THERAPEUTIC TREATMENT FOR CARDIOVASCULAR DISEASES

This application is a continuation-in-part of Heath et al., application U.S. Serial No. 08/643,706 filed May 6, 1996, which is a divisional of Heath et al., U.S. Serial No. 08/413,735, filed March 30, 1995, which is a continuation-in-part of Heath et al., U.S. Serial No. 08/316,973, filed October 3, 1994, which is a continuation-in-part of Heath et al., U.S. Serial No. 08/163,060, filed December 7, 1993.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is broadly directed to a method for treating vascular endothelial cell dysfunction, especially dysfunction induced by hyperglycemia. The present invention is particularly directed to the use of a particular class of isozyme selective Protein Kinase C (PKC) inhibitors for treating atherosclerotic disease states especially cardiovascular diseases associated with vascular endothelial cell dysfunction.

2. Description of Related Art

Injury or dysfunction of the vascular endothelium is a common feature shared by many conditions that predispose an individual to accelerated development of atherosclerotic cardiovascular disease. One of the most prevalent factors that causes endothelial cell dysfunction is hyperglycemia. Evidence suggests that hyperglycemia

is directly toxic to endothelial cells. Using techniques such as acetylcholine induced vasodilation as an indicator of endothelial cell function, multiple studies have demonstrated that endothelial cell dysfunction is apparent in nonhuman models of diabetes. Several studies in humans have demonstrated that a similar dysfunction of the endothelium exists in humans with diabetes. Although certain types of diabetes are accompanied with other cardiovascular risk factors such as obesity, hypertension and dyslipidemias, these concomitant risk factors do not account for the increased risk of developing the clinical manifestations of atherosclerosis seen in diabetic patients.

Several groups have suggested that the occurrence of microalbuminuria in both diabetic and non-diabetic patients reflects a generalized worsening of their endothelial cell function. In diabetic patients, the onset of microalbuminuria is associated with a large increase in the risk of exhibiting the clinical manifestations of atherosclerotic macrovascular disease that is independent of other conventional cardiovascular risk factors. In non-diabetic populations, the onset of microalbuminuria is associated with an increase in the risk of developing macrovascular atherosclerosis and cardiovascular disease. Thus, the widespread endothelial cell dysfunction associated with the onset of microalbuminuria strongly correlates with a dramatic increase in cardiovascular disease. These findings suggest that vascular endothelial cell dysfunction may be the etiology explaining the increase in cardiovascular disease seen in both diabetic and non-diabetic patients with microalbuminuria. Furthermore, the treatment of microalbuminuria has been associated with a lowering of blood lipids and blood pressure.

In addition to predisposing a patient to chronic complications of

atherosclerosis, vascular endothelial cell dysfunction also is associated with acute sequela of atherosclerosis such as ischemic-reperfusion injury. Both non-diabetic and diabetic patients are at increased risk of sudden death due mainly to cardiovascular causes. Diabetic patients also have an increased mortality rate following a myocardial infarction. The increased mortality rate after a myocardial infarction and the increased incidence of sudden death in diabetic patients can be related to a higher degree of vascular endothelial dysfunction imparted by hyperglycemia in addition to the intrinsic endothelial cell dysfunction associated with ischemia-reperfusion injury.

Populations without overt diabetes, but exhibiting milder elevations in their glucose levels, are also at an increased risk for the development of the clinical manifestations of atherosclerosis, *e.g.*, cerebrovascular disease, peripheral vascular disease, myocardial ischemic states, and sudden death. Populations with impaired glucose tolerance have a higher prevalence of atherosclerotic diseases.

Data obtained in several disease demonstrates that predispose to the development of atherosclerosis such as hypertension and hypercholesterolemia are associated with a dysfunctional endothelium and reversal of these factors that predispose the patient to atherosclerosis ameliorates the endothelial cell dysfunction. Correlating with the improvement in endothelial cell function, seen with reduction of hypercholesterolemia, is a reduction in cardiovascular events. Thus, treatments improving vascular endothelial cell function should reduce the risk of developing clinical manifestations of cardiovascular disease.

Protein kinase C activation occurs during ischemia-reperfusion in non-diabetic animal models and has been implicated in the pathogenesis of myocardial

injury occurring in the ischemia-reperfusion model. In non-diabetic models of ischemia-reperfusion injury which simulates the pathologic processes occurring during acute myocardial ischemia, endothelial cell dysfunction occurs and is involved in worsening cardiac damage after this injury. Protection against endothelial cell damage in this model reduces myocardial injury after ischemia-reperfusion induced damage.

Given that the ischemia-reperfusion myocardial injury model is thought to reflect the processes occurring during acute myocardial ischemic states, such as myocardial infraction, treatment of non-diabetics patients suffering from acute myocardial ischemia with a PKC inhibitor are expected to exhibit a reduction in myocardial injury and the sequela related to this injury (e.g., arrhythmia, sudden death, increased infarction size, congestive heart failure, recurrent ischemia, etc.

The ubiquitous nature of the protein kinase C isozymes and their important roles in physiology provide incentives to produce highly selective PKC inhibitors. Given the evidence demonstrating linkage of certain isozymes to disease states, it is reasonable to assume that inhibitory compounds that are selective to one or two protein kinase C isozymes relative to the other PKC isozymes and other protein kinases are superior therapeutic agents. Such compounds should demonstrate greater efficacy and lower toxicity by virtue of their specificity.

At present, there are limited means to treat vascular endothelial cell dysfunction and the atherosclerotic disease states, especially cardiovascular diseases associated with it. Thus there is a need in the art to employ new therapeutic agents to treat atherosclerotic disease states especially cardiovascular diseases.

SUMMARY OF INVENTION

It is an object of the invention to provide a method for treating vascular endothelial cell dysfunction.

It is another object of the invention to provide a method for treating cardiovascular disease.

It is yet another object of the invention to provide a method for inhibiting onset of cardiovascular disease.

It is still another object of the invention to provide a method for treating microalbuminuria.

It is another object of the invention to provide a method for treating central ischemia brain injury.

It is yet another object of the invention to provide a method for treating restenosis.

It is still another object of the invention to provide a method for treating atherosclerosis.

It is another object of the invention to provide a method for treating congestive heart failure.

These and other objects of the invention are provided by one or more of the embodiments described below.

In one embodiment of the invention there is provided a method for treating vascular endothelial cell dysfunction which comprises contacting said vascular endothelial cells with a cell dysfunction inhibiting amount of a particular protein kinase C inhibitor.

In another embodiment of the invention there is provided a method for treating cardiovascular disease which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a particular protein kinase C inhibitor.

In still another embodiment of the invention there is provided a method for inhibiting onset of cardiovascular disease in a mammal, which comprises administering to the mammal in need of such treatment, a therapeutically effective amount of a particular protein kinase C inhibitor.

In another embodiment of the invention there is provided a method for treating microalbuminuria which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a particular protein kinase C inhibitor.

In still another embodiment of the invention there is provided a method for treating central ischemia brain injury which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a particular protein kinase C inhibitor.

In yet another embodiment of the invention there is provided a method for treating restenosis which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a particular protein kinase C inhibitor.

In yet another embodiment of the invention there is provided a method for treating atherosclerosis which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a particular protein kinase C inhibitor.

