DESCRIPTION

SYNTHETIC TRITERPENOIDS AND METHODS OF USE IN THE TREATMENT OF DISEASE

BACKGROUND OF THE INVENTION

The present application claims the benefit of priority to U.S. Provisional Application Nos. 61/020,624, filed January 11, 2008, and 61/109,114, filed October 28, 2008, the entire contents of each of which are incorporated by reference herein.

I. Field of the Invention

The present invention relates generally to the fields of biology and medicine. More particularly, it concerns compositions and methods for treating and/or preventing renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, fatty liver disease, and cardiovascular disease (CVD).

II. Description of Related Art

Renal failure, resulting in inadequate clearance of metabolic waste products from the blood and abnormal concentrations of electrolytes in the blood, is a significant medical problem throughout the world, especially in developed countries. Diabetes and hypertension are among the most important causes of chronic renal failure, also known as chronic kidney disease (CKD), but it is also associated with other conditions such as lupus or systemic cardiovascular disease. Dysfunction of the vascular endothelium commonly occurs in such conditions and is believed to be a major contributing factor in the development of chronic kidney disease. Acute renal failure may arise from exposure to certain drugs (*e.g.*, acetaminophen) or toxic chemicals or from ischemia-reperfusion injury associated with shock or surgical procedures such as transplantation, and may ultimately result in CKD. In many patients, CKD advances to end-stage renal disease (ESRD) in which the patient requires kidney transplantation or regular dialysis to continue living. Both of these procedures are highly invasive and associated with significant side effects and quality of life issues. Although there are effective treatments for some complications of renal failure, such as hyperparathyroidism and hyperphosphatemia, no available treatment has been shown to halt or reverse the underlying progression of renal failure. Thus, agents that can improve

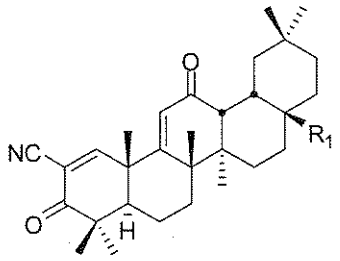
compromised renal function would represent a significant advance in the treatment of renal failure.

Triterpenoids, biosynthesized in plants by the cyclization of squalene, are used for medicinal purposes in many Asian countries; and some, like ursolic and oleanolic acids, are known to be anti-inflammatory and anti-carcinogenic (Huang *et al.*, 1994; Nishino *et al.*, 1988). However, the biological activity of these naturally-occurring molecules is relatively weak, and therefore the synthesis of new analogs to enhance their potency was undertaken (Honda *et al.*, 1997; Honda *et al.*, 1998). An ongoing effort for the improvement of anti-inflammatory and antiproliferative activity of oleanolic and ursolic acid analogs led to the discovery of 2-cyano-3,12-dioxooleane-1,9(11)-dien-28-oic acid (CDDO) and related compounds (Honda *et al.*, 1997, 1998, 1999, 2000a, 2000b, 2002; Suh *et al.*, 1998; 1999; 2003; Place *et al.*, 2003; Liby *et al.*, 2005). Several potent derivatives of oleanolic acid were identified, including methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO-Me; RTA 402). RTA 402 suppresses the induction of several important inflammatory mediators, such as iNOS, COX-2, TNFα, and IFNγ, in activated macrophages. RTA 402 has also been reported to activate the Keap1/Nrf2/ARE signaling pathway resulting in the production of several anti-inflammatory and antioxidant proteins, such as heme oxygenase-1 (HO-1). These properties have made RTA 402 a candidate for the treatment of neoplastic and proliferative diseases, such as cancer. The ability of this compound and related molecules to treat and/or prevent kidney disease and cardiovascular disease remains untested.

SUMMARY OF THE INVENTION

The present invention provides new methods for treating and/or preventing renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, fatty liver disease, cardiovascular disease (CVD), and related disorders. Compounds covered by the generic or specific formulas below or specifically named are referred to as "compounds of the invention," "compounds of the present invention," or "synthetic triterpenoids" in the present application.

In one aspect of the present prevention, methods are provided for treating or preventing renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, fatty liver disease, or cardiovascular disease (CVD) in a subject comprising, administering to said subject a pharmaceutically effective amount of a compound having the structure:



, Formula I

wherein R_1 is: –CN, or C_1-C_{15}-acyl or C_1-C_{15}-alkyl, wherein either of these groups is heteroatom-substituted or heteroatom-unsubstituted; or a pharmaceutically acceptable salt, hydrate or solvate thereof.

In some embodiments, methods are provided for treating RKD. In some variations, the RKD is diabetic nephropathy (DN). In other variations, the RKD results from a toxic insult, for example, wherein the toxic insult results from an imaging agent or a drug. For example, the drug may be a chemotherapeutic agent. In a further variation, the RKD results from ischemia/reperfusion injury. In yet a further variation, the RKD results from diabetes or hypertension. In still further variations, the RKD results from an autoimmune disease. In other variations, the RKD is chronic RKD. In still other variations, the RKD is acute RKD.

In some embodiments, the subject has undergone or is undergoing dialysis. In some embodiments, the subject has undergone or is a candidate to undergo kidney transplant. In some embodiments, the subject has RKD and insulin resistance. In some variations on the above embodiments, the subject has RKD, insulin resistance and endothelial dysfunction. In some embodiments, the subject has RKD and diabetes. In some embodiments, the subject has insulin resistance.

In some embodiments, the subject has diabetes. The pharmaceutically effective amount of the compound may also effectively treat one or more complications associated with diabetes. For example, the complications can be selected from the group consisting of obesity, hypertension, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, myonecrosis, diabetic foot ulcers and other diabetic ulcers, retinopathy and metabolic syndrome (syndrome X). Also, for example, the complication can be metabolic syndrome (syndrome X). In some variations, the diabetes results from insulin resistance.

In some embodiments, the subject has RKD and endothelial dysfunction. In other embodiments, the subject has RKD and cardiovascular disease. In some embodiments, the subject has CVD. In some variations, the CVD results from endothelial dysfunction.

In some embodiments, the subject has endothelial dysfunction and/or insulin resistance. In some embodiments, the subject has fatty liver disease. In some variations, the fatty liver disease is non-alcoholic fatty liver disease. In other variations, the fatty liver disease is alcoholic fatty liver disease. In some variations, the subject has fatty liver disease and one or more of the following disorders: renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, and cardiovascular disease (CVD).

In some embodiments, the methods further comprise identifying a subject in need of treatment of any of the diseases, dysfunctions, resistances or disorders listed herein. In some embodiments, the subject has a family or patient history of any of the diseases, dysfunctions, resistances or disorders listed herein. In some embodiments, the subject exhibits symptoms of any of the diseases, dysfunctions, resistances or disorders listed herein.

In another aspect of the invention, a method is provided for improving glomerular filtration rate or creatinine clearance in a subject comprising, administering to said subject a pharmaceutically effective amount of a compound having the structure of Formula I, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

In some embodiments, the compound is administered locally. In some embodiments, the compound is administered systemically. In some embodiments, the compound is administered orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularally, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, orally, parenterally, rectally, subconjunctivally, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof. For example, in some variations, the compound is administered intravenously, intra-arterially or orally. For example, in some variations, the compound is administered orally.

In some embodiments, the compound is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a solid dispersion, a wafer, or an elixir. In some variations, the soft capsule is a gelatin capsule. In variations, the compound is formulated as a solid dispersion. In some variations the hard capsule, soft capsule, tablet or wafer further comprises a protective coating. In some variations, the formulated compound comprises an agent that delays absorption. In some variations, the formulated compound further comprises an agent

that enhances solubility or dispersibility. In some variations, the compound is dispersed in a liposome, an oil in water emulsion or a water in oil emulsion.

In some embodiments, the pharmaceutically effective amount is a daily dose from about 0.1 mg to about 500 mg of the compound. In some variations, the daily dose is from about 1 mg to about 300 mg of the compound. In some variations, the daily dose is from about 10 mg to about 200 mg of the compound. In some variations, the daily dose is about 25 mg of the compound. In other variations, the daily dose is about 75 mg of the compound. In still other variations, the daily dose is about 150 mg of the compound. In further variations, the daily dose is from about 0.1 mg to about 30 mg of the compound. In some variations, the daily dose is from about 0.5 mg to about 20 mg of the compound. In some variations, the daily dose is from about 1 mg to about 15 mg of the compound. In some variations, the daily dose is from about 1 mg to about 10 mg of the compound. In some variations, the daily dose is from about 1 mg to about 5 mg of the compound.

In some embodiments, the pharmaceutically effective amount is a daily dose is 0.01 – 25 mg of compound per kg of body weight. In some variations, the daily dose is 0.05 – 20 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 10 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 5 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 2.5 mg of compound per kg of body weight.

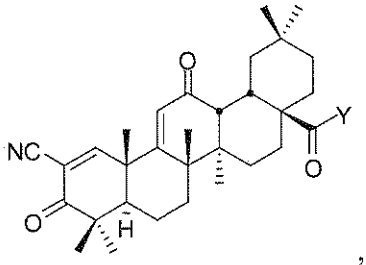
In some embodiments, the pharmaceutically effective amount is administered in a single dose per day. In some embodiments, the pharmaceutically effective amount is administered in two or more doses per day.

In some embodiments, the treatment method further comprises a second therapy. In some variations, the second therapy comprises administering to said subject a pharmaceutically effective amount of a second drug. In some embodiments, the second drug is a cholesterol lowering drug, an anti-hyperlipidemic, a calcium channel blocker, an anti-hypertensive, or an HMG-CoA reductase inhibitor. Non-limiting examples of second drugs are amlodipine, aspirin, ezetimibe, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine and nitrendipine. Further non-limiting examples of second drugs are atenolol, bucindolol, carvedilol, clonidine, doxazosin, indoramin, labetalol, methyldopa, metoprolol, nadolol, oxprenolol, phenoxybenzamine, phentolamine, pindolol, prazosin, propranolol, terazosin, timolol and tolazoline. In some variations, the second drug is a statin. Non-limiting examples of statins are atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. In some

variations, the second drug is a dipeptidyl peptidase-4 (DPP-4) inhibitor. Non-limiting examples of DPP-4 inhibitors are sitagliptin, vildagliptin, SYR-322, BMS 477118 and GSK 823093. In some variations, the second drug is a biguanide. For example, the biguanide can be metformin. In some variations, the second drug is a thiazolidinedione (TZD). Non-limiting examples of TZDs are pioglitazone, rosiglitazone and troglitazone. In some variations, the second drug is a sulfonylurea derivative. Non-limiting examples of sulfonyl urea derivatives are tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride and gliclazide. In some variations, the second drug is a meglitinide. Non-limiting examples of meglitinides include repaglinide, mitiglinide and nateglinide. In some variations, the second drug is insulin. In some variations, the second drug is an alpha-glucosidase inhibitor. Non-limiting examples of alpha-glucosidase inhibitors are acarbose, miglitol and voglibose. In some variations, the second drug is a glucagon-like peptide-1 analog. Non-limiting examples of glucagon-like peptide-1 analogs are exenatide and liraglutide. In some variations, the second drug is a gastric inhibitory peptide analog. In some variations, the second drug is a GPR40 agonist. In some variations, the second drug is a GPR119 agonist. In some variations the second drug is a GPR30 agonist. In some variations, the second drug is a glucokinase activator. In some variations, the second drug is a glucagon receptor antagonist. In some variations, the second drug is an amylin analog. A non-limiting example of an amylin analog is pramlintide. In some variations, the second drug is an IL-1β receptor antagonist. A non-limiting examples of a IL-1β receptor antagonist is anakinra. In some variations, the second drug is an endocannabinoid receptor antagonist or inverse agonist. A non-limiting example of a endocannabinoid receptor antagonist or inverse agonist is rimonabant. In some variations, the second drug is Orlistat. In some variations, the second drug is Sibutramine. In some variations, the second drug is a growth factor. Non-limiting examples of growth factors are TGF-β1, TGF-β2, TGF-β1.2, VEGF, insulin-like growth factor I or II, BMP2, BMP4, BMP7, a GLP-1 analog, a GIP analog, a DPP-IV inhibitor, a GPR119 agonist, a GPR40 agonist, gastrin, EGF, betacellulin, KGF, NGF, insulin, growth hormone, HGF, an FGF, an FGF homologue, PDGF, Leptin, prolactin, placental lactogen, PTHrP, activin, inhibin, and INGAP. Further non-limiting examples of growth factors are parathyroid hormone, calcitonin, interleukin-6, and interleukin-11.

In some embodiments, the subject is a primate. In some variations, the primate is a human. In other variations, the subject is a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

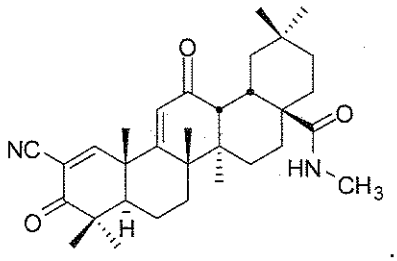
In some embodiments, the compound is defined as:



, Formula II

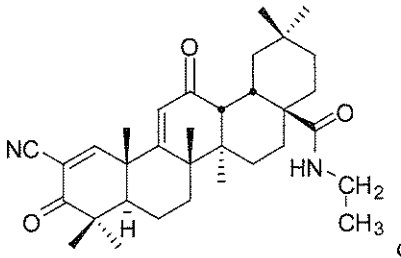
wherein Y is: –H, hydroxy, amino, halo, or C_1-C_{14}-alkoxy, C_2-C_{14}-alkenyloxy, C_2-C_{14}-alkynyloxy, C_1-C_{14}-aryloxy, C_2-C_{14}-aralkoxy, C_1-C_{14}-alkylamino, C_2-C_{14}-alkenylamino, C_2-C_{14}-alkynylamino, C_1-C_{14}-arylamino, C_3-C_{10}-aryl, or C_2-C_{14}-aralkylamino, wherein any of these groups is heteroatom-substituted or heteroatom-unsubstituted; or a pharmaceutically acceptable salt, hydrate or solvate thereof.

In some embodiments, Y is a heteroatom-unsubstituted C_1-C_4-alkylamino, such that the compound of the invention is, for example:

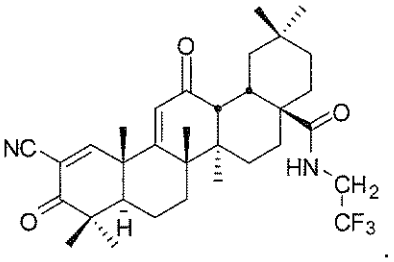


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In some embodiments, Y is a heteroatom-substituted or heteroatom-unsubstituted C_2-C_4-alkylamino, such that the compound of the invention is, for example:

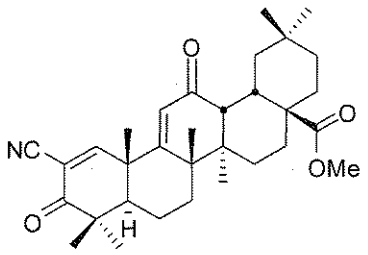


or



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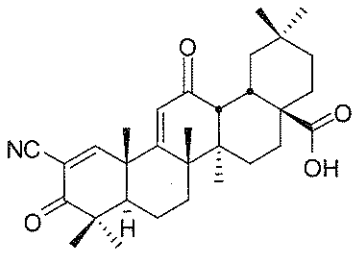
In some embodiments, Y is a heteroatom-substituted or heteroatom-unsubstituted C_1-C_4-alkoxy, such as a heteroatom-unsubstituted C_1-C_2-alkoxy. For example, one non-limiting example of such a compound is:



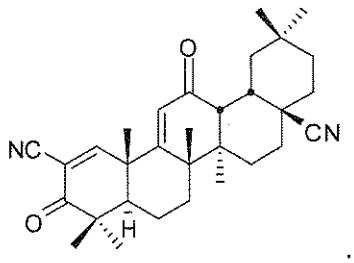
(CDDO-Me, RTA 402).

In some embodiments, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ. In non-limiting examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 12A or FIG. 12B. In other variations, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 12C, and a T_g. In some variations, the compound is an amorphous form. In some variations, the compound is a glassy solid form of CDDO-Me, having an X-ray powder diffraction pattern with a halo peak at about 13.5 °2θ, as shown in FIG. 12C, and a T_g. In some variations, the T_g value falls within a range of about 120 °C to about 135 °C. In some variations, the T_g value is from about 125 °C to about 130 °C.

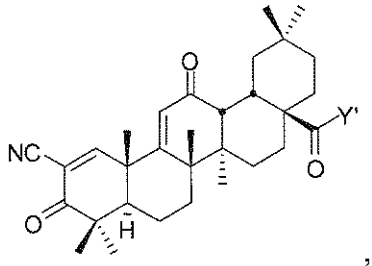
In some embodiments, Y is hydroxy, such that the compound of the invention is, for example:



In some embodiments, the compound is:



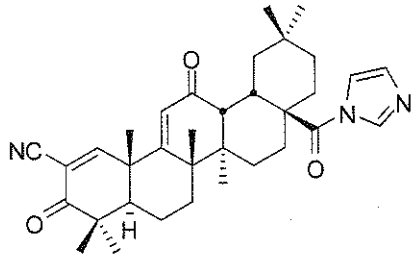
In some embodiments, the compound is defined as:



, Formula III

wherein Y' is a heteroatom-substituted or heteroatom-unsubstituted C_1-C_{14}-aryl; or a pharmaceutically acceptable salt, hydrate or solvate thereof.

