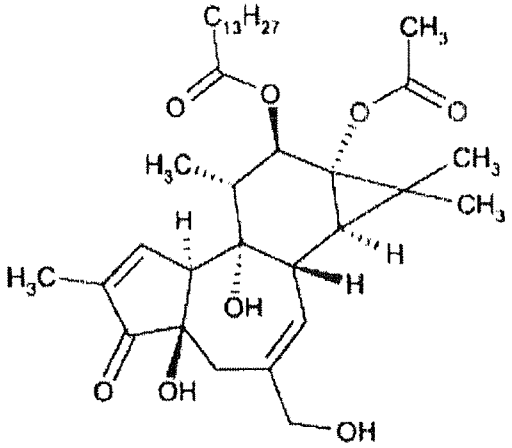
substituted derivatives thereof and R_3 may be hydrogen or —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

[028] In some embodiments, at least one of R_1 and R_2 are other than hydrogen and R_3 is hydrogen or —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof. In another embodiment, either R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

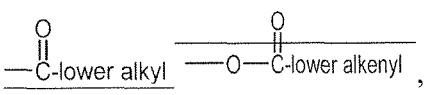
[029] The alkyl, alkenyl, phenyl and benzyl groups of the formulas herein may be unsubstituted or substituted with halogens, preferably, chlorine, fluorine or bromine; nitro; amino; and/or similar type radicals.

[030] In a further embodiment, the invention achieves these objects and satisfies additional objects and advantages by providing novel and surprisingly effective methods and compositions for modulating cell signaling pathways and/or treating diseases or conditions associated with diseases using an exemplary phorbol ester composition such as 12-O-tetradecanoylphorbol-13-acetate (TPA) of Formula II, below:



Formula II

[031] Useful phorbol esters and related compounds and derivatives within the formulations and methods of the invention include, but are not limited to, other

substituted derivatives thereof and R_3 may be hydrogen or , including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel HIV and AIDS treating compounds.

[079] Viral load decreasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel viral load decreasing agents.

[080] Immune responsiveness increasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as immune stimulatory compounds.

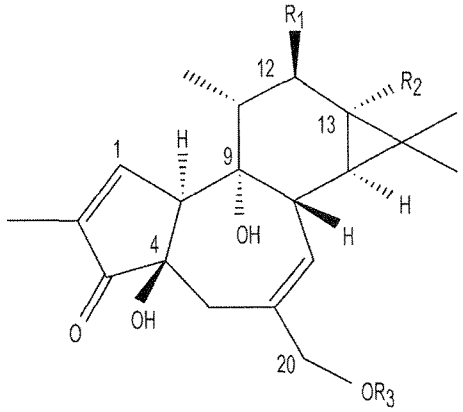
[081] Th1 cytokine increasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel Th1 cytokine increasing agents.

[082] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of neoplastic diseases.

[083] Apoptosis inducing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically

enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of urinary incontinence and symptoms thereof.

[0138] Phorbol is a natural, plant-derived polycyclic alcohol of the tigliane family of diterpenes. It was first isolated in 1934 as the hydrolysis product of croton oil derived from the seeds of *Croton tiglium.* It is well soluble in most polar organic solvents and in water. Esters of phorbol have the general structure of Formula I, below:



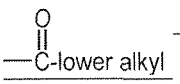
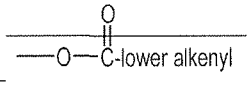
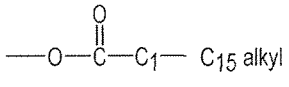
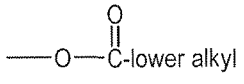
FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen; —O—C(=O)-alkyl, wherein the alkyl group contains 1 to 15 carbon atoms, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof and R_3 may be hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl or substituted derivatives thereof.

[0139] The term "lower alkyl" or "lower alkenyl" as used herein means moieties containing 1-7 carbon atoms. In the compounds of the Formula I, the alkyl or alkenyl groups may be straight or branched chain. In some embodiments, either or both R_1 or R_2, are a long chain carbon moiety (i.e., Formula I is decanoate or myristate).