In still another embodiment of the invention there is provided a method for treating congestive heart failure which comprises administering to a mammal in need

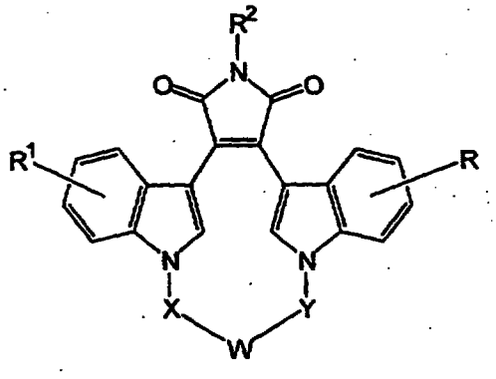
of such treatment, a therapeutically effective amount of a particular protein kinase C inhibitor.

The present invention provides the art with compounds which are prophylactic and effective in treating vascular endothelial cell dysfunction. Consequently, the compounds can be used to treat or inhibit the onset of atherosclerotic disease states, especially cardiovascular diseases associated with vascular endothelial cell dysfunction.

DETAILED DESCRIPTION OF THE INVENTION

It is a discovery of the present invention that using a particular class of protein kinase C inhibitors reduces vascular endothelial cell dysfunction associated with atherosclerotic disease states, and in particular the endothelial cell dysfunction induced by hyperglycemia. Consequently, such compounds can be used therapeutically to treat a variety of atherosclerotic disease states especially cardiovascular diseases, and prophylactically to inhibit the development of such diseases.

The method of this invention preferably utilizes the isozyme selective protein kinase C inhibitor compounds of formula I:



(I)

wherein:

W is -O-, -S-, -SO-, $-SO_2-$, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_mO$-, -heterocycle-, -heterocycle-$(CH_2)_mO$-, -fused bicyclic-, -fused bicyclic-$(CH_2)_mO$-, $-NR^3-$, $-NOR^3-$, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form $-(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), $-CONR^4R^5$, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), $-SO_2$ (NR^4R^5), or $-SO_2$ (C_1-C_4 alkyl);

R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

These compounds, and methods for their preparation, are known and have been disclosed in Heath *et al.*, EP publication 0 657 458 A1 which is incorporated herein by reference. These compounds are administered in a therapeutically effective amount, *e.g.*, a vascular endothelial cell dysfunction inhibiting amount, to a mammal

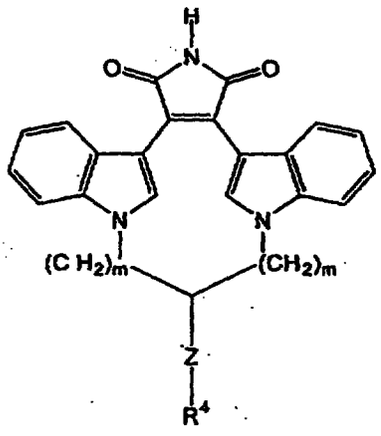
to treat endothelial cell dysfunction. The endothelial cell dysfunction can be induced by a variety of factors, *e.g.*, hyperglycemia, hypertension, hypercholesterolemia, and ischemic-reperfusion injury.

Such endothelial cell dysfunction can be associated with atherosclerotic disease states including cerebrovascular diseases, *e.g.*, central ischemia brain injury, cerebrovascular accidents and transient ischemic attacks; peripheral vascular diseases, *e.g.*, nontraumatic amputations and intermittent claudication, and cardiovascular diseases, *e.g.*, stable angina, unstable angina, variant angina, sudden death, myocardial infarction, restenosis, and ischemia-reperfusion injury. Consequently, these compounds can be used to treat these various atherosclerotic disease states, especially the cardiovascular diseases discussed above.

The compounds also can be administered in a prophylactically effective amount to patients at risk of developing atherosclerotic disease states, especially cardiovascular diseases, such as patients with hyperglycemia, hypertension, or hypercholesterolemia, as a prophylactic.

The preferred compounds for use in this invention are those of formula I wherein the moieties -X-W-Y- contain 4 to 8 atoms, which may be substituted or unsubstituted. Most preferably, the moieties -X-W-Y- contain 6 atoms.

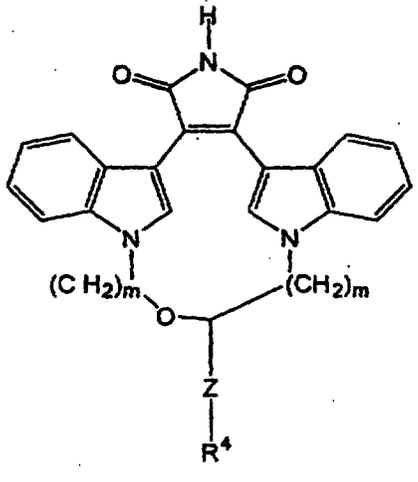
Other preferred compounds for use in this invention are those compounds of formula I wherein R^1 and R^2 are hydrogen; and W is a substituted alkylene, -O-, S-, -CONH-, -NHCO- or -NR^3-. Particularly preferred compounds are compounds of the formula Ia:



(Ia)

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable sale, prodrug or ester thereof. Most preferred compounds of the formula Ia are those wherein Z is $-CH_2$; and R^4 is $-NH_2$, $-NH(CF_3)$, or $-N(CH_3)_2$.

Other preferred compounds for use in the present invention are compounds wherein W in formula I is -O-, Y is a substituted alkylene, and X is an alkylene. These preferred compounds are represented by formula Ib:



(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof. Most preferred compounds of formula Ib are those wherein p is 1; and R^5 and R^6 are methyl.

Because they contain a basic moiety, the compounds of formula I, Ia and Ib can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4-dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like.

In addition to pharmaceutically-acceptable salts, other salts also can exist.

They may serve as intermediates in the purification of the compounds, in the preparation of other salts, or in the identification and characterization of the compounds or intermediates.

The pharmaceutically acceptable salts of compounds of formulae I, Ia and Ib can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

It is recognized that various stereoisomeric forms of the compounds of formulae I, Ia and Ib may exist; for example, W may contain a chiral carbon atom in the substituted alkylene moiety. The compounds are normally prepared as racemates and can conveniently be used as such. Alternatively, both individual enantiomers can be isolated or synthesized by conventional techniques if so desired. Such racemates and individual enantiomers and mixtures thereof form part of the compounds used in the methods of the present invention.

The compounds utilized in this invention also encompass the pharmaceutically acceptable prodrugs of the compounds of formulae I, Ia and Ib. A prodrug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which may be degraded or modified by one or more enzymatic or other *in vivo* processes to the parent bioactive form. This prodrug likely may have a different pharmacokinetic profile than the parent, enabling easier absorption across the mucosal epithelium, better salt formation or solubility, and/or improved systemic stability (an

increase in plasma half-life, for example). Typically, such chemical modifications include the following:

1) ester or amide derivatives which may be cleaved by esterases or lipases;

2) peptides which may be recognized by specific or nonspecific proteases; or

3) derivatives that accumulate at a site of action through membrane selection of a prodrug form or a modified prodrug form; or any combination of 1 to 3, supra. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in H. Bundgaard, Design of Prodrugs, (1985).