In some embodiments, the compound is:



In some variations of the above methods, the compound is substantially free from optical isomers thereof. In some variations of the above methods, the compound is in the form of a pharmaceutically acceptable salt. In other variations of the above methods, the compound is not a salt.

In some embodiments, the compound is formulated as a pharmaceutical composition comprising (i) a therapeutically effective amount of the compound and (ii) an excipient is selected from the group consisting of (A) a carbohydrate, carbohydrate derivative, or carbohydrate polymer, (B) a synthetic organic polymer, (C) an organic acid salt, (D) a protein, polypeptide, or peptide, and (E) a high molecular weight polysaccharide. In some variations, the excipient is a synthetic organic polymer. In some variations, the excipient is selected from the group consisting of a hydroxpropyl methyl cellulose, a poly[1-(2-oxo-1-pyrrolidinyl)ethylene or copolymer thereof, and a methacrylic acid – methylmethacrylate copolymer. In some variations, the excipient is hydroxpropyl methyl cellulose phthalate ester. In some variations, the excipient is PVP/VA. In some variations, the excipient is a methacrylic acid – ethyl acrylate copolymer (1:1). In some variations, the excipient is copovidone.

Any embodiment discussed herein with respect to one aspect of the invention applies to other aspects of the invention as well, unless specifically noted.

Other objects, features and advantages of the present invention will become apparent from the following detailed description and any accompanying drawings. It should be understood, however, that the detailed description and any specific examples or drawings provided, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1a-d – RTA 402 reduces renal damage following ischemia-reperfusion. Mice were administered RTA 402 at 2 mg/kg or simply the vehicle (sesame oil) daily by oral gavage beginning on Day 2. On Day 0, a clamp was placed on the left renal artery for 17 minutes and then removed to induce ischemia-reperfusion. (FIG. 1a) On Day 1, blood was collected from animals that were subjected to clamping and "sham" control animals that underwent surgery without clamping of the renal artery. Blood urea nitrogen (BUN) levels were measured as a surrogate for renal damage. (FIGS. 1b-d) Sections of kidneys from RTA 402-treated or vehicle-treated mice were scored for histological damage (FIGS. 1b & 1d) and inflammation (FIG. 1c). (FIG. 1d) Black arrows (vehicle group) show two of many severely damaged tubules in the outer medulla. Red arrows (RTA 402 group) show two of many undamaged tubules in the outer medulla.

FIGS. 2a-c – RTA 402 reduces cisplatin-induced renal toxicity. Rats were administered RTA 402 at 10 mg/kg or simply the vehicle (sesame oil) every day by oral gavage beginning on Day -1. On Day 0, the rats received an intravenous injection of cisplatin at 6 mg/kg. Blood samples were drawn on the indicated days and the levels of creatinine (FIG. 2a) and blood urea nitrogen (BUN) (FIG. 2b) were measured as markers of renal damage. A statistically significant difference was observed between the vehicle-treated and RTA 402-treated groups on Day 3 (creatinine) and Day 5 (creatinine and BUN). (FIG. 2c) Less damage to the proximal tubules is observed in RTA 402-treated animals compared to vehicle-treated animals.

FIGS. 3a-d – RTA 402 reduces serum creatinine levels in monkeys, dogs, and rats. (FIG. 3a) Cynomolgus monkeys were administered RTA 402 orally at the indicated doses once daily for 28 days. The percent reduction of serum creatinine on Day 28 in RTA 402-treated monkeys relative to vehicle-treated control monkeys is shown. (FIG. 3b) RTA 402 was administered orally to beagle dogs at the indicated doses daily for three months. Control animals received vehicle (sesame oil). The percent change in serum creatinine at the three-month time point relative to baseline is shown. (FIG. 3c) Sprague-Dawley rats were administered RTA 402 orally at the indicated doses once daily for a period of one month. The percent reduction of serum creatinine at study completion in RTA 402-treated rats relative to vehicle-treated control rats is shown. (FIG. 3d) Sprague-Dawley rats were administered the amorphous form of RTA 402 orally at the indicated doses once daily for a period of three months. The percent reduction of serum creatinine at study completion in RTA 402-treated rats relative to vehicle-treated control rats is shown. Note: in FIGS. 3A, 3C and 3D, "% reduction" on the vertical axis indicates percent change. For example, a reading of –15 on this axis indicates a 15% reduction in serum creatinine.

FIGS. 4A-B – RTA 402 reduces serum creatinine levels and increases the estimated glomerular filtration rate (eGFR) in human patients with cancer. FIG. 4A: Serum creatinine was measured in RTA 402-treated patients enrolled in a Phase I clinical trial for the treatment of cancer. The patients were administered RTA 402 (p.o.) once daily for 21 days at doses ranging from 5 to 1,300 mg/day. The percent reduction of serum creatinine relative to baseline levels is shown for the indicated study days. Significant decreases in serum creatinine levels were observed on Days 15 and 21. FIG. 4B: The estimated glomerular filtration rate (eGFR) was calculated for the patients in FIG. 4A. Significant improvements in the eGFR were observed in both groups. All patients: n = 24; patients with baseline $\geq$ 1.5: n = 5. For FIGS. 4A and 4B, * indicates $p \leq 0.04$; † indicates $p = 0.01$, and ‡ indicates $p \leq 0.01$. Note: in FIG. 4A, "% Reduction from Baseline" on the vertical axis indicates percent change. For example, a reading of -15 on this axis indicates a 15% reduction in serum creatinine.

FIG. 5 – RTA 402 increases GFR in human patients with cancer. Estimated glomerular filtration rate (eGFR) was measured in RTA 402-treated patients enrolled in a multi-month clinical trial for the treatment of cancer. All patients (n = 11) dosed through six months were included in the analysis. The dosing information for these patients is provided in Example 5, below.

FIG. 6 – RTA 402 Activity Correlates with Severity. Reduction of hemoglobin A1c is presented as a fraction of the initial baseline value. Groups with higher baselines, *e.g.*, mean baseline ≥ 7.0% A1c or ≥ 7.6% A1c, showed greater reduction. The intent-to-treat (ITT) group includes all patients (n = 53), including those starting at a normal A1c value.

FIG. 7 – RTA 402 Activity is Dose Dependent. Reduction of hemoglobin A1c is presented relative to the initial baseline value. The bar graph shows mean results for all patients, all patients with baseline A1c values ≥ 7.0%, individual dose cohorts from the ≥ 7.0% group, and patients with Stage 4 renal disease (GFR 15-29 mL/min), wherein n is the number of patients in each group.

FIG. 8 – RTA 402 Reduces Circulating Endothelial Cells (CECs) and iNOS-positive CECs. The change in the mean number of CECs in cells/mL is shown for intent-to-treat (ITT) and elevated baseline groups, both before and after the 28 day RTA treatment. The reduction for the Intent-to-treat group was approximately 20%, and the reduction in the elevated baseline group (>5 CECs/ml) was approximately 33%. The fraction of iNOS-positive CECs was reduced approximately 29%.

FIG. 9 – Reversible Dose Dependent GFR Increase in 28 Days. Treatment with RTA 402 increases GFR dose-dependently. All evaluable patients were included. An improvement of >30% was noted in patients with Stage 4 renal disease.

FIGS. 10A-B – Reduction of Markers of Diabetic Nephropathy Severity and Outcome. Improvements in Adiponectin (FIG. 10A) and Angiotensin II (FIG. 10B), which are elevated in diabetic nephropathy (DN) patients and correlate with renal disease severity. Adiponectin predicts all-cause mortality and end stage renal disease in DN patients. All available data included.

FIGS. 11A-C – RTA 402 Significantly Reduces Uremic Solutes. The graphs present mean changes in BUN (FIG. 11A), phosphorus (FIG. 11B), and uric acid (FIG. 11C) for all patients and for those patients showing elevated baseline values of a particular solute.

FIGS. 12A-C – X-ray Powder Diffraction (XRPD) Spectra of Forms A and B of RTA 402. FIG. 12A shows unmicronized Form A; FIG. 12B shows micronized Form A; FIG. 12C shows Form B.

FIG. 13 – Modulated Differential Scanning Calorimetry (MDSC) Curve of Form A RTA 402. The section of the curve shown in the expanded view is consistent with a glass transition temperature (T_g).

FIG. 14 – Modulated Differential Scanning Calorimetry (MDSC) Curve of Form B RTA 402. The section of the curve shown in the expanded view is consistent with a glass transition temperature (T_g).

FIG. 15 – Improved Bioavailability of Form B (Amorphous) in Cynomolgus Monkeys. The figure shows a representative plot of the area under the curve for Form A and Form B, following a 4.1 mg/kg oral administration to cynomolgus monkeys. Each data point represents the mean plasma concentration of CDDO methyl ester in 8 animals. Error bars represent the standard deviation within the sampled population.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. The Present Invention

The present invention concerns new methods for the treatment and prevention of renal disease and related disorders, including diabetes and cardiovascular disease, involving the use of triterpenoids.

II. Definitions

As used herein, the term "amino" means $-NH_2$; the term "nitro" means $-NO_2$; the term "halo" designates –F, –Cl, –Br or –I; the term "mercapto" means –SH; the term "cyano" means –CN; the term "silyl" means $-SiH_3$, and the term "hydroxy" means –OH.

The term "heteroatom-substituted," when used to modify a class of organic radicals (*e.g.*, alkyl, aryl, acyl, *etc.*), means that one, or more than one, hydrogen atom of that radical has been replaced by a heteroatom, or a heteroatom containing group. Examples of heteroatoms and heteroatom containing groups include: hydroxy, cyano, alkoxy, =O, =S, $-NO_2$, $-N(CH_3)_2$, amino, or –SH. Specific heteroatom-substituted organic radicals are defined more fully below.

The term "heteroatom-unsubstituted," when used to modify a class of organic radicals (*e.g.*, alkyl, aryl, acyl, *etc.*) means that none of the hydrogen atoms of that radical have been replaced with a heteroatom or a heteroatom containing group. Substitution of a hydrogen atom with a carbon atom, or a group consisting of only carbon and hydrogen atoms, is not sufficient to make a group heteroatom-substituted. For example, the group $-C_6H_4C{\equiv}CH$ is an example of a heteroatom-unsubstituted aryl group, while $-C_6H_4F$ is an example of a heteroatom-substituted aryl group. Specific heteroatom-unsubstituted organic radicals are defined more fully below.

The term "alkyl" includes straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl heteroatom-substituted cycloalkyl groups, and cycloalkyl heteroatom-substituted alkyl groups. The term "heteroatom-unsubstituted C_n-alkyl" refers to a radical having a linear or branched, cyclic or acyclic structure, further having no carbon-carbon double or triple bonds, further having a total of n carbon atoms, all of which are nonaromatic, 3 or more hydrogen atoms, and no heteroatoms. For example, a heteroatom-unsubstituted C_1-C_{10}-alkyl has 1 to 10 carbon atoms. The groups, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH(CH_2)_2$ (cyclopropyl), $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$, cyclobutyl, cyclopentyl, and cyclohexyl, are all examples of heteroatom-unsubstituted alkyl groups. The term "heteroatom-substituted C_n-alkyl" refers to a radical having a single saturated carbon atom as the point of attachment, no carbon-carbon double or triple bonds, further having a linear or branched, cyclic or acyclic structure, further having a total of n carbon atoms, all of which are nonaromatic, 0, 1, or more than one hydrogen atom, at least one heteroatom, wherein each heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_1-C_{10}-alkyl has 1 to 10 carbon atoms. The following groups are all examples of heteroatom-substituted alkyl groups: trifluoromethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2OCH_2CH_2CH_3$, $-CH_2OCH(CH_3)_2$, $-CH_2OCH(CH_2)_2$, $-CH_2OCH_2CF_3$, $-CH_2OCOCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2NHCH_2CH_3$, $-CH_2N(CH_3)CH_2CH_3$, $-CH_2NHCH_2CH_2CH_3$, $-CH_2NHCH(CH_3)_2$, $-CH_2NHCH(CH_2)_2$, $-CH_2N(CH_2CH_3)_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2Br$, $-CH_2CH_2I$, $-CH_2CH_2OH$, $-CH_2CH_2OCOCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_2CH_3$, $-CH_2CH_2N(CH_3)CH_2CH_3$, $-CH_2CH_2NHCH_2CH_2CH_3$, $-CH_2CH_2NHCH(CH_3)_2$, $-CH_2CH_2NHCH(CH_2)_2$, $-CH_2CH_2N(CH_2CH_3)_2$, $-CH_2CH_2NHCO_2C(CH_3)_3$, and $-CH_2Si(CH_3)_3$.

The term "heteroatom-unsubstituted C_n-alkenyl" refers to a radical having a linear or branched, cyclic or acyclic structure, further having at least one nonaromatic carbon-carbon double bond, but no carbon-carbon triple bonds, a total of n carbon atoms, three or more hydrogen atoms, and no heteroatoms. For example, a heteroatom-unsubstituted C_2-C_{10}-alkenyl has 2 to 10 carbon atoms. Heteroatom-unsubstituted alkenyl groups include: $-CH=CH_2$, $-CH=CHCH_3$, $-CH=CHCH_2CH_3$, $-CH=CHCH_2CH_2CH_3$, $-CH=CHCH(CH_3)_2$, $-CH=CHCH(CH_2)_2$, $-CH_2CH=CH_2$, $-CH_2CH=CHCH_3$, $-CH_2CH=CHCH_2CH_3$, $-CH_2CH=CHCH_2CH_2CH_3$, $-CH_2CH=CHCH(CH_3)_2$, $-CH_2CH=CHCH(CH_2)_2$, and $-CH=CH-C_6H_5$. The term "heteroatom-substituted C_n-alkenyl" refers to a radical having a

single nonaromatic carbon atom as the point of attachment and at least one nonaromatic carbon-carbon double bond, but no carbon-carbon triple bonds, further having a linear or branched, cyclic or acyclic structure, further having a total of n carbon atoms, 0, 1, or more than one hydrogen atom, and at least one heteroatom, wherein each heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_2-C_{10}-alkenyl has 2 to 10 carbon atoms. The groups, $-CH=CHF$, $-CH=CHCl$ and $-CH=CHBr$, are examples of heteroatom-substituted alkenyl groups.

The term "heteroatom-unsubstituted C_n-alkynyl" refers to a radical having a linear or branched, cyclic or acyclic structure, further having at least one carbon-carbon triple bond, a total of n carbon atoms, at least one hydrogen atom, and no heteroatoms. For example, a heteroatom-unsubstituted C_2-C_{10}-alkynyl has 2 to 10 carbon atoms. The groups, $-C\equiv CH$, $-C\equiv CCH_3$, and $-C\equiv CC_6H_5$ are examples of heteroatom-unsubstituted alkynyl groups. The term "heteroatom-substituted C_n-alkynyl" refers to a radical having a single nonaromatic carbon atom as the point of attachment and at least one carbon-carbon triple bond, further having a linear or branched, cyclic or acyclic structure, and having a total of n carbon atoms, 0, 1, or more than one hydrogen atom, and at least one heteroatom, wherein each heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_2-C_{10}-alkynyl has 2 to 10 carbon atoms. The group, $-C\equiv CSi(CH_3)_3$, is an example of a heteroatom-substituted alkynyl group.

The term "heteroatom-unsubstituted C_n-aryl" refers to a radical having a single carbon atom as a point of attachment, wherein the carbon atom is part of an aromatic ring structure containing only carbon atoms, further having a total of n carbon atoms, 5 or more hydrogen atoms, and no heteroatoms. For example, a heteroatom-unsubstituted C_6-C_{10}-aryl has 6 to 10 carbon atoms. Examples of heteroatom-unsubstituted aryl groups include phenyl, methylphenyl, (dimethyl)phenyl, $-C_6H_4CH_2CH_3$, $-C_6H_4CH_2CH_2CH_3$, $-C_6H_4CH(CH_3)_2$, $-C_6H_4CH(CH_2)_2$, $-C_6H_3(CH_3)CH_2CH_3$, $-C_6H_4CH=CH_2$, $-C_6H_4CH=CHCH_3$, $-C_6H_4C\equiv CH$, $-C_6H_4C\equiv CCH_3$, naphthyl, and the radical derived from biphenyl. The term "heteroatom-unsubstituted aryl" includes carbocyclic aryl groups, biaryl groups, and radicals derived from polycyclic fused hydrocarbons (PAHs). The term "heteroatom-substituted C_n-aryl" refers to a radical having either a single aromatic carbon atom or a single aromatic heteroatom as the point of attachment, further having a total of n carbon atoms, at least one hydrogen atom, and at least one heteroatom, further wherein each heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-unsubstituted

C_1-C_{10}-heteroaryl has 1 to 10 carbon atoms. The term "heteroatom-substituted aryl" includes heteroaryl groups. It also includes those groups derived from the compounds: pyrrole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, isothiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like. Further examples of heteroatom-substituted aryl groups include the groups: $-C_6H_4F$, $-C_6H_4Cl$, $-C_6H_4Br$, $-C_6H_4I$, $-C_6H_4OH$, $-C_6H_4OCH_3$, $-C_6H_4OCH_2CH_3$, $-C_6H_4OCOCH_3$, $-C_6H_4OC_6H_5$, $-C_6H_4NH_2$, $-C_6H_4NHCH_3$, $-C_6H_4NHCH_2CH_3$, $-C_6H_4CH_2Cl$, $-C_6H_4CH_2Br$, $-C_6H_4CH_2OH$, $-C_6H_4CH_2OCOCH_3$, $-C_6H_4CH_2NH_2$, $-C_6H_4N(CH_3)_2$, $-C_6H_4CH_2CH_2Cl$, $-C_6H_4CH_2CH_2OH$, $-C_6H_4CH_2CH_2OCOCH_3$, $-C_6H_4CH_2CH_2NH_2$, $-C_6H_4CH_2CH{=}CH_2$, $-C_6H_4CF_3$, $-C_6H_4CN$, $-C_6H_4C{\equiv}CSi(CH_3)_3$, $-C_6H_4COH$, $-C_6H_4COCH_3$, $-C_6H_4COCH_2CH_3$, $-C_6H_4COCH_2CF_3$, $-C_6H_4COC_6H_5$, $-C_6H_4CO_2H$, $-C_6H_4CO_2CH_3$, $-C_6H_4CONH_2$, $-C_6H_4CONHCH_3$, $-C_6H_4CON(CH_3)_2$, furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazoyl, quinolyl and indolyl.