[0140] The alkyl, alkenyl, phenyl and benzyl groups of the formulas herein may be unsubstituted or substituted with halogens, preferably, chlorine, fluorine or bromine; nitro; amino and similar type radicals.

[0141] Organic and synthetic forms of phorbol esters, including any preparations or extracts from herbal sources such as *croton tiglium*, are contemplated as useful compositions comprising phorbol esters (or phorbol ester analogs, related compounds and/or derivatives) for use within the embodiments herein. Useful phorbol esters and/or related compounds for use within the embodiments herein will typically have a structure as illustrated in Formula I, although functionally equivalent analogs, complexes, conjugates, and derivatives of such compounds will also be appreciated by those skilled in the art as within the scope of the invention.

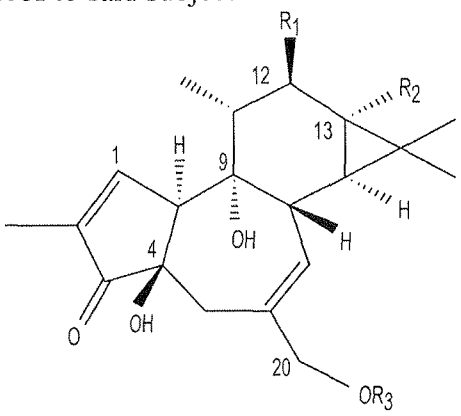
[0142] In more detailed embodiments, illustrative structural modifications according to Formula I above will be selected to provide useful candidate compounds for treating and/or preventing HIV and AIDS and/or neoplastic diseases, wherein: at least one of R_1 and R_2 are other than hydrogen and R_3 is selected from the group consisting of hydrogen   and substituted derivatives thereof. In another embodiment, either R_1 or R_2 is  the remaining R_1 or R_2 is  and R_3 is hydrogen.

[0143] An exemplary embodiment of a phorbol ester compound of Formula I useful in the treatment of cytopathic diseases such as HIV and AIDS and/or neoplastic diseases, particularly AML, is found in phorbol 12-myristate-13-acetate (also known as PMA or 12-O-tetradecanoyl-phorbol-13-acetate (TPA)) shown in Formula II, below.

We claim:

~~Claims 1-48 cancelled.~~

49. A method of treating or preventing neoplasms in a mammalian subject comprising administering an effective amount of a phorbol ester or derivative of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is selected from hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula 1 to treat or prevent neoplasms in said subject.

50. The method of claim 49, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

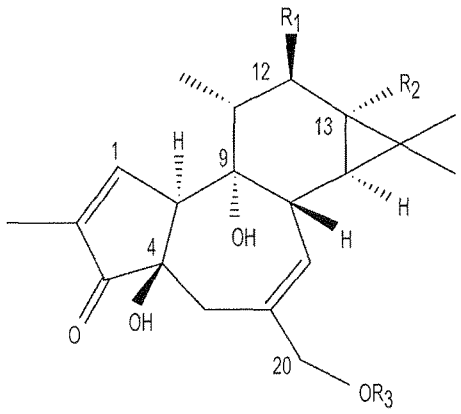
51. The method of claim 49, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoal:e, phorbol 12,13-dibutyrate, phorbol 12,13-

62. The method of claim 49, wherein the neoplasm is a solid tumor.

63. The method of claim 49, wherein the neoplasm is a relapsing neoplasm.

64. The method of claim 49, wherein the neoplasm is refractory.

65. A method for preventing or treating one or more symptoms or conditions of neoplastic disease in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

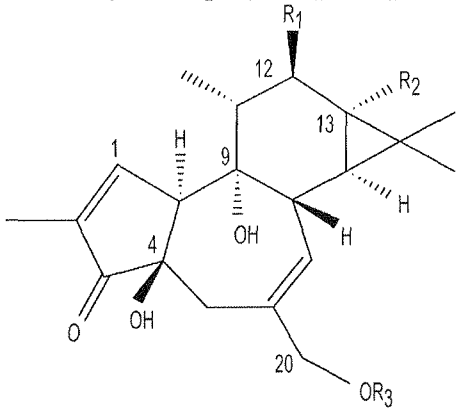


FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent symptoms of neoplastic disease in said subject.