The synthesis of various bis-indole-N-maleimide derivatives is described in Davis *et al.* U.S. Patent 5,057,614 and the synthesis of the preferred compounds suitable for use in this invention are described in the previously identified Heath *et al.0* EP publication 657 458 and in Faul *et al.* EP publication 0 657 411 A1, both of which are incorporated herein by reference.

One particularly preferred protein kinase C inhibitor for use in the method of this invention is the compound described in Example 5s ((S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3"'(O)-4"'-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione Hydrochloride Salt) of the aforementioned EP publication 0 657 458 A1. This compound is a potent protein kinase C inhibitor. It is selective to protein kinase C over other kinases and is highly isozyme-selective, i.e., it is selective for the beta-1 and beta -2 isozymes. This compound is shown to normalize endothelial cell

dysfunction in animal models of diabetes at doses predictive to selectively inhibit PKC-β. The data are reported in Hidehiro et al., *Science* Vol. 272, page 728-731, 1996 and is incorporated herein by reference.

In streptozotocin and alloxan diabetic rodents, this compound normalized changes induced by diabetes in retinal blood flow and vascular Na/K-ATPase activity. Changes in retinal blood flow reflect hyperglycemic induced abnormalities in endothelial cell regulation of blood flow. Decreases in Na/K-ATPase activity is a indication of abnormal endothelial cell function (Gupta, *et al., J. Clin. Invest.*, 90:727-732 (1991)). The ability of this compound to normalize these diabetic induced abnormalities demonstrates its protective effect on the endothelium in hyperglycemic states. In addition, this compound blocked microalbuminuria, a marker of widespread endothelial cell dysfunction. Thus, in the rodent model of diabetes, this compound reduces the glucose-mediated endothelial cell toxicity and inhibited the endothelial cell dysfunction that is associated with the development of atherosclerotic macrovascular disease.

Vascular endothelial cell dysfunction is strongly associated with atherosclerotic cardiovascular disease in diabetic and nondiabetic patients. The compounds of this invention, being active for normalizing vascular endothelia cell dysfunctions are particularly useful for treating cardiovascular diseases *e.g.*, stable angina, unstable angina, variant angina, cardiovascular ischemia, sudden death, and myocardial infarction, especially the cardiovascular diseases associated with hyperglycemia. In addition to predisposing individuals to chronic complications of atherosclerosis, endothelial cell dysfunction also is associated with acute sequela of

atherosclerosis such as ischemic-reperfusion injury (Ku, *Science*, 218:576-578 (1982); Van Benthuysen, *et al., J. Clin. Invest.*, 79:265-274 (1987); Mehta, *et al., Cir. Res.*, 64:43-54 (1989)). The compounds useful in the method of this invention are therapeutically effective for reducing endothelial cell dysfunction occurring after an ischemic episode and on reducing the clinical sequela associated with this abnormality, *e.g.*, sudden death and a higher mortality rate after a myocardial infarction.

The compounds of this invention also can be used to reduce the risk of cardiovascular disease seen in persons exhibiting hyperglycemia. A normal range of plasma glucose level is 75 to 105 mg/dl (4.2 to 5.8 mmol per liter) in fasting condition and up to 140 mg/dl (up to 7.8 mmol per liter) two hours postprandial. The compounds thus can be used prophylactively to treat patients where glucose levels are in the upper range of normal and in patients exhibiting impaired glucose tolerance, hypertension, hypercholesterolemia, and diabetes.

Microalbuminuria and macrovascular endothelial cell dysfunction reflect a generalized worsening of vascular endothelial cell function in diabetic and non-diabetic patients. The compounds in the present invention can be used therapeutically to treat these conditions.

The term "treating," as used herein, describes the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications (prophylactic uses), alleviating the symptoms or complications, or eliminating the disease, condition, or disorder.

The term "isozyme selective" means the preferential inhibition of protein kinase C beta-1 or beta-2 isozyme over protein kinase C isozymes, alpha, gamma, delta, epsilon, zeta, and eta. In general, the compounds useful in the invention demonstrate a minimum of a eight fold differential (preferably a ten fold differential) in the dosage required to inhibit PKC beta-1 or beta-2 isozyme and the dosage required for equal inhibition of the alpha protein kinase C isozyme as measured in the PKC assay. The compounds demonstrate this differential across the range of inhibition and are exemplified at the IC_{50}, i.e., a 50% inhibition. Thus, isozyme-selective compounds inhibit the beta-1 and beta-2 isozymes of protein kinase C at much lower concentrations with lower toxicity by virtue of their minimal inhibition of the other PKC isozymes.

One skilled in the art will recognize that a therapeutically effective amount, e.g., an endothelial cell dysfunction inhibiting amount, of the protein kinase C inhibitor of the present invention is an amount sufficient to inhibit the endothelial cell dysfunction or inhibit development of cardiovascular disease and that this amount varies *inter alia*, depending upon an affected tissue size, the concentration of the compound in the therapeutic formulation, and the body weight of the patient. Generally, an amount of protein kinase C inhibitor to be administered as a therapeutic agent for treating cardiovascular disease, and for inhibiting onset of cardiovascular disease as discussed above, will be determined on a case by case basis by the attending physician. As a guideline, the extent of the vascular endothelial cell dysfunctions, the body weight, and age of the patient will be considered when setting an appropriate dose.

Generally, a suitable dose is one that results in a concentration of the protein kinase C inhibitor at the treatment site in the range of 0.5 nM to 200 μM, and more usually 0.5 nM to 200 nM. It is expected that serum concentrations of 0.5 nM to 10 nM should be sufficient in most circumstances.

To obtain these treatment concentrations, a patient in need of treatment likely will be administered between about 0.001 mg per day per kg of body weight and 50.0 mg per day per kg. Usually, not more than about 10.0 mg per day per kg of body weight of protein kinase C inhibitor need be needed. As noted above, the above amounts may vary on a case-by-case basis.

One skilled in the art will also recognize that a prophylactically effective amount of the protein kinase C inhibitor of the present invention is an amount sufficient to inhibit or reduce the risk of onset of cardiovascular disease. This amount varies depending on the degrees of exhibited risk factors. Generally, an amount of protein kinase C inhibitor to be administered as a prophylactic agent for cardiovascular disease will be determined on a case by case basis by the attending physicians. As a guideline, a suitable dose is determined on the dose of the PKC inhibitors used as therapeutic agents. It normally would range from 50% - 150% of the therapeutic dosage discussed above.

The compounds of formula I, and the preferred compounds of formulae Ia and Ib, are preferably formulated prior to administration. Suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. In making the compositions suitable for use in the method of the present invention, the active ingredient will usually be mixed with a carrier, or

diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders for either oral or topical application.

Some examples of suitable carriers, excipient, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphates, alginate, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents.

The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 mg to about 3 g, more usually about 750 mg of the active ingredient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances, including the severity of the condition to be treated, the choice of compound to be administered and the chosen route of administration. Therefore, the above dosage ranges are not intended to limit the scope of the invention in any way. The term "unit

dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

In addition to the above formulations, most of which may be administered orally, the compounds used in the method of the present invention also may be administered topically. Topical formulations include ointments, creams and gels.