The term "heteroatom-unsubstituted C_n-aralkyl" refers to a radical having a single saturated carbon atom as the point of attachment, further having a total of n carbon atoms, wherein at least 6 of the carbon atoms form an aromatic ring structure containing only carbon atoms, 7 or more hydrogen atoms, and no heteroatoms. For example, a heteroatom-unsubstituted C_7-C_{10}-aralkyl has 7 to 10 carbon atoms. Examples of heteroatom-unsubstituted aralkyls include phenylmethyl (benzyl) and phenylethyl. The term "heteroatom-substituted C_n-aralkyl" refers to a radical having a single saturated carbon atom as the point of attachment, further having a total of n carbon atoms, 0, 1, or more than one hydrogen atom, and at least one heteroatom, wherein at least one of the carbon atoms is incorporated in an aromatic ring structure, further wherein each heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_2-C_{10}-heteroaralkyl has 2 to 10 carbon atoms.

The term "heteroatom-unsubstituted C_n-acyl" refers to a radical having a single carbon atom of a carbonyl group as the point of attachment, further having a linear or branched, cyclic or acyclic structure, further having a total of n carbon atoms, 1 or more hydrogen atoms, a total of one oxygen atom, and no additional heteroatoms. For example, a heteroatom-unsubstituted C_1-C_{10}-acyl has 1 to 10 carbon atoms. The groups, $-COH$, $-COCH_3$, $-COCH_2CH_3$, $-COCH_2CH_2CH_3$, $-COCH(CH_3)_2$, $-COCH(CH_2)_2$, $-COC_6H_5$, $-COC_6H_4CH_3$, $-COC_6H_4CH_2CH_3$, $-COC_6H_4CH_2CH_2CH_3$, $-COC_6H_4CH(CH_3)_2$, $-COC_6H_4CH(CH_2)_2$, and $-COC_6H_3(CH_3)_2$, are examples of heteroatom-unsubstituted acyl groups. The term "heteroatom-substituted C_n-acyl" refers to a radical having a single carbon

atom as the point of attachment, the carbon atom being part of a carbonyl group, further having a linear or branched, cyclic or acyclic structure, further having a total of n carbon atoms, 0, 1, or more than one hydrogen atom, at least one additional heteroatom in addition to the oxygen of the carbonyl group, wherein each additional heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_1-C_{10}-acyl has 1 to 10 carbon atoms. The term heteroatom-substituted acyl includes carbamoyl, thiocarboxylate, and thiocarboxylic acid groups. The groups, $-COCH_2CF_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, $-CO_2CH(CH_3)_2$, $-CO_2CH(CH_2)_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CONHCH_2CH_2CH_3$, $-CONHCH(CH_3)_2$, $-CONHCH(CH_2)_2$, $-CON(CH_3)_2$, $-CON(CH_2CH_3)CH_3$, $-CON(CH_2CH_3)_2$ and $-CONHCH_2CF_3$, are examples of heteroatom-substituted acyl groups.

The term "heteroatom-unsubstituted C_n-alkoxy" refers to a group, having the structure $-OR$, in which R is a heteroatom-unsubstituted C_n-alkyl, as that term is defined above. Heteroatom-unsubstituted alkoxy groups include: $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, and $-OCH(CH_2)_2$. The term "heteroatom-substituted C_n-alkoxy" refers to a group, having the structure $-OR$, in which R is a heteroatom-substituted C_n-alkyl, as that term is defined above. For example, $-OCH_2CF_3$ is a heteroatom-substituted alkoxy group.

The term "heteroatom-unsubstituted C_n-alkenyloxy" refers to a group, having the structure $-OR$, in which R is a heteroatom-unsubstituted C_n-alkenyl, as that term is defined above. The term "heteroatom-substituted C_n-alkenyloxy" refers to a group, having the structure $-OR$, in which R is a heteroatom-substituted C_n-alkenyl, as that term is defined above.

The term "heteroatom-unsubstituted C_n-alkynyloxy" refers to a group, having the structure $-OR$, in which R is a heteroatom-unsubstituted C_n-alkynyl, as that term is defined above. The term "heteroatom-substituted C_n-alkynyloxy" refers to a group, having the structure $-OR$, in which R is a heteroatom-substituted C_n-alkynyl, as that term is defined above.

The term "heteroatom-unsubstituted C_n-aryloxy" refers to a group, having the structure $-OAr$, in which Ar is a heteroatom-unsubstituted C_n-aryl, as that term is defined above. An example of a heteroatom-unsubstituted aryloxy group is $-OC_6H_5$. The term "heteroatom-substituted C_n-aryloxy" refers to a group, having the structure $-OAr$, in which Ar is a heteroatom-substituted C_n-aryl, as that term is defined above.

The term "heteroatom-unsubstituted C_n-aralkyloxy" refers to a group, having the structure $-OR_{Ar}$, in which R_{Ar} is a heteroatom-unsubstituted C_n-aralkyl, as that term is defined above. The term "heteroatom-substituted C_n-aralkyloxy" refers to a group, having the structure $-OR_{Ar}$, in which R_{Ar} is a heteroatom-substituted C_n-aralkyl, as that term is defined above.

The term "heteroatom-unsubstituted C_n-acyloxy" refers to a group, having the structure –OAc, in which Ac is a heteroatom-unsubstituted C_n-acyl, as that term is defined above. A heteroatom-unsubstituted acyloxy group includes alkylcarbonyloxy and arylcarbonyloxy groups. For example, $-OCOCH_3$ is an example of a heteroatom-unsubstituted acyloxy group. The term "heteroatom-substituted C_n-acyloxy" refers to a group, having the structure –OAc, in which Ac is a heteroatom-substituted C_n-acyl, as that term is defined above. A heteroatom-substituted acyloxy group includes alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, and alkylthiocarbonyl groups.

The term "heteroatom-unsubstituted C_n-alkylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having one or two saturated carbon atoms attached to the nitrogen atom, further having a linear or branched, cyclic or acyclic structure, containing a total of n carbon atoms, all of which are nonaromatic, 4 or more hydrogen atoms, a total of 1 nitrogen atom, and no additional heteroatoms. For example, a heteroatom-unsubstituted C_1-C_{10}-alkylamino has 1 to 10 carbon atoms. The term "heteroatom-unsubstituted C_n-alkylamino" includes groups, having the structure –NHR, in which R is a heteroatom-unsubstituted C_n-alkyl, as that term is defined above. A heteroatom-unsubstituted alkylamino group would include $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH(CH_2)_2$, $-NHCH_2CH_2CH_2CH_3$, $-NHCH(CH_3)CH_2CH_3$, $-NHCH_2CH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(CH_3)CH_2CH_3$, $-N(CH_2CH_3)_2$, *N*-pyrrolidinyl, and *N*-piperidinyl. The term "heteroatom-substituted C_n-alkylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having one or two saturated carbon atoms attached to the nitrogen atom, no carbon-carbon double or triple bonds, further having a linear or branched, cyclic or acyclic structure, further having a total of n carbon atoms, all of which are nonaromatic, 0, 1, or more than one hydrogen atom, and at least one additional heteroatom, that is, in addition to the nitrogen atom at the point of attachment, wherein each additional heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_1-C_{10}-alkylamino has 1 to 10 carbon atoms. The term "heteroatom-substituted C_n-alkylamino" includes groups, having the

structure –NHR, in which R is a heteroatom-substituted C_n-alkyl, as that term is defined above.

The term "heteroatom-unsubstituted C_n-alkenylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having one or two carbon atoms attached to the nitrogen atom, further having a linear or branched, cyclic or acyclic structure, containing at least one nonaromatic carbon-carbon double bond, a total of n carbon atoms, 4 or more hydrogen atoms, a total of one nitrogen atom, and no additional heteroatoms. For example, a heteroatom-unsubstituted C_2-C_{10}-alkenylamino has 2 to 10 carbon atoms. The term "heteroatom-unsubstituted C_n-alkenylamino" includes groups, having the structure –NHR, in which R is a heteroatom-unsubstituted C_n-alkenyl, as that term is defined above. Examples of heteroatom-unsubstituted C_n-alkenylamino groups also include dialkenylamino and alkyl(alkenyl)amino groups. The term "heteroatom-substituted C_n-alkenylamino" refers to a radical having a single nitrogen atom as the point of attachment and at least one nonaromatic carbon-carbon double bond, but no carbon-carbon triple bonds, further having one or two carbon atoms attached to the nitrogen atom, further having a linear or branched, cyclic or acyclic structure, further having a total of n carbon atoms, 0, 1, or more than one hydrogen atom, and at least one additional heteroatom, that is, in addition to the nitrogen atom at the point of attachment, wherein each additional heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_2-C_{10}-alkenylamino has 2 to 10 carbon atoms. The term "heteroatom-substituted C_n-alkenylamino" includes groups, having the structure –NHR, in which R is a heteroatom-substituted C_n-alkenyl, as that term is defined above.

The term "heteroatom-unsubstituted C_n-alkynylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having one or two carbon atoms attached to the nitrogen atom, further having a linear or branched, cyclic or acyclic structure, containing at least one carbon-carbon triple bond, a total of n carbon atoms, at least one hydrogen atoms, a total of one nitrogen atom, and no additional heteroatoms. For example, a heteroatom-unsubstituted C_2-C_{10}-alkynylamino has 2 to 10 carbon atoms. The term "heteroatom-unsubstituted C_n-alkynylamino" includes groups, having the structure –NHR, in which R is a heteroatom-unsubstituted C_n-alkynyl, as that term is defined above. An alkynylamino group includes dialkynylamino and alkyl(alkynyl)amino groups. The term "heteroatom-substituted C_n-alkynylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having one or two carbon atoms attached to the nitrogen atom, further having at least one nonaromatic carbon-carbon triple bond, further having a

linear or branched, cyclic or acyclic structure, and further having a total of n carbon atoms, 0, 1, or more than one hydrogen atom, and at least one additional heteroatom, that is, in addition to the nitrogen atom at the point of attachment, wherein each additional heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_2-C_{10}-alkynylamino has 2 to 10 carbon atoms. The term "heteroatom-substituted C_n-alkynylamino" includes groups, having the structure –NHR, in which R is a heteroatom-substituted C_n-alkynyl, as that term is defined above.

The term "heteroatom-unsubstituted C_n-arylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having at least one aromatic ring structure attached to the nitrogen atom, wherein the aromatic ring structure contains only carbon atoms, further having a total of n carbon atoms, 6 or more hydrogen atoms, a total of one nitrogen atom, and no additional heteroatoms. For example, a heteroatom-unsubstituted C_6-C_{10}-arylamino has 6 to 10 carbon atoms. The term "heteroatom-unsubstituted C_n-arylamino" includes groups, having the structure –NHR, in which R is a heteroatom-unsubstituted C_n-aryl, as that term is defined above. A heteroatom-unsubstituted arylamino group includes diarylamino and alkyl(aryl)amino groups. The term "heteroatom-substituted C_n-arylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having a total of n carbon atoms, at least one hydrogen atom, at least one additional heteroatoms, that is, in addition to the nitrogen atom at the point of attachment, wherein at least one of the carbon atoms is incorporated into one or more aromatic ring structures, further wherein each additional heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_6-C_{10}-arylamino has 6 to 10 carbon atoms. The term "heteroatom-substituted C_n-arylamino" includes groups, having the structure –NHR, in which R is a heteroatom-substituted C_n-aryl, as that term is defined above. A heteroatom-substituted arylamino group includes heteroarylamino groups.

The term "heteroatom-unsubstituted C_n-aralkylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having one or two saturated carbon atoms attached to the nitrogen atom, further having a total of n carbon atoms, wherein at least 6 of the carbon atoms form an aromatic ring structure containing only carbon atoms, 8 or more hydrogen atoms, a total of one nitrogen atom, and no additional heteroatoms. For example, a heteroatom-unsubstituted C_7-C_{10}-aralkylamino has 7 to 10 carbon atoms. The term "heteroatom-unsubstituted C_n-aralkylamino" includes groups, having the structure –NHR, in which R is a heteroatom-unsubstituted C_n-aralkyl, as that term is defined above. An

aralkylamino group includes diaralkylamino groups. The term "heteroatom-substituted C_n-aralkylamino" refers to a radical having a single nitrogen atom as the point of attachment, further having at least one or two saturated carbon atoms attached to the nitrogen atom, further having a total of n carbon atoms, 0, 1, or more than one hydrogen atom, at least one additional heteroatom, that is, in addition to the nitrogen atom at the point of attachment, wherein at least one of the carbon atom incorporated into an aromatic ring, further wherein each heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_7-C_{10}-aralkylamino has 7 to 10 carbon atoms. The term "heteroatom-substituted C_n-aralkylamino" includes groups, having the structure –NHR, in which R is a heteroatom-substituted C_n-aralkyl, as that term is defined above. The term "heteroatom-substituted aralkylamino" includes the term "heteroaralkylamino."

The term amido includes *N*-alkyl-amido, *N*-aryl-amido, *N*-aralkyl-amido, acylamino, alkylcarbonylamino, arylcarbonylamino, and ureido groups. The group, $-NHCOCH_3$, is an example of a heteroatom-unsubstituted amido group. The term "heteroatom-unsubstituted C_n-amido" refers to a radical having a single nitrogen atom as the point of attachment, further having a carbonyl group attached via its carbon atom to the nitrogen atom, further having a linear or branched, cyclic or acyclic structure, further having a total of n carbon atoms, 1 or more hydrogen atoms, a total of one oxygen atom, a total of one nitrogen atom, and no additional heteroatoms. For example, a heteroatom-unsubstituted C_1-C_{10}-amido has 1 to 10 carbon atoms. The term "heteroatom-unsubstituted C_n-amido" includes groups, having the structure –NHR, in which R is a heteroatom-unsubstituted C_n-acyl, as that term is defined above. The term "heteroatom-substituted C_n-amido" refers to a radical having a single nitrogen atom as the point of attachment, further having a carbonyl group attached via its carbon atom to the nitrogen atom, further having a linear or branched, cyclic or acyclic structure, further having a total of n aromatic or nonaromatic carbon atoms, 0, 1, or more than one hydrogen atom, at least one additional heteroatom in addition to the oxygen of the carbonyl group and the nitrogen atom at the point of attachment, wherein each additional heteroatom is independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. For example, a heteroatom-substituted C_1-C_{10}-amido has 1 to 10 carbon atoms. The term "heteroatom-substituted C_n-amido" includes groups, having the structure –NHR, in which R is a heteroatom-unsubstituted C_n-acyl, as that term is defined above. The group, $-NHCO_2CH_3$, is an example of a heteroatom-substituted amido group.

In addition, atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C. Similarly, it is contemplated that one or more carbon atom(s) of a compound of the present invention may be replaced by a silicon atom(s). Similarly, it is contemplated that one or more oxygen atom(s) of a compound of the present invention may be replaced by a sulfur or a selenium atom(s).

Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to the atom.

The use of the word "a" or "an," when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

The term "effective," as that term is used in the specification and/or claims, means adequate to accomplish a desired, expected, or intended result.

The term "hydrate" when used as a modifier to a compound means that the compound has less than one (*e.g.*, hemihydrate), one (*e.g.*, monohydrate), or more than one (*e.g.*, dihydrate) water molecules associated with each compound molecule, such as in solid forms of the compound.

As used herein, the term "IC_{50}" refers to an inhibitory dose which is 50% of the maximum response obtained.

An "isomer" of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term "patient" or "subject" refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic

species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylicacids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, *o*-(4-hydroxybenzoyl)benzoic acid, oxalic acid, *p*-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, *p*-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (P. H. Stahl & C. G. Wermuth eds., Verlag Helvetica Chimica Acta, 2002),

As used herein, "predominantly one enantiomer" means that a compound contains at least about 85% of one enantiomer, or more preferably at least about 90% of one enantiomer,

or even more preferably at least about 95% of one enantiomer, or most preferably at least about 99% of one enantiomer. Similarly, the phrase "substantially free from other optical isomers" means that the composition contains at most about 15% of another enantiomer or diastereomer, more preferably at most about 10% of another enantiomer or diastereomer, even more preferably at most about 5% of another enantiomer or diastereomer, and most preferably at most about 1% of another enantiomer or diastereomer.

"Prevention" or "preventing" includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

The term "saturated" when referring to an atom means that the atom is connected to other atoms only by means of single bonds.

A "stereoisomer" or "optical isomer" is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers.

"Therapeutically effective amount" or "pharmaceutically effective amount" means that amount which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

As used herein, the term "water soluble" means that the compound dissolves in water at least to the extent of 0.010 mole/liter or is classified as soluble according to literature precedence.