66. The method of claim 65, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

72. A method for inducing remission in a mammalian subject suffering from neoplastic disease comprising administering to said subject an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

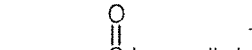


FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof; R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester of derivative compound of Formula I to induce remission in said subject.

73. The method of claim 72, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to induce remission in said subject.

74. The method of claim 72, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate., phorbol 13,20-

wherein R_1 and R_2 are selected from the group consisting of hydrogen, , , , and substituted derivatives thereof, R_3 is hydrogen,  and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or~~of~~ derivative compound of Formula 1 to induce apoptosis in a neoplasm in said subject.

79. The method of claim 78, wherein R_1 or R_2 is  the remaining R_1 or R_2 is  and R_3 is hydrogen and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent malignancy in said subject.

80. The method of claim 78, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-rnyristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

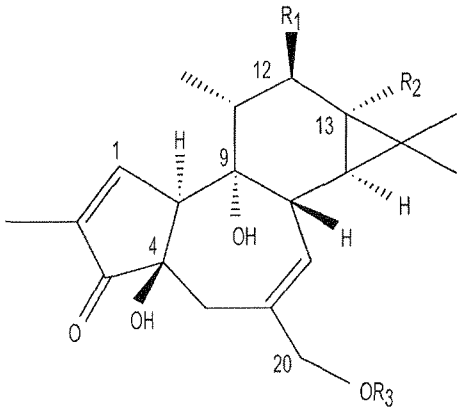
81. The method of claim 78, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

82. The method of claim 78, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

83. The method of claim 82, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside~~,~~, daunorubicin, cyclophosphamide, gemtuzumab

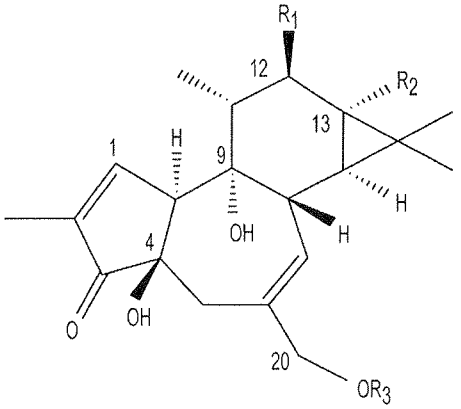
ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

84. A composition for preventing or treating neoplastic disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a neoplasm in said subject.



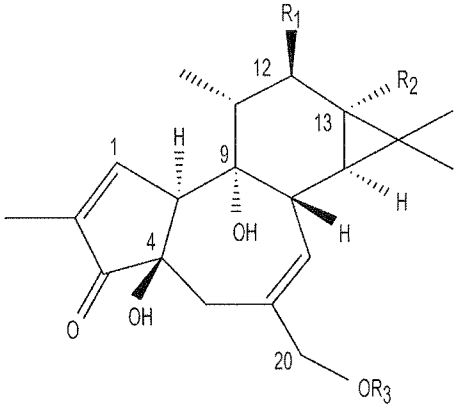
FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

92. The method of claim 91, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

93. The method of claim 91, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

94. The method of claim 91, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.



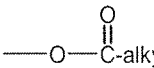
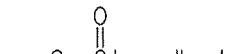
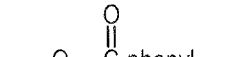
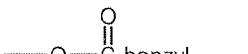
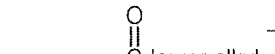
FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

102. The composition of claim 101, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

103. The composition of claim 101, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

104. The composition of claim 101, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

wherein R_1 and R_2 are selected from the group consisting of hydrogen, , , ,  and substituted derivatives thereof, R_3 is hydrogen,  and substituted derivatives thereof.

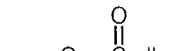
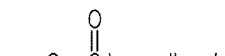
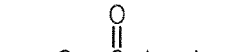
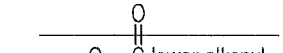
109. The method of claim 108, wherein R_1 or R_2 is  the remaining R_1 or R_2 is  and R_3 is hydrogen.

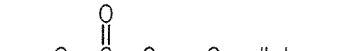
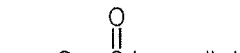
110. The method of claim 108, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

111. The method of claim 108, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

112. The method of claim 108, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent side effects of radiation therapy to said subject.

