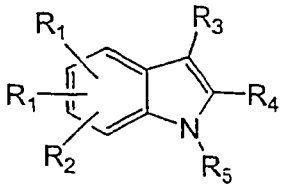
SUBSTITUTED DIHYDROPYRANO INDOLE-3,4-DIONE DERIVATIVES AS INHIBITORS OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1)

This invention relates to substituted dihydropyrano indole-3,4-dione derivatives useful as inhibitors of plasminogen activator inhibitor-1 (PAI-1) and therapeutic compositions containing such compounds for treating conditions resulting from fibrinolytic disorders such as deep vein thrombosis and coronary heart disease, and pulmonary fibrosis.

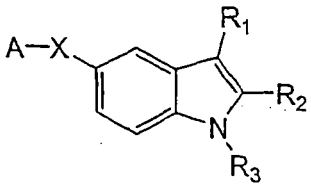
BACKGROUND OF INVENTION

Plasminogen activator inhibitor-1 (PAI-1) is a major regulatory component of the plasminogen-plasmin system. PAI-1 is the principal physiologic inhibitor of both tissue type plasminogen activator (tPA) and urokinase type plasminogen activator (uPA). Elevated plasma levels of PAI-1 have been associated with thrombotic events as indicated by animal experiments (Krishnamurti, *Blood,* 69, 798 (1987); Reilly, *Arteriosclerosis and Thrombosis*, 11, 1276 (1991); Carmeliet, *Journal of Clinical Investigation*, 92, 2756 (1993)) and clinical studies (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 of women such as polycystic ovary syndrome (Nordt, *Journal of clinical Endocrinology and Metabolism*, 85, 4, 1563 (2000)) and bone loss induced by estrogen deficiency (Daci, *Journal of Bone and Mineral Research*, 15, 8, 1510 (2000)). Accordingly, agents that inhibit PAI-1 would be of utility in treating conditions originating from fibrinolytic disorder such as deep vein thrombosis, coronary heart disease, pulmonary fibrosis, Alzheimer's disease, polycystic ovary syndrome, etc.

WO 99/43654 and WO 99/43651 disclose indole derivatives of the following formula as inhibitors of phospholipase enzymes useful in preventing inflammatory conditions.

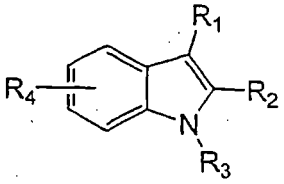


US 4,851,406 discloses cardiotonic compounds of the following formula:



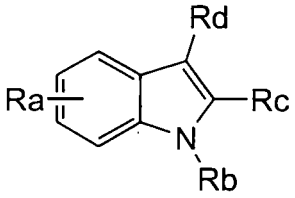
wherein: A is a five-membered, or six-membered ring heterocycle; X is a bond, an alkylene, or a vinylene radical; R_1 is a H, alkyl, alkenyl, cycloalkyl, cycloalkenyl, carboxyl, cyano, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl or aryl radical; R_2 is H, alkyl, trihalogenomethyl, hydroxyl, cycloalkyl, cyano, carboxyl, cycloalkenyl, carboxyl, cyano, alkylcarbonyl, alkoxy-carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl or aryl radical; and R_3 is a hydrogen atom.

WO 96/32379 teaches PDE-inhibitor compounds of the following formula:



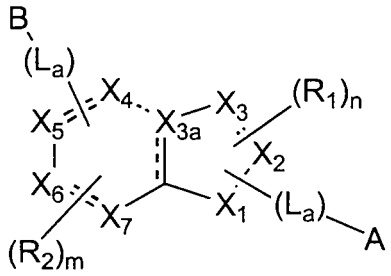
wherein R_1 is a H, halogen, nitro, carboxy, protected carboxy, lower alkenyl, or acyl; R_2 is H, halogen, carboxy, lower alkenyl, or acyl; R_3 is a lower alkenyl, or lower alkenyl, both optionally substituted; and R_4 is carboxy, protected carboxy, or acyl.

WO 9928297 relates to substituted indoles of the following formula with thrombin inhibiting effect and fibrinogen receptor antagonist effect.



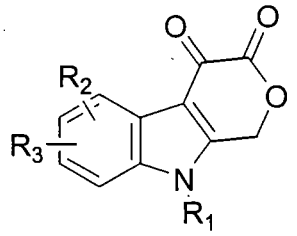
where: Ra is halogen, carboxy, R_3R_4N-CO-, $R_3R_4SO_2$-, or R_4R5N-; Rb and Rd are either alkyl or R_2-A where R_2 is a phenyl optionally substituted and A is an alkylene or a substituted alkylene; and Rc is a hydrogen, or alkyl.

EP 0 655 439 teaches 5,6 fused ring bicyclic compounds inclusive of indoles, benzofurans, and benzothiophenes corresponding the following formula as platelet aggregation inhibitors.



SUMMARY OF THE INVENTION

This invention is directed to compounds of formula I:



(I)

wherein:

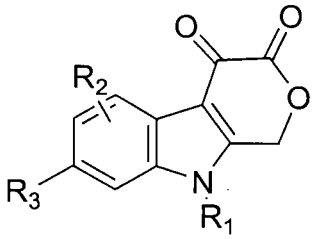
R_1 is C_1-C_8 alkyl, preferably C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, pyridinyl, -CH_2-pyridinyl, phenyl or benzyl, wherein the rings of the

cycloalkyl, pyridinyl, phenyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from, halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, $-NH_2$, or $-NO_2$;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, $-CH_2$-C_3-C_6 cycloalkyl, hydroxy, $-NH_2$, or $-NO_2$;

R_3 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, CH_2-C_3-C_6 cycloalkyl, hydroxy, $-NH_2$, $-NO_2$, phenyl, benzyl, benzyloxy, pyridinyl, or $-CH_2$-pyridinyl, wherein the rings of these groups may be optionally substituted by from 1 to 3 groups independently selected from phenyl, halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, $-NH_2$, or $-NO_2$; or a pharmaceutically acceptable salt or ester form thereof.

The present invention also provides a compound of formula III:



(III)

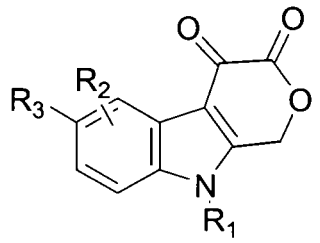
wherein:

R_1 is C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, pyridinyl, -CH_2-pyridinyl, phenyl or benzyl, wherein the rings of the cycloalkyl, pyridinyl, phenyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, -NH_2, or -NO_2;

R_3 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, -NO_2, phenyl, benzyl, benzyloxy, pyridinyl, or -CH_2-pyridinyl, wherein the rings of these groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

The present invention also provides a compound of formula (IV)



(IV)

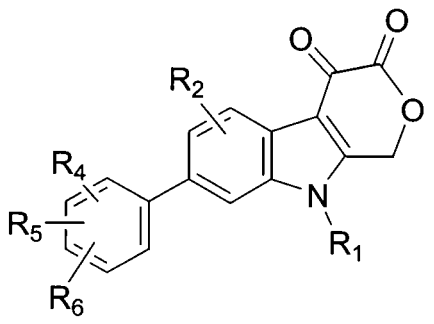
wherein:

R_1 is C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, pyridinyl, -CH_2-pyridinyl, phenyl or benzyl, wherein the rings of the cycloalkyl, pyridinyl, phenyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, -NH_2, or -NO_2;

R_3 is phenyl, benzyl, benzyloxy, pyridinyl, or -CH_2-pyridinyl, with the rings of these groups being optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

The present invention also provides a compound of formula (V):



(V)

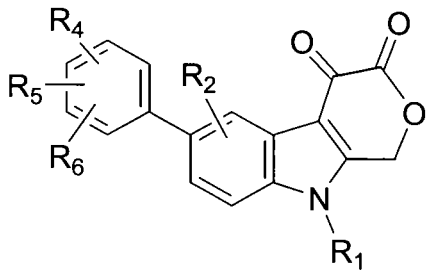
wherein:

R_1 is C_1-C_8 alkyl, preferably C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, or benzyl, wherein the rings of the cycloalkyl and benzyl groups may be optionally substituted by from 1 to 3 groups selected independently from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, or -NO_2;

R_4, R_5 and R_6 are each independently hydrogen, phenyl, halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, -O-C_1-C_3 perfluoroalkyl, C_1-C_3 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

The present invention also provides a compound of formula VI:



(VI)

wherein:

R_1 is C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, or benzyl, wherein the rings of the cycloalkyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, preferably –CF_3, -O-C_1-C_6 perfluoroalkyl, preferably –O-CF_3, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, or -NO_2; and

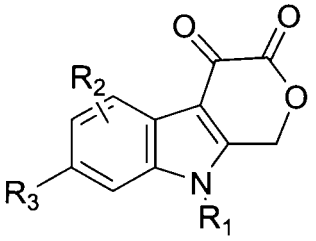
R_4, R_5 and R_6 are each independently hydrogen, phenyl, halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, -O-C_1-C_3 perfluoroalkyl, preferably –O-CF_3, C_1-C_3 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

The present invention also provides a pharmaceutical composition comprising a compound as described above and a pharmaceutical carrier.

The present invention also provides the use of a compound as described above in the manufacture of a medicament for the treatment of thrombosis, fibrinolytic impairment, peripheral arterial disease, stroke associated with or resulting from atrial fibrillation, deep vein thrombosis, myocardial ischemia, cardiovascular disease caused by non-insulin dependent diabetes mellitus, the formation of atherosclerotic plaques, chronic obstructive pulmonary disease, renal fibrosis, polycystic ovary syndrome, Alzheimer's disease, or cancer in a mammal.

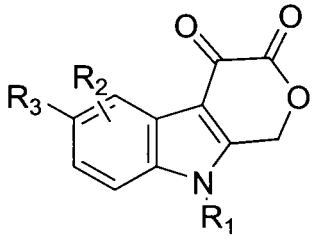
DETAILED DESCRIPTION OF THE INVENTION

Preferred forms of the compounds of this invention are those of formulas (III) and (IV) :



(III)

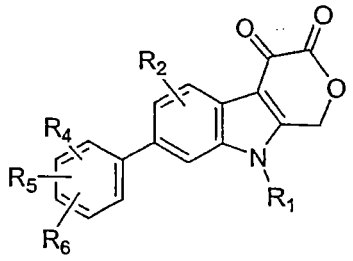
or



(IV)

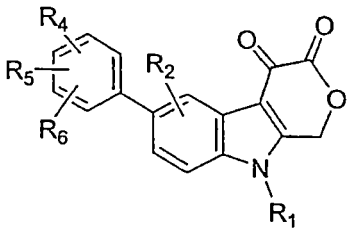
wherein R_1, R_2, and R_3 are as defined above, or a pharmaceutically acceptable salt or ester form thereof.

More preferred compounds of this invention are those of formulas (V) and (VI):



(V)

or



(VI)

wherein:

R_1 is C_1-C_8 alkyl, preferably C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, or benzyl, wherein the rings of the cycloalkyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

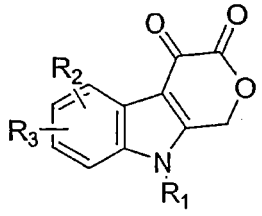
R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, or -NO_2;

R_4, R_5 and R_6 are each independently hydrogen, phenyl, halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, -O-C_1-C_3 perfluoroalkyl, C_1-C_3 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

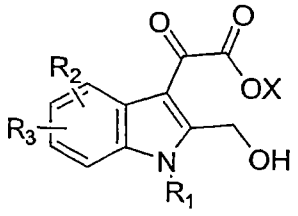
The alkali metals suitable for use in the present invention include: sodium, potassium, lithium, calcium, magnesium, etc.. The basic amine moieties include: amonia, primary amines, secondary amines, tertiary amines, pyridine, aromatic amines, benzyl amines, etc. The term "alkyl" includes both straight and branched carbon chains. The preferred C_1-C_3 perfluoroalkyl substituent is -CF_3 and the preferred O-C_1-C_3 perfluoroalkyl substituent is -OCF_3.