Other abbreviations used herein are as follows: DMSO, dimethyl sulfoxide; NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NGF, nerve growth

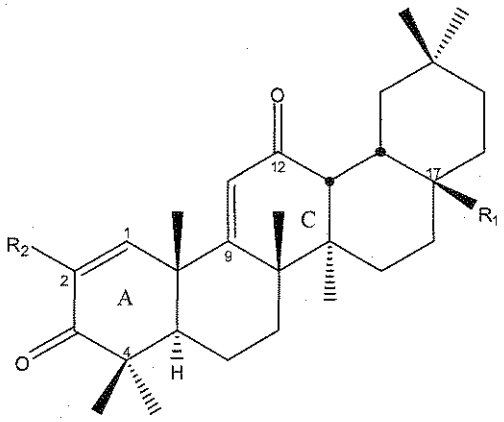
factor; IBMX, isobutylmethylxanthine; FBS, fetal bovine serum; GPDH, glycerol 3-phosphate dehydrogenase; RXR, retinoid X receptor; TGF-β, transforming growth factor-β; IFNγ or IFN-γ, interferon-γ; LPS, bacterial endotoxic lipopolysaccharide; TNFα or TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MTBE, methyl-*tert*-butylether; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; TCA, trichloroacetic acid; HO-1, inducible heme oxygenase.

The above definitions supersede any conflicting definition in any of the reference that is incorporated by reference herein.

III. Synthetic Triterpenoids

Triterpenoids, biosynthesized in plants by the cyclization of squalene, are used for medicinal purposes in many Asian countries; and some, like ursolic and oleanolic acids, are known to be anti-inflammatory and anti-carcinogenic (Huang *et al.*, 1994; Nishino *et al.*, 1988). However, the biological activity of these naturally-occurring molecules is relatively weak, and therefore the synthesis of new analogs to enhance their potency was undertaken (Honda *et al.*, 1997; Honda *et al.*, 1998). Subsequent research has identified a number of synthetic compounds that have improved activity as compared to the naturally-occurring triterpenoids.

The ongoing efforts for the improvement of anti-inflammatory and antiproliferative activity of oleanolic and ursolic acid analogs led to the discovery of 2-cyano-3,12-dioxooleane-1,9(11)-dien-28-oic acid (CDDO, RTA 402) and related compounds (*e.g.*, CDDO-Me, TP-225, CDDO-Im) (Honda *et al.*, 1997, 1998, 1999, 2000a, 2000b, 2002; Suh *et al.*, 1998; 1999; 2003; Place *et al.*, 2003; Liby *et al.*, 2005). In the case of inducing cytoprotective genes through Keap1-Nrf2-antioxidant response element (ARE) signaling, a recent structure activity evaluation of 15 triterpenoids noted the importance of Michael acceptor groups on both the A and C rings, a nitrile group at C-2 of the A ring, and that substituents at C-17 affected pharmacodynamic action *in vivo* (Yates *et al.*, 2007).



In general, CDDO is the prototype for a large number of compounds in a family of agents that have been shown useful in a variety of contexts. For example, CDDO-Me and CDDO-Im are reported to possess the ability to modulate transforming growth factor-β (TGF-β)/Smad signaling in several types of cells (Suh *et al.*, 2003; Minns *et al.*, 2004; Mix *et al.*, 2004). Both are known to be potent inducers of heme-oxygenase-1 and Nrf2/ARE signaling (Liby *et al.*, 2005), and a series of synthetic triterpenoid (TP) analogs of oleanolic acid have also been shown to be potent inducers of the phase 2 response, that is elevation of NAD(P)H-quinone oxidoreductase and heme oxygenase 1 (HO-1), which is a major protector of cells against oxidative and electrophile stress (Dinkova-Kostova *et al.*, 2005). Like previously identified phase 2 inducers, the TP analogs were shown to use the antioxidant response element–Nrf2–Keap1 signaling pathway.

RTA 402 (bardoxolone methyl), one of the compounds for use with the methods of this invention, is an Antioxidant Inflammation Modulator (AIM) in clinical development for inflammation and cancer-related indications that inhibits immune-mediated inflammation by restoring redox homeostasis in inflamed tissues. It induces the cytoprotective transcription factor Nrf2 and suppresses the activities of the pro-oxidant and pro-inflammatory transcription factors NF-κB and STAT3. *In vivo*, RTA 402 has demonstrated significant single agent anti-inflammatory activity in several animal models of inflammation such as renal damage in the cisplatin model and acute renal injury in the ischemia-reperfusion model. In addition, significant reductions in serum creatinine have been observed in patients treated with RTA 402.

In one aspect of the invention, the compounds of the present invention may be used for treating a subject having a renal disease or condition caused by elevated levels of oxidative stress in one or more tissues. The oxidative stress may be accompanied by either

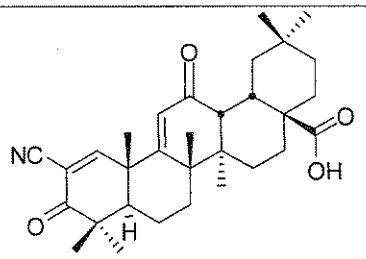
acute or chronic inflammation. The oxidative stress may be caused by acute exposure to an external agent such as ionizing radiation or a cytotoxic chemotherapy agent (*e.g.*, doxorubicin), by trauma or other acute tissue injury, by ischemia/reperfusion injury, by poor circulation or anemia, by localized or systemic hypoxia or hyperoxia, or by other abnormal physiological states such as hyperglycemia or hypoglycemia.

Accordingly, in pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation, treatment may comprise administering to a subject a therapeutically effective amount of a compound of this invention, such as those described above or throughout this specification. Treatment may be administered preventively in advance of a predictable state of oxidative stress (*e.g.*, organ transplantation or the administration of therapy to a cancer patient), or it may be administered therapeutically in settings involving established oxidative stress and inflammation.

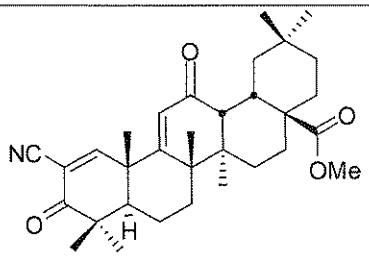
Newer amide derivatives of CDDO have now also been found to be promising agents, for example for their ability to pass through the blood brain barrier. In addition to the methyl amide of CDDO (CDDO-MA), as reported in Honda *et al.* (2002), the invention provides for the use of additional CDDO amide derivatives, such as the ethyl amide (CDDO-EA), as well fluorinated amide derivatives of CDDO, such as the 2,2,2-trifluoroethyl amide derivative of CDDO (CDDO-TFEA).

The compounds of the present invention can be prepared according to the methods taught by Honda *et al.* (1998), Honda *et al.* (2000b), Honda *et al.* (2002), Yates *et al.* (2007), and U.S. Patents 6,326,507 and 6,974,801, which are all incorporated herein by reference.

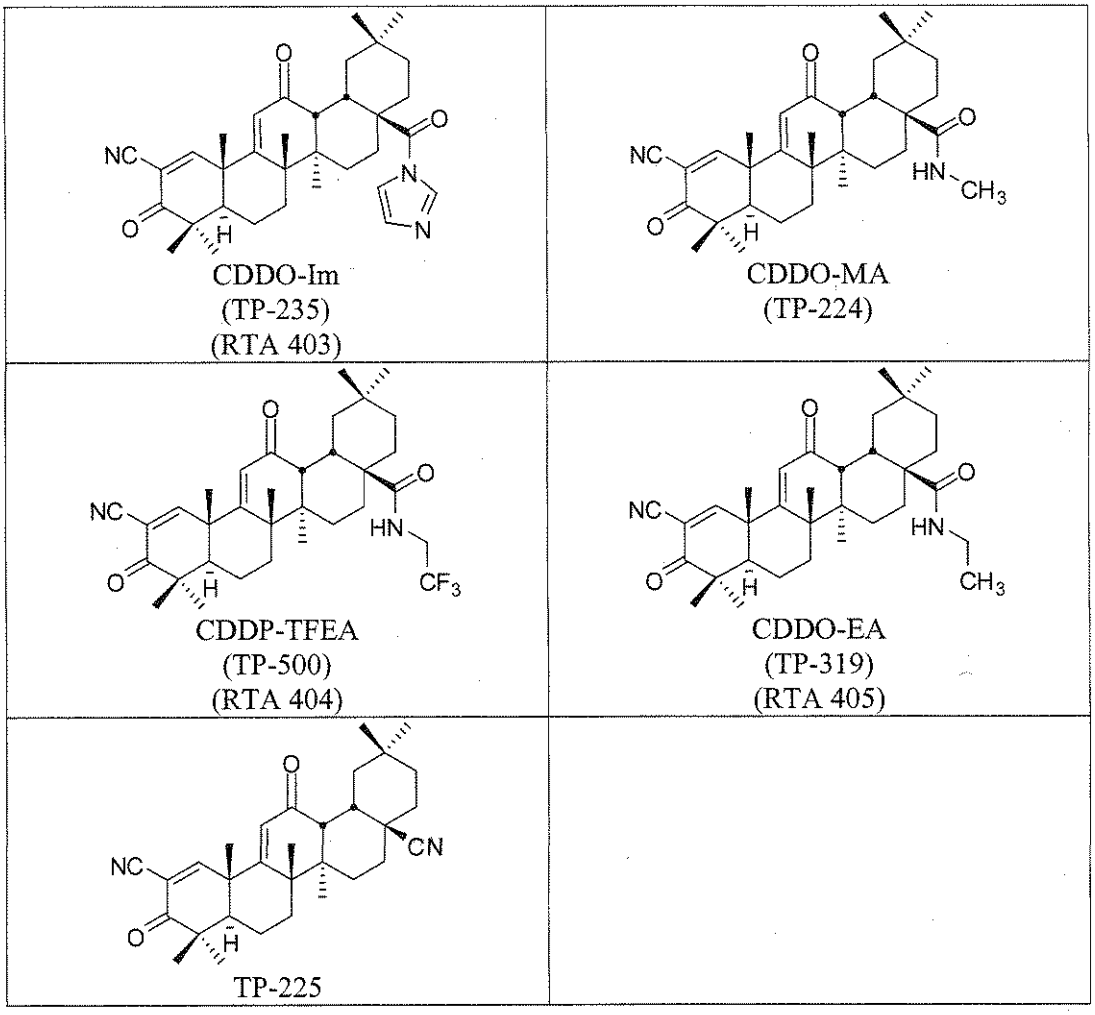
Non-limiting examples of triterpenoids that may be used in accordance with the methods of this invention are shown here.



CDDO
(TP-151)
(RTA 401)



CDDO-Me
bardoxolone methyl
(TP-155)
(RTA 402)



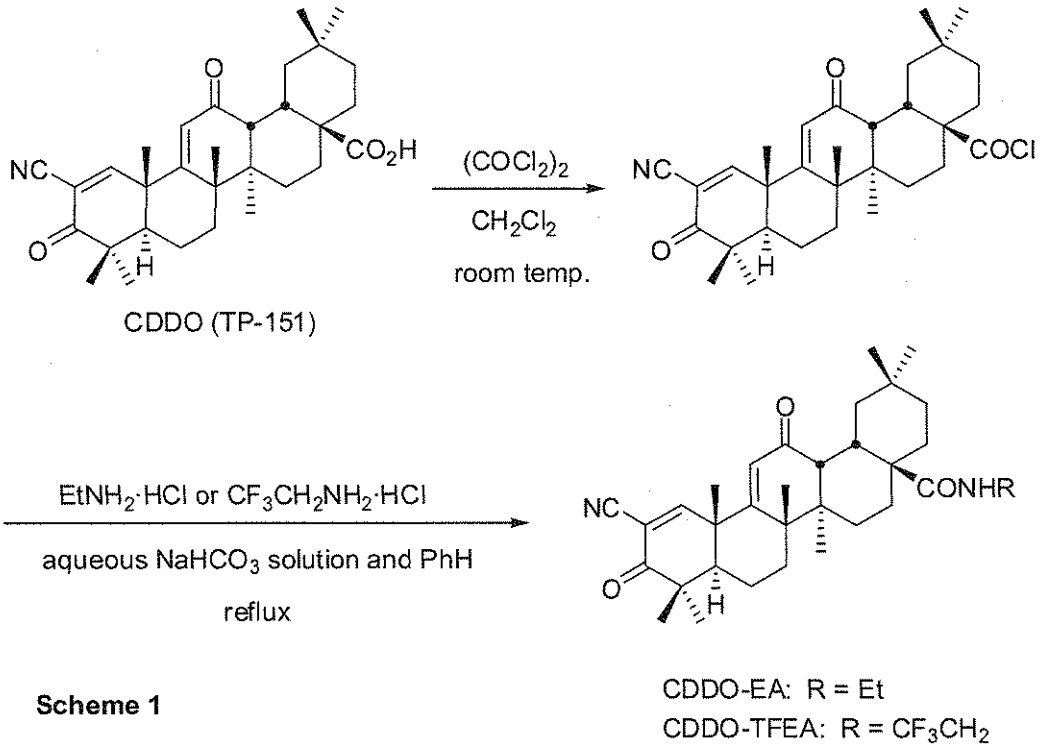
The compounds for use with the present invention, such as those of the table above, are structurally similar to RTA 402 and in many cases exhibit similar biological properties, as has been noted above. As additional examples, Table 1 summarizes *in vitro* results for several of these compounds in which RAW264.7 macrophages were pre-treated with DMSO or drugs at various concentrations (nM) for 2 hours, then treated with 20 ng/ml IFNγ for 24 hours. NO concentration in media was determined using a Griess reagent system; cell viability was determined using WST-1 reagent. NQO1 CD represents the concentration required to induce a two-fold increase in the expression of NQO1, an Nrf2-regulated antioxidant enzyme, in Hepa1c1c7 murine hepatoma cells (Dinkova-Kostova *et al.*, 2005). All these results are orders of magnitude more active than, for example, the parent oleanolic acid molecule. In part because induction of antioxidant pathways resulting from Nrf2 activation provides important protective effects against oxidative stress and inflammation, compounds related to RTA 402 may also provide significant benefits similar to those presented for RTA 402 in this application, and these related compounds may, therefore, be

used for the treatment and/or prevention of diseases, such as: renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, fatty liver disease, cardiovascular disease (CVD), and related disorders.

Table 1. Suppression of IFNγ-induced NO production.

Working ID	RAW264.7 (20 ng/ml IFNγ)		Hepa1c1c7 cells
	NO IC_{50}	WST-1 IC_{50}	NQO1 CD
RTA 401	~10 nM	> 200 nM	2.3 nM
RTA 402	2.2 nM	80 nM	1.0 nM
RTA 403	~0.6 nM	100 nM	3.3 nM
RTA 404	5.8 nM	100 nM	n/a
RTA 405	6 nM	~200 nM	n/a
TP-225	~0.4 nM	75 nM	0.28 nM

The synthesis of CDDO-MA is discussed in Honda *et al.* (2002), which is incorporated herein by reference. The syntheses of CDDO-EA and CDDO-TFEA are presented in Yates *et al.* (2007), which is incorporated herein by reference, and shown in the Scheme 1 below.



CDDO (TP-151)

CDDO-EA: R = Et
CDDO-TFEA: R = CF_3CH_2

Scheme 1

IV. Polymorphic Forms of CDDO-Me

Polymorphic forms of the compounds of the present invention, *e.g.*, Forms A and B of CDDO-Me, may be used in accordance with the methods of this inventions. Form B displays a bioavailability that is surprisingly better than that of Form A (FIG. 15). Specifically the bioavailability of Form B was higher than that of Form A CDDO-Me in monkeys when the monkeys received equivalent dosages of the two forms orally, in gelatin capsules (U.S. Application No. 12/191,176, filed August 13, 2008).

"Form A" of CDDO-Me (RTA 402) is unsolvated (non-hydrous) and can be characterized by a distinctive crystal structure, with a space group of $P4_3\,2_12$ (no. 96) unit cell dimensions of a = 14.2 Å, b = 14.2 Å and c = 81.6 Å, and by a packing structure, whereby three molecules are packed in helical fashion down the crystallographic *b* axis. In some embodiments, Form A can also be characterized by X-ray powder diffraction (XRPD) pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ. In some variations, the X-ray powder diffraction of Form A is substantially as shown in FIG. 12A or FIG. 12B.

Unlike Form A, "Form B" of CDDO-Me is in a single phase but lacks such a defined crystal structure. Samples of Form B show no long-range molecular correlation, *i.e.*, above roughly 20 Å. Moreover, thermal analysis of Form B samples reveals a glass transition temperature (T_g) in a range from about 120 °C to about 130 °C (FIG. 14). In contrast, a disordered nanocrystalline material does not display a T_g but instead only a melting temperature (T_m), above which crystalline structure becomes a liquid. Form B is typified by an XRPD spectrum (FIG 12C) differing from that of Form A (FIG. 12A or FIG. 12B). Since it does not have a defined crystal structure, Form B likewise lacks distinct XRPD peaks, such as those that typify Form A, and instead is characterized by a general "halo" XRPD pattern. In particular, the non-crystalline Form B falls into the category of "X-ray amorphous" solids because its XRPD pattern exhibits three or fewer primary diffraction halos. Within this category, Form B is a "glassy" material.