113. The method of claim 112, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

wherein R_1 and R_2 are selected from the group consisting of hydrogen, , , ,  and substituted derivatives thereof, R_3 is hydrogen,   and substituted derivatives thereof.

119. The composition of claim 118, wherein R_1 or R_2 is  the remaining R_1 or R_2 is  and R_3 is hydrogen.

120. The composition of claim 118, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

121. The composition of claim 118, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

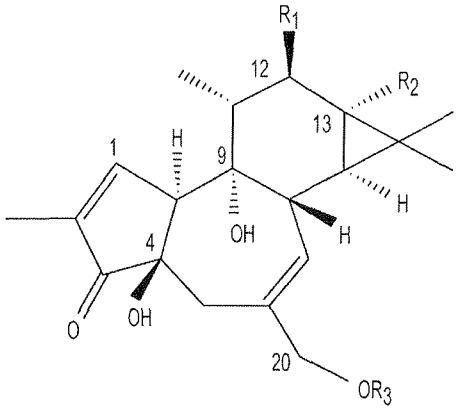
122. The composition of claim 118 further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a side effect of radiation therapy in said subject.

123. The composition of claim 118, wherein the one or more secondary or adjunctive therapeutic agents are steroids, amifostine, chlorhexidine, benzydamine, sucralfate, KGF, palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

124. The composition of claim 118, wherein the one or more side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, or mucosal dryness.

125. A method for preventing or treating one or more of the effects of stroke in a mammalian subject comprising administering an effective amount of phorbol ester or

derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

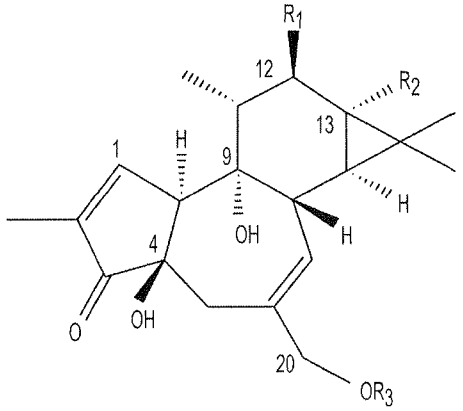
126. The method of claim 125, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

127. The method of claim 125, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-

135. The method of claim 125, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

136. The method of claim 135, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

137. A composition for the prevention or treatment of one or more effects of stroke in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

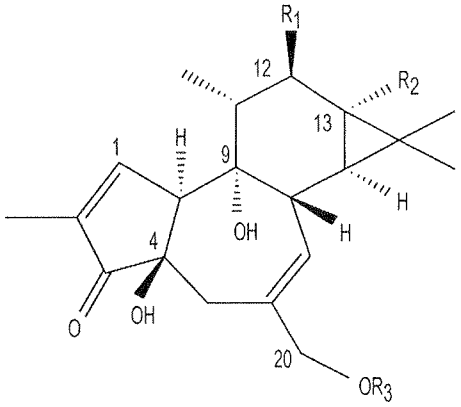


FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

138. The composition of claim 137, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

139. The composition of claim 138, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-



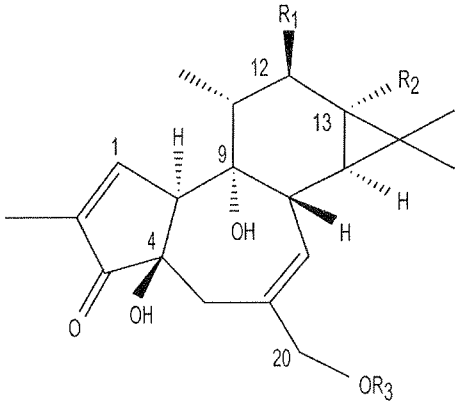
FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

145. The method of claim 144, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

146. The method of claim 144, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

147. The method of claim 144, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

157. The composition of claim 156, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

158. The composition of claim 156, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

159. The composition of claim 156, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

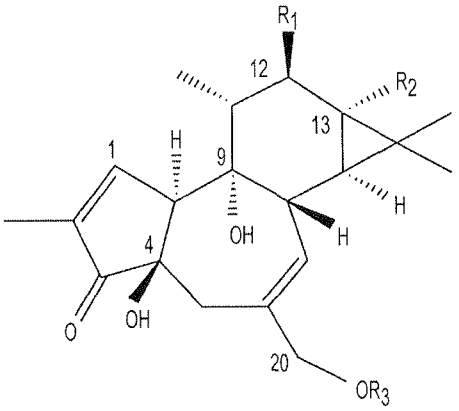
160. The composition of claim 156, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said

phorbol ester or derivative compound of Formula I to treat or prevent an effect of stroke in said subject.