The present invention further comprises a method of inhibiting in a mammal plasminogen activator type 1 (PAI-I) comprising administering to a mammal in need

thereof a therapeutically effective amount of a compound of formulas (I) and (II):



(II)



(II)

wherein:

X is an alkali metal or a basic amine moiety as defined above;

R_1 is C_1-C_8 alkyl, preferably C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, pyridinyl, -CH_2-pyridinyl, phenyl or benzyl, wherein the rings of the cycloalkyl, pyridinyl, phenyl and benzyl groups may be optionally substituted by, from 1 to 3 groups selected from, halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, -O-C_1-C_3 perfluoroalkyl, C_1-C_3 alkoxy, -OH, -NH_2, or -NO_2;

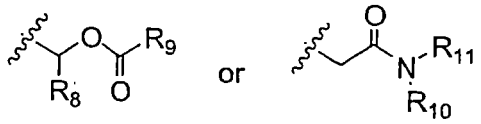
R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, or -NO_2;

R_3 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 pperfluoroalkyl, C_1-C_6, C_3-C_6 cycloalkyl I, CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, -NO_2, phenyl, benzyl, benzyloxy, pyridinyl, or -CH_2-pyridinyl, wherein the rings of these groups may be optionally substituted by from 1 to 3 groups selected from halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, -O-C_1-C_3 perfluoroalkyl, C_1-C_3 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

The preferred salt forms of the compounds herein include but are not limited to sodium salts, and potassium salts. Other useful salt forms of these compounds include those formed with pharmaceutically acceptable inorganic and organic bases known in the art. 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 benzylzmine, 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 triethanol-amine. Also useful are alkylene diamines containing up to 6 carbon atoms, such as hexamethylenediamine; cyclic saturated or unsaturated bases containing up to 6 carbon atoms, including pyrrolidine, peperidine, morpholine, piperazine and their N-alkyl and N-hydroxyalkyl derivatives, such as N-methyl-morpholine and N-(2-hyroxyethyl)-piperidine, or pyridine. Quaternary salts may 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-methyl-morpholinium, N-mehtyl-N-(2-hydroxyethyl)-morpholinium, or N,N-dimethyl-piperidinium salt forms. These salt forms may be prepared using the acidic compound(s) of Formula I and procedures known in the art.

Ester forms of the compounds of this invention include straight chain alkyl esters having from 1 to 6 carbon atoms or branched chain alkyl groups containing 3 or 6 carbon atoms, including methyl, ethyl, propyl, butyl, 2-methylpropyl and 1,1-dimethylethyl esters. Other esters useful with this invention include those of the formula $-COOR_7$ wherein R_7 is selected from the formulae:



(1) or (2)

wherein R_8, R_9, R_{10}, R_{11} are independently selected from hydrogen, alkyl of from 1 to 10 carbon atoms, aryl of 6 to 12 carbon atoms, arylalkyl of from 6 to 12 carbon atoms; heteroaryl or alkylheteroaryl wherein the heteroaryl ring is bound by an alkyl chain of from 1 to 6 carbon atoms.

Among the preferred ester forms of the compounds herein include but not limited to C_1-C_6 alkyl esters, C_3-C_6 branched alkyl esters, benzyl esters, etc.

As used herein, "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryl groups include phenyl, naphthyl and the like. As used herein, "heteroaryl" refers to an aromatic heterocyclic ring system (monocyclic or bicyclic) where the heteroaryl moieties are five or six membered rings containing 1 to 4 heteroatoms selected from the group consisting of S, N, and O,. Such heteroaryl groups can have a single ring, such as pyridyl, pyrrolyl or furyl groups, or multiple condensed rings, such as indolyl, indolizinyl, benzofuranyl or benzothienyl groups. Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

Unless otherwise limited by the definition for the aryl or heteroaryl groups herein, such groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, amino substituted by one or two alkyl groups of from 1 to 6 carbon atoms, aminoacyl, acylamino, azido, cyano, halo, nitro, thioalkoxy of from 1 to 6 carbon atoms, substituted thioalkoxy of from 1 to 6 carbon atoms, and trihalomethyl. Substituents on the alkyl, alkenyl, alkynyl, thioalkoxy and alkoxy groups mentioned above include halogens, CN, OH, and amino groups. Preferred substituents on the aryl groups herein include alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The compounds of the present invention are inhibitors of the serine protease inhibitor PAI-1, and are therefore useful in the treatment, inhibition, prevention or prophylaxis in a mammal, preferably in a human, of those processes which involve the production and/or action of PAI-1. Thus, the compounds of the invention are useful in the treatment or prevention of noninsulin dependent diabetes mellitus and prevention of thrombotic events associated with coronary artery and cerebrovascular disease. These compounds would also be useful for inhibiting the disease process involving the 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

fibrosis, cerebral thrombosis, thromboembolic complications of surgery (such as joint replacement), and peripheral arterial occlusion. These compounds are also useful in treating stroke associated with aor resulting from atrial fibrillation.

The compounds of the invention may also be useful in the treatment of 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.

The compounds of the invention may also be useful in the treatment of malignancies, and diseases associated with neoangiogenesis (such as diabetic retinopathy).

The compounds in the invention may also be used in conjunction with and following processes or procedures involving maintaining blood vessel patency, including vascular surgery, vascular graft and stent patency, organ, tissue and cell implantation and transplantation.

The compounds of the invention may also be used in the treatment of Alzheimer's disease. This method may also be characterized as the inhibition of plasminogen activator by PAI-1 in a mammal, particularly a human, experiencing or subject to Alzhemier's disease. This method may also be characterized as a method of increasing or normalizing levels of plasmin concentration in a mammal, particularly those experiencing or subject to Alzheimer's disease.

The compounds of the present invention are useful for the treatment of blood and blood products used in dialysis, blood storage in the fluid phase, especially *ex vivo* platelet aggregation. The present compounds may also be added to human plasma during the analysis of blood chemistry in hospital settings to determine the fibrinolytic capacity thereof.

The compounds in the present invention may also be used in combination with prothrombolytic, fibrinolytic and anticoagulant agent.

The compounds of the present invention may also be used to treat cancer including, but not limited to, breast and ovarian cancer, and as imaging agents for the identification of metastatic cancers.

The compounds of the invention may also be useful in the treatment of myelofibrosis with myeloid metaplasia by regulating stromal cell hyperplasia and increases in extracellular matrix proteins.

The present compounds may also be used in conjunction with protease inhibitors containing highly active antiretroviral therapy (HAART) for the treatment of diseases which originate from fibrinolytic impairment and by hypercoagulability of HIV-1 infected patients receiving such therapy.

The compounds of the invention may be used for the treatment of diabetic neuropathy and renal dialysis associated with nephropathy.

The compounds of the invention may be used to treat cancer, septicemia, obesity, insulin resistance, proliferative diseases, such as psoriasis, improving coagulation homeostasis, cerebrovascular diseases, microvascular disease, hypertension, dementia, osteoporosis, arthritis, asthma, heart failure, arrhythmia, angina, as a hormone replacement agent, treating, preventing or reversing progression of atherosclerosis, Alzheimer's disease, osteopenia, reducing inflammatory markers, reducing C-reactive protein, preventing or treating low grade vascular inflammation, stroke, coronary heart disease, primary and secondary prevention of myocardial infarction, stable and unstable angina, primary prevention of cardiovascular events, secondary prevention of cardiovascular events, peripheral vascular disease, peripheral arterial disease, acute vascular syndromes, reducing the risk of undergoing a myocardial revascularization procedure, micromuscular diseases such as nephropathy, neuropathy, retinopathy, nephrotic syndrome, Type I and Type 2 diabetes and related diseases, hyperglycemia, hyperinsulinemia, malignant lesions, pre malignant lesions, gastro intestinal malignancies, liposarcomas and epithelial

tumors, proliferative diseases such as psoriasis, improving coagulation, homeostasis and/or improving endothelial function and all forms of cerebrovascular diseases.

The compounds of the invention may also be used for topical application in wound healing for the prevention of scarring.

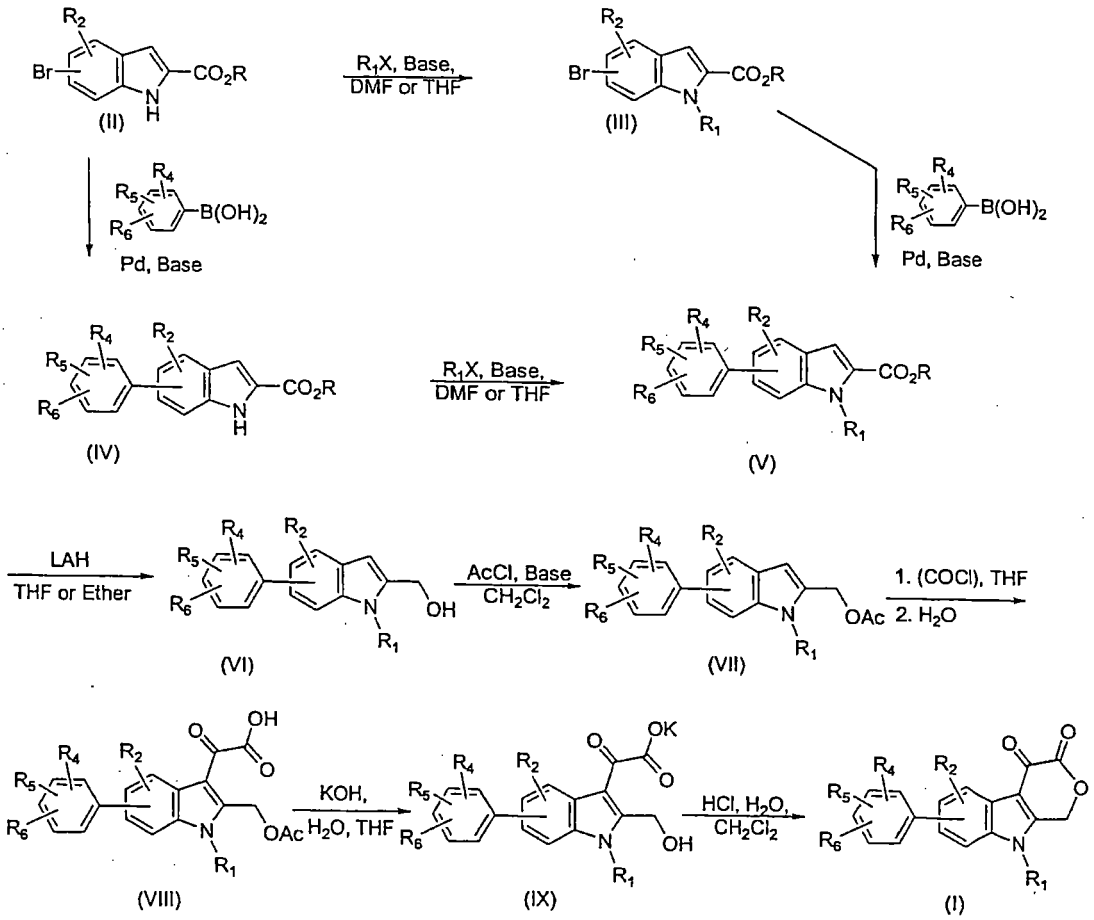
Methods for the treatment, inhibition, prevention or prophylaxis in a mammal of each of the conditions or maladies listed herein are part of this invention. Each method comprises administering to a mammal in need thereof a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt or ester form thereof.

The compounds of the present invention can be prepared according to the method described in Scheme I or modification thereof using readily available starting materials, reagents and conventional synthetic procedures. It is also possible to make use of variants of these process steps, which in themselves are known to and well within the preparatory skill of the medicinal chemist. In the following reaction schemes, R_1, R_2, R_4, R_5 and R_6 are selected from the groups defined above.

In Scheme I, the bromo-indole-2-carboxylates (II) were reacted with alkyl halides or aryl-alkyl halides using a base such as sodium hydride in DMF or THF to give the *N*-substituted bromo-indole carboxylates (III). The *N*-substituted bromo-indole carboxylates (III) were then subjected to palladium catalyzed cross-coupling with various substituted aryl-halides affording the *N*-substituted Aryl-indole carboxylates (V). Alternatively, reaction of bromo-indole-2-carboxylates (II) with various substituted aryl-boronic acids under the palladium catalyzed cross-coupling conditions afforded the aryl-indole carboxylates (IV). Alkylation of (IV) with alkyl-halides or aryl-alkyl-halides under basic conditions as described above afforded the *N*-substituted Aryl-indole carboxylates (V). Reduction of V to the corresponding alcohol (VI) was accomplished by treating V with lithium aluminum hydride in ether or THF. Reaction of the alcohol (VI) with acetyl chloride in presence of a base such as triethyl amine or *N,N*-diisopropyl ethyl amine in an inert solvent such as methylene chloride afforded the acetate VII. Reaction of VII with oxalyl chloride in THF or

dichloromethane and subsequent quenching with water furnished the keto acid VIII. Treatment of the acetate (VIII) with an aqueous base such as KOH or NaOH in a solvent such as THF furnished the carboxylate salt (IX). Lactonization of (IX) to the corresponding pyrano indole derivatives (I) was accomplished by treating IX with an aqueous acid such as hydrogen chloride in an organic solvent such as dichloromethane.