Form A and Form B of CDDO-Me are readily prepared from a variety of solutions of the compound. For example, Form B can be prepared by fast evaporation or slow evaporation in MTBE, THF, toluene, or ethyl acetate. Form A can be prepared in several ways, including via fast evaporation, slow evaporation, or slow cooling of a CDDO-Me solution in ethanol or methanol. Preparations of CDDO-Me in acetone can produce either Form A, using fast evaporation, or Form B, using slow evaporation.

Various means of characterization can be used together to distinguish Form A and Form B CDDO-Me from each other and from other forms of CDDO-Me. Illustrative of the techniques suitable for this purpose are solid state Nuclear Magnetic Resonance (NMR), X-ray powder diffraction (compare FIGS. 12A & B with FIG. 12C), X-ray crystallography, Differential Scanning Calorimetry (DSC) (compare FIG. 13 with FIG. 14), dynamic vapor sorption/desorption (DVS), Karl Fischer analysis (KF), hot stage microscopy, modulated differential screening calorimetry, FT-IR, and Raman spectroscopy. In particular, analysis of the XRPD and DSC data can distinguish Form A, Form B, and a hemibenzenate forms of CDDO-Me (U.S. Application No. 12/191,176, filed August 13, 2008.)

Additional details regarding polymorphic forms of CDDO-Me are described in U.S. Provisional Application No. 60/955,939, filed August 15, 2007, and the corresponding non-provisional U.S. Application No. 12/191,176, filed August 13, 2008, which are both incorporated herein by reference in their entireties.

V. Use of Triterpenoids for the Treatment of Chronic Kidney Disease, Insulin Resistance/Diabetes and Endothelial Dysfunction/Cardiovascular Disease

The compounds and methods of this invention may be used for treating various aspects of renal/kidney disease, including both acute and chronic indications. In general, the method will comprise administering to the subjects pharmaceutically effective amounts of a compound of this invention.

Inflammation contributes significantly to the pathology of chronic kidney disease (CKD). There is also a strong mechanistic link between oxidative stress and renal dysfunction. The NF-κB signaling pathway plays an important role in the progression of CKD as NF-κB regulates the transcription of MCP-1, a chemokine that is responsible for the recruitment of monocytes/macrophages resulting in an inflammatory response that ultimately injures the kidney (Wardle, 2001). The Keap1/Nrf2/ARE pathway controls the transcription of several genes encoding antioxidant enzymes, including heme oxygenase-1 (HO-1). Ablation of the Nrf2 gene in female mice results in the development of lupus-like glomerular nephritis (Yoh *et al.*, 2001; Ma *et al.*, 2006). Furthermore, several studies have demonstrated that HO-1 expression is induced in response to renal damage and inflammation and that this enzyme and its products – bilirubin and carbon monoxide – play a protective role in the kidney (Nath *et al.*, 2006).

The glomerulus and the surrounding Bowman's capsule constitute the basic functional unit of the kidney. Glomerular filtration rate (GFR) is the standard measure of renal function.

Creatinine clearance is commonly used to measure GFR. However, the level of serum creatinine is commonly used as a surrogate measure of creatinine clearance. For instance, excessive levels of serum creatinine are generally accepted to indicate inadequate renal function and reductions in serum creatinine over time are accepted as an indication of improved renal function. Normal levels of creatinine in the blood are approximately 0.6 to 1.2 milligrams (mg) per deciliter (dl) in adult males and 0.5 to 1.1 milligrams per deciliter in adult females.

Acute kidney injury (AKI) can occur following ischemia-reperfusion, treatment with certain pharmacological agents such as cisplatin and rapamycin, and intravenous injection of radiocontrast media used in medical imaging. As in CKD, inflammation and oxidative stress contribute to the pathology of AKI. The molecular mechanisms underlying radiocontrast-induced nephropathy (RCN) are not well understood; however, it is likely that a combination of events including prolonged vasoconstriction, impaired kidney autoregulation, and direct toxicity of the contrast media all contribute to renal failure (Tumlin *et al.*, 2006). Vasoconstriction results in decreased renal blood flow and causes ischemia-reperfusion and the production of reactive oxygen species. HO-1 is strongly induced under these conditions and has been demonstrated to prevent ischemia-reperfusion injury in several different organs, including the kidney (Nath *et al.*, 2006). Specifically, induction of HO-1 has been shown to be protective in a rat model of RCN (Goodman *et al.*, 2007). Reperfusion also induces an inflammatory response, in part though activation of NF-κB signaling (Nichols, 2004). Targeting NF-κB has been proposed as a therapeutic strategy to prevent organ damage (Zingarelli *et al.*, 2003).

Without being bound by theory, the potency of the compounds of the present invention, *e.g.*, RTA 402, is largely derived from the addition of α,β-unsaturated carbonyl groups. In *in vitro* assays, most activity of the compounds can be abrogated by the introduction of dithiothreitol (DTT), N-acetyl cysteine (NAC), or glutathione (GSH); thiol containing moieties that interact with α,β-unsaturated carbonyl groups (Wang *et al.*, 2000; Ikeda *et al.*, 2003; 2004; Shishodia *et al.*, 2006). Biochemical assays have established that RTA 402 directly interacts with a critical cysteine residue (C179) on IKKβ (see below) and inhibits its activity (Shishodia *et al.*, 2006; Ahmad *et al.*, 2006). IKKβ controls activation of NF-κB through the "classical" pathway which involves phosphorylation-induced degradation of IκB resulting in release of NF-κB dimers to the nucleus. In macrophages, this pathway is

responsible for the production of many pro-inflammatory molecules in response to TNFα and other pro-inflammatory stimuli.

RTA 402 also inhibits the JAK/STAT signaling pathway at multiple levels. JAK proteins are recruited to transmembrane receptors (*e.g.*, IL-6R) upon activation by ligands such as interferons and interleukins. JAKs then phosphorylate the intracellular portion of the receptor causing recruitment of STAT transcription factors. The STATs are then phosphorylated by JAKs, form dimers, and translocate to the nucleus where they activate transcription of several genes involved in inflammation. RTA 402 inhibits constitutive and IL-6-induced STAT3 phosphorylation and dimer formation and directly binds to cysteine residues in STAT3 (C259) and in the kinase domain of JAK1 (C1077). Biochemical assays have also established that the triterpenoids directly interact with critical cysteine residues on Keap1 (Dinkova-Kostova *et al.*, 2005). Keap1 is an actin-tethered protein that keeps the transcription factor Nrf2 sequestered in the cytoplasm under normal conditions (Kobayashi & Yamamoto, 2005). Oxidative stress results in oxidation of the regulatory cysteine residues on Keap1 and causes the release of Nrf2. Nrf2 then translocates to the nucleus and binds to antioxidant response elements (AREs) resulting in transcriptional activation of many antioxidant and anti-inflammatory genes. Another target of the Keap1/Nrf2/ARE pathway is heme oxygenase 1 (HO-1). HO-1 breaks down heme into bilirubin and carbon monoxide and plays many antioxidant and anti-inflammatory roles (Maines & Gibbs, 2005). HO-1 has recently been shown to be potently induced by the triterpenoids (Liby *et al.*, 2005), including RTA 402. RTA 402 and many structural analogs have also been shown to be potent inducers of the expression of other Phase 2 proteins (Yates *et al.*, 2007).

RTA 402 is a potent inhibitor of NF-κB activation. Furthermore, RTA 402 activates the Keap1/Nrf2/ARE pathway and induces expression of HO-1. As described below, RTA 402 has demonstrated activity in two animal models of AKI. Furthermore, reduced serum creatinine levels and improvement of glomerular filtration have been observed in the majority of human patients that have been treated with RTA 402 (see Examples below). Significant improvements have now been observed in a Phase II study of patients with diabetic nephropathy. The findings indicate that RTA 402 may be used to improve renal function in patients with diabetic nephropathy through suppression of renal inflammation and improvement of glomerular filtration.

As noted above, both diabetes and essential hypertension are major risk factors for the development of chronic kidney disease and, ultimately, renal failure. Both of these conditions, along with indicators of systemic cardiovascular disease such as hyperlipidemia,

are frequently present in the same patient, especially if that patient is clinically obese. Although the unifying factors are not completely understood, dysfunction of the vascular endothelium has been implicated as a significant pathological factor in systemic cardiovascular disease, chronic kidney disease, and diabetes (see, *e.g.*, Zoccali, 2006). Acute or chronic oxidative stress in vascular endothelial cells has been implicated in the development of endothelial dysfunction, and is strongly associated with chronic inflammatory processes. Therefore, an agent capable of relieving oxidative stress and concomitant inflammation in the vascular endothelium may alleviate dysfunction and restore endothelial homeostasis. Without being bound by theory, compounds of the invention, by stimulating Nrf2-regulated endogenous antioxidant mechanisms, have shown the highly unusual ability to improve parameters related to renal function (*e.g.*, serum creatinine and estimated glomerular filtration rate), glycemic control and insulin resistance (*e.g.*, hemoglobin A1c), and systemic cardiovascular disease (*e.g.*, circulating endothelial cells) in patients having abnormal clinical values for these parameters. Currently, combination therapy is typically required in such patients to achieve improvements in measures of glycemic control and cardiovascular disease, including the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers to alleviate hypertension and slow the progression of chronic kidney disease. By achieving simultaneous and clinically meaningful improvements in all of these parameters, especially measures of renal function, compounds of the invention represent a significant improvement over currently available therapies. In some aspects, the compounds of the present invention may be used to treat a combination of the above conditions as a single therapy, or in combination with fewer additional therapies than would currently be used.

These findings also indicate that administration of RTA 402 may be used to protect patients from kidney damage such as from exposure to radiocontrast agents, as in the case of radiocontrast-induced nephropathy (RCN), as well as in other contexts. In one aspect, the compounds of this invention may be used to treat ischemia-reperfusion- and/or chemotherapy-induced acute renal injury. For example, the results shown in Examples 2 and 3 below demonstrate that RTA 402 is protective in animal models of ischemia-reperfusion- and chemotherapy-induced acute renal injury.

Serum creatinine has been measured in several animal models treated with RTA 402. Significant reductions of serum creatinine levels relative to baseline levels or levels in control animals have been observed in cynomolgus monkeys, beagle dogs, and Sprague-Dawley rats (FIGS. 3A-D). This effect has been observed in rats with both forms of RTA 402 (crystalline and amorphous).

RTA 402 reduces serum creatinine in patients. For example, improvements were observed in cancer patients receiving RTA 402. In humans, nephrotoxicity is a dose-limiting side-effect of treatment with cisplatin. Cisplatin-induced damage to the proximal tubules is thought to be mediated by increased inflammation, oxidative stress, and apoptosis (Yao *et al.*, 2007). Serum creatinine has also been measured in patients with chronic kidney disease (CKD) enrolled in an open label Phase II clinical trial of RTA 402 (Example 6). This study was designed with multiple endpoints, in categories of insulin resistance, endothelial dysfunction/CVD, and CKD, including measurements of hemoglobin A1c (A1c), a widely used phase 3 endpoint for glycemic control.

A1c is a minor component of hemoglobin to which glucose is bound. A1c also is referred to as glycosylated or glucosylated hemoglobin. A1c may be separated by charge and size from the other hemoglobin A components in blood using high performance liquid chromatography (HPLC). Because A1c is not affected by short-term fluctuations in blood glucose concentrations, for example, due to meals, blood can be drawn for A1c testing without regard to when food was eaten. In healthy, non-diabetic patients the A1c level is less than 7% of total hemoglobin. The normal range is 4-5.9%. In poorly controlled diabetes, it can be 8.0% or above. It has been demonstrated that the complications of diabetes can be delayed or prevented if the A1c level can be kept close to 7%.

Recently approved agents typically only reduce A1c levels an amount of 0.4 to 0.80 over six months of treatment, with 28 day improvements typically smaller. The table below shows six-month Hemoglobin A1c Reductions by two approved agents, sitagliptin and pramlintide acetate (Aschner *et al.*, 2006; Goldstein *et al.*, 2007; Pullman *et al.*, 2006).

Drug	**Duration of DM (years)**	**Study Design**	**Mean A1c**	**Change**
Sitagliptin	4.3	+/- placebo with A1c $\geq$ 7.0	8.0	-0.8
	4.4	+/- metformin with A1c $\geq$ 7.5	8.9	-0.7
	6.1	pioglitazone +/- sitagliptin; A1c $\geq$ 7.0	8.1	-0.7
Pramlintide acetate	13	+/- insulin	9.1	-0.4

In comparison, RTA 402 reduces A1c in 28 days in refractory diabetics on top of standard of care. The treatment showed an intent-to-treat reduction of 0.34 (n = 21) and an elevated baseline (≥ 7.0 at baseline) reduction of 0.50 (n = 16). These results are presented in greater detail in the Examples section below. See also FIGS. 6 and 7.

In another aspect, the compounds of this invention may also be used to improve insulin sensitivity and/or glycemic control. For example, hyperinsulinemic euglycemic clamp test results in the study detailed in Example 6 showed that treatment with RTA 402 improved glycemic control. The hyperinsulinemic euglycemic clamp test is a standard method for investigating and quantifying insulin sensitivity. It measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia (DeFronzo *et al.*, 1979).

The typical procedure is as follows: Through a peripheral vein, insulin is infused at 10-120 mU per m^2 per minute. In order to compensate for the insulin infusion, glucose 20% is infused to maintain blood sugar levels between 5 and 5.5 mmol/liter. The rate of glucose infusion is determined by checking the blood sugar levels every 5 to 10 minutes.

Typically, low-dose insulin infusions are more useful for assessing the response of the liver, whereas high-dose insulin infusions are useful for assessing peripheral (*i.e.*, muscle and fat) insulin action.

Results are typically evaluated as follows: The rate of glucose infusion during the last 30 minutes of the test determines insulin sensitivity. If high levels (7.5 mg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/min or lower) indicate that the body is resistant to insulin action. Levels between 4.0 and 7.5 mg/min may not be definitive and may suggest "impaired glucose tolerance," an early sign of insulin resistance.

The methods of this invention may be used to improve renal function. As shown in Example 6, treatment using RTA 402 has been shown to improve six measures of renal function and status, including serum creatinine based eGFR, creatinine clearance, BUN, Cystatin C, Adiponectin, and Angiotensin II. RTA 402 was shown to increase GFR in a dose-dependent manner and with high response rate (86%; n = 22). As also shown in FIG. 9, the 28 day GFR improvements were reversible after the drug was withdrawn.

In some embodiments, treatment methods of this invention result in improved levels of Adiponectin and/or Angiotensin II. Adiponectin and Angiotensin II are typically elevated in DN patients and correlate with renal disease severity. Adiponectin (also referred to as Acrp30, apM1) is a hormone known to modulate a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin is secreted from adipose tissue into

the bloodstream and is abundant in plasma relative to many other hormones. Levels of the hormone are inversely correlated with body fat percentage in adults, while the association in infants and young children is more unclear. The hormone plays a role in the suppression of the metabolic derangements that may result in type 2 diabetes, obesity, atherosclerosis and non-alcoholic fatty liver disease (NAFLD). Adiponectin can be used to predict all-cause mortality and end stage renal disease in DN patients.

The compounds and methods of this invention may be used for treating various aspects of cardiovascular disease (CVD). The treatment methods of this invention have been found to reduce circulating endothelial cells (CECs) in human patients. CECs are markers of endothelial dysfunction and vascular injury. Endothelial dysfunction is a systemic inflammatory process that is linked to cardiovascular and end-organ damage. Elevated CECs typically correlate with the development, progression, and death from CVD. They also typically correlate with chronic kidney disease and decreased GFR. Historical normal levels are ≤ 5 cells/mL.

Typical features of endothelial dysfunction include the inability of arteries and arterioles to dilate fully in response to an appropriate stimulus. This creates a detectable difference in subjects with endothelial dysfunction versus a normal, healthy endothelium. Such a difference can be tested by a variety of methods including iontophoresis of acetylcholine, intra-arterial administration of various vasoactive agents, localised heating of the skin or temporary arterial occlusion by inflating a blood pressure cuff to high pressures. Testing can also take place in the coronary arteries themselves. These techniques are thought to stimulate the endothelium to release nitric oxide (NO) and possibly some other agents, which diffuse into the surrounding vascular smooth muscle causing vasodilation.

For example, according to the Phase II study results (Example 6), patients treated with RTA 402 for 28 days showed a reduction in cardiovascular inflammatory markers in the form of a reduction in the number of circulating endothelial cells. The reduction in CECs for the intent-to-treat group (n=20) was 27%; the reduction for the elevated baseline group (n=14) was 40% (p=0.02) and nine of those patients showed a normal level for CECs post-treatment. These results are consistent with a reversal of endothelial dysfunction.

The treatment methods of this invention have been found to reduce matrix metallopeptidase 9 (MMP-9), soluble adhesion molecules and tumor necrosis factor (TNFα) in most patients. High levels of these typically correlate with poor cardiovascular outcomes.

VI. Pharmaceutical Formulations and Routes of Administration

Administration of the compounds of the present invention to a patient will follow general protocols for the administration of pharmaceuticals, taking into account the toxicity, if any, of the drug. It is expected that the treatment cycles would be repeated as necessary.

The compounds of the present invention may be administered by a variety of methods, *e.g.*, orally or by injection (*e.g.* subcutaneous, intravenous, intraperitoneal, *etc.*). Depending on the route of administration, the active compounds may be coated by a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. They may also be administered by continuous perfusion/infusion of a disease or wound site. Specific examples of formulations, including a polymer-based dispersion of CDDO-Me that showed improved oral bioavailability, are provided in U.S. Application No. 12/191,176, filed August 13, 2008, which is incorporated herein by reference in its entirety. It will be recognized by those skilled in the art that other methods of manufacture may be used to produce dispersions of the present invention with equivalent properties and utility (see Repka *et al.*, 2002 and references cited therein). Such alternative methods include but are not limited to solvent evaporation, extrusion, such as hot melt extrusion, and other techniques.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a patient in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.*, 1984).