161. The composition of claim 160, wherein the at least one secondary or adjunctive therapeutic agent is levodopa, carbidopa, pyridoxine, seleyiline, rasagiline, tolcapone, dopamine agonist, MAO-B inhibitors, amantidine, or anticholinergics.

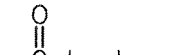
162. The composition of claim 156, wherein the one or more symptoms of Parkinson's disease is tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia or postural instability.

163. A method for treating or preventing one or more of the symptoms of prostate hypertrophy in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

wherein R_1 and R_2 are selected from the group consisting of hydrogen, , , ,  and substituted derivatives thereof, R_3 is hydrogen,  and substituted derivatives thereof.

176. The composition of claim 175, wherein R_1 or R_2 is the remaining R_1 or R_2 is  and R_3 is hydrogen.

177. The composition of claim 175, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

178. The composition of claim 175, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

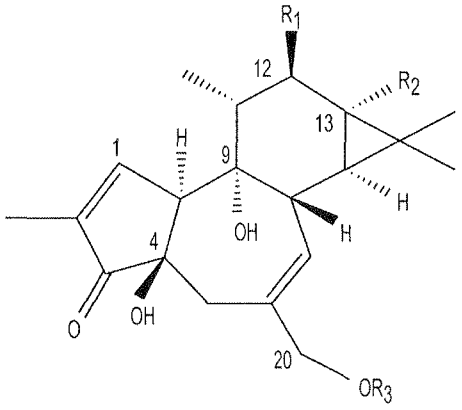
179. The composition of claim 175, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of prostate hypertrophy.

180. The composition of claim 179, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.

181. The composition of claim 179, wherein the one or more symptoms of prostate hypertrophy are dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, stopping and starting of urine stream, straining to urinate, weak urine stream, or strong and sudden urge to urinate.

182. A method for treating or preventing one or more of the symptoms of rheumatoid arthritis in a mammalian subject comprising administering an effective amount of

phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject



FORMULA I

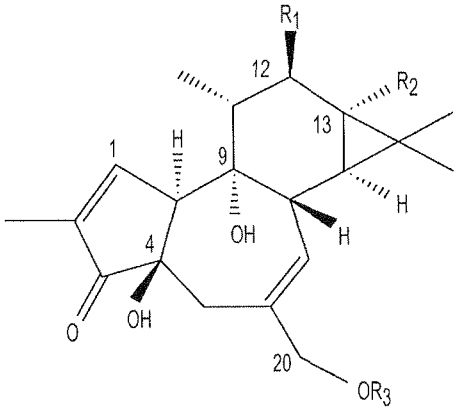
wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

183. The method of claim 182, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

184. The method of claim 182, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-

191. The method of claim 182, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

192. A composition for the prevention or treatment of one or more symptoms of rheumatoid arthritis in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

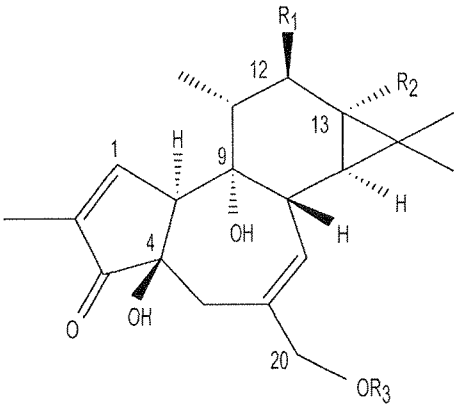


FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

193. The composition of claim 192, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

194. The composition of claim 192, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate., phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