Scheme I



This invention also provides pharmaceutical compositions comprising a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt or ester form thereof, either alone or in

combination with one or more pharmaceutically acceptable carriers or excipients (i.e. pharmaceutically acceptable materials with no pharmacological effects). It will be understood that a pharmaceutically or therapeutically effective amount of a compound herein refers to an amount of the compound in question which will sufficiently inhibit the serine protease inhibitor PAI-1in the mammal in need thereof to a sufficient extent to provide a desirable improvement in the condition in question or provide sufficient inhibition of the serine protease inhibitor PAI-1 to prevent, inhibit or limit the onset of the physiological basis for the malady or condition in question.

The precise dosage to be employed depends upon several factors including the host, whether in veterinary medicine or human medicine, the nature and severity of the condition being treated, the mode of administration and the particular active substance employed. The compounds may be administered by any conventional route, in particular enterally, preferably orally in the form of tablets or capsules. Administered compounds can be in the free form or pharmaceutically acceptable salt form as appropriate, for use as a pharmaceutical, particularly for use in the prophylactic or curative treatment of atherosclerosis and sequelae (angina pectoris, myocardial infarction, arrhythmias, heart failure, kidney failure, stroke, peripheral arterial occlusion, and related disease states). These measures will slow the rate of progress of the disease state and assist the body in reversing the process direction in a natural manner.

Any suitable carrier known to the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as a flavoring agent, lubricant, solubilizer, suspending agent, binder, or tablet disintegrant. In powders, the carrier is a finely divided solid, which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, hydroxymethyl cellulose, sodium carboxymethyl

cellulose, a low melting wax, cocoa butter, and the like. Encapsulating materials may also be employed with the compounds of this invention, and the term "composition" is intended to include the active ingredient in combination with an encapsulating material as a formulation, with or without other carriers. Cachets may also be used in the delivery of the anti-atherosclerotic medicament of this invention.

Sterile liquid compositions include solutions, suspensions, emulsions, syrups and elixirs. The compounds of this invention may be dissolved or suspended in the pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably the liquid carrier is one suitable for parental injection. 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. If desired, dispersions of the finely divided compounds can be made-up in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, such as arachis oil. Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by intramuscular, intraperitoneal or subcutaneous injection. In many instances a liquid composition form may be used instead of the preferred solid oral method of administration.

It is preferred to prepare unit dosage forms of the compounds for standard administration regimens. In this way, the composition can be subdivided readily into smaller doses at the physicians direction. For example, unit dosages may 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 may be present in an amount 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. The daily dose of active compound will vary depending upon the route of administration, the size, age and sex of the patient, the severity of the disease state, and the response to the therapy as traced by blood analysis and the patients recovery rate. By initiating the treatment regimen with a minimal daily dose of about one gram, the blood levels of PAI-1 and the patients symptomatic relief analysis may be used to determine whether a larger dose is indicated. Based upon the data presented below, the projected daily dose for both human and veterinary use will be

from about 25 to about 200 milligrams/kilogram per day, and more usually, from about 50 to about 100 milligrams/kilogram per day.

The ability of the compounds of this invention to inhibit plasminogen activator inhibitor-1 was established by the following experimental procedures:

PRIMARY SCREEN FOR THE PAI-1 INHIBITION

Test compounds were dissolved in DMSO at a final concentration of 10mM, then diluted 100X in physiologic buffer. The inhibitory assay was initiated by the addition of the test compound (1 – 100 μM final concentration, maximum DMSO concentration of 0.2%) in a pH 6.6 buffer containing 140 nM recombinant human plasminogen activator inhibitor-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 was equal to the residual tPA activity in the presence of the test compound and PAI-1. Control treatments included 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.

ASSAY FOR DETERMINING IC_{50} OF INHIBITION OF PAI-1

This assay is based upon the non-SDS dissociable interaction between tPA and active PAI-1. Assay plates were initially coated with human tPA (10 μg/ml). Test compounds were dissolved in DMSO at 10 mM, then diluted with physiologic buffer (pH 7.5) to a final concentration of 1-50μM. Test compounds were incubated with human PAI-1 (50 ng/ml) for 15 minutes at room temperature. The tPA-coated plate was washed with a solution of 0.05% Tween 20 and 0.1% BSA, then the plate was blocked with a solution of 3% BSA. An aliquot of the test compound/PAI-1 solution was then added to the tPA-coated plate, incubated at room temperature for 1 hour, and washed. Active PAI-1 bound to the plate was assessed by adding an aliquot of a

1:1000 dilution of the 33B8 monoclonal antibody against human PAI-1, and incubating the plate at room temperature for 1 hour (*Molecular Innovations, Royal Oak, MI*). The plate was again washed, and a solution of goat anti-mouse IgG-alkaline phosphatase conjugate is added at a 1:50,000 dilution in goat serum. The plate was incubated 30 minutes at room temperature, washed, and a solution of alkaline phosphatase substrate is added. The plate was incubated 45 minutes at room temperature, and color development is determined at OD_{405nm}. The quantitation of active PAI-1 bound to tPA at varying concentrations of the test compound was used to determine the IC_{50}. Results were analyzed using a logarithmic best-fit equation. The assay sensitivity was 5 ng/ml of human PAI-1 as determined from a standard curve ranging from 0-100 ng/ml.

The compounds of the present invention inhibited Plasminogen Activator Inhibitor-1 as summarized in Table I.

Table I

Example	IC_{50} uM	% inhibition at 25 uM
1	2.3	
2	--	34
3	--	22
4	29.5	--
5	26.6	--
6	34.8	--
7	--	6
8	4.83	--
9	--	40
10	--	59
11	--	30
12	--	40
13	--	36

Example 1

9-(4-Methylbenzyl)-6-[4-(trifluoromethoxy)phenyl]-1,9-dihydropyrano[3,4-*b*]-indole-3,4-dione

Step 1

Ethyl 5-bromo-1-(4-methylbenzyl)-1*H*-indole-2-carboxylate

NaH (60%, 3.88 g, 96.98 mmol) was added portionwise to a stirring solution of ethyl 5-bromo-1*H*-indole-2-carboxylate (20.0 g, 74.6 mmol) in DMF (140 mL) at 0°C under a nitrogen atmosphere over a period of 10 min. The mixture was then warmed to room temperature. After the reaction mixture was stirred at room temperature for one hour, 4-methylbenzyl bromide (14.2 g, 74.6 mmol) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with aqueous ammonium chloride and diluted with water. The aqueous mixture was extracted with ethyl acetate. The organic extract was washed with water and brine, dried over anhydrous magnesium sulfate. This mixture was concentrated to give a semi-solid contained 0.8 mole equivalent DMF. Mass spectrum (ESI, $[M+H]^+$) *m/z* 372. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 7.93 (d, 1H, *J* = 7.94 Hz), 7.55 (d, 1H, *J* = 9.01 Hz), 7.40 (dd, 1H, *J* = 8.85 and 1.98 Hz), 7.32 (s, 1H), 7.04 (d, 2H, *J* = 7.96 Hz), 6.90 (d, 2H, *J* = 7.94 Hz), 5.79 (s, 2H), 4.28 (q, 2H), 2.20 (s, 3H), and 1.28 ppm (t, 3H).

Step 2

Ethyl 1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indole-2-carboxylate

A mixture of ethyl 5-bromo-1-(4-methylbenzyl)-1*H*-indole-2-carboxylate (5.8 g, 15.54 mmol), 4-(trifluoromethoxy)phenylboronic acid (8.2 g, 38.85 mmol), potassium carbonate (5.4 g, 38.85 mmol), [1'1'-bis(diphenylphosphino)-ferrocene]dichloro-palladium (II) complex with methylene (1:1) (4.41 g, 5.44 mmol) in dioxane-water (10:1, 154 mL) was stirred at 70°C for two days. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with water and brine, and then concentrated to an oil. This residue was crystallized from

ethyl ether to afford the title compound as an off-white solid, m.p. 77-78°C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 454. ^{1}H NMR (400 *MHz*, DMSO-*d*6) δ 8.00 (s, 1H), 7.78 (d, 2H, *J* = 8.70 Hz), 7.67 (d, 1H, *J* = 8.85 Hz), 7.61 (dd, 1H, *J* = 8.70 and 1.68 Hz), 7.44 (s, 1H), 7.42-7.41 (m, 3H), 7.06 (d, 2H, *J* = 7.94 Hz), 6.94 (d, 2H, *J* = 8.09 Hz), 5.83 (s, 2H), 4.29 (q, 2H), 2.21 (s, 3H), and 1.30 ppm (t, 3H).

Elemental Analysis for $C_{26}H_{22}F_3NO_3$:

Calculated: C, 68.87; H, 4.89; N, 3.09.

Found: C, 69.00; H, 4.66; N, 3.06.

Step 3

{1-(4-Methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methanol

Lithium aluminum hydride (0.244 g, 6.1 mmol) was added portionwise to a stirring solution of ethyl 1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indole-2-carboxylate (2.0 g, 4.4 mmol) in ethyl ether (17 mL) at 0°C under a nitrogen atmosphere over a period of 5 minutes. The mixture was then warmed up to room temperature. After the reaction mixture was stirred at room temperature for 5 hours, the reaction was carefully quenched with water and filtered. The filtrate was extracted with ethyl acetate. The organic extract was washed with water and brine, dried over anhydrous magnesium sulfate and evaporated to afford the title compound as a white solid (1.56 g, 86 %). Mass spectrum (ESI, $[M+H]^+$) *m/z* 412. ^{1}HNMR (400 *MHz*, DMSO-*d*6): δ 7.81 (s, 1H), 7.76 (d, 2H, *J* = 6.71 Hz), 7.45-7.35 (m, 4H), 7.08 (d, 2H, *J* = 7.74 Hz), 6.96 (d, 2H, *J* = 8.09 Hz), 6.50 (s, 1H), 5.44 (s, 2H), 5.35 (t, 1H), 4.60 (d, 2H), and 2.23 ppm (t, 3H).

Elemental Analysis for $C_{24}H_{20}F_3NO_2$:

Calculated: C, 70.07; H, 4.90; N, 3.40.

Found: C, 69.80; H, 4.75; N, 3.34.

Step 4

{1-(4-Methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methyl acetate

Acetyl chloride (0.222 mL, 3.08 mmol) was added to a stirring solution of {1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methanol (0.507 g, 1.23

mmol) and N,N-diisopropylethylamine (0.547 mL, 3.08 mmol) in methylene chloride (8 mL) at 0 °C under a nitrogen atmosphere over a period of 5 minutes. After the reaction mixture was stirred at room temperature overnight, the reaction was quenched carefully with water. The aqueous mixture was extracted with ethyl acetate. The organic extract was washed with water and brine, dried over anhydrous magnesium sulfate and evaporated to afford the title compound as a solid (0.557 g, 99.6 %), mp: 125-126 °C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 454. ^{1}HNMR (400 *MHz*, DMSO-*d*$_6$): δ 7.86 (s, 1H), 8.77 (d, 2H, *J* = 8.96 Hz), 7.48-7.40 (m, 4H), 7.09 (d, 2H, *J* = 7.94 Hz), 6.90 (d, 2H, *J* = 7.94 Hz), 6.70 (s, 1H), 5.44 (s, 2H), 5.23 (s, 2H), 2.23 (s, 3H), and 1.85 ppm (s, 3H).

Elemental Analysis for $C_{26}H_{22}F_3NO_3$:

Calculated: C, 68.32; H, 4.94; N, 3.07.

Found: C, 67.96; H, 4.57; N, 2.96.