Ointments generally are prepared using either (1) an oleaginous base, i.e., one consisting of fixed oils or hydrocarbons, such as white petrolatum or mineral oil, or (2) an absorbent base, i.e., one consisting of an anhydrous substance or substances which can absorb water, for example anhydrous lanolin. Customarily, following formation of the base, whether oleaginous or absorbent, the active ingredient (compound) is added to an amount affording the desired concentration.

Creams are oil/water emulsions. They consist of an oil phase (internal phase), comprising typically fixed oils, hydrocarbons, and the like, such as waxes, petrolatum, mineral oil, and the like, and an aqueous phase (continuous phase), comprising water and any water-soluble substances, such as added salts. The two phases are stabilized by use of an emulsifying agent, for example, a surface active agent, such as sodium lauryl sulfate; hydrophilic colloids, such as acacia colloidal clays, veegum, and the like. Upon formation of the emulsion, the active ingredient (compound) customarily is added in an amount to achieve the desired concentration.

Gels comprise a base selected from an oleaginous base, water, or an emulsion-suspension base. To the base is added a gelling agent which forms a matrix in the

base, increasing its viscosity. Examples of gelling agents are hydroxypropyl cellulose, acrylic acid polymers, and the like. Customarily, the active ingredient (compounds) is added to the formulation at the desired concentration at a point preceding addition of the gelling agent.

The amount of PKC inhibitor compound incorporated into a topical formulation is not critical; the concentration should be within a range sufficient to permit ready application of the formulation to the affected tissue area in an amount which will deliver the desired amount of compound to the desired treatment site.

The customary amount of a topical formulation to be applied to an affected tissue will depend upon an affected tissue size and concentration of compound in the formulation. Generally, the formulation will be applied to the effected tissue in an amount affording from about 1 to about 500 μg compound per cm^2 of an affected tissue. Preferably, the applied amount of compound will range from about 30 to about 300 μg/cm^2, more preferably, from about 50 to about 200 μg/cm^2, and, most preferably, from about 60 to about 100 μg/cm^2.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active agent	250
starch, dried	200
magnesium stearate	10

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 4

Capsules each containing 80 mg of medicament are made as follows:

	Quantity (mg/capsule)
Active agent	80 mg
starch	59 mg
microcrystalline cellulose	59 mg
magnesium stearate	2 mg
Total	200 mg

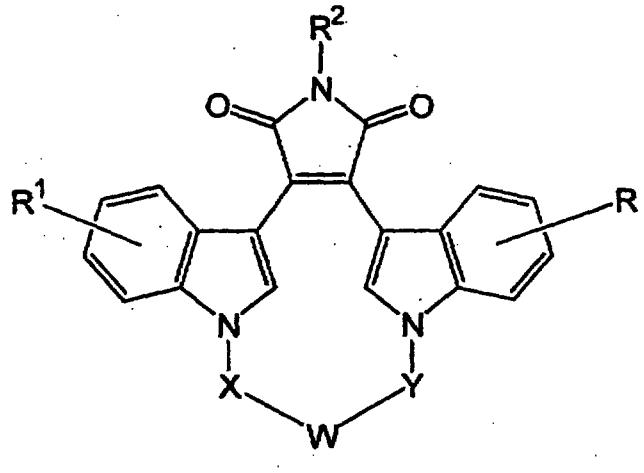
The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without

departing from the spirit of the invention.

CLAIMS:

1. A method for treating vascular endothelial cell dysfunction in a mammal comprising administering to a mammal in need of such treatment a cell dysfunction inhibiting amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_m$O-, -heterocycle-, -heterocycle-$(CH_2)_m$O-, -fused bicyclic-, -fused bicyclic-$(CH_2)_m$O-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -$COO(C_1$-C_4 alkyl), -$CONR^4R^5$, -$(C=NH)NH_2$, -$SO(C_1$-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

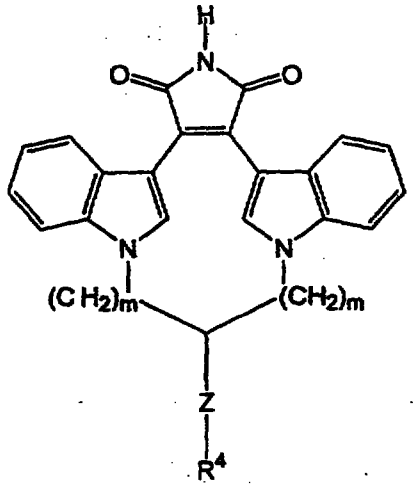
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

2. The method of claim 1 wherein the protein kinase C inhibitor has the following formula:

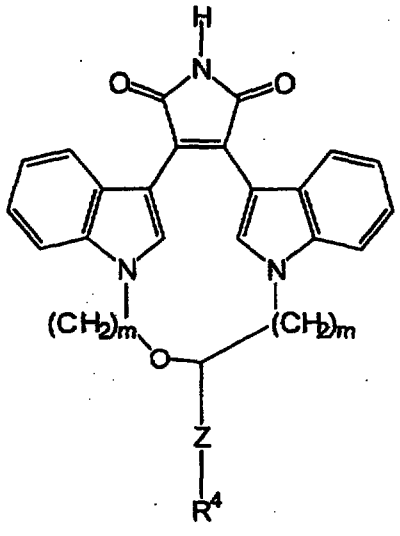


(Ia)

wherein Z is -$(CH_2)_p$- or -$(CH_2)_p$-O-$(CH_2)_p$-; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), -$N(CH_3)(CF_3)$, -$NH(CF_3)$, or -NR^5R^6; R^5 is hydrogen or C_1-C_4

alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

3. The method of claim 1 wherein the protein kinase C inhibitor has the following formula:



(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

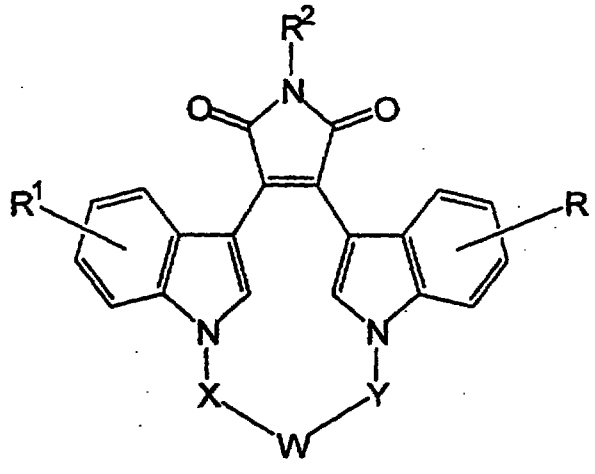
4. The method of claim 1, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione or its acid salt.

5. The method of claim 1 wherein the endothelial cell dysfunction is associated with hyperglycemia.

6. The method of claim 1 wherein the endothelial cell dysfunction is

associated with ischemic-reperfusion injury.