The therapeutic compound may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Dispersions may be prepared in, *e.g.*, glycerol, liquid polyethylene glycols, mixtures thereof, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol,

propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile carrier which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient (*i.e.*, the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent

on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of a selected condition in a patient.

The therapeutic compound may also be administered topically to the skin, eye, or mucosa. Alternatively, if local delivery to the lungs is desired the therapeutic compound may be administered by inhalation in a dry-powder or aerosol formulation.

The actual dosage amount of a compound of the present invention or composition comprising a compound of the present invention administered to a subject may be determined by physical and physiological factors such as age, sex, body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the subject and on the route of administration. These factors may be determined by a skilled artisan. The practitioner responsible for administration will typically determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. The dosage may be adjusted by the individual physician in the event of any complication.

In some embodiments, the pharmaceutically effective amount is a daily dose from about 0.1 mg to about 500 mg of the compound. In some variations, the daily dose is from about 1 mg to about 300 mg of the compound. In some variations, the daily dose is from about 10 mg to about 200 mg of the compound. In some variations, the daily dose is about 25 mg of the compound. In other variations, the daily dose is about 75 mg of the compound. In still other variations, the daily dose is about 150 mg of the compound. In further variations, the daily dose is from about 0.1 mg to about 30 mg of the compound. In some variations, the daily dose is from about 0.5 mg to about 20 mg of the compound. In some variations, the daily dose is from about 1 mg to about 15 mg of the compound. In some variations, the daily dose is from about 1 mg to about 10 mg of the compound. In some variations, the daily dose is from about 1 mg to about 5 mg of the compound.

In some embodiments, the pharmaceutically effective amount is a daily dose is 0.01 – 25 mg of compound per kg of body weight. In some variations, the daily dose is 0.05 – 20 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 10 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 5 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 2.5 mg of compound per kg of body weight.

In some embodiments, the pharmaceutically effective amount is a daily dose is of 0.1 – 1000 mg of compound per kg of body weight. In some variations, the daily dose is 0.15 –

20 mg of compound per kg of body weight. In some variations, the daily dose is 0.20 – 10 mg of compound per kg of body weight. In some variations, the daily dose is 0.40 – 3 mg of compound per kg of body weight. In some variations, the daily dose is 0.50 – 9 mg of compound per kg of body weight. In some variations, the daily dose is 0.60 – 8 mg of compound per kg of body weight. In some variations, the daily dose is 0.70 – 7 mg of compound per kg of body weight. In some variations, the daily dose is 0.80 – 6 mg of compound per kg of body weight. In some variations, the daily dose is 0.90 – 5 mg of compound per kg of body weight. In some variations, the daily dose is from about 1 mg to about 5 mg of compound per kg of body weight.

An effective amount typically will vary from about 0.001 mg/kg to about 1,000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 0.1 mg/kg to about 500 mg/kg, from about 0.2 mg/kg to about 250 mg/kg, from about 0.3 mg/kg to about 150 mg/kg, from about 0.3 mg/kg to about 100 mg/kg, from about 0.4 mg/kg to about 75 mg/kg, from about 0.5 mg/kg to about 50 mg/kg, from about 0.6 mg/kg to about 30 mg/kg, from about 0.7 mg/kg to about 25 mg/kg, from about 0.8 mg/kg to about 15 mg/kg, from about 0.9 mg/kg to about 10 mg/kg, from about 1 mg/kg to about 5 mg/kg, from about 100 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, or from about 10.0 mg/kg to about 150 mg/kg, in one or more dose administrations daily, for one or several days (depending, of course, of the mode of administration and the factors discussed above). Other suitable dose ranges include 1 mg to 10,000 mg per day, 100 mg to 10,000 mg per day, 500 mg to 10,000 mg per day, and 500 mg to 1,000 mg per day. In some particular embodiments, the amount is less than 10,000 mg per day with a range, for example, of 750 mg to 9,000 mg per day.

The effective amount may be less than 1 mg/kg/day, less than 500 mg/kg/day, less than 250 mg/kg/day, less than 100 mg/kg/day, less than 50 mg/kg/day, less than 25 mg/kg/day, less than 10 mg/kg/day, or less than 5 mg/kg/day. It may alternatively be in the range of 1 mg/kg/day to 200 mg/kg/day. For example, regarding treatment of diabetic patients, the unit dosage may be an amount that reduces blood glucose by at least 40% as compared to an untreated subject. In another embodiment, the unit dosage is an amount that reduces blood glucose to a level that is within ± 10% of the blood glucose level of a non-diabetic subject.

In other non-limiting examples, a dose may also comprise from about 1 microgram/kg/body weight, about 5 microgram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500

microgram/kg/body weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, to about 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers listed herein, a range of about 1 mg/kg/body weight to about 5 mg/kg/body weight, a range of about 5 mg/kg/body weight to about 100 mg/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, *etc.*, can be administered, based on the numbers described above.

In certain embodiments, a pharmaceutical composition of the present invention may comprise, for example, at least about 0.1% of a compound of the present invention. In other embodiments, the compound of the present invention may comprise between about 2% to about 75% of the weight of the unit, or between about 25% to about 60%, for example, and any range derivable therein.

Single or multiple doses of the agents are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the agent is administered once a day.

The agent(s) may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks there-between. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months, *etc.* In other embodiments, the invention provides that the agent(s) may taken orally and that the timing of which is or is not dependent upon food intake. Thus, for example, the agent can be taken every morning and/or every evening, regardless of when the subject has eaten or will eat.

Non-limiting specific formulations include CDDO-Me polymer dispersions (see U.S. Application No. 12/191,176, filed August 13, 2008, which is incorporated herein by reference). Some of the formulations reported therein exhibited higher bioavailability than either the micronized Form A or nanocrystalline Form A formulations. Additionally, the

polymer dispersion based formulations demonstrated further surprising improvements in oral bioavailability relative to the micronized Form B formulations. For example, the methacrylic acid copolymer, Type C and HPMC-P formulations showed the greatest bioavailability in the subject monkeys.

VII. Combination Therapy

In addition to being used as a monotherapy, the compounds of the present invention may also find use in combination therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, administered at the same time, wherein one composition includes a compound of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

Various combinations may be employed, such as when a compound of the present invention is "A" and "B" represents a secondary agent, non-limiting examples of which are described below:

A/B/A	B/A/B	B/B/A	A/A/B	A/B/B	B/A/A	A/B/B/B	B/A/B/B
B/B/B/A	B/B/A/B	A/A/B/B	A/B/A/B	A/B/B/A	B/B/A/A		
B/A/B/A	B/A/A/B	A/A/A/B	B/A/A/A	A/B/A/A	A/A/B/A		

It is contemplated that other anti-inflammatory agents may be used in conjunction with the treatments of the current invention. For example, other COX inhibitors may be used, including arylcarboxylic acids (salicylic acid, acetylsalicylic acid, diflunisal, choline magnesium trisalicylate, salicylate, benorylate, flufenamic acid, mefenamic acid, meclofenamic acid and triflumic acid), arylalkanoic acids (diclofenac, fenclofenac, alclofenac, fentiazac, ibuprofen, flurbiprofen, ketoprofen, naproxen, fenoprofen, fenbufen, suprofen, indoprofen, tiaprofenic acid, benoxaprofen, pirprofen, tolmetin, zomepirac, clopinac, indomethacin and sulindac) and enolic acids (phenylbutazone, oxyphenbutazone, azapropazone, feprazone, piroxicam, and isoxicam. See also U.S. Patent 6,025,395, which is incorporated herein by reference.

Dietary and nutritional supplements with reported benefits for treatment or prevention of Parkinson's, Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel disease, and all other diseases whose pathogenesis is believed

to involve excessive production of either nitric oxide (NO) or prostaglandins, such as acetyl-L-carnitine, octacosanol, evening primrose oil, vitamin B6, tyrosine, phenylalanine, vitamin C, L-dopa, or a combination of several antioxidants may be used in conjunction with the compounds of the current invention.

Other particular secondary therapies include immunosuppressants (for transplants and autoimmune-related RKD), anti-hypertensive drugs (for high blood pressure-related RKD, *e.g.*, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), insulin (for diabetic RKD), lipid/cholesterol-lowering agents (*e.g.*, HMG-CoA reductase inhibitors such as atorvastatin or simvastatin), treatments for hyperphosphatemia or hyperparathyroidism associated with CKD (*e.g.*, sevelamer acetate, cinacalcet), dialysis, and dietary restrictions (*e.g.*, protein, salt, fluid, postassium, phosphorus).

VIII. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1 - Materials and Methods

Chemicals. Triterpenoids were synthesized as previously described in Honda *et al.* (1998), Honda *et al.* (2000b), Honda *et al.* (2002) and Yates *et al.* (2007), which are all incorporated herein by reference.

Example 2 – Mouse Ischemia-Reperfusion Results

In a mouse model of ischemic acute renal failure, the renal artery is clamped for approximately twenty minutes. After this time, the clamp is removed and the kidney is reperfused with blood. Ischemia-reperfusion results in renal damage and decreased renal function which can be assessed by blood urea nitrogen (BUN) levels, which become elevated following renal damage. As shown in FIGS. 1a-d, surgically-induced ischemia-reperfusion increased BUN levels by approximately 2-fold. However, in animals treated with 2 mg/kg

RTA 402 orally once daily beginning two days prior to the surgery, the BUN levels were significantly reduced ($p<0.01$) relative to vehicle-treated animals and were similar to the levels in animals that underwent sham surgeries (FIGS. 1a-c). Histological measures of kidney damage and inflammation were also significantly improved by treatment with RTA 402 (FIG. 1d). These data indicate that RTA 402 is protective against ischemia-reperfusion induced tissue damage.

Example 3 – Rat Chemotherapy-Induced Acute Renal Injury Results

In another model of acute renal injury, rats were injected intravenously with the antineoplastic agent cisplatin. In humans, nephrotoxicity is a dose-limiting side effect of treatment with cisplatin. Cisplatin-induced damage to the proximal tubules is thought to be mediated by increased inflammation, oxidative stress, and apoptosis (Yao *et al.*, 2007). Rats treated with a single dose of cisplatin at 6 mg/kg developed renal insufficiency as measured by increased blood levels of creatinine and BUN. Treatment with 10 mg/kg RTA 402 by oral gavage beginning one day prior to treatment with cisplatin and continuing every day significantly reduced blood levels of creatinine and BUN (FIGS. 2a-b). Histological evaluation of the kidneys demonstrated an improvement in the extent of proximal tubule damage in RTA 402-treated animals compared to vehicle-treated animals (FIG. 2c).

Example 4 – Reduction of Serum Creatinine Levels in Several Species

Serum creatinine has been measured in several animal species treated with RTA 402 in the course of toxicology studies. Significant reductions of serum creatinine levels relative to baseline levels or levels in control animals have been observed in cynomolgus monkeys, beagle dogs, and Sprague-Dawley rats (FIGS. 3a-d). This effect has been observed in rats with crystalline and amorphous forms of RTA 402.

Example 5 – Reduced Serum Creatinine and Increased eGFR in Cancer Patients

Serum creatinine has also been measured in patients with cancer enrolled in a Phase I clinical trial of RTA 402. These patients received RTA 402 once daily at doses from 5 to 1,300 mg/day for a total of twenty-one days every 28 days. A reduction in serum creatinine by greater than 15% was observed as early as eight days following treatment initiation and persisted through the end of the cycle (FIG. 4A). This reduction was maintained in those patients that received six or more cycles of treatment with RTA 402. A subset of patients with pre-existing renal damage (baseline serum creatinine levels of at least 1.5 mg/dl) also

had significant reductions in serum creatinine levels following treatment with RTA 402. In these patients, serum creatinine levels decreased progressively throughout the cycle such that the Day 21 levels were approximately 25% lower than baseline levels (FIG. 4A). These results can be summarized as shown in the table below.

	All patients	Sub-set with elevated baseline serum creatinine levels
Number of patients who received drug for at least 3 weeks	45	8
% of Patients with Decrease on Day 21	87%	100%
% Serum Creatinine Decrease from Baseline	-18.3%	-24.5%
p-value (Baseline versus Day 21)	0.001	0.0007

The estimated glomerular filtration rate (eGFR) significantly improved in the patients treated with RTA 402 (FIG. 4B).

FIG. 5 shows the results following at least six months of RTA 402 treatment in eleven cancer patients, showing that eGFR improved in an approximately continuous manner. Some of these patients were enrolled in the Phase I study, whereas others were enrolled in a study of RTA 402 (in combination with gemcitabine) in patients with pancreatic cancer. The results can be summarized as shown in Table 2, below.

Table 2: eGFR in Patients Receiving RTA 402 for 6 Cycles.

		Solid Tumor Study							Pancreatic Study			
	Pt ID:	**402**	**406**	**408**	**409**	**410**	**421**	**427**	**1001**	**1104**	**1105**	**1106**
	Dose (mg):	5	80	150	150/300	300/600	1300/900	1300	150	300/150	300	300
Cycle (each cycle is 28 days)	BL	109.7	94.2	73.2	48.4	49.9	52.5	70.1	68.8	67.3	82.4	89.0
	1	109.7	125.9	82.1	62.6	69.6	58.6	101.3	78.9	95.7	106.6	106.3
	2	109.7	107.9	77.4	62.6	63.4	66.2	78.3	109.9	71.6	89.3	106.3
	3	95.7	107.9	69.4	62.6	63.4	75.8	88.4	135.7	141.2	106.6	106.3
	4	95.7	125.9	77.4	57.0	69.6	N/A	101.3	175.5	95.7	106.6	131.2
	5	109.7	107.9	77.4	69.2	63.4	88.4	101.3	175.5	114.4	131.6	131.2
	6	95.7	125.9	87.4	69.2	69.6	75.8	101.3	135.7	114.4	170.3	131.2

Example 6 – Phase 2 Study in Patients with Diabetic Nephropathy

Serum creatinine has also been measured in patients with chronic kidney disease (CKD) enrolled in an open label Phase II clinical trial of RTA 402. These patients received RTA 402 once daily at three dose levels, 25 mg, 75 mg and 150 mg, for a total of 28 days.

The study was designed with multiple endpoints, in categories of insulin resistance, endothelial dysfunction/CVD, and CKD. These can be summarized as follows:

Insulin Resistance/ Diabetes	**Endothelial Dysfunction/ Cardiovascular**	**Chronic Kidney Disease**
Hgb A1c	CECs	GFR
GDR/Euglycemic Clamp	C-Reactive Protein (CRP)	Serum Creatinine
Glucose	E-Selectin	Creatinine Clearance
	VCAM	Cystatin C
	Cytokines	Adiponectin
		Angiotensin II

A primary outcome measure for this study is determining the effects of RTA 402 administered orally at the three dose strengths on the glomerular filtration rate (as estimated by the MDRD formula) in patients with diabetic nephropathy.

Secondary outcome measures include: (1) an evaluation of the safety and tolerability of oral RTA 402 administered orally at the three different doses, in this patient population; (2) an evaluation of the effects of RTA 402 administered orally at the three dose strengths on the serum creatinine level, creatinine clearance, and urine albumin/creatinine ratio in patients with diabetic nephropathy; (3) an evaluation of the effects of RTA 402 administered orally at the three dose strengths on hemoglobin A1c in all patients enrolled and on insulin response by the hyperinsulinemic euglycemic clamp test in patients enrolled at only one of the study centers; (4) an evaluation of the effects of RTA 402 at the three different doses on a panel of markers of inflammation, renal injury, oxidative stress, and endothelial cell dysfunction.

The patient population selected for this study all had type 2 diabetes with CKD. Most had been diagnosed with poor glycemic control for two decades. CKD was established through elevated serum creatinine (SCr) levels. Most of the patients had been diagnosed with cardiovascular disease (CVD) and most were receiving standard of care (SOC) treatment for

diabetes, CKD and CVD, (*e.g.*, insulin, ACEI/ARB, β-blocker, diuretic, and statin). The baseline demographic can be summarized as follows:

Age	59
Diabetes Duration (yrs)	15.4
Diabetic Nephropathy	100%
Non-renal Diabetic Complications[1]	100%
Hypertensive	100%
Hgb A1c(%)	7.9%
Failed Oral Antihyperglycemics	90%
ACEI/ARB Use	80%
Statin Use	50%

[1]Includes neuropathy and retinopathy
All values represent the mean; n = 10; 1st 10 patients to complete study

The patient inclusion criteria were as follows: (1) diagnosis of type 2 diabetes; (2) serum creatinine in women 1.3 - 3.0 mg/dL (115-265 μmol/L), inclusive, and in men 1.5 - 3.0 mg/dL (133-265 μmol/L), inclusive; (3) patient must agree to practice effective contraception; (4) patient must have a negative urine pregnancy test within 72 hours prior to the first dose of study medication; (5) patient is willing and able to cooperate with all aspects of the protocol and is able to communicate effectively; (6) patient is willing and able to provide written informed consent to participate in this clinical study.