Step 5

{2-[(Acetyloxy)methyl]-1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1H-indol-3-yl}(oxo)acetic acid

Oxalyl chloride (1.05 mL) was added dropwise to a stirring solution of {1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methyl acetate (0.515 g) in THF (17 mL) at room temperature over a period of 5 minutes under a nitrogen atmosphere. After the reaction mixture was stirred at room temperature for 4 hours, the reaction was quenched carefully with water. The aqueous mixture was extracted with ethyl acetate. The extract was washed with water, and brine, dried over anhydrous magnesium sulfate, and concentrated to give the title compound as a light brown solid, mp: 79-80 °C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 524. ^{1}HNMR (400 *MHz*, DMSO-*d*$_6$): δ 14.50 (br s, 1H), 8.20 (s, 1H), 7.74 (d, 2H, *J* = 8.55 Hz), 7.70 (d, 1H, *J* = 8.69 Hz), 7.62 (d, 1H, *J* = 8.55 Hz), 7.47 (d, 2H, *J* = 8.25 Hz), 7.15 (d, 2H, *J* = 7,88 Hz), 6.99 (d, 2H, *J* = 7.78 Hz), 5.64 (s, 2H), 5.53 (s, 2H), 2.25 (s, 3H), and 1.83 ppm (s, 3 H).

Elemental Analysis for $C_{28}H_{22}F_3NO_6$:

Calculated: C, 64.00; H, 2.67; N, 2.67.

Found: C, 63.77; H, 3.99; N, 2.65.

Step 6

{2-(Hydroxymethyl)-1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-3-yl}(oxo)acetic acid, potassium salt

A solution of {2-[(acetyloxy)methyl]-1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-3-yl}(oxo)acetic acid (0.50 g, 0.96 mmol) and aqueous potassium hydroxide (1.0 N, 2.38 mL, 2.38 mmol) in THF : water (1 : 1, 16 mL) was stirred at room temperature for 4 h. The reaction mixture was evaporated to dryness. The residual solid was stirred in water : hexane (8 : 92, 100 mL) and filtered to give the title compound as a white solid (0.4 g), mp: 248-249.5 °C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 482. ^{1}HNMR (400 *MHz*, DMSO-*d6*): δ 8.51 (s, 1H), 7.73 (d, 2H, *J* = 8.86 Hz), 7.50 (d, 1H, *J* = 8.56 Hz), 7.45 (d, 1H, *J* = 8.55 Hz), 7.43 (d, 2H, *J* = 7.94 Hz), 7.09 (d, 2H, *J* = 8.09 Hz), 7.05 (d, 2H, *J* = 8.09 Hz), 5.74 (t, 1H), 5.55 (s, 2H), 4.80 (d, 2H, *J* = 6.80 Hz), and 2.23 ppm (s, 3 H).

Elemental Analysis for $C_{26}H_{20}F_3NO_5 \cdot 1.0\ K \cdot 0.8\ H_2O$:

Calculated: C, 58.27; H, 3.87; N, 2.61.

Found: C, 58.14; H, 3.82; N, 2.59.

Step 7

9-(4-Methylbenzyl)-6-[4-(trifluoromethoxy)phenyl]-1,9-dihydropyrano[3,4-*b*]-indole-3,4-dione

{2-(Hydroxymethyl)-1-(4-methylbenzyl)-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-3-yl}-(oxo) acetic acid, potassium salt (0.355 g) was partitioned between methylene chloride (400 mL) and 15 % aqueous HCl (100 mL) with stirring. The organic layer was separated, washed with water and evaporated to afford the title compound as an off-white solid (0.304 g), mp: 243-244°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 464. ^{1}HNMR (400 *MHz*, DMSO-*d6*): δ 8.23 (s, 1H), 7.81 (d, 2H, *J* = 7.49 Hz), 7.77 (d, 1H, *J* = 8.40 Hz), 7.67 (d, 1H, *J* = 8.71 Hz), 7.46 (d, 2H, *J* = 7.94 Hz), 7.16 (s, 4H,), 5.92 (s, 2H), 5.50 (s, 2H), and 2.25 ppm (s, 3H).

Elemental Analysis for $C_{26}H_{18}F_3NO_4$:

Calculated: C, 67.10; H, 3.90; N, 3.01.

Found: C, 66.82; H, 3.71; N, 2.91.

Example 2

9-Benzyl-6-[4-(trifluoromethoxy)phenyl]-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

Ethyl 5-bromo-1-benzyl-1*H*-indole-2-carboxylate

The title compound was prepared from ethyl 5-bromo-1*H*-indole-2-carboxylate and benzyl bromide in substantially the same manner, as described in step 1 of Example 1. The product was obtained as a light yellow solid. Mass spectrum (ESI, $[M+H]^+$) *m/z* 358. ^1H NMR (300 *MHz*, DMSO-*d6*) δ 7.94 (s, 1H), 7.55 (d, 1H, *J* = 9.01 Hz), 7.42 (d, 1H, *J* = 8.85 Hz), 7.34 (s, 1H), 7.30-7.21 (m, 3H), 6.99 (d, 2H, *J* = 7.94 Hz), 5.85 (s, 2H), 4.28 (q, 2H), and 1.28 ppm (t, 3H).

Elemental Analysis for $C_{18}H_{16}BrNO_2$:
Calculated: C, 60.35; H, 4.50; N, 3.91.
Found: C, 69.19; H, 4.51; N, 3.75.

Step 2

Ethyl 1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indole-2-carboxylate

The title compound was prepared from ethyl 5-bromo-1-benzyl-1*H*-indole-2-carboxylate and 4-(trifluoromethoxy)phenylboronic acid in substantially the same manner, as described in step 2 of Example 1. The product was obtained as an oil. Mass spectrum (ESI, $[M+H]^+$) *m/z* 440. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 8.01 (s, 1H), 7.79 (d, 2H, *J* = 8.86 Hz), 7.67 (d, 1H, *J* = 8.85 Hz), 7.62 (dd, 1H, *J* = 8.70 and 1.68 Hz), 7.44-7.42 (m, 2H), 7.28-7.20 (m, 3H), 7.04 (d, 2H, *J* = 7.94 Hz), 5.88 (s, 2H), 4.28 (q, 2H), 1.29 (t, 3H).

Step 3

{1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methanol

The title compound was prepared from ethyl 1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indole-2-carboxylate (step 3 of Example 1) and lithium aluminum in substantially

the same manner, as described in step 1 of Example 21. The product was obtained as a white solid, mp: 108-109 °C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 398. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 7.82 (s, 1H), 7.76 (d, 2H, *J* = 8.86 Hz), 7.42-7.36 (m, 4H), 7.29 (d, 1H, *J* = 7.03 Hz), 7.27 (d, 1H, *J* = 7.63 Hz), 7.23-7.20 (m, 1H), 7.06 (d, 2H, *J* = 7.03 Hz), 6.52 (s, 1H), 5.50 (s, 2H), 5.36 (t, 1H), and 4.60 ppm (d, 2H).

Elemental Analysis for $C_{23}H_{18}F_3NO_2$:

Calculated: C, 69.52; H, 4.57; N, 3.52.

Found: C, 69.21; H, 4.38; N, 3.40.

Step 4

{1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methyl acetate

The title compound was prepared from {1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methanol and acetyl chloride in substantially the same manner, as described in step 4 of Example 1. The product was obtained as an oil. Mass spectrum (ESI, $[M+H]^+$) *m/z* 440. ^{1}H NMR (300 *MHz*, DMSO-*d6*) δ 7.88 (s, 1H), 7.77 (d, 2H, *J* = 8.87 Hz), 7.48-7.40 (m, 4H), 7.29-7.22 (m, 3H), 7.00 (d, 2H, *J* = 7.01 Hz), 6.72 (s, 1H), 5.50 (s, 2H), 5.24 (s, 2H), and 1.80 ppm (s, 3H).

Elemental Analysis for $C_{25}H_{20}F_3NO_3$:

Calculated: C, 68.33; H, 4.59; N, 3.19.

Found: C, 68.19; H, 4.70; N, 3.06.

Step 5

{2-[(Acetyloxy)methyl]-1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-3-yl}-(oxo)acetic acid

The title compound was prepared from {1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-2-yl}methyl acetate and oxalyl chloride in substantially the same manner, as described in step 5 of Example 1. The product was obtained as a brown solid; mp: 85-86 °C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 510. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 14.40 (br s, 1H), 8.20 (s, 1H), 7.76 (d, 2H, *J* = 6.72 Hz), 7.72 (d, 1H, *J* = 8.70 Hz), 7.63 (d, 1H, *J* = 8.70 Hz), 7.48 (d, 2H, *J* = 8.24 Hz), 7.34-7.25(m, 3H), 7.08(d, 1H, *J* = 7.23 Hz), 5.70 (s, 2H), 5.53 (s, 2H), and 1.78 ppm (s, 3 H).

Elemental Analysis for $C_{27}H_{20}F_3NO_6$:
Calculated: C, 63.41; H, 3.94; N, 2.74.
Found: C, 63.02; H, 3.97; N, 2.64.

Step 6

{2-(Hydroxymethyl)-1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-3-yl}-(oxo)acetic acid, potassium salt

The title compound was prepared from {2-[(acetyloxy)methyl]-1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-3-yl}(oxo)acetic acid and aqueous potassium hydroxide in substantially the same manner, as described in step 6 of Example 1. The product was obtained as a white solid; mp: 280-282°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 468. ^1H NMR (400 *MHz*, DMSO-d_6) δ 8.51 (s, 1H), 7.72 (d, 2H, *J* = 8.70 Hz), 7.52 (d, 1H, *J* = 8.55 Hz), 7.47-7.43 (m, 3H), 7.31-28 (m, 2H), 7.23 (d, 1H, *J* = 7.18 Hz), 7.15 (d, 2H, *J* = 7.18 Hz), 5.75 (t, 1H), 5.62 (s, 2H), and 4.81 ppm (d, 2H, *J* = 6.72 Hz).
Elemental Analysis for $C_{25}H_{18}F_3NO_5 \cdot 1.0\ K \cdot 1.0\ H_2O$:
Calculated: C, 57.14; H, 3.64; N, 2.67.
Found: C, 57.05; H, 3.42; N, 2.55.

Step 7

9-Benzyl-6-[4-(trifluoromethoxy)phenyl]-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from {2-(Hydroxymethyl)-1-benzyl-5-[4-(trifluoromethoxy)phenyl]-1*H*-indol-3-yl}(oxo)acetic acid, potassium salt and aqueous HCl in substantially the same manner, as described in step 7 of Example 1. The product was obtained as an off-white solid; mp: 239-240°C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 452. ^1H NMR (400 *MHz*, DMSO-d_6) δ 8.24 (s, 1H), 7.81 (dd, 2H, *J* = 8.86 and 2.14 Hz), 7.74 (d, 1H, *J* = 8.56 Hz), 7.68 (dd, 1H, *J* = 8.54 and 1.83 Hz), 7.46 (d, 2H, *J* = 7.94 Hz), 7.37-7.26 (m, 5H,), 5.93 (s, 2H), and 5.56 ppm (s, 2H).
Elemental Analysis for $C_{25}H_{16}F_3NO_4$:
Calculated: C, 66.52; H, 3.57; N, 3.10.
Found: C, 66.59; H, 3.50; N, 3.04.

Example 3

9-(4-Methylbenzyl)-6-(3-methylphenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

Ethyl 1-(4-methylbenzyl)-5-(3-methylphenyl)-1*H*-indole-2-carboxylate

The title compound was prepared from ethyl 5-bromo-1-(4-methylbenzyl)-1*H*-indole-2-carboxylate (step 1 of Example 1) and 3-methylphenylboronic acid in substantially the same manner, as described in step 2 of Example 1. The product was obtained as a solid. Mass spectrum (ESI, $[M+H]^+$) *m/z* 384. ^{1}H NMR (400 *MHz*, DMSO-d_6) δ 7.95 (s, 1H), 7.63 (d, 1H, *J* = 7.70 Hz), 7.60 (d, 1H, *J* = 8.47 Hz), 7.48 (s, 1H), 7.44 (d, 1H, *J* = 7.95 Hz), 7.39 (s, 1H), 7.33 (t, 1H, *J* = 7.63 Hz), 7.14 (d, 1H, *J* = 7.49 Hz), 7.07 (d, 2H, *J* = 7.94 Hz), 6.93 (d, 2H, *J* = 7.94 Hz), 5.82 (s, 2H), 4.29 (q, 2H, *J* = 7.17 Hz), 2.37 (s, 3H), 2.21 (s, 3H), and 1.30 ppm (t, 3H, *J* = 7.18 Hz).