7. A method for treating cardiovascular disease, which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_m$O-, -heterocycle-, -heterocycle-$(CH_2)_m$O-, -fused bicyclic-, -fused bicyclic-$(CH_2)_m$O-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -CONR^{4}R^5, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

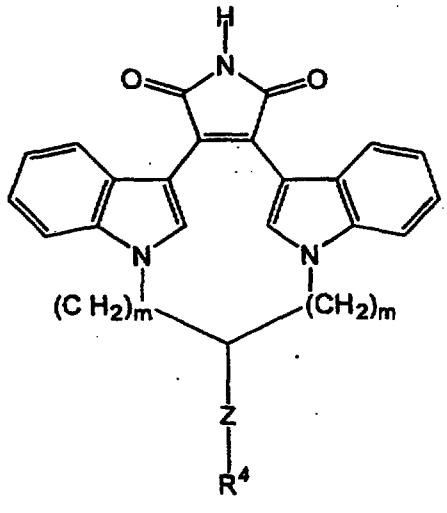
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

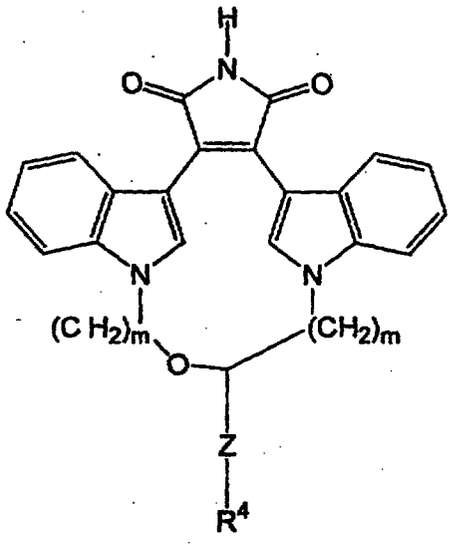
8. The method of claim 7 wherein the protein kinase C inhibitor has the following formula:



(Ia)

wherein Z is -$(CH_2)_p$- or -$(CH_2)_p$-O-$(CH_2)_p$-; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), -N(CH_3) (CF_3), -NH(CF_3), or -NR^5R^6; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

9. The method of claim 7 wherein the protein kinase C inhibitor has the following formula:



(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

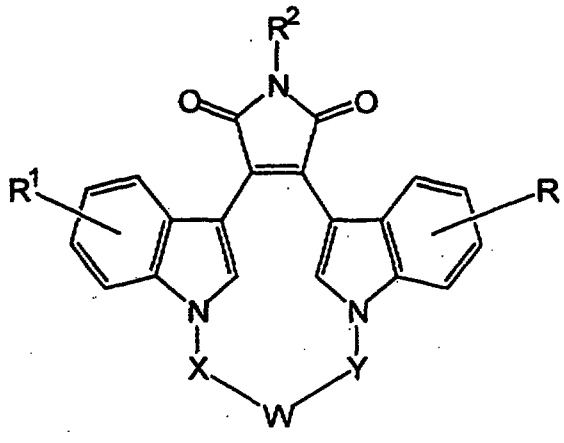
10. The method of claim 7, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indolyl)]-1(H)-pyrrole-2,5-dione or its acid salt.

11. The method of claim 7, wherein the cardiovascular disease is selected from a group consisting of stable angina, unstable angina, variant angina, cardiovascular ischemia, ischemia-reperfusion injury, sudden death, and myocardial infarction.

12. The method of claim 7, wherein the cardiovascular disease is

associated with hyperglycemia.

13. A method for inhibiting onset of cardiovascular disease in a mammal, which comprises administering to a mammal a prophylactically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_m$O-, -heterocycle-, -heterocycle-$(CH_2)_m$O-, -fused bicyclic-, -fused bicyclic-$(CH_2)_m$O-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -$CONR^4R^5$, -

$(C=NH)NH_2$, $-SO(C_1-C_4$ alkyl), $-SO_2(NR^4R^5)$, or $-SO_2(C_1-C_4$ alkyl);

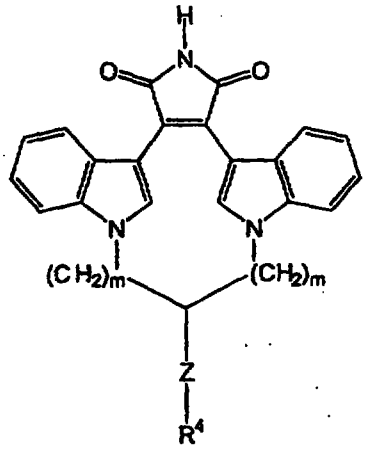
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

14. The method of claim 13 wherein the protein kinase C inhibitor has the following formula:

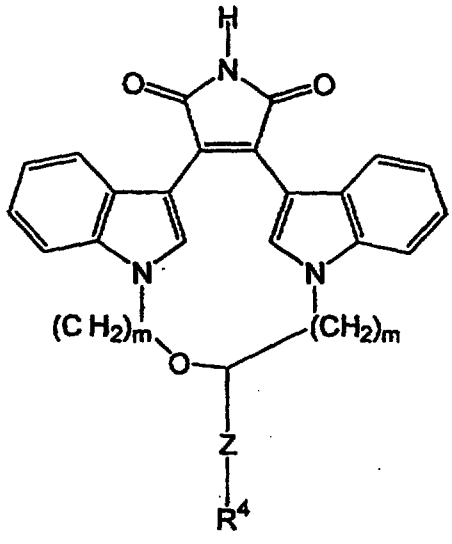


(Ia)

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

15. The method of claim 13 wherein the protein kinase C inhibitor has the

following formula:



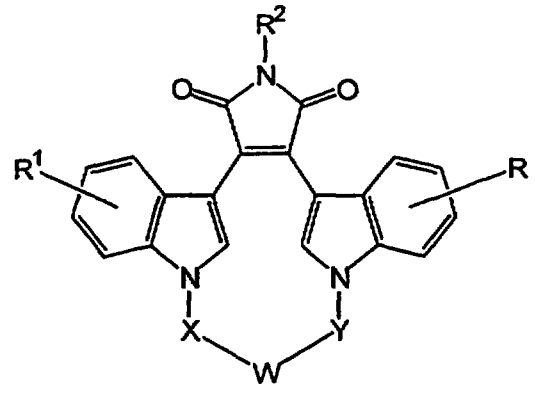
(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

16. The method of claim 13, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione or it acid salt.

17. A method for treating microalbuminuria, which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:





(I)

wherein:

W is -O-, -S-, -SO-, $-SO_2$-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_mO$-, -heterocycle-, -heterocycle-$(CH_2)_mO$-, -fused bicyclic-, -fused bicyclic-$(CH_2)_mO$-, $-NR^3$-, $-NOR^3$-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form $-(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), $-CONR^4R^5$, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), $-SO_2$ (NR^4R^5), or $-SO_2$ (C_1-C_4 alkyl);

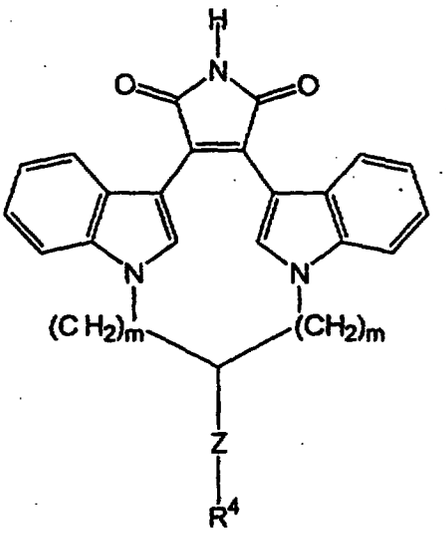
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

