. The compound of claim 11 with the proviso that when R₁₄ is -OH or C₁₋₆ alkoxy, R₁₆ or R₁₇ is substituted with OCF₃, benzyl, phenyl, or heterocyclyl.
13. The compound of claim 11 or claim 12, wherein:
R₁₄ is alpha amino acid or NR₁₈R₁₉ wherein R₁₈ and R₁₉ are joined together with the nitrogen to which they are attached to form a 3 to 9 membered saturated ring comprising 2 to 8 carbon ring atoms and substituted with CO₂H or C(O)C₁₋₆ alkoxy.
14. The compound of claim 11 that is one of the following:
{5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl}acetic acid;
N-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl}acetyl)-*L*-phenylalanine;
N-[{5-}[(4-*tert*-butylphenyl)sulfonyl]amino]-1*H*-indol-1-yl]acetyl]-*L*-phenylalanine;
N-({5-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl}acetyl)-*L*-leucine;
N-[{5-}[(4-*tert*-butylphenyl)sulfonyl]amino]-1*H*-indol-1-yl]acetyl]-*L*-leucine;
N-[{5-}([4-(trifluoromethoxy)phenyl]sulfonyl)amino]-1*H*-indol-1-yl]acetyl]-*L*-phenylalanine;
N-({5-[(quinolin-8-ylsulfonyl)amino]-1*H*-indol-1-yl}acetyl)-*L*-phenylalanine;
N-[{5-}([4-(trifluoromethoxy)phenyl]sulfonyl)amino]-1*H*-indol-1-yl]acetyl]-*L*-leucine;
1-{{5-}([4-(trifluoromethoxy)phenyl]sulfonyl)amino]-1*H*-indol-1-yl]acetyl}piperidine-4-carboxylic acid;
1-{{5-}[(quinolin-8-ylsulfonyl)amino]-1*H*-indol-1-yl}acetyl)piperidine-4-carboxylic acid;
1-{{5-}[(1,1'-biphenyl-4-ylsulfonyl)amino]-1*H*-indol-1-yl}acetyl)piperidine-4-carboxylic acid;
1-{{5-}[(4-*tert*-butylphenyl)sulfonyl]amino]-1*H*-indol-1-yl]acetyl}piperidine-4-carboxylic acid;
N-({5-[(quinolin-8-ylsulfonyl)amino]-1*H*-indol-1-yl}acetyl)-*L*-leucine;
or a pharmaceutically acceptable salt or ester form thereof.

15. A method of inhibiting PAI-1 activity, comprising the step of:
administering to a subject in need thereof a pharmaceutically effective amount of a compound of any one of claims 1 to 14.
16. A method for treating a PAI-1 related disorder, comprising the step of:
administering to a subject in need thereof a pharmaceutically effective amount of a compound of any one of claims 1 to 14.
17. The method of claim 16,
wherein the PAI-1 related disorder is impairment of the fibrinolytic system.
18. The method of claim 16,
wherein the PAI-1 related disorder is thrombosis, atrial fibrillation, pulmonary fibrosis, myocardial ischemia, stroke, thromboembolic complication of surgery, cardiovascular disease, atherosclerotic plaque formation, chronic obstructive pulmonary disease, renal fibrosis, polycystic ovary syndrome, diabetes, Alzheimer's disease, or cancer.
19. The method of claim 18,
wherein the thrombosis is selected from the group consisting of venous thrombosis, arterial thrombosis, cerebral thrombosis, and deep vein thrombosis.
20. The method of claim 16,
wherein the PAI-1 related disorder is cardiovascular disease caused by noninsulin dependent diabetes mellitus in a subject.
21. The method of any one of claims 15 to 20,
wherein the pharmaceutically effective amount is from 25 mg/kg/day to 200 mg/kg/day.
22. A method, comprising the step of:
contacting a cell with a compound of any one of claims 1 to 14.