Step 2

[1-(4-Methylbenzyl)-5-(3-methylphenyl)-1*H*-indol-2-yl]methanol

The title compound was prepared from ethyl 1-(4-methylbenzyl)-5-(3-methylphenyl)-1*H*-indole-2-carboxylate and lithium aluminum in substantially the same manner, as described in step 3 of Example 1. The product was obtained as a white solid. Mass spectrum (ESI, $[M+H]^+$) *m/z* 342. ^{1}H NMR (400 *MHz*, DMSO-d_6) δ 7.77 (s, 1H), 7.46 (s, 1H), 7.42 (d, 1H, *J* = 7.79 Hz), 7.37 (d, 1H, *J* = 8.55 Hz), 7.33 (d, 1H, *J* = 8.56 Hz), 7.31 (d, 1H, *J* = 7.02 Hz), 7.29 (d, 1H, *J* = 7.48 Hz), 7.10-7.07 (m, 4H), 6.96 (d, 2H, *J* = 7.94 Hz), 6.48 (s, 1H), 5.54 (s, 2H), 5.33 (s, 1H), 4.60 (s, 2H), 2.36 (s, 3H), and 2.23 ppm (s, 3H).

Elemental Analysis for $C_{24}H_{23}NO \cdot 0.5\ H_2O$:

Calculated: C, 82.25; H, 6.90; N, 4.00.

Found: C, 82.05; H, 6.98; N, 3.88.

Step 3

[1-(4-Methylbenzyl)-5-(3-methylphenyl)-1*H*-indol-2-yl]methyl acetate

The title compound was prepared from [1-(4-methylbenzyl)-5-(3-methylphenyl)-1*H*-indol-2-yl]methanol and acetyl chloride in substantially the same manner, as

described in step 4 of Example 1. The product was obtained as a brown oil. Mass spectrum (ESI, $[M+H]^+$) *m/z* 384. ^1H NMR (400 *MHz*, DMSO-d_6) δ 7.82 (s, 1H), 7.47 (s, 1H), 7.45-7.40 (m, 3H), 7.31 (t, 1H, *J* = 7.74 Hz), 7.13-7.08 (m, 3H), 6.90 (d, 2H, *J* = 8.09 Hz), 6.68 (s, 1H), 5.43 (s, 2H), 5.22 (s, 2H), 2.36 (s, 3H), 2.23 (s, 3H), and 1.85 ppm (s, 3H).

Elemental Analysis for $C_{26}H_{25}NO_2$:

Calculated: C, 81.43; H, 6.57; N, 3.65.

Found: C, 81.75; H, 6.67; N, 3.26.

Step 4

[2-[(Acetyloxy)methyl]-1-(4-methylbenzyl)-5-(3-methylphenyl)-1*H*-indol-3-yl]-(oxo)acetic acid

The title compound was prepared from [1-(4-methylbenzyl)-5-(3-methylphenyl)-1*H*-indol-2-yl]methyl acetate and oxalyl chloride in substantially the same manner, as described in step 5 of Example 1. The product was obtained as a brown solid; mp: 89-90°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 454. ^1H NMR (400 *MHz*, DMSO-d_6) δ 8.18 (s, 1H), 7.67 (d, 1H, *J* = 8.69 Hz), 7.59 (dd, 1H, *J* = 7.17 and 1.53 Hz), 7.44-7.41 (m, 2H),), 7.36 (t, 1H, *J* = 7.48 Hz), 7.18 (d, 1H, *J* = 7.23 Hz), 7.13 (d, 1H, *J* = 7.94 Hz), 5.63 (s, 2H), 5.53 (s, 2H), 2.39 (s, 3H), 2.24 (s, 3H), and 1.83 ppm (s, 3H).

Elemental Analysis for $C_{28}H_{25}NO_5 \cdot 0.5\ H_2O$:

Calculated: C, 72.40; H, 5.64; N, 3.02.

Found: C, 72.41; H, 5.44; N, 2.96.

Step 5

9-(4-Methylbenzyl)-6-(3-methylphenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from [2-[(acetyloxy)methyl]-1-(4-methylbenzyl)-5-(3-methylphenyl)-1*H*-indol-3-yl](oxo)acetic acid and aqueous potassium hydroxide in substantially the same manner, as described in step 6 of Example 1 followed by the treatment with aqueous HCl in substantially the same manner, as described in step 7 of Example 1. The product was obtained as a white solid; mp: 216-217°C. Mass

spectrum (ESI, $[M+H]^+$) *m/z* 396. ^1H NMR (400 *MHz*, DMSO-d_6) δ 8.21 (s, 1H), 7.71 (d, 1H, *J* = 8.56 Hz), 7.64 (dd, 1H, *J* = 8.75 and 1.28 Hz), 7.49 (s, 1H), 7.46 (d, 1H, *J* = 8.09 Hz), 7.36 (t, 1H, *J* = 7.63 Hz), 7.19-7.14 (m, 5H,), 5.91 (s, 2H), and 5.49 (s, 2H), 2.39 (s, 3H), 2.26 ppm (s, 3H),

Elemental Analysis for $C_{26}H_{21}NO_3 \cdot 0.4\ H_2O$:
Calculated: C, 77.56; H, 5.46; N, 3.48.
Found: C, 77.41; H, 5.46; N, 3.49.

Example 4

9-(4-*tert*-butylbenzyl)-6-(3-methylphenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

(5-Bromo-1*H*-indol-2-yl)methanol

The title compound was prepared from ethyl 5-bromo-1*H*-indole-2-carboxylate and lithium aluminum in substantially the same manner, as described in step 3 of Example 1. The product was obtained as a solid; mp: 111-112°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 224. ^1H NMR (400 *MHz*, DMSO-d_6) δ 7.62 (s, 1H), 7.27 (d, 1H, *J* = 8.02 Hz), 7.12 (d, 1H, *J* = 8.02 Hz), 6.25 (s, 1H), 5.29 (t, 1H, *J* = 5.50 Hz), 4.59 ppm (d, 2H, *J* = 5.65 Hz).

Elemental Analysis for C_9H_8BrNO:
Calculated: C, 47.82; H, 3.57; N, 6.20.
Found: C, 47.94; H, 3.42; N, 6.20.

Step 2

[5-(3-Methylphenyl)-1*H*-indol-2-yl]methyl acetate

A mixture of (5-bromo-1*H*-indol-2-yl) methanol (9 g, 39.8 mmol), 3-methylbenzeneboronic acid (6.14 g, 43.78 mmol), potassium carbonate (13.75 g, 99.5 mmol), palladium(II) acetate (0.045 g) and tetrabutylammonium bromide (12.84 g, 39.8 mmol) in 10 % dioxane in water (degassed, 0.38 L) was stirred at 70 °C. The reaction was monitored by TLC. Additional 3-methylbenzeneboronic acid (5.6 g, 39.8

mmol) was added. After no 5-bromo-1-(4-tert-butylbenzyl)-1*H*-indole was detected by TLC, the reaction was cooled to room temperature and the solvent was decanted. The residual thick oil was stirred with hexane. The hexane was decanted and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was separated, washed with water filtered and concentrated. The residue was purified by flash column chromatography using hexane/ethyl acetate (55 : 45) as an eluant to give [5-(3-Methylphenyl)-1*H*-indol-2-yl]methanol as a brown solid (6.0 g). Reaction of [5-(3-Methylphenyl)-1*H*-indol-2-yl]methanol with acetyl chloride according to the procedure described in step 4 of Example 1 afforded the title compound as an oil (3.94 g); Mass spectrum (ESI, $[M-H]^-$) *m/z* 278. ^{1}H NMR (400 *MHz*, DMSO-d_6) δ 7.76 (s, 1H), 7.46 (s, 1H), 7.42-7.36 (m, 3H), 7.30 (s, 1H), 7.10 (d, 1H, *J* = 7.48 Hz), 6.50 (s, 1H), 2.37 (s, 3H), and 2.07 ppm (s, 3H).

Step 3

[1-(4-*tert*-Butylbenzyl)-5-(3-methylphenyl)-1*H*-indol-2-yl]methyl acetate

Potassium carbonate (0.3 g, 2.15 mmol) was added to a stirring solution of 5-(3-methylphenyl)-1*H*-indol-2-yl]methyl acetate (0.5 g, 1.79 mmol) in DMF (5 mL) at room temperature under a nitrogen atmosphere. 4-*tert*-Butylbenzyl bromide (0.356 g, 1.88 mmol) was added and the mixture was stirred at room temperature overnight. The reaction was monitored by TLC. An additional amount of 4-*tert*-butylbenzyl bromide (0.34 g, 1.8 mmol) was added and stirring continued at room temperature for three days. The reaction was quenched with aqueous ammonium chloride, diluted with water and extracted with ethyl acetate. The organic extract was washed with water and brine, dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was purified by flash column chromatography using hexane/ethyl acetate (85:15) as an eluant to give the title compound as a light brown oil (0.284 g). Mass spectrum (ESI, $[M+H]^+$) *m/z* 426. ^{1}H NMR (400 *MHz*, DMSO-d_6) δ 7.83 (s, 1H), 7.49-7.47 (m, 2H), 7.44-7.41 (m, 2H), 7.32-7.29 (m, 3H), 7.11 (d, 1H, *J* = 7.49 Hz), 6.91 (d, 2H, *J* = 8.24 Hz), 6.69 (s, 1H), 5.44 (s, 2H), 5.23 (s, 2H), 2.36 (s, 3H), 1.78 (s, 3H), and 1.21 ppm (s, 9H).

Elemental Analysis for $C_{29}H_{31}NO_2 \cdot 0.3\ H_2O$:

Found: C, 80.82; H, 7.39; N, 3.25.

Calculated: C, 80.90; H, 7.45; N, 3.17.

Step 4

[2-[(Acetyloxy)methyl]-1-(4-*tert*-butylbenzyl)-5-(3-methylphenyl)-1*H*-indol-3-yl]-(oxo)acetic acid

The title compound was prepared from [1-(4-*tert*-butylbenzyl)-5-(3-methylphenyl)-1*H*-indol-2-yl]methyl acetate and oxalyl chloride in substantially the same manner, as described in step 5 of Example 1. The product was obtained as a light brown solid; mp: 91-92°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 496. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 8.18 (s, 1H), 7.72 (d, 2H, *J* = 8.71 Hz), 7.61 (dd, 1H, *J* = 8.70 and 1.38 Hz), 7.45-7.41 (m, 2H), 7.38-7.33 (m, 3H), 7.18 (d, 1H, *J* = 8.70 Hz), 7.00 (d, 2H, *J* = 8.24 Hz), 5.64 (s, 2H), 5.53 (s, 2H), 2.39 (s, 3H), 1.76 (s, 3H), and 1.22 ppm (s, 9H).
Elemental Analysis for $C_{31}H_{31}NO_5 \cdot 0.5\ H_2O$:
Calculated: C, 73.50; H, 6.37; N, 2.77.
Found: C, 73.43; H, 6.57; N, 2.64.

Step 5

9-(4-*tert*-Butylbenzyl)-6-(3-methylphenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

A solution of [2-[(acetyloxy)methyl]-1-(4-*tert*-butylbenzyl)-5-(3-methylphenyl)-1*H*-indol-3-yl](oxo)acetic acid (0.27 g, 0.63 mmol) and aqueous potassium hydroxide (1.0 N, 1.1 mL, 1.1 mmol) in THF:MeOH (1:1, 6.6 mL) was stirred at room temperature for 4 h. The reaction mixture was evaporated to dryness. The residue was washed with water and hexane to give an oil. This oil was partitioned between methylene chloride (80 mL) and 15 % aqueous HCl (15 mL) with stirring. The organic layer was separated, washed with water and evaporated to afford the title compound as an off-white solid, mp: 196-197°C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 438. ^{1}HNMR (400 *MHz*, DMSO-*d6*): δ 8.21 (s, 1H), 7.75 (d, 2H, *J* = 8.55 Hz), 7.66 (dd, 1H, *J* = 8.70 and 1.52 Hz), 7.50 (s, 1H), 7.47 (d, 1H, *J* = 8.71 Hz), 7.38-7.35 (m, 3H), 7.20-7.17 (m, 3H), 5.92 (s, 2H), 5.50 (s, 2H), and 2.39 ppm (s, 3H).
Elemental Analysis for $C_{29}H_{27}NO_3 \cdot 0.5\ H_2O$:
Calculated: C, 78.64; H, 6.28; N, 3.16.
Found: C, 78.54; H, 6.46; N, 3.04

Example 5

6-(Benzyloxy)-9-(4-methylbenzyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

[5-(Benzyloxy)-1*H*-indol-2-yl]methanol

The title compound was prepared from ethyl 5-(benzyloxy)-1*H*-indole-2-carboxylate and lithium aluminum hydride according to the procedure described in step 3 of Example 1. The product was obtained as a white solid, mp: 106-107°C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 254. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 10.80 (s, 1H), 7.45 (d, 2H, *J* = 7.33 Hz), 7.37 (t, 2H, *J* = 7.49 Hz), 7.30 (d, 1H, *J* = 7.18 Hz), 7.20 (d, 1H, *J* = 8.71 Hz), 7.04 (s, 1H), 6.74 (dd, 1H, *J* = 8.70 and 1.46 Hz), 6.16 (s, 1H), 5.16 (t, 1H, *J* = 5.49 Hz), 5.01 (s, 2H), 4.55 ppm (d, 2H, *J* = 5.50 Hz).