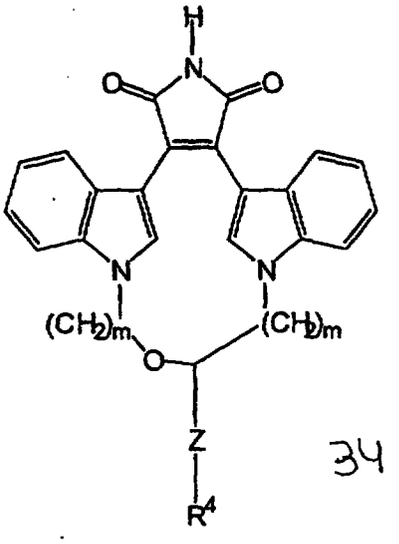
18. The method of claim 17 wherein the protein kinase C inhibitor has the following formula:



(Ia)

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

19. The method of claim 17 wherein the protein kinase C inhibitor has the following formula:



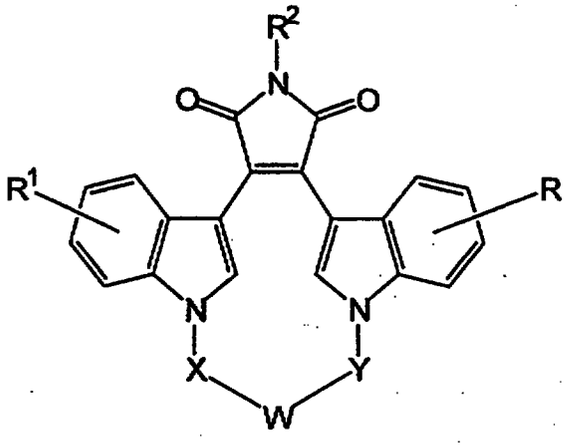
(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

20. The method of claim 17, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indolyl)]-1(H)-pyrrole-2,5-dione or its acid salt.

21. The method of claim 17, wherein microalbuminuria is associated with diabetes.

22. A method for treating central ischemia brain injury, which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_mO$-, -heterocycle-, -heterocycle-$(CH_2)_mO$-, -fused bicyclic-, -fused bicyclic-$(CH_2)_mO$-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C $_1$C $_4$ alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C $_1$C $_4$alkyl, -COO(C $_1$C $_4$alkyl), -$CONR^4R^5$, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

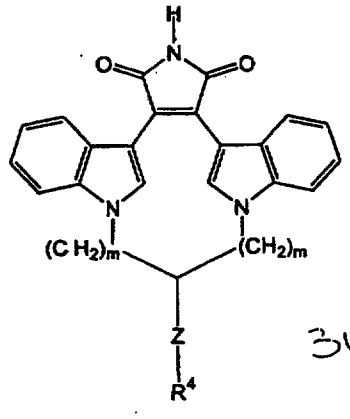
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

23. The method of claim 22 wherein the protein kinase C inhibitor has the following formula:

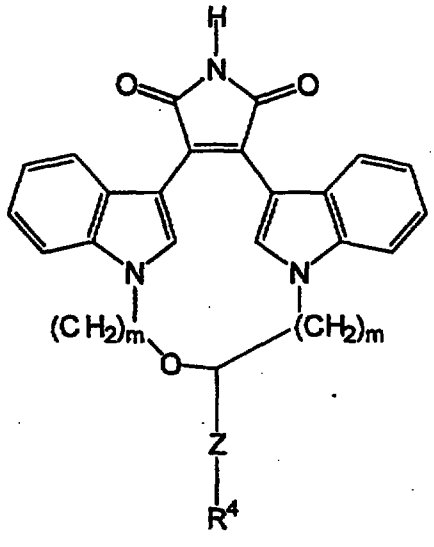


(Ia)

36

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

24. The method of claim 22 wherein the protein kinase C inhibitor has the following formula:



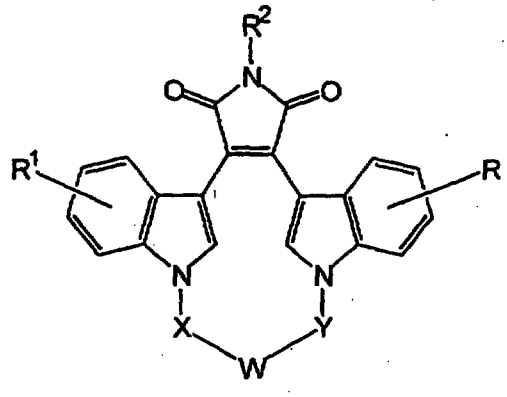
(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

25. The method of claim 22, wherein the protein kinase C inhibitor

comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indolyl)]-1(H)-pyrrole-2,5-dione or its acid salt.

26. A method for treating restenosis, which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_m$O-, -heterocycle-, -heterocycle-$(CH_2)_m$O-, -fused bicyclic-, -fused bicyclic-$(CH_2)_m$O-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -CONR $R^{4,5}$-

* C L M S *

$(C=NH)NH_2$, $-SO(C_1-C_4$ alkyl), $-SO_2(NR^4R^5)$, or $-SO_2(C_1-C_4$ alkyl);

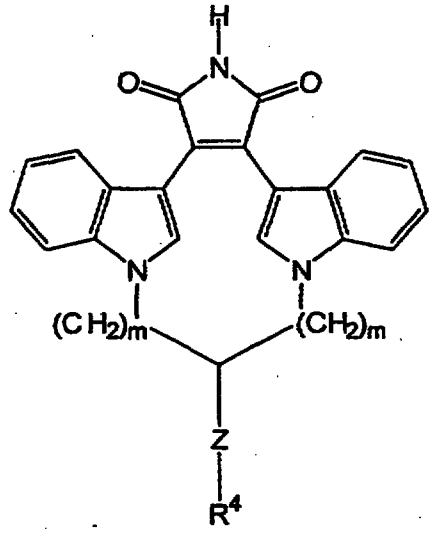
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

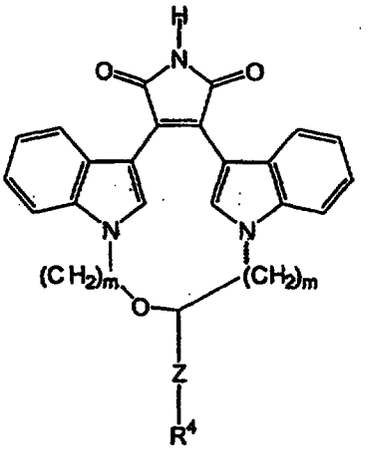
27. The method of claim 26 wherein the protein kinase C inhibitor has the following formula:



(Ia)

