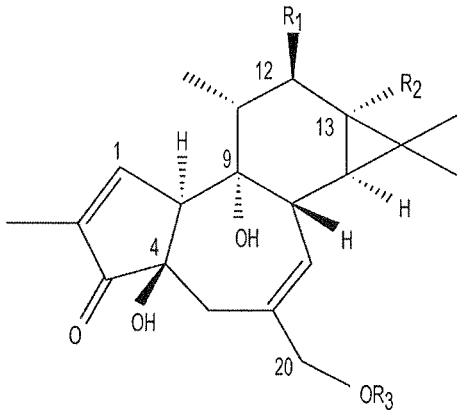
We claim:

491. Use~~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, hydroxyl, —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 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 in the manufacture of a medicament for~~o~~ treating or preventing neoplasms in a mammalian~~said~~ subject.

250. The use~~method~~ of claim 491, 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.

513. The usemethod of claim 491, 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-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.

524. The usemethod of claim 491, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

~~53. The method of claim 49, 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.~~

545. The usemethod of claim 491, 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.

556. The usemethod of claim 491, wherein two secondary or adjunctive therapeutic agents are used in the manufacture of the medicamentadministered to said subject.

~~56~~7. The use~~method~~ of claim ~~55~~6, wherein the two secondary or adjunctive therapeutic agents are dexamethasone and choline magnesium trisalicylate.

~~57~~8. The use~~method~~ of claim ~~49~~1, wherein the medicament~~said effective amount~~ comprises between about 10 and 1500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~58~~9. The use~~method~~ of claim ~~49~~1, wherein the medicament~~said effective amount~~ comprises between about 150 to 500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~59~~10. The use~~method~~ of claim ~~49~~1 wherein the neoplasm is caused by a haematological malignancy/bone marrow disorder.

~~60~~11. The use~~method~~ of claim ~~59~~10, wherein the hematological malignancy/bone marrow disorder is leukemia.

~~61~~12. The use~~method~~ of claim ~~60~~11, wherein the leukemia is acute myeloid leukemia.

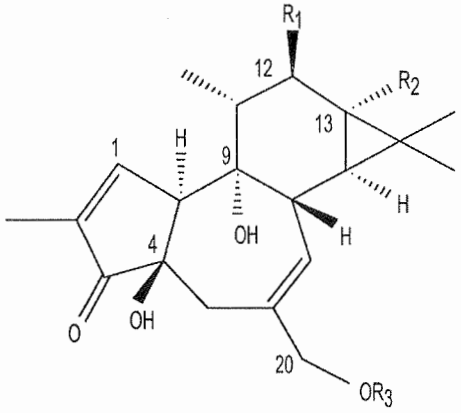
~~62~~13. The use~~method~~ of claim ~~49~~1, wherein the neoplasm is a solid tumor.

~~63~~14. The use~~method~~ of claim ~~49~~1, wherein the neoplasm is a relapsing neoplasm.

~~64~~15. The use~~method~~ of claim ~~49~~1, wherein the neoplasm is refractory.

~~65~~16. Use~~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 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, hydroxyl, —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 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 in the manufacture of a medicament for~~to~~ treating or preventing one or more symptoms or conditions of neoplastic disease in a mammalian~~said~~ subject.

~~66~~17. The use~~method~~ of claim ~~65~~16, 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.

~~67~~18. The use~~method~~ of claim ~~65~~16, 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-dipropionatc, 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.

~~68~~19. The use~~method~~ of claim ~~65~~16, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

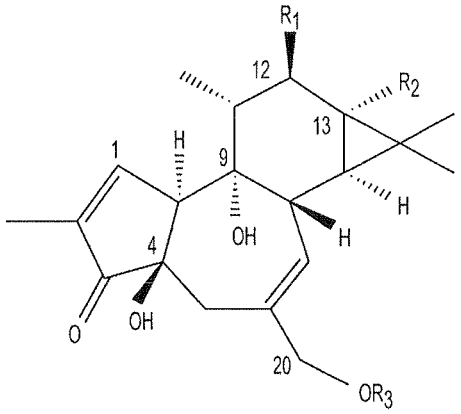
~~69. The method of claim 68, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.~~

~~70~~20. The use~~method~~ of claim ~~68~~16, 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.

~~71~~21. The use~~method~~ of claim ~~68~~19, wherein the one or more symptoms or conditions of neoplastic disease are anemia, chronic fatigue, excessive or easy bleeding, easy bruising, shortness of breath, petechiae, recurrent fever, swollen gums, slow healing of cuts, bone and joint discomfort, recurrent infections, weight loss, itching, night sweats, lymph node swelling, fever, abdominal pain and discomfort, disturbances in vision,

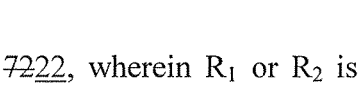
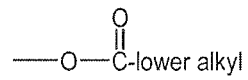
coughing, loss of appetite, pain in the chest, difficulty swallowing, swelling, a need to urinate frequently, difficulty starting urination, difficulty holding back urine, weak or interrupted flow of urine, painful or burning urination, difficulty in having an erection, painful ejaculation, blood in urine or semen, frequent pain or stiffness, or weakness.

~~72~~22. Use~~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, hydroxyl, —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 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 in the manufacture of a medicament for~~to~~ inducinge remission in a mammalian~~said~~ subject suffering from neoplastic disease.

~~73~~23. The use~~method~~ of claim ~~72~~22, 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 induce remission in said subject.

~~74~~24. The use~~method~~ of claim ~~72~~22, 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.

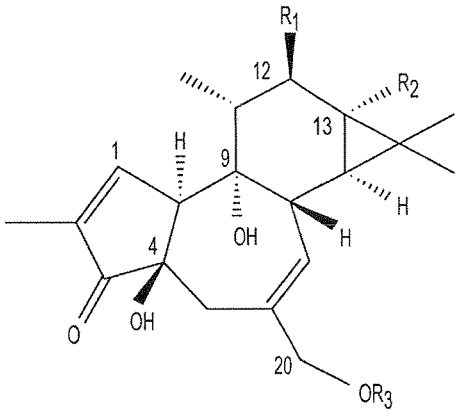
~~75~~25. The use~~method~~ of claim ~~72~~22, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

~~76. The method of claim 72, 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.~~

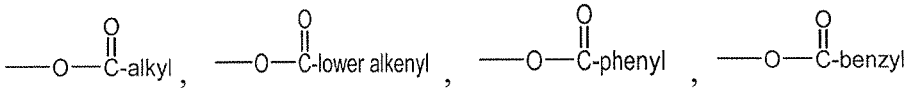
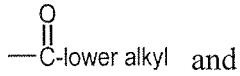
~~77~~26. The use~~method~~ of claim ~~72~~22, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3,

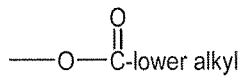
cytarabine, cytosine arabinoside,~~,~~ daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

~~7827~~. Use~~A method for inducing apoptosis in a neoplasm 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, hydroxyl,  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 derivative compound of Formula I in the manufacture of a medicament for~~to~~ inducinge apoptosis in a neoplasm in a mammalian~~said~~ subject suffering from neoplastic disease.

~~79~~28. The use~~method~~ of claim ~~78~~27, 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.