Elemental Analysis for $C_{16}H_{15}NO_2$:

Calculated: C, 75.87; H, 5.97; N, 5.53.

Found: C, 75.96; H, 6.11; N, 5.41.

Step 2

[5-(Benzyloxy)-1*H*-indol-2-yl]methyl acetate

The title compound was prepared from [5-(benzyloxy)-1*H*-indol-2-yl]methanol and acetyl chloride in substantially the same manner, as described in step 4 of Example 1. The product was obtained as a gray solid. Mass spectrum (ESI, $[M+H]^+$) *m/z* 296. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 11.03 (s, 1H), 7.45 (d, 2H, *J* = 7.33 Hz), 7.38 (t, 2H, *J* = 7.49 Hz), 7.30 (d, 1H, *J* = 7.20 Hz), 7.24 (d, 1H, *J* = 8.71 Hz), 7.08 (s, 1H), 6.81 (dd, 1H, *J* = 8.70 and 1.45 Hz), 6.34 (s, 1H), 5.13 (s, 2H), 5.06 (s, 2H), 2.04 ppm (s, 3H).

Elemental Analysis for $C_{18}H_{17}NO_3 \cdot 0.2\ H_2O$:

Calculated: C, 72.32; H, 5.87; N, 4.69.

Found: C, 72.21; H, 5.75; N, 4.66.

Step 3

[5-(Benzyloxy)-1-(4-methylbenzyl)-1*H*-indol-2-yl]methyl acetate

The title compound was prepared from [5-(benzyloxy)-1*H*-indol-2-yl]methyl acetate and 4-methylbenzyl bromide in substantially the same manner, as described in step 3 of Example 4. The product was obtained as a white solid. Mass spectrum (ESI, $[M+H]^+$) *m/z* 400. ^{1}H NMR (300 *MHz*, DMSO-*d6*) δ 7.45 (d, 2H, *J* = 8.34 Hz), 7.37 (t, 2H, *J* = 7.19 Hz), 7.31 (d, 1H, *J* = 7.30 Hz), 7.26 (d, 1H, *J* = 7.56 Hz), 7.15 (d, 1H, *J* = 2.44 Hz), 7.07 (d, 2H, *J* = 8.76 Hz), 6.85 (d, 2H, *J* = 8.81 Hz), 6.84 (s, 1H), 6.25 (s, 1H), 5.35 (s, 2H), 5.17 (s, 2H), 5.09 (s, 2H), 2.22 (s, 3H), 1.84 ppm (s, 3H).
Elemental Analysis for $C_{26}H_{25}NO_3$:
Calculated: C, 78.17; H, 6.31; N, 3.51.
Found: C, 78.01; H, 6.35; N, 3.46.

Step 4

[2-[(Acetyloxy)methyl]-5-(benzyloxy)-1-(4-methylbenzyl)-1*H*-indol-3-yl](oxo)-acetic acid

The title compound was prepared from [5-(benzyloxy)-1-(4-methylbenzyl)-1*H*-indol-2-yl]methyl acetate and oxalyl chloride in substantially the same manner, as described in step 5 of Example 1. The product was obtained as an off-white solid; mp: 91-92°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 470. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 7.61 (s, 1H), 7.50 (s, 1H), 7.47 (d, 2H, *J* = 8.24 Hz), 7.39 (t, 2H, *J* = 7.64 Hz), 7.32 (d, 1H, *J* = 7.02 Hz), 7.11 (d, 2H, *J* = 8.10 Hz),), 7.03 (d, 1H, *J* = 8.99 Hz), 6.95 (d, 2H, *J* = 7.79 Hz), 5.54 (s, 2H), 5.46 (s, 2H), 5.10 (s, 2H), 2.23 (s, 3H), 1.82 ppm (s, 3H).
Elemental Analysis for $C_{28}H_{25}NO_6 \cdot 0.6\ H_2O$:
Calculated: C, 69.73; H, 5.48; N, 2.90.
Found: C, 69.60; H, 5.30; N, 2.80.

Step 5

6-(Benzyloxy)-9-(4-methylbenzyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from [2-[(acetyloxy)methyl]-5-(benzyloxy)-1-(4-methylbenzyl)-1*H*-indol-3-yl](oxo)acetic acid and aqueous potassium hydroxide according to the procedure described in step 6 of Example 1, followed by the treatment with aqueous HCl in substantially the same manner, as described in step 7 of Example 1. The product was obtained as an off-white solid; mp: 206-207°C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 412. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 7.58 (s, 1H), 7.54 (d, 1H, *J* = 9.01 Hz), 7.47 (d, 2H, *J* = 7.33 Hz), 7.38 (t, 2H, *J* = 8.63 Hz), 7.31 (t, 1H, *J* = 7.18 Hz), 7.15-7.11 (m, 4H,), 7.05 (dd, 2H, *J* = 9.44 and 2.44 Hz), 5.86 (s, 2H), 5.41 (s, 2H), 5.16 (s, 2H), 2.25 ppm (s, 3H).

Elemental Analysis for $C_{26}H_{21}NO_4 \cdot 0.8\ H_2O$:

Calculated: C, 73.33; H, 5.35; N, 3.29.

Found: C, 73.16; H, 4.95; N, 3.20.

Example 6

6-(Benzyloxy)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

[2-[(Acetyloxy)methyl]-5-(benzyloxy)-1*H*-indol-3-yl](oxo)acetic acid

The title compound was prepared from [5-(benzyloxy)-1*H*-indol-2-yl]methyl acetate (step 2 of Example 5) and oxalyl chloride following the procedure described in step 5 of Example 1. The product was obtained as a brown solid; mp: > 165°C (dec.). Mass spectrum (ESI, $[M-H]^-$) *m/z* 366. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 12.42 (s, 1H), 7.51 (s, 1H), 7.48 (d, 2H, *J* = 7.33 Hz), 7.43 (d, 1H, *J* = 8.85 Hz), 7.39 (t, 2H, *J* = 7.33 Hz), 7.32 (d, 1H, *J* = 7.17 Hz), 6.99 (d, 1H, *J* = 7.86 Hz), 5.41 (s, 2H), 5.10 (s, 2H), 2.13 ppm (d, 3H).

Elemental Analysis for $C_{20}H_{17}NO_6$:

Calculated: C, 65.39; H, 4.66; N, 3.81.

Found: C, 65.37; H, 4.68; N, 3.83.

Step 2

6-(Benzyloxy)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from [2-[(acetyloxy)methyl]-5-(benzyloxy)-1*H*-indol-3-yl](oxo)acetic acid and aqueous potassium hydroxide in substantially the same manner, as described in step 6 of Example 1, followed by the treatment with aqueous HCl, as described in step 7 of Example 1. The product was obtained as a yellow solid; mp: > 291°C (dec.). Mass spectrum (ESI, $[M-H]^-$) *m/z* 306. ^1H NMR (400 *MHz*, DMSO-d_6) δ 12.37 (s, 1H), 7.54 (s, 1H), 7.49 (s, 1H), 7.48 (d, 2H, *J* = 8.86 Hz), 7.39 (t, 2H, *J* = 7.64 Hz), 7.32 (d, 1H, *J* = 7.18 Hz), 7.04 (dd, 1H, *J* = 8.71 and 2.59 Hz), 5.82 (s, 2H), and 5.16 ppm (s, 2H).

Elemental Analysis for $C_{18}H_{13}NO_4$:

Calculated: C, 70.35; H, 4.26; N, 4.56.

Found: C, 70.07; H, 4.17; N, 4.49.

Example 7

6-(Benzyloxy)-9-(4-*tert*-butylbenzyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

[5-(Benzyloxy)-1-(4-*tert*-butylbenzyl)-1*H*-indol-2-yl]methyl acetate

The title compound was prepared from [5-(benzyloxy)-1*H*-indol-2-yl]methyl acetate and 4-*tert*-butylbenzyl bromide in substantially the same manner, as described in step 3 of Example 4. The product was obtained as a white solid; mp: 132-133°C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 442. ^1H NMR (400 *MHz*, DMSO-d_6) δ 7.45 (d, 2H, *J* = 7.33 Hz), 7.38 (t, 2H, *J* = 7.33 Hz), 7.32-7.27 (m, 4H), 7.16 (d, 1H, *J* = 2.30 Hz), 6.88-6.84 (m, 3H), 6.53 (s, 1H), 5.36 (s, 2H), 5.18 (s, 2H), 5.08 (s, 2H), 1.77 (s, 3H), and 1.21 ppm (s, 9H).

Elemental Analysis for $C_{29}H_{31}NO_3$:

Calculated: C, 78.88; H, 7.08; N, 3.17.

Found: C, 78.79; H, 7.07; N, 3.04.

Step 2

[2-[(Acetyloxy)methyl]-5-(benzyloxy)-1-(4-*tert*-butylbenzyl)-1*H*-indol-3-yl](oxo)-acetic acid

The title compound was prepared from [5-(Benzyloxy)-1-(4-*tert*-butylbenzyl)-1*H*-indol-2-yl]methyl acetate and oxalyl chloride in substantially the same manner, as described in step 5 of Example 1. The product was obtained as an off-white solid; mp: 145-146°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 512. ^{1}H NMR (400 *MHz*, DMSO-d_6) δ 7.61 (d, 1H, *J* = 2.14 Hz), 7.56 (d, 1H, *J* = 9.16 Hz), 7.48 (d, 2H, *J* = 7.18 Hz), 7.39 (t, 2H, *J* = 7.33 Hz), 7.33-7.31 (m, 4H) 7.05 (dd, 1H, *J* = 9.01 and 2.45 Hz), 6.96 (d, 1H, *J* = 8.25 Hz), 5.56 (s, 2H), 5.46 (s, 2H), 5.11 (s, 2H), 1.75 (s, 3H), and 1.21 ppm (s, 9H).

Elemental Analysis for $C_{31}H_{31}NO_6 \cdot 0.7\ H_2O$:

Calculated: C, 70.76; H, 6.21; N, 2.66.

Found: C, 70.76; H, 6.39; N, 2.64.

Step 3

6-(Benzyloxy)-9-(4-*tert*-butylbenzyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from [2-[(acetyloxy)methyl]-5-(benzyloxy)-1-(4-*tert*-butylbenzyl)-1*H*-indol-3-yl](oxo)acetic acid and aqueous potassium hydroxide in substantially the same manner, as described in step 6 of Example 1, followed by the treatment with aqueous HCl, as described in step 7 of Example 1. The product was obtained as an off-white solid; mp: 233-234 °C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 454. ^{1}H NMR (400 *MHz*, DMSO-d_6) δ 7.59-7.56 (m, 2H), 7.47 (d, 1H, *J* = 7.33 Hz), 7.39 (t, 2H, *J* = 7.33 Hz), 7.35-7.30 (m, 3H), 7.15 (d, 2H, *J* = 8.40 Hz), 7.07 (dd, 1H, *J* = 9.05 and 2.45 Hz), 5.87 (s, 2H), 5.42 (s, 2H), 5.16 (s, 2H), and 1.22 ppm (s, 9H).

Elemental Analysis for $C_{29}H_{27}NO_4$:

Calculated: C, 76.80; H, 6.00; N, 3.09.

Found: C, 76.55; H, 6.07; N, 2.98.

