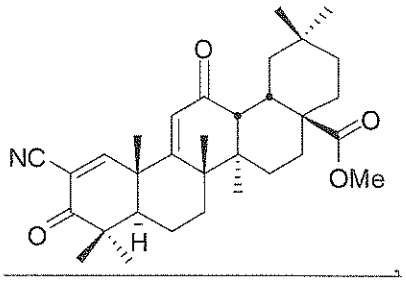
compromised renal function would represent a significant advance in the treatment of renal failure.

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~~

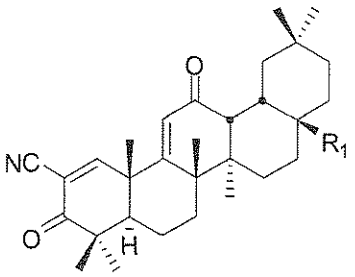
The present ~~invention provides~~disclosure describes new methods for treating and/or preventing renal/kidney disease (RKD), insulin resistance, diabetes, endothelial dysfunction, fatty liver disease, cardiovascular disease (CVD), and related disorders. Compounds covered by the generic or specific formulas 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, the present invention refers to the use of a compound of the formula:



in the manufacture of a medicament for treating renal/kidney disease (RKD), insulin resistance, endothelial dysfunction, fatty liver disease, or cardiovascular disease (CVD), in a subject.

In one example~~aspect of the present prevention~~, disclosed herein are 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~~examples, methods are ~~provided~~disclosed 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~~examples, the subject has undergone or is undergoing dialysis. In some ~~embodiments~~examples, the subject has undergone or is a candidate to undergo kidney transplant. In some ~~embodiments~~examples, the subject has RKD and insulin resistance. In some variations on the above ~~embodiments~~examples, the subject has RKD, insulin resistance and endothelial dysfunction. In some ~~embodiments~~examples, the subject has RKD and diabetes. In some ~~embodiments~~examples, the subject has insulin resistance.

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

In some ~~embodiments~~examples, the subject has endothelial dysfunction and/or insulin resistance. In some ~~embodiments~~examples, 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~~examples, 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~~examples, the subject has a family or patient history of any of the diseases, dysfunctions, resistances or disorders listed herein. In some ~~embodiments~~examples, the subject exhibits symptoms of any of the diseases, dysfunctions, resistances or disorders listed herein.

In another example~~aspect of the invention~~, disclosed herein is 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~~examples, the compound is administered locally. In some ~~embodiments~~examples, the compound is administered systemically. In some ~~embodiments~~examples, 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~~examples, 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~~examples, 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~~examples, 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.

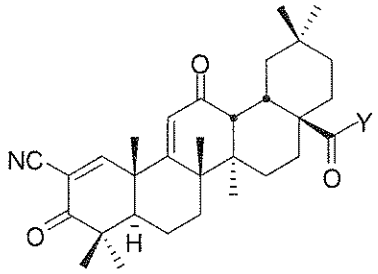
In some ~~embodiments~~examples, the pharmaceutically effective amount is administered in a single dose per day. In some ~~embodiments~~examples, the pharmaceutically effective amount is administered in two or more doses per day.

In some ~~embodiments~~examples, 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~~examples, 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~~examples, 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.

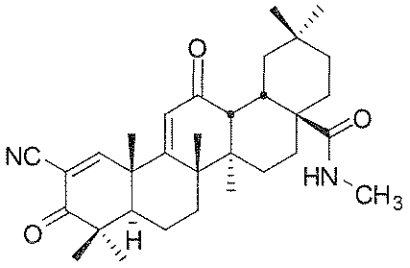
In some ~~embodiments~~examples, the compound is defined as:



, Formula II

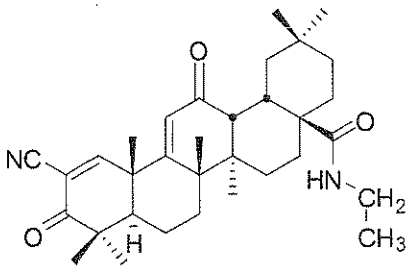
wherein Y is: –H, hydroxy, amino, halo, or C_1-C_{14}-alkoxy, C_2-C_{14}-alkenyloxy, C_2-C_{14}-alkynyloxy, C_1-C_{14}-aryloxy, C_2-C_{14}-aralkoxy, C_1-C_{14}-alkylamino, C_2-C_{14}-alkenylamino, C_2-C_{14}-alkynylamino, C_1-C_{14}-arylamino, C_3-C_{10}-aryl, or C_2-C_{14}-aralkylamino, wherein any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

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

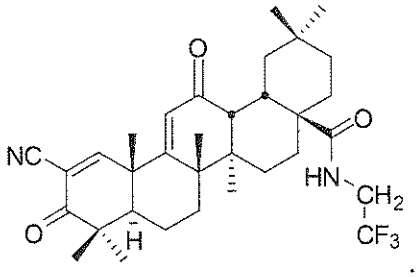


.

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

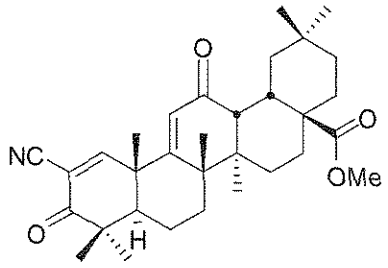


or



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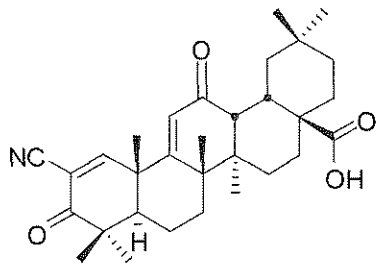
In some ~~embodiments~~examples, Y is a heteroatom-substituted or heteroatom-unsubstituted C_1-C_4-alkoxy, such as a heteroatom-unsubstituted C_1-C_2-alkoxy. For example, one non-limiting example of such a compound is:



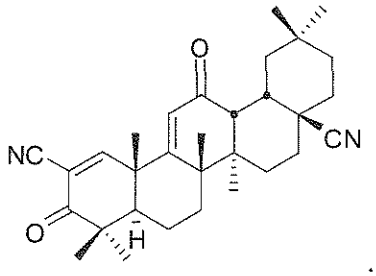
(CDDO-Me, RTA 402).

In some ~~embodiments~~examples, 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.

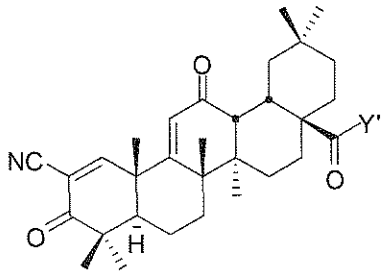
In some ~~embodiments~~examples, Y is hydroxy, such that the compound of the invention is, for example:



In some ~~embodiments~~examples, the compound is:



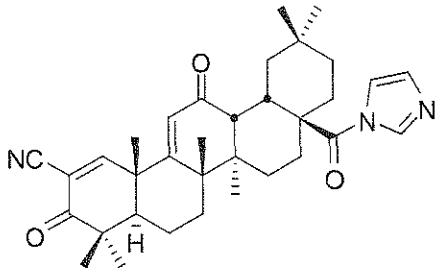
In some ~~embodiments~~examples, the compound is defined as:



, 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~~examples, 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~~examples, 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.