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

28. The method of claim 26 wherein the protein kinase C inhibitor has the following formula:

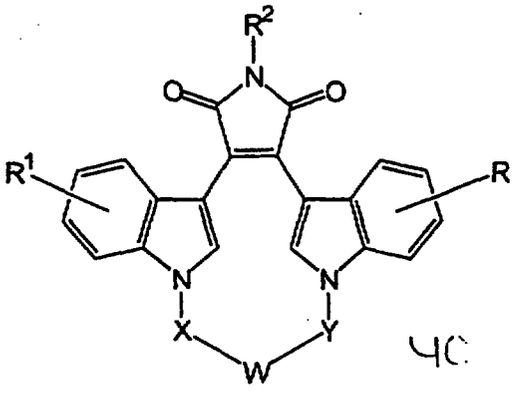


(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

29. The method of claim 26, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione or its acid salt.

30. A method for treating atherosclerotic disease state, which comprises administering to a mammal in need of such treatment, a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

* C L M S *

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_mO$-, -heterocycle-, -heterocycle-$(CH_2)_mO$-, -fused bicyclic-, -fused bicyclic-$(CH_2)_mO$-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -$CONR^4R^5$, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

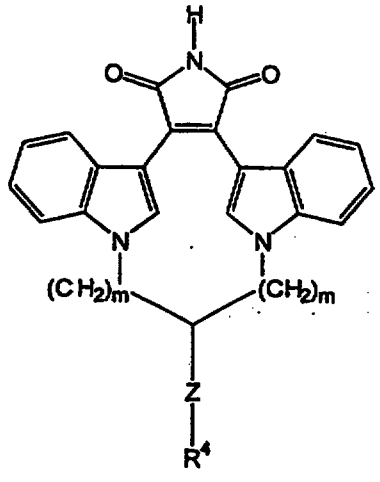
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

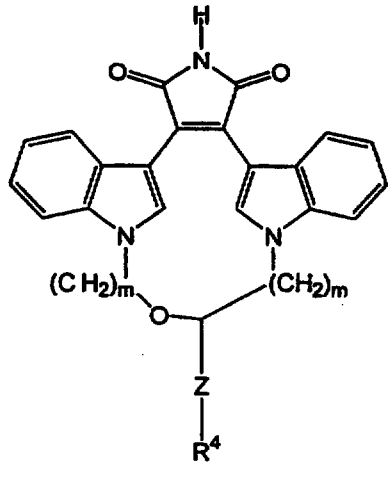
31. The method of claim 30 wherein the protein kinase C inhibitor has the following formula:



(Ia)

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

32. The method of claim 30 wherein the protein kinase C inhibitor has the following formula:



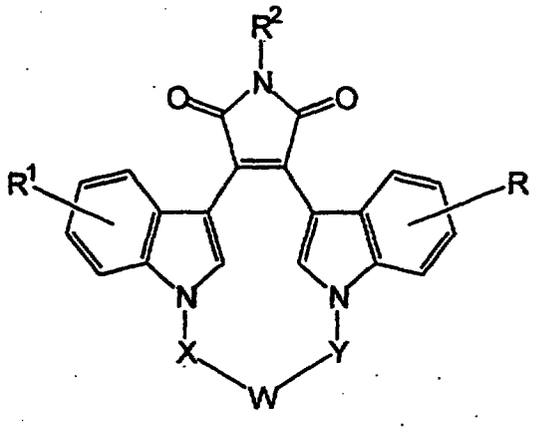
(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable sale, prodrug or ester thereof.

33. The method of claim 30, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione or its acid salt.

34. The method of claim 30, wherein the atherosclerotic disease state is selected from a group consisting of: cerebrovascular disease, peripheral vascular disease, and cardiovascular disease.

35. A method for treating congestive heart failure in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, $-SO_2-$, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6

alkenylene, -aryl-, -aryl$(CH_2)_mO$-, -heterocycle-, -heterocycle-$(CH_2)_mO$-, -fused bicyclic-, -fused bicyclic-$(CH_2)_mO$-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -$CONR^4R^5$, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

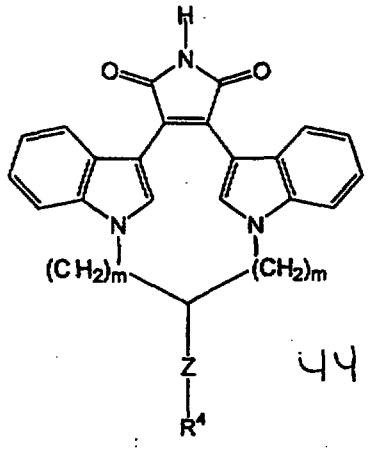
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

36. The method of claim 35 wherein the protein kinase C inhibitor has the following formula:

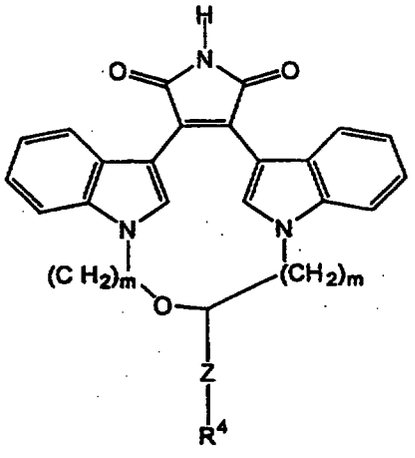


(Ia)

44

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

37. The method of claim 35 wherein the protein kinase C inhibitor has the following formula:

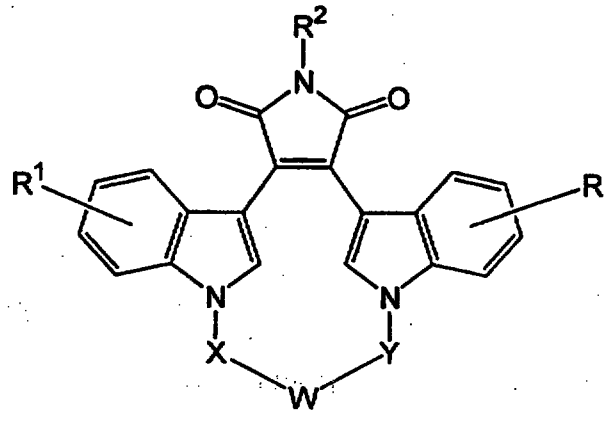


(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

38. The method of claim 35, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione or its acid salt.

39. A method for treating congestive heart failure associated with vascular endothelial cell dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, $-SO_2-$, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, $-aryl(CH_2)_mO-$, -heterocycle-, -heterocycle-$(CH_2)_mO-$, -fused bicyclic-, -fused bicyclic-$(CH_2)_mO-$, $-NR^3-$, $-NOR^3-$, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form $-(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -$COO(C_1$-C_4 alkyl), -$CONR^4R^5$, -$(C=NH)NH_2$, -$SO(C_1$-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

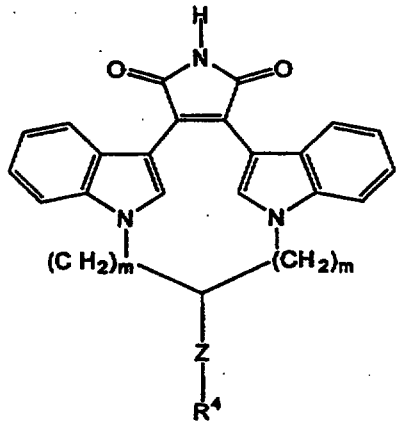
R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