The patient exclusion criteria were the following: (1) patients having type 1 (insulin-dependent; juvenile onset) diabetes; (2) patients with known non-diabetic renal disease (nephrosclerosis superimposed on diabetic nephropathy acceptable), or with renal allograft; (3) patients having cardiovascular disease as follows: unstable angina pectoris within 3 months of study entry; myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty/stent within 3 months of study entry; transient ischemic attack within 3 months of study entry; cerebrovascular accident within 3 months of study entry; obstructive valvular heart disease or hypertrophic cardiomyopathy; second or third degree atrioventricular block not successfully treated with a pacemaker; (4) patients with need for chronic (> 2 weeks) immunosuppressive therapy, including corticosteroids (excluding inhaled or nasal steroids) within 3 months of study entry; (5)

patients with evidence of hepatic dysfunction including total bilirubin > 1.5 mg/dL (> 26 micromole/L) or liver transaminase (aspartate aminotransferase [AST] or alanine transferase [ALT]) > 1.5 times upper limit of normal; (6) if female, patient is pregnant, nursing or planning a pregnancy; (7) patients with any concurrent clinical conditions that in the judgment of the investigator could either potentially pose a health risk to the patient while involved in the study or could potentially influence the study outcome; (8) patients having known hypersensitivity to any component of the study drug; (9) patients having known allergy to iodine; (10) patients having undergone diagnostic or intervention procedure requiring a contrast agent within the last 30 days prior to entry into the study; (11) patients with change or dose-adjustment in any of the following medications: ACE inhibitors, angiotensin II blockers, non-steroidal anti inflammatory drugs (NSAIDs), or COX-2 inhibitors within 3 months; other anti-hypertensive, and other anti-diabetic medications within 6 weeks prior to entry into the study; (12) patients having a history of drug or alcohol abuse or having positive test results for any drug of abuse (positive urine drug test and/or alcohol breathalyzer test); (13) patients having participated in another clinical study involving investigational or marketed products within 30 days prior to entry into the study or would concomitantly participate in such a study; (14) patients unable to communicate or cooperate with the Investigator due to language problems, poor mental development or impaired cerebral function.

As of the end of September 2008, there were 32 of 60 patients enrolled in this study. All but one patient was receiving insulin and standard-of-care oral antihyperglycemics.

Treatment with RTA 402 was observed to reduce hemoglobin % A1c in 28 days in refractory diabetics on top of standard of care. The treatment showed an intent-to-treat reduction of approximately 0.25 (n = 56) and an elevated baseline (≥ 7.0 at baseline) reduction of 0.50 (n = 35). Hemoglobin % A1c reduction as a function of baseline severity is shown in FIG. 6, and reduction as a function of dosage is shown in FIG. 7. Patients with advanced (Stage 4) renal disease (GFR from 15-29 ml/min) showed a mean % A1c reduction of approximately 0.77. All reductions were statistically significant.

Hyperinsulinemic euglycemic clamp test results showed that the 28 day treatment also improved glycemic control and insulin sensitivity in the patients, as measured by glucose disposal rate (GDR). Patients exhibited improvements in GDR after the 28 day treatment, with more severely impaired patients (GDR < 4) showing statistically significant improvements ($p \leq 0.02$). The hyperinsulinemic euglycemic clamp test was performed at Baseline (Day −1) and at the end of the study on Day 28. The test measures the rate of

glucose infusion (GINF) necessary to compensate for an increased insulin level without causing hypoglycemia; this value is used to derive the GDR.

In short, the hyperinsulinemic euglycemic clamp test takes about 2 hours. Through a peripheral vein, insulin is infused at 10-120 mU per m^2 per minute. In order to compensate for the insulin infusion, glucose 20% is infused to maintain blood sugar levels between 5 and 5.5 mmol/L. The rate of glucose infusion is determined by checking the blood sugar levels every 5 to 10 minutes. The rate of glucose infusion during the last 30 minutes of the test is used to determine insulin sensitivity as determined by the glucose metabolism rate (M) in mg/kg/min.

The following protocol guidelines are in place for the hyperinsulinemic euglycemic clamp test:

1) Subject to fast 8-10 hours prior to the clamp procedure.
2) The morning of the clamp measure vital signs and weight.
3) Start a retrograde line in one hand with 1¼", 18-20 gauge catheter for drawing samples.
4) Prepare IV tubing with 2 three-way stop cocks and j-loop extension tubing. Spike tubing to a liter bag of 0.9% NaCl to run at KVO (keep vein open, about 10 cc/hr) until the start of the procedure.
5) Apply a heating pad covered in a pillow case with a pad separating the heating pad from the subject's hand. (Enables the collection of shunted arterialized blood from venous catheterization)
6) Monitor the temperature (approximately 150 °F / 65 °C) generated by the heating pad before and during the clamp, to maintain arterialization.
7) Start another line opposite the draw side in the distal forearm with 1¼", 18-20 gauge catheter for the infusion line. Prepare IV tubing with 2 three-way stop cocks.
8) Hang a 500 ml bag of 20% dextrose and attach to port on the infusion side
9) Prepare the insulin infusion
    a. Remove 53 cc (50 cc of overfill) of saline from a 500 cc bag of 0.9% NaCl and discard
    b. Draw 8 cc of blood from subject using sterile technique and inject into a tiger top tube
    c. Centrifuge the tiger top tube. Withdraw 2 cc of serum and inject into the 500 cc bag of 0.9% NaCl

d. Add 100 units of insulin to the bag with the serum and mix well (0.2 U insulin/ml)

e. Connect IV tubing with duo-vent spike into the 0.9% NaCl bag

f. Place on Baxter pump

10) Time and draw all basal blood samples (Baseline fasting blood glucose values will be obtained prior to beginning the insulin prime).

11) Perform insulin infusion rate calculations for a priming dose and 60 mU/m^2 insulin infusion. This background insulin is to suppress endogenous hepatic glucose production. Lean subjects can be suppressed with 40 mU/m^2; obese, insulin resistant subjects require 80 mU/m^2. 60 mU/m^2 should be sufficient to suppress the suggested study population with a BMI of 27-40 kg/m^2. The suggested 60 mU/m^2 insulin infusion may need to be adjusted if the BMI is amended.

12) 0.5 mL samples will be drawn every five minutes and the readings from the YSI Blood Glucose Analyzer will be used to determine/adjust the glucose infusion rate (mg/kg/min). Any additional laboratory tests required by the protocol will be in addition to the blood volume. The clamp will last 120 minutes which is believed to be a sufficient duration for determining insulin sensitivity.

13) Label and save all YSI printouts for source documents.

14) The glucose infusion rates from the last 30 minutes of the euglycemic clamp will be adjusted using space correction. This will be used to determine the glucose metabolism rate (M mg/kg/min), which represents the subject's sensitivity to insulin.

As shown in FIG. 8, RTA 402 reduces circulating endothelial cells (CECs). The mean number of CECs in cells/mL is shown for intent-to-treat (ITT) and elevated baseline groups, both before and after the 28 day RTA treatment. The reduction for the Intent-to-treat group was approximately 20%, and the reduction in the elevated baseline group (>5 CECs/ml) was approximately 33%. The fraction of iNOS-positive CECs was reduced approximately 29%. Normalization of CEC values (≤ 5 cells/mL) was observed in 11 out of the 19 patients with elevated baseline.

CECs were isolated from whole blood by using CD146 Ab (an antibody to the CD146 antigen that is expressed on endothelial cells and leukocytes). After CEC isolation, a FITC (fluorescein isothiocyanate) conjugated CD105 Ab (a specific antibody for endothelial cells) is used to identify CECs using the CellSearch™ system. A fluorescent conjugate of CD45

Ab was added to stain the leukocytes, and these were then gated out. For a general overview of this method, see Blann *et al.*, (2005), which is incorporated herein by reference in its entirety. CEC samples were also assessed for the presence of iNOS by immunostaining. Treatment with RTA 402 reduced iNOS-positive CECs by approximately 29%, further indicating that RTA 402 reduces inflammation in endothelial cells.

RTA 402 was shown to improve significantly eight measures of renal function and status, including serum creatinine based eGFR (FIG. 9), creatinine clearance, BUN (FIG. 11A), serum phosphorus (FIG. 11B), serum uric acid (FIG. 11C), Cystatin C, Adiponectin (FIG. 10A), and Angiotensin II (FIG. 10B). Adiponectin predicts all-cause mortality and end stage renal disease in DN patients. Adiponectin and Angiotensin II, which are elevated in DN patients, correlate with renal disease severity (FIGS. 10A-B). Effects on BUN, phosphorus, and uric acid are shown in FIGS. 11A-C.

Patients treated with higher doses (75 or 150 mg) of RTA 402 showed modest elevations (approximately 20 to 25%) in proteinuria. This is consistent with studies indicating that better GFR performance correlates with increased proteinuria. For example, in a long-term clinical study of more than 25,000 patients, treatment with ramipril (an ACE inhibitor) slowed the rate of eGFR decline more effectively than either telmisartan (an angiotensin receptor blocker) or the combination of ramipril and telmisartan (Mann *et al.*, 2008). Conversely, proteinuria increased more in the ramipril group than in the other two groups. Major renal outcomes were also better with either drug alone than with combination therapy, although proteinuria increased least in the combination therapy group. Other studies have shown that drugs that reduce GFR, such as ACE-inhibitors, also reduce proteinuria (Lozano *et al.*, 2001; Sengul *et al.*, 2006). Other studies have shown that drugs that acutely increase GFR, such as certain calcium channel blockers, increase proteinuria up to 60% during short-term dosing (Agodoa *et al.*, 2001; Viberti *et al.*, 2002).

* * * * * * * * * * * * * * * *

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More

specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

IX. References

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

U.S. Patent 6,025,395

U.S. Patent 6,326,507

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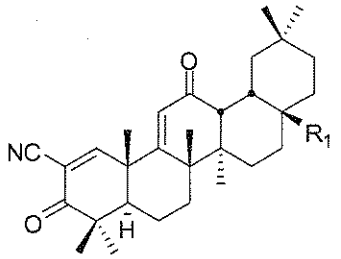
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CLAIMS

1. A method for treating renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, fatty liver disease, or cardiovascular disease (CVD) in a subject comprising, administering to said subject a pharmaceutically effective amount of a compound having the structure:



,

wherein R_1 is:

–CN, or

C_1-C_{15}-acyl or C_1-C_{15}-alkyl, wherein either of these groups is heteroatom-substituted or heteroatom-unsubstituted; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. The method of claim 1, wherein the subject has RKD.

3. The method of claim 2, wherein the RKD is diabetic nephropathy (DN).

4. The method of claim 2, wherein the RKD results from a toxic insult.

5. The method of claim 4, wherein the toxic insult results from an imaging agent or a drug.

6. The method of claim 5, wherein the drug is a chemotherapeutic.

7. The method of claim 2, wherein the RKD results from ischemia/reperfusion injury.

8. The method of claim 2, wherein the RKD results from diabetes or hypertension.

9. The method of claim 2, wherein the RKD results from an autoimmune disease.

10. The method of claim 2, wherein the RKD is chronic RKD.

11. The method of claim 2, wherein the RKD is acute RKD.

12. The method of claim 1, wherein the subject has undergone or is undergoing dialysis.

13. The method of claim 1, wherein the subject has undergone or is a candidate to undergo kidney transplant.

14. The method of claim 1, wherein the subject has RKD and insulin resistance.

15. The method of claim 14, wherein the subject has RKD, insulin resistance and endothelial dysfunction.

16. The method of claim 1, wherein the subject has RKD and diabetes.

17. The method of claim 1, wherein the subject has insulin resistance.

18. The method of claim 1, wherein the subject has diabetes.

19. The method of claim 18, wherein the pharmaceutically effective amount of the compound also effectively treats one or more complications associated with diabetes.

20. The method of claim 19, wherein the complications are selected from the group consisting of obesity, hypertension, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, myonecrosis, retinopathy and metabolic syndrome (syndrome X).

21. The method of claim 20, wherein the complication is metabolic syndrome (syndrome X).

22. The method of claim 18, wherein the diabetes results from insulin resistance.

23. The method of claim 1, wherein the subject has RKD and endothelial dysfunction.

24. The method of claim 1, wherein the subject has RKD and cardiovascular disease.

25. The method of claim 1, wherein the subject has CVD.

26. The method of claim 25, wherein the CVD results from endothelial dysfunction.

27. The method of claim 1, wherein the subject has endothelial dysfunction.

28. The method of claim 27, wherein the subject has endothelial dysfunction and insulin resistance.

29. The method of claim 1, wherein the subject has fatty liver disease.

30. The method of claim 29, wherein the fatty liver disease is non-alcoholic fatty liver disease.

31. The method of claim 29, wherein the fatty liver disease is alcoholic fatty liver disease.

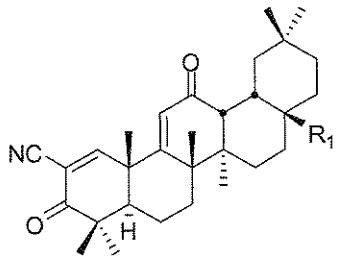
32. The method of claim 29, wherein the subject has fatty liver disease and one or more of the following disorders: renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, and cardiovascular disease (CVD).

33. The method according to any of claims 1-32, further comprising identifying a subject in need of treatment of any of the listed diseases, dysfunctions, resistances or disorders.

34. The method according to any of claims 1-32, wherein the subject has a family or patient history of any of the listed diseases, dysfunctions, resistances or disorders.

35. The method according to any of claims 1-32, wherein the subject exhibits symptoms of any of the listed diseases, dysfunctions, resistances or disorders.

36. A method for improving glomerular filtration rate or creatinine clearance in a subject comprising, administering to said subject a pharmaceutically effective amount of a compound having the structure:



,

wherein R_1 is:

–CN, or

C_1-C_{15}-acyl or C_1-C_{15}-alkyl, wherein either of these groups is heteroatom-substituted or heteroatom-unsubstituted; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

37. The method according to any of claims 1-36, wherein the compound is administered locally.

38. The method according to any of claims 1-36, wherein the compound is administered systemically.

39. The method according to any of claims 1-36, wherein the compound is administered orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularally, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, orally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

40. The method of claim 39, wherein the compound is administered intravenously, intra-arterially or orally.

41. The method of claim 40, wherein the compound is administered orally.

42. The method of claim 41, wherein the compound is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a solid dispersion, a wafer, or an elixir.

43. The method of claim 42, wherein the compound is formulated as a solid dispersion.

44. The method of claim 42, wherein the soft capsule is a gelatin capsule.

45. The method of claim 44, further comprising a protective coating.

46. The method of claim 44, further comprising an agent that delays absorption.

47. The method of claim 42, further comprising an agent that enhances solubility or dispersibility.

48. The method of claim 39, wherein the compound is dispersed in a liposome, an oil in water emulsion or a water in oil emulsion.

49. The method according to any of claims 1-36, wherein the pharmaceutically effective amount is a daily dose from about 0.1 mg to about 500 mg of the compound.

50. The method of claim 49, wherein the daily dose is from about 1 mg to about 300 mg of the compound.

51. The method of claim 50, wherein the daily dose is from about 10 mg to about 200 mg of the compound.

52. The method of claim 51, wherein the daily dose is about 25 mg of the compound.

53. The method of claim 51, wherein the daily dose is about 75 mg of the compound.

54. The method of claim 51, wherein the daily dose is about 150 mg of the compound.

55. The method of claim 49, wherein the daily dose is from about 0.1 mg to about 30 mg of the compound.

56. The method of claim 55, wherein the daily dose is from about 0.5 mg to about 20 mg of the compound.

57. The method of claim 56, wherein the daily dose is from about 1 mg to about 15 mg of the compound.

58. The method of claim 57, wherein the daily dose is from about 1 mg to about 10 mg of the compound.

59. The method of claim 58, wherein the daily dose is from about 1 mg to about 5 mg of the compound.

60. The method according to any of claims 1-36, wherein the pharmaceutically effective amount is a daily dose is 0.01 – 25 mg of compound per kg of body weight.

61. The method of claim 60, wherein the daily dose is 0.05 – 20 mg of compound per kg of body weight.

62. The method of claim 61, wherein the daily dose is 0.1 – 10 mg of compound per kg of body weight.

63. The method of claim 62, wherein the daily dose is 0.1 – 5 mg of compound per kg of body weight.

64. The method of claim 63, wherein the daily dose is 0.1 – 2.5 mg of compound per kg of body weight.

65. The method according to any of claims 1-36, wherein the pharmaceutically effective amount is administered in a single dose per day.

66. The method according to any of claims 1-36, wherein the pharmaceutically effective amount is administered in two or more doses per day.

67. The method according to any of claims 1-36, further comprising a second therapy.

68. The method of claim 67, wherein the second therapy comprises administering to said subject a pharmaceutically effective amount of a second drug.

69. The method of claim 68, wherein the second drug is a cholesterol lowering drug, an anti-hyperlipidemic, a calcium channel blocker, an anti-hypertensive, or an HMG-CoA reductase inhibitor.

70. The method of claim 69, wherein the second drug is amlodipine, aspirin, ezetimibe, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine or nitrendipine.

71. The method of claim 69, wherein the second drug is atenolol, bucindolol, carvedilol, clonidine, doxazosin, indoramin, labetalol, methyldopa, metoprolol, nadolol, oxprenolol, phenoxybenzamine, phentolamine, pindolol, prazosin, propranolol, terazosin, timolol or tolazoline.