Example 8

9-(4-*tert*-Butylbenzyl)-6-hydroxy-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

Ethyl 1-(4-*tert*-butylbenzyl)-5-methoxy-1*H*-indole-2-carboxylate

The title compound was prepared from ethyl 5-methoxy-1*H*-indole-2-carboxylate and 4-(*tert*-butyl) benzyl bromide in substantially the same manner, as described in step 1 of Example 1. The product was obtained as a solid. Mass spectrum (ESI, $[M-H]^-$) *m/z* 364. ^1H NMR (400 *MHz*, DMSO-d_6) δ 7.48 (d, 1H, *J* = 9.20 Hz), 7.27 (s, 1H), 7.24 (d, 2H, *J* = 7.18 Hz), 7.16 (d, 1H, *J* = 2.44 Hz), 6.96-6.92 (m, 3H), 5.77 (s, 2H), 4.28 (q, 2H), 3.76 (s, 3H), 1.28 (s, 3H), and 1.20 ppm (s, 9H).

Elemental Analysis for $C_{23}H_{27}NO_3$:

Calculated: C, 75.59; H, 7.45; N, 3.83.

Found: C, 75.94; H, 7.67; N, 3.66.

Step 2

[1-(4-*tert*-Butylbenzyl)-5-methoxy-1*H*-indol-2-yl]methanol

The title compound was prepared from ethyl 1-(4-*tert*-butylbenzyl)-5-methoxy-1*H*-indole-2-carboxylate and lithium aluminum hydride in substantially the same manner, as described in step 3 of Example 1. The product was obtained as an oil. Mass spectrum (ESI, $[M-H]^-$) *m/z* 322. ^1H NMR (400 *MHz*, DMSO-d_6) δ 7.27 (d, 2H, *J* = 8.14 Hz), 7.20 (d, 1H, *J* = 8.70 Hz), 7.01 (d, 1H, *J* = 2.45 Hz), 6.94 (d, 2H, *J* = 8.24 Hz), 6.68 (dd, 1H, *J* = 8.85 and 2.44 Hz), 6.34 (s, 1H), 5.37 (s, 2H), 5.26 (t, 1H), 4.56 (d, 2H, *J* = 4.43 Hz), 3.72 (s, 3H), and 1.21 ppm (s, 9H).

Step 3

[1-(4-*tert*-Butylbenzyl)-5-methoxy-1*H*-indol-2-yl]methyl acetate

The title compound was prepared from [1-(4-*tert*-butylbenzyl)-5-methoxy-1*H*-indol-2-yl]methanol and acetyl chloride in substantially the same manner, as described in

step 4 of Example 1. The product was obtained as a white solid. Mass spectrum (ESI, $[M+H]^+$) *m/z* 366. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 7.30 (s, 1H), 7.28 (d, 2H, *J* = 8.10 Hz), 7.07 (d, 1H, *J* = 2.45 Hz), 7.86 (d, 2H, *J* = 8.24 Hz), 7.76 (dd, 1H, *J* = 8.86 and 2.29 Hz), 6.54 (s, 1H), 5.36 (s, 2H), 5.18 (s, 2H), 3.74 (s, 3H), 1.77 (s, 3H), and 1.20 ppm (s, 9H).

Elemental Analysis for $C_{23}H_{27}NO_3$:

Calculated: C, 75.59; H, 7.45; N, 3.83.

Found: C, 75.37; H, 7.65; N, 3.70.

Step 4

[2-[(Acetyloxy)methyl]-1-(4-*tert*-butylbenzyl)-5-methoxy-1*H*-indol-3-yl](oxo)-acetic acid

The title compound was prepared from [1-(4-*tert*-butylbenzyl)-5-methoxy-1*H*-indol-2-yl]methyl acetate and oxalyl chloride in substantially the same manner, as described in step 5 of Example 1. The product was obtained as a brown solid; mp: > 105°C (decomposed). Mass spectrum (ESI, $[M-H]^-$) *m/z* 436. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 7.54 (d, 1H, *J* = 8.10 Hz), 7.51 (d, 1H, *J* = 1.68 Hz), 7.32 (d, 2H, *J* = 8.25 Hz), 6.97-6.94 (m, 3H), 5.56 (s, 2H), 5.46 (s, 2H), 3.78 (s, 3H), 1.75 (s, 3H), and 1.21 ppm (s, 9H).

Elemental Analysis for $C_{25}H_{27}NO_6 \cdot 0.12\ H_2O$:

Calculated: C, 68.3; H, 6.25; N, 3.19.

Found: C, 69.00; H, 6.66; N, 2.99.

Step 5

9-(4-*tert*-Butylbenzyl)-6-methoxy-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from [2-[(acetyloxy)methyl]-1-(4-*tert*-butylbenzyl)-5-methoxy-1*H*-indol-3-yl](oxo)acetic acid and aqueous potassium hydroxide in substantially the same manner as described in step 6 of Example 1, followed by the treatment with aq HCl in substantially the same manner as described in step 7 of Example 1. The product was obtained as an off-white solid; mp: 238-239°C. Mass spectrum (ESI, $[M-H]^-$) *m/z* 376. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 7.56 (d, 1H, *J* =

9.01 Hz), 7.48 (d, 1H, *J* = 2.45 Hz), 7.35 (d, 2H, *J* = 8.40 Hz), 7.14 (d, 2H, *J* = 8.25 Hz), 6.98 (dd, 1H, *J* = 8.86 and 2.44 Hz), 5.87 (s, 2H), 5.42 (s, 2H), 3.81 (s, 3H), 1.22 ppm (s, 9H).

Elemental Analysis for $C_{23}H_{23}NO_4$:

Calculated: C, 73.19; H, 6.14; N, 3.71.

Found: C, 73.23; H, 6.11; N, 3.60.

Step 6

9-(4-*tert*-Butylbenzyl)-6-hydroxy-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Boron tribromide (2.2 mL, 23.3 mmol) was added dropwise to a stirring suspension of 9-(4-*tert*-Butylbenzyl)-6-methoxy-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione (4.92 g, 13.0 mmol) in methylene chloride (25 mL) at -78 °C under a nitrogen atmosphere over a period of 20 minutes. The mixture was then warmed up to room temperature. After stirring at room temperature for 6.5 hours, the reaction mixture was carefully quenched with a small amount of water and the evaporated to dryness. The residue was stirred in ether and filtered to afford a brown solid. Crystallization from aqueous methanol afforded the title compound as a brown solid (1.72 g). Mass spectrum (ESI, $[M-H]^-$) *m/z* 362. ^{1}HNMR (400 *MHz*, DMSO-*d6*): δ 9.39 (s, 1H), 7.44 (d, 1H, *J* = 8.85 Hz), 7.40 (d, 1H, *J* = 2.29 Hz), 7.34 (d, 2H, *J* = 8.25 Hz), 6.80 (dd, 1H, *J* = 8.86 and 2.29 Hz), 5.84 (s, 2H), 5.37 (s, 2H), 1.22 ppm (s, 9H).

Elemental Analysis for $C_{22}H_{21}NO_4 \cdot 0.7\ H_2O$:

Calculated: C, 70.27; H, 6.00; N, 3.73.

Found: C, 70.01; H, 5.62; N, 3.81.

Example 9

9-Benzyl-6-(4-chlorophenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

(1-Benzyl-5-bromo-1*H*-indol-2-yl)methanol

The title compound was prepared from ethyl 5-bromo-1-benzyl-1*H*-indole-2-carboxylate and lithium aluminum hydride in substantially the same manner, as described in step 3 of Example 1. The product was obtained as a semi-solid. Mass

spectrum (ESI, $[M-H]^-$) *m/z* 314. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 7.67 (s, 1H), 7.58-7.15 (m, 4H), 7.12 (d, 1H, *J* = 8.69 and 1.97 Hz), 6.98 (d, 2H, *J* = 8.34 Hz), 6.41 (s, 1H), 5.43 (s, 2H), 5.33 (t, 1H, *J* = 5.57 Hz), and 4.54 ppm (d, 2H, *J* = 5.43 Hz).

Step 2

(1-Benzyl-5-bromo-1*H*-indol-2-yl)methyl acetate

The title compound was prepared from (1-benzyl-5-bromo-1*H*-indol-2-yl)methanol and acetyl chloride in substantially the same manner, as described in step 4 of Example 1. The product was obtained as a semi-solid. Mass spectrum (ESI, $[M-H]^-$) *m/z* 356. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 7.78 (d, 1H, *J* = 2.13 Hz), 7.38 (d, 1H, *J* = 8.86 Hz), 7.29-7.20 (m, 4H), 6.94 (d, 2H, *J* = 7.17 Hz), 6.64 (s, 1H), 5.47 (s, 2H), 5.21 (s, 2H), and 1.79 ppm (s, 3H).

Step 3

[1-Benzyl-5-bromo-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt

Oxalyl chloride (30.2 mL) was added dropwise to a stirring solution of (1-benzyl-5-bromo-1*H*-indol-2-yl)methyl acetate (31.5 g, 88.0 mmol) in THF (890 mL) at room temperature over a period of 30 minutes under a nitrogen atmosphere. The reaction was monitored by TLC. More oxalyl chloride was added as needed. After the reaction completed, the reaction mixture was quenched carefully with water and extracted with ethyl acetate. The organic extracts were washed with water, and brine, dried over anhydrous magnesium sulfate, and evaporated to give a solid. This solid was treated with aqueous potassium hydroxide (2.0 N, 96.8 mL, 193.6 mmol) in THF : MeOH (1 : 1, 800 mL) with stirring at room temperature for 2 h. The mixture was concentrated to yield a semi-solid. Trituration with water and collection of the solid by filtration afforded the title compound as a light brown solid (32.2 g), mp: >160°C (dec); Mass spectrum (ESI, $[M-H]^-$) *m/z* 386. ^{1}H NMR (400 *MHz*, DMSO-*d6*) δ 8.35 (d, 1H, *J* = 1.99 Hz), 7.40 (d, 1H, *J* = 8.70 Hz), 7.29-7.26 (m, 4H), 7.23 (d,

2H, *J* = 7.33 Hz), 7.10 (d, 2H, *J* = 7.18 Hz), 5.72 (b, 1H), 5.59 (s, 2H), and 4.81 ppm (s, 2H).

Elemental Analysis for $C_{18}H_{13}BrNO_4 \cdot 1.0\ K \cdot 1.0\ H_2O$:

Calculated: C, 48.66; H, 3.40; N, 3.15.

Found: C, 48.61; H, 3.36; N, 2.89.

Step 4

9-Benzyl-6-(4-chlorophenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

A mixture of [1-benzyl-5-bromo-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt (3.15 g, 7.4 mmol), 4-chlorophenylboronic acid (1.74 g, 2.6 mmol), potassium carbonate (2.55 g, 13.7 mmol), palladium(II) acetate (0.032 g) and tetrabutylammonium bromide (2.4 g, 7.4 mmol) in 15 % dioxane in water (45 mL) was stirred at 70°C. The reaction was monitored by TLC. After no [1-benzyl-5-bromo-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, was detected by TLC, the reaction was cooled down and solvent was decanted. The dark gum-like oil was partitioned between ethyl acetate and 10 % aqueous HCl. The upper organic layer was separated, washed with water, and filtered. This filtrate was evaporated to give a solid. This solid was triturated with ethyl ether with stirring and dried in vacuum at 60°C for 8 hours. to afford the title compound as an off-white solid (0.77 g), m.p. 263-264°C. Mass spectrum (ESI, $[M+H]^+$) *m/z* 402. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 8.19 (s, 1H), 7.71-7.67 (m, 3H), 7.63 (dd, 1H, *J* = 8.66 and 1.83 Hz),), 7.49 (dd, 2H, *J* = 8.54 and 1.95 Hz), 7.34-7.25 (m, 3H), 7.22 (d, 2H, *J* = 7.46 Hz), 5.88 (s, 2H), and 5.52 ppm (s, 2H).

Elemental Analysis for $C_{24}H_{16}ClNO_3 \cdot 0.4\ H_2O$:

Calculated: C, 70.47; H, 4.14; N, 3.42.

Found: C, 70.57; H, 4.19; N, 3.12.