40. The method of claim 39 wherein the protein kinase C inhibitor has the following formula:

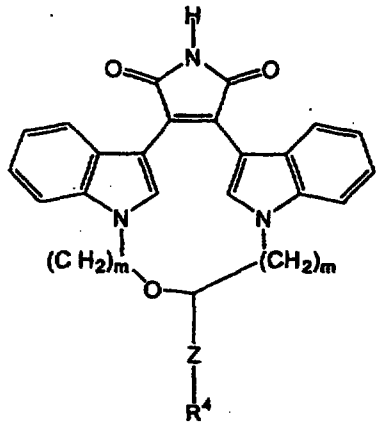


(Ia)

wherein Z is -$(CH_2)_p$- or -$(CH_2)_p$-O-$(CH_2)_p$-; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), -$N(CH_3)(CF_3)$, -$NH(CF_3)$, or -NR^5R^6; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2

or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

41. The method of claim 39 wherein the protein kinase C inhibitor has the following formula:



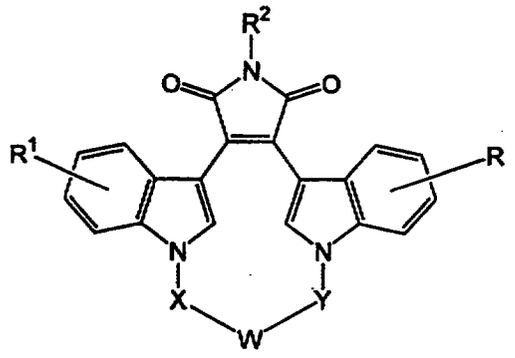
(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

42. The method of claim 39, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indolyl)]-1(H)-pyrrole-2,5-dione or its acid salt.

43. A method for treating congestive heart failure associated with myocardial injury in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:





(I)

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_mO$-, -heterocycle-, -heterocycle-$(CH_2)_mO$-, -fused bicyclic-, -fused bicyclic-$(CH_2)_mO$-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -CONR R^5, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

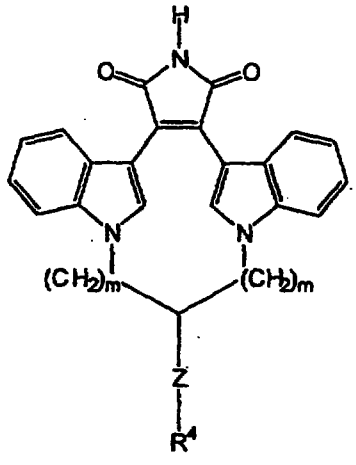
AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug

or ester thereof.

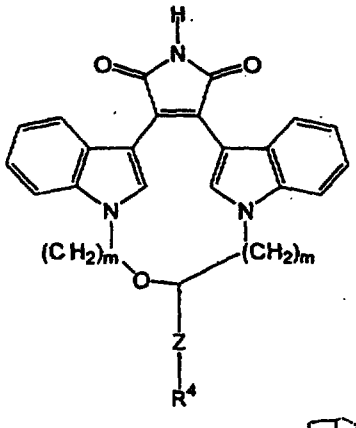
44. The method of claim 43 wherein the protein kinase C inhibitor has the following formula:



(Ia)

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

45. The method of claim 43 wherein the protein kinase C inhibitor has the following formula:

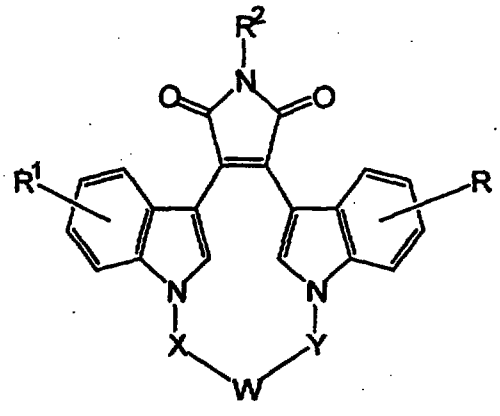


(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

46. The method of claim 43, wherein the protein kinase C inhibitor comprises (S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione or its acid salt.

47. A method for treating congestive heart failure associated with atherosclerosis in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a protein kinase C inhibitor, wherein the protein kinase C inhibitor has the following formula:



(I)

wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_m$O-, -heterocycle-, -heterocycle-$(CH_2)_m$O-, -fused bicyclic-, -fused bicyclic-$(CH_2)_m$O-, -NR^3-, -NOR^3-, -CONH-, or -NHCO-;

X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form -$(CH_2)_n$-AA-;

R^1s are hydrogen or up to four optional substituents independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR^4R^5, or -NHCO(C_1-C_4 alkyl);

R^2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R^3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -$CONR^4R^5$, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), -SO_2 (NR^4R^5), or -SO_2 (C_1-C_4 alkyl);

R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

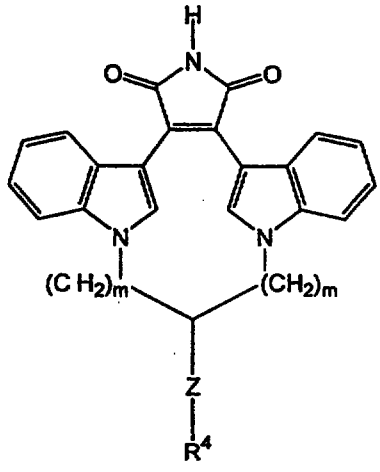
AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5 or a pharmaceutically acceptable salt, prodrug or ester thereof.

48. The method of claim 47 wherein the protein kinase C inhibitor has the following formula:

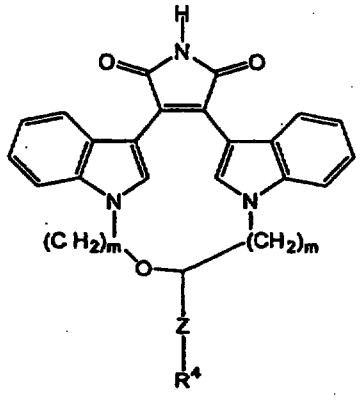




(Ia)

wherein Z is $-(CH_2)_p-$ or $-(CH_2)_p-O-(CH_2)_p-$; R^4 is hydroxy, -SH, C_1-C_4 alkyl, $(CH_2)_m$aryl, -NH(aryl), $-N(CH_3)(CF_3)$, $-NH(CF_3)$, or $-NR^5R^6$; R^5 is hydrogen or C_1-C_4 alky; R^6 is hydrogen, C_1-C_4 alkyl or benzyl; p is 0, 1, or 2; and m is independently 2 or 3 or a pharmaceutically acceptable salt, prodrug or ester thereof.

49. The method of claim 47 wherein the protein kinase C inhibitor has the following formula:



(Ib)

wherein Z is $-(CH_2)_p-$; R^4 is $-NR^5R^6$, $-NH(CF_3)$, or $-N(CH_3)(CF_3)$; R^5 and R^6 are independently H or C_1-C_4 alkyl; p is 0, 1, or 2; and m is independently 2 or 3, or a pharmaceutically acceptable salt, prodrug or ester thereof.

50. The method of claim 47, wherein the protein kinase C inhibitor comprises

(S)-3,4-[N, N'-1,1'-((2"-ethoxy)-3'"(O)-4'"-(N,N-dimethylamino)-butane)-bis-(3,3'-indoly1)]-1(H)-pyrrole-2,5-dione or its acid salt.