200. The method of claim 199, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

201. The method of claim 199, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

202. The method of claim 199 further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of myasthenia gravis.

203. The method of claim 202, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

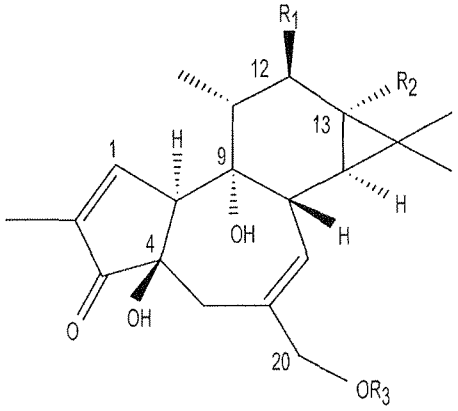
204. The method of claim 202, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.

205. The method of claim 199, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

206. The method of claim 199, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

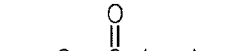
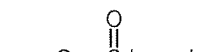
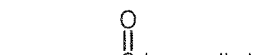
207. The method of claim 199, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

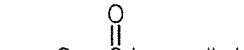
208. A composition for the prevention or treatment of one or more symptoms of myasthenia gravis in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

wherein R_1 and R_2 are selected from the group consisting of hydrogen, , , ,  and substituted derivatives thereof, R_3 is hydrogen,  and substituted derivatives thereof.

215. The method of claim 214, wherein R_1 or R_2 is  the remaining R_1 or R_2 is  and R_3 is hydrogen.

216. The method of claim 214, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

217. The method of claim 214, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent symptoms of kidney disease.

218. The method of claim 217, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

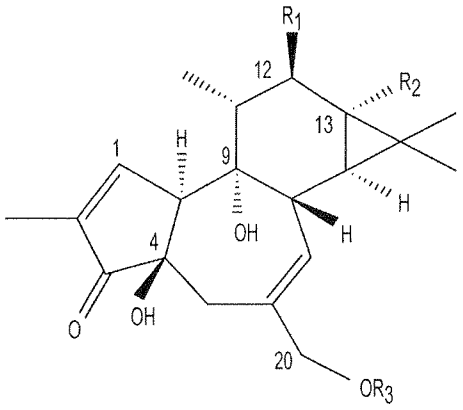
219. The method of claim 217, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

220. The method of claim 214, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

221. The method of claim 214, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

222. The method of claim 214, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

223. A composition for the prevention or treatment of kidney disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

224. The composition of claim 223, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

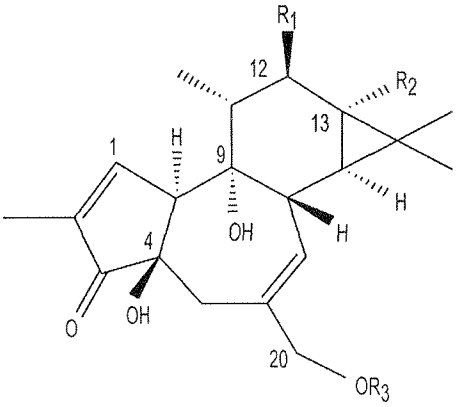
225. The composition of claim 223, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

226. The composition of claim 223, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula 1 to treat or prevent a symptom of kidney disease.

227. The composition of claim 226, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

228. The composition of claim 223, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

229. A method for treating or preventing urinary incontinence in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject



FORMULA I

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

230. The method of claim 229, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

231. The method of claim 229, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

232. The method of claim 229, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation

wherein R_1 and R_2 are selected from the group consisting of hydrogen, —O—C(=O)-alkyl, —O—C(=O)-lower alkenyl, —O—C(=O)-phenyl, —O—C(=O)-benzyl and substituted derivatives thereof, R_3 is hydrogen, —C(=O)-lower alkyl —O—C(=O)-lower alkenyl and substituted derivatives thereof.

238. The composition of claim 237, wherein R_1 or R_2 is —O—C(=O)—C_1— C_{15} alkyl the remaining R_1 or R_2 is —O—C(=O)-lower alkyl and R_3 is hydrogen.

239. The composition of claim 237, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13 -acetate.

240. The composition of claim 237, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent urinary incontinence.

241. The composition of claim 240, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.