Example 10

[1-Benzyl-5-(4-chlorophenyl)-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt

Step 1

[1-Benzyl-5-(4-chlorophenyl)-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt

A solution of 9-benzyl-6-(4-chlorophenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione (0.613 g, 0.1.53 mmol) and (1.0 N, 1.6 mL, 1.6 mmol) in THF:MeOH (1:1, 14 mL) was stirred at room temperature for 2 hours. The reaction was followed by NMR. More aqueous potassium hydroxide was added as needed. After no starting material was detected, the reaction mixture was evaporated to dryness. The residual solid was triturated with ethyl ether to afford the title compound as a light grey solid, mp: 225-226°C; Mass spectrum (ESI, $[M-H]^-$) *m/z* 418. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 8.51 (s, 1H), 7.64 (d, 2H, *J* = 8.55 Hz), 7.52-7.49 (m, 3H), 7.45 (d, 1H, *J* = 8.55 Hz), 7.31-7.28 (m, 2H), 7.18 (d, 1H, *J* = 7.64 Hz), 7.15 (d, 2H, *J* = 7.64 Hz), 5.75 (t, 1H, *J* = 7.57 Hz),), 5.61 (s, 2H), and 4.81 ppm (d, 2H, *J* = 5.95 Hz).
Elemental Analysis for $C_{24}H_{17}ClNO_4 \cdot 1.0\ K \cdot 1.6\ H_2O$:
Calculated: C, 59.22; H, 4.18; N, 2.88.
Found: C, 59.02; H, 3.90; N, 2.70.

Example 11

9-Benzyl-6-(3-methylphenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

9-Benzyl-6-(3-methylphenyl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from [1-benzyl-5-bromo-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt and *m*-tolylboronic acid in substantially the same manner, as described in step 4 of Example 9. The product was obtained as a grey solid, mp: 225-226°C; Mass spectrum (ESI, $[M+H]^+$) *m/z* 382. ^1H NMR (400 *MHz*, DMSO-*d6*) δ 8.22 (s, 1H), 7.22 (d, 1H, *J* = 8.40 Hz), 7.65 (dd, 1H, *J* = 8.45 and

1.83 Hz), 7.49 (s, 1H), 7.47-7.34 (m, 3H), 7.31 (d, 1H, J = 7.33 Hz), 7.27 (d, 2H, J = 8.40 Hz), 7.18 (d, 1H, J = 7.48 Hz), 5.92 (s, 2H), 5.55 (s, 2H), and 2.39 ppm (s, 3H).
Elemental Analysis for $C_{25}H_{19}NO_3 \cdot 0.4\ H_2O$:
Calculated: C, 77.26; H, 5.14; N, 3.60.
Found: C, 77.45; H, 5.09; N, 3.51.

Example 12

9-Benzyl-6-(1,1'-biphenyl-4-yl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

Step 1

9-Benzyl-6-(1,1'-biphenyl-4-yl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione

The title compound was prepared from [1-benzyl-5-bromo-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt and 4-biphenylboronic acid in substantially the same manner, as described in step 4 of Example 9. The product was obtained as a white solid, mp: 254-255 °C; Mass spectrum (ESI, $[M+H]^+$) *m/z* 444. ^{1}H NMR (400 *MHz*, DMSO-d_6) δ 8.26(s, 1H), 7.75-7.68 (m, 8H), 7.45-7.43 (m, 2H), 7.36-7.23 (m, 6H), 5.89 (s, 2H), 5.53 ppm (s, 2H).
Elemental Analysis for $C_{30}H_{21}NO_3 \cdot 0.2\ H_2O$:
Calculated: C, 80.59; H, 4.82; N, 3.13.
Found: C, 80.70; H, 4.60; N, 2.82.

Example 13

[1-Benzyl-5-(1,1'-biphenyl-4-yl)-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt

Step 1

[1-Benzyl-5-(1,1'-biphenyl-4-yl)-2-(hydroxymethyl)-1*H*-indol-3-yl](oxo)acetic acid, potassium salt

The title compound was prepared from 9-benzyl-6-(1,1'-biphenyl-4-yl)-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione and aqueous potassium hydroxide in substantially the same manner, as described in step 1 of Example 10. The product

was obtained as a light yellow solid, mp: 266-268 °C; Mass spectrum (ESI, $[M-H]^-$) *m/z* 460. ^1H NMR (400 *MHz*, DMSO-d_6) δ 8.58 (s, 1H), 7.70-7.72 (m, 6H), 7.52 (s, 2H), 7.48 (t, 2H, *J* = 7.63 Hz), 7.36 (t, 1H, *J* = 7.33 Hz), 7.32-7.29 (m, 2H),), 7.24 (t, 1H, *J* = 7.02 Hz), 7.17 (d, 1H, *J* = 7.63 Hz), 5.76 (t, 1H), 5.62 (s, 2H), and 4.83 ppm (d, 2H, *J* = 5.34 Hz).

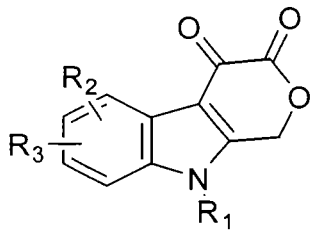
Elemental Analysis for $C_{30}H_{23}NO_4 \cdot 1.0\ K \cdot 1.50\ H_2O$:

Calculated: C, 68.42; H, 4.79; N, 2.66.

Found: C, 68.24; H, 4.85; N, 2.46.

CLAIMS:

1. A compound of formula I:



(I)

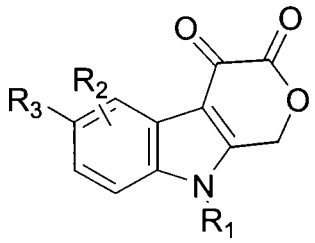
wherein:

R_1 is C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, pyridinyl, -CH_2-pyridinyl, phenyl or benzyl, wherein the rings of the cycloalkyl, pyridinyl, phenyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, or -NO_2;

R_3 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, -NO_2, phenyl, benzyl, benzyloxy, pyridinyl, or -CH_2-pyridinyl, wherein the rings of these groups may be optionally substituted by from 1 to 3 groups independently selected from phenyl, halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

2. A compound according to Claim 1 of the formula (IV)



(IV)

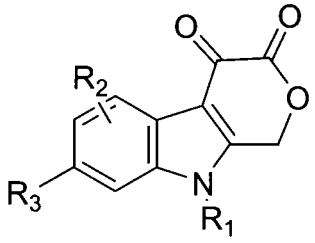
wherein R_1, R_2 and R_3 are as defined in Claim 1; or a pharmaceutically acceptable salt or ester form thereof.

3. A compound according to Claim 1 or 2 wherein R_3 is hydroxyl, phenyl or benzyloxy, wherein the rings of the phenyl and benzyloxy groups may be optionally independently substituted by from 1 to 3 groups independently selected from phenyl, halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, -O-C_1-C_3 perfluoroalkyl, C_1-C_3 alkoxy, -OH, $-NH_2$, or $-NO_2$; or a pharmaceutically acceptable salt or ester form thereof.

4. A compound according to any one of Claims 1 to 3 wherein R_2 is hydrogen; or a pharmaceutically acceptable salt or ester form thereof.

5. A compound according to any one of Claims 1 to 4 wherein R_1 is benzyl, wherein the ring of the benzyl group may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, -O-C_1-C_3 perfluoroalkyl, C_1-C_3 alkoxy, -OH, $-NH_2$, or $-NO_2$; or a pharmaceutically acceptable salt or ester form thereof.

6. A compound of formula III:



(III)

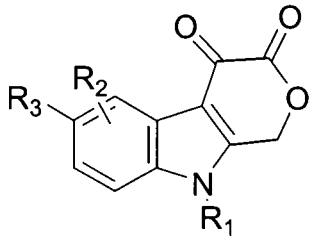
wherein:

R_1 is C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, pyridinyl, -CH_2-pyridinyl, phenyl or benzyl, wherein the rings of the cycloalkyl, pyridinyl, phenyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, -NH_2, or -NO_2;

R_3 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, -NO_2, phenyl, benzyl, benzyloxy, pyridinyl, or -CH_2-pyridinyl, wherein the rings of these groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

7. A compound of formula (IV)



(IV)

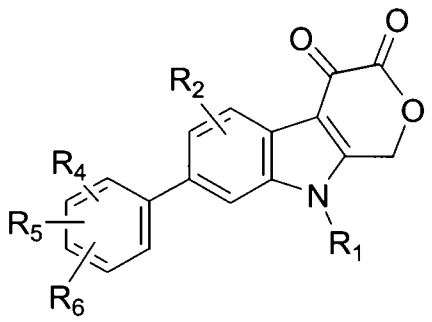
wherein:

R_1 is C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, pyridinyl, -CH_2-pyridinyl, phenyl or benzyl, wherein the rings of the cycloalkyl, pyridinyl, phenyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, -NH_2, or -NO_2;

R_3 is phenyl, benzyl, benzyloxy, pyridinyl, or -CH_2-pyridinyl, with the rings of these groups being optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

8. A compound of formula (V):



(V)

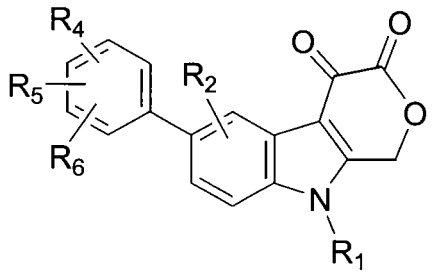
wherein:

R_1 is C_1-C_8 alkyl, preferably C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, or benzyl, wherein the rings of the cycloalkyl and benzyl groups may be optionally substituted by from 1 to 3 groups selected independently from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, -O-C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, or -NO_2;

R_4, R_5 and R_6 are each independently hydrogen, phenyl, halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, -O-C_1-C_3 perfluoroalkyl, C_1-C_3 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

9. A compound of formula VI:



(VI)

wherein:

R_1 is C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, or benzyl, wherein the rings of the cycloalkyl and benzyl groups may be optionally substituted by from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, preferably –CF_3, -O-C_1-C_6 perfluoroalkyl, preferably –O-CF_3, C_1-C_6 alkoxy, -OH, -NH_2, or -NO_2;

R_2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -CH_2-C_3-C_6 cycloalkyl, hydroxy, -NH_2, or -NO_2; and

R_4, R_5 and R_6 are each independently hydrogen, phenyl, halogen, C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, preferably –CF_3, -O-C_1-C_3 perfluoroalkyl, preferably –O-CF_3, C_1-C_3 alkoxy, -OH, -NH_2, or -NO_2; or a pharmaceutically acceptable salt or ester form thereof.

10. The compound of Claim 1 which is any one of
9-(4-Methylbenzyl)-6-[4-(trifluoromethoxy)phenyl]-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione,
9-Benzyl-6-[4-(trifluoromethoxy)phenyl]-1,9-dihydropyrano[3,4-*b*]indole-3,4-dione,
9-(4-Methylbenzyl)-6-(3-Methylphenyl)-1,9-dihydropyrano[3,4-b]indole-3,3-dione,
9-(4-tert-butylbenzyl)-6-(3-Methylphenyl)-1,9-dihydropyrano[3,4-b] indole-3,4-dione,
6-(Benzyloxy)-9-(4-methylbenzyl)-1,9-dihydropyrano[3,4-b]indole-3,4-dione,
6-(Benzyloxy)-9-(4-tertbutylbenzyl)-1,9-dihydropyrano[3,4-b]indole-3,4-dione,
9-(4-tertbutybenzyl)-6-hydroxy-1,9-dihydropyrano[3,4-b]indole-3,4-dione,
9-benzyl-6-(4-chlorophenyl)-1,9-dihydropyrano[3,4-b]indole-3,4-dione,
9-benzyl-6-(3-Methylphenyl)-1,9-dihydropyrano[3,4-b]indole-3,4-dione, or
9-benzyl-6-(1-1-bi-phenyl-4-yl)-1,9-dihydropyrano[3,4-b]indole-3,4-dione,
or a pharmaceutically acceptable salt or ester form thereof.

11. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 10 and a pharmaceutical carrier.

12. The use of a compound according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment of thrombosis, fibrinolytic impairment, peripheral arterial disease, stroke associated with or resulting from atrial fibrillation, deep vein thrombosis, myocardial ischemia, cardiovascular disease caused by non-insulin dependent diabetes mellitus, the formation of atherosclerotic plaques, chronic obstructive pulmonary disease, renal fibrosis, polycystic ovary syndrome, Alzheimer's disease, or cancer in a mammal.

13. The use of Claim 12 wherein the thrombosis or fibrinolytic impairment is associated with formation of atherosclerotic plaques, venous and arterial thrombosis, myocardial ischemia, atrial fibrillation, deep vein thrombosis, coagulation syndromes, pulmonary fibrosis, cerebral thrombosis, thromboembolic complications of surgery or peripheral arterial occlusion.