72. The method of claim 68, wherein the second drug is a statin.

73. The method of claim 72, wherein the statin is atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin.

74. The method of claim 68, wherein the second drug is a dipeptidyl peptidase-4 (DPP-4) inhibitor.

75. The method of claim 74, wherein the DPP-4 inhibitor is sitagliptin, vildagliptin, SYR-322, BMS 477118 or GSK 823093.

76. The method of claim 68, wherein the second drug is a biguanide.

77. The method of claim 76, wherein the biguanide is metformin.

78. The method of claim 68, wherein the second drug is a thiazolidinedione (TZD).

79. The method of claim 78, wherein the TZD is pioglitazone, rosiglitazone or troglitazone.

80. The method of claim 68, wherein the second drug is a sulfonylurea derivative.

81. The method of claim 80, wherein the sulfonyl urea derivative is selected from the group consisting of tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride and gliclazide.

82. The method of claim 68, wherein the second drug is a meglitinide.

83. The method of claim 82, wherein the meglitinide is selected from the group consisting of repaglinide, mitiglinide and nateglinide.

84. The method of claim 68, wherein the second drug is insulin.

85. The method of claim 68, wherein the second drug is an alpha-glucosidase inhibitor.

86. The method of claim 85, wherein the alpha-glucosidase inhibitor is selected from the group consisting of acarbose, miglitol and voglibose.

87. The method of claim 68, wherein the second drug is a glucagon-like peptide-1 analog.

88. The method of claim 87, wherein the glucagon-like peptide-1 analog is selected from the group consisting of exenatide and liraglutide.

89. The method of claim 68, wherein the second drug is a gastric inhibitory peptide analog.

90. The method of claim 68, wherein the second drug is a GPR40 agonist.

91. The method of claim 68, wherein the second drug is a GPR119 agonist.

92. The method of claim 68, wherein the second drug is a GPR30 agonist.

93. The method of claim 68, wherein the second drug is a glucokinase activator.

94. The method of claim 68, wherein the second drug is a glucagon receptor antagonist.

95. The method of claim 68, wherein the second drug an amylin analog.

96. The method of claim 95, wherein the amylin analog is pramlintide.

97. The method of claim 68, wherein the second drug is an IL-1β receptor antagonist.

98. The method of claim 97, wherein the IL-1β receptor antagonist is anakinra.

99. The method of claim 68, wherein the second drug is an endocannabinoid receptor antagonist or inverse agonist.

100. The method of claim 99, wherein the endocannabinoid receptor antagonist or inverse agonist is rimonabant.

101. The method of claim 68, wherein the second drug is Orlistat.

102. The method of claim 68, wherein the second drug is Sibutramine.

103. The method of claim 68, wherein the second drug is a growth factor.

104. The method of claim 103, wherein the growth factor is TGF-β1, TGF-β2, TGF-β1.2, VEGF, insulin-like growth factor I or II, BMP2, BMP4, BMP7, GLP-1 analog, a GIP analog, a DPP-IV inhibitor, a GPR119 agonist, a GPR40 agonist, gastrin, EGF, betacellulin, KGF, NGF, insulin, growth hormone, HGF, an FGF, an FGF homologue, PDGF, Leptin, prolactin, placental lactogen, PTHrP, activin, inhibin, or INGAP.

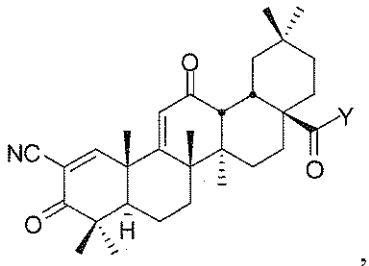
105. The method of claim 103, wherein the growth factor is parathyroid hormone, calcitonin, interleukin-6, or interleukin-11.

106. The method according to any of claims 1-36, wherein the subject is a primate.

107. The method of claim 106, wherein the primate is a human.

108. The method according to any of claims 1-36, wherein the subject is a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

109. The method according to any of claims 1-108, wherein the compound is further defined as



,

wherein Y is:

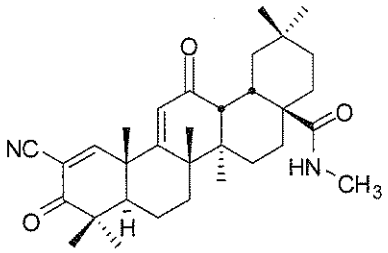
–H, hydroxy, amino, halo, or

C_1-C_{14}-alkoxy, C_2-C_{14}-alkenyloxy, C_2-C_{14}-alkynyloxy, C_1-C_{14}-aryloxy, C_2-C_{14}-aralkoxy, C_1-C_{14}-alkylamino, C_2-C_{14}-alkenylamino, C_2-C_{14}-alkynylamino, C_1-C_{14}-arylamino, C_3-C_{10}-aryl, or C_2-C_{14}-aralkylamino, wherein any of these groups is heteroatom-substituted or heteroatom-unsubstituted; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

110. The method of claim 109, wherein Y is a heteroatom-unsubstituted C_1-C_4-alkylamino.

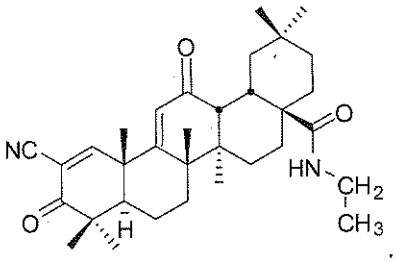
111. The method of claim 110, wherein the compound is further defined as:



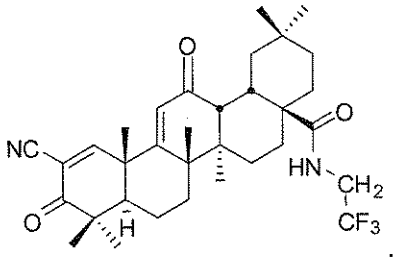
.

112. The method of claim 110, wherein Y is a heteroatom-substituted or heteroatom-unsubstituted C_2-C_4-alkylamino.

113. The method of claim 112, wherein the compound is further defined as:



114. The method of claim 112, wherein the compound is further defined as:

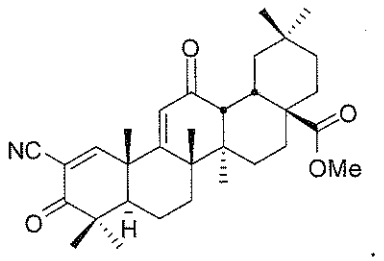


115. The method of claim 109, wherein Y is a heteroatom-substituted or heteroatom-unsubstituted C_1-C_4-alkoxy.

116. The method of claim 115, wherein Y is a heteroatom-unsubstituted C_1-C_4-alkoxy.

117. The method of claim 116, wherein Y is a heteroatom-unsubstituted C_1-C_2-alkoxy.

118. The method of claim 115, wherein the compound is further defined as:



119. The method of claim 118, wherein at least a portion of the compound of claim 118 is present as a polymorphic form, wherein the polymorphic form is a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ.

120. The method of claim 119, wherein the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 12A or FIG. 12B.

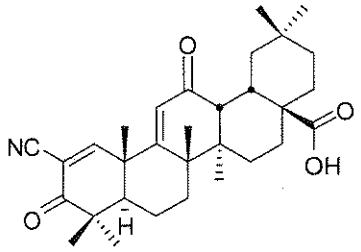
121. The method of claim 118, wherein at least a portion of the compound of claim 118 is present as a polymorphic form, wherein the polymorphic form is an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 12C, and a T_g.

122. The method of claim 121, wherein the T_g value is in the range of about 120 °C to about 135 °C.

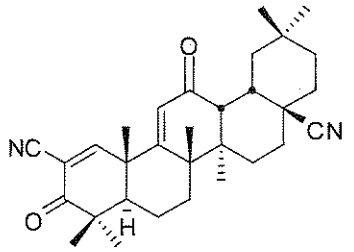
123. The method of claim 122, wherein the T_g value is in the range of about 125 °C to about 130 °C.

124. The method of claim 109, wherein Y is hydroxy.

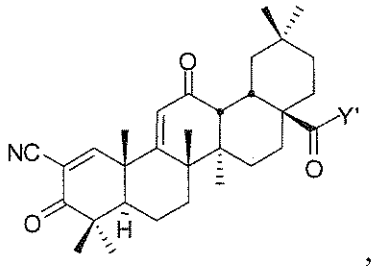
125. The method of claim 124, wherein the compound is further defined as:



126. The method according to any of claims 1-108, wherein the compound is further defined as:

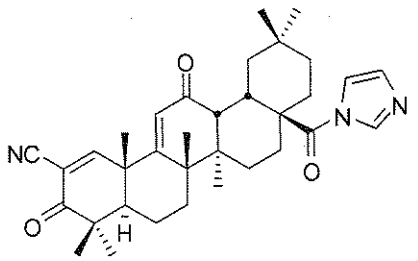


127. The method according to any of claims 1-108, wherein the compound is further defined as



wherein Y' is a heteroatom-substituted or heteroatom-unsubstituted C_1-C_{14}-aryl; or a pharmaceutically acceptable salt, hydrate or solvate thereof.

128. The method of claim 127, wherein the compound is further defined as:



129. The method according to any of claims 1, 36, 109-128, wherein the compound is substantially free from optical isomers thereof.

130. The method according to any of claims 1, 36, 109, 110, 112, 115 and 127, wherein the compound is in the form of a pharmaceutically acceptable salt.

131. The method according to any of claims 1, 36, 109, 110, 112, 115 and 127, wherein the compound is not a salt.

132. The method according to any of claims 1, 36, 109, 110, 112, 115 and 127, wherein the compound is formulated as a pharmaceutical composition comprising (i) a therapeutically effective amount of the compound and (ii) an excipient is (A) a carbohydrate, carbohydrate derivative, or carbohydrate polymer, (B) a synthetic organic polymer, (C) an organic acid salt, (D) a protein, polypeptide, or peptide, or (E) a high molecular weight polysaccharide.

133. The method of claim 132, wherein the excipient is a synthetic organic polymer.

134. The method of claim 133, wherein the excipient is selected from the group consisting of a hydroxpropyl methyl cellulose, a poly[1-(2-oxo-1-pyrrolidinyl)ethylene or copolymer thereof, and a methacrylic acid – methylmethacrylate copolymer.

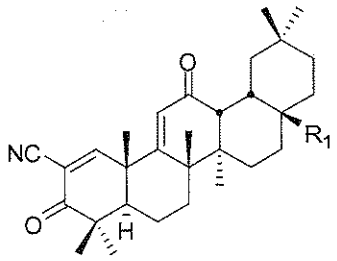
135. The method of claim 134, wherein the excipient is hydroxpropyl methyl cellulose phthalate ester.

136. The method of claim 134, wherein the excipient is PVP/VA.

137. The method of claim 134, wherein the excipient is a methacrylic acid – ethyl acrylate copolymer (1:1).

138. The method of claim 133, wherein the excipient is copovidone.

139. A compound having the structure:



,

wherein R_1 is:

–CN, or

C_1-C_{15}-acyl or C_1-C_{15}-alkyl, wherein either of these groups is heteroatom-substituted or heteroatom-unsubstituted; or

a pharmaceutically acceptable salt, hydrate or solvate thereof for use in a method for improving the glomerular filtration rate or the creatinine clearance in a subject.

140. The compound for the use of claim 139, wherein the subject is in need of a treatment of renal/kidney disease (RKD), insulin resistance, diabetes, a complication associated with diabetes, endothelial dysfunction, fatty liver disease, or cardiovascular disease (CVD).

141. The compound for the use of claim 140, wherein the RKD

(a) is diabetic nephropathy (DN),

(b) is chronic RKD,

(c) is acute RKD,

(d) results from ischemia/reperfusion injury,

(e) results from diabetes or hypertension,

(f) results from an autoimmune disease, or

(g) results from a toxic insult, in particular from a toxic insult resulting from an imaging agent or a drug such as a chemotherapeutic.

142. The compound for the use of any of claims 139 to 141, wherein the subject has undergone or is undergoing dialysis, or wherein the subject has undergone or is a candidate to undergo kidney transplant.

143. The compound for the use of claim 140, wherein the complication is obesity, hypertension, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, myonecrosis, retinopathy, or metabolic syndrome (syndrome X).

144. The compound for the use of claim 140, wherein the diabetes results from insulin resistance, wherein the CVD results from endothelial dysfunction, and/or wherein the fatty liver disease is a non- alcoholic or an alcoholic fatty liver disease.

145. The compound for the use of any of claims 139-144, wherein the compound is administered locally or systemically, in particular wherein the compound is administered orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularally, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, orally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

146. The compound for the use of claim 145, wherein the compound is administered orally and is formulated as a hard or soft capsule such as a gelatin capsule, said gelatin capsule optionally further comprising a protective coating or an agent that delays absorption; is formulated as a tablet, a syrup, a suspension, a solid dispersion, a wafer, or an elixir.

147. The compound for the use of claim 146, the formulation further comprising an agent that enhances solubility or dispersibility.

148. The compound for the use of claim 145, wherein the compound is dispersed in a liposome, an oil in water emulsion or a water in oil emulsion.

149. The compound for the use of any of claims 139-148, wherein the daily dose is 25 mg to 500 mg of the compound, 0.01 – 25 mg of the compound per kg of body weight, in

particular 0.05 – 20 mg, 0.10 – 10 mg, or 0.1 – 5 mg of the compound per kg of body weight.

150. The compound for the use of any of claims 139-149, wherein the compound is administered in a single dose per day or in two or more doses per day.

151. The compound for the use of any of claims 139-150, wherein treatment with the compound is in combination with a second therapy, in particular wherein the second therapy comprises treatment with a second drug such as a cholesterol lowering drug, an anti-hyperlipidemic, a calcium channel blocker, an anti-hypertensive, or an HMG-CoA reductase inhibitor, in particular amlodipine, aspirin, ezetimibe, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, atenolol, bucindolol, carvedilol, clonidine, doxazosin, indoramin, labetalol, methyldopa, metoprolol, nadolol, oxprenolol, phenoxybenzamine, phentolamine, pindolol, prazosin, propranolol, terazosin, timolol, tolazoline, or a statin including atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

152. The compound for the use of any of claims 139-150, wherein treatment with the compound is in combination with a second therapy comprising treatment with a dipeptidyl peptidase-4 (DPP-4) inhibitor such as sitagliptin, vildagliptin, SYR-322, BMS 477118, or GSK 823093; with a biguanide such as metformin, or with a thiazolidinedione (TZD) such as pioglitazone, rosiglitazone, and troglitazone; with a sulfonylurea derivative such as tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, and gliclazide; with a meglitinide such as repaglinide, mitiglinide and nateglinide; with insulin; with an alpha-glucosidase inhibitor such as acarbose, miglitol, and voglibose; with a glucagon-like peptide-1 analog such as exenatide and liraglutide; with a gastric inhibitory peptide analog; with a GPR40 agonist; with a GPR119 agonist; with a GPR30 agonist; with a glucokinase activator; with a glucagon receptor antagonist; with an amylin analog such as pramlintide; with an IL-1β receptor antagonist such as anakinra; with an endocannabinoid receptor antagonist or inverse agonist such as rimonabant; with Orlistat; with Sibutramine; with a growth factor such as TGF-β1, TGF-β2, TGF-β1.2, VEGF, insulin-like growth factor I or II, BMP2, BMP4, BMP7, GLP-1 analog, a GIP analog, a DPP-IV inhibitor, a GPR119 agonist, a GPR40 agonist, gastrin, EGF,

betacellulin, KGF, NGF, insulin, growth hormone, HGF, an FGF, an FGF homologue, PDGF, Leptin, prolactin, placental lactogen, PTHrP, activin, inhibin, INGAP, parathyroid hormone, calcitonin, interleukin-6, or interleukin-11.

153. The compound for the use of any of claims 139-152, wherein the subject is a primate, in particular a human a cow, a horse, a dog, a cat, a pig, a mouse, a rat, or a guinea pig.

154. The compound for the use of any of claims 139-153, wherein R_1 is $-C(=O)-Y$ and Y is:

$-H$, hydroxy, amino, halo, or

C_1-C_{14}-alkoxy, C_2-C_{14}-alkenyloxy, C_2-C_{14}-alkynyloxy, C_1-C_{14}-aryloxy, C_2-C_{14}-aralkoxy, C_1-C_{14}-alkylamino, C_2-C_{14}-alkenylamino, C_2-C_{14}-alkynylamino, C_1-C_{14}-arylamino, C_3-C_{10}-aryl, or C_2-C_{14}-aralkylamino, wherein any of these groups is heteroatom-substituted or heteroatom-unsubstituted, in particular wherein Y is

(a) a heteroatom-unsubstituted C_1-C_4-alkylamino such as $-NHCH_3$,

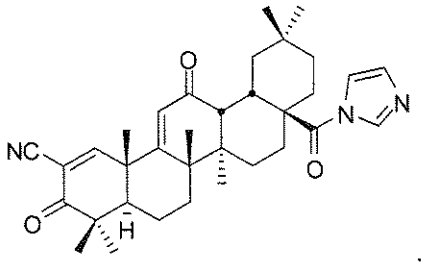
(b) a heteroatom-substituted or heteroatom-unsubstituted C_2-C_4-alkylamino such as $-NHCH_2CH_3$ or $-NHCH_2CF_3$,

(c) a heteroatom-unsubstituted C_1-C_4-alkoxy such as $-OCH_3$, or

(d) hydroxy.

155. The compound for the use of any of claims 139-153, wherein R_1 is $-CN$.

156. The compound for the use of any of claims 139-153, wherein R_1 is $-C(=O)-Y'$ and Y' is a heteroatom-substituted or heteroatom-unsubstituted C_1-C_{14}-aryl, in particular wherein the compound is:



157. The compound for the use of any of claims 139-156, wherein the compound is a substantially pure optical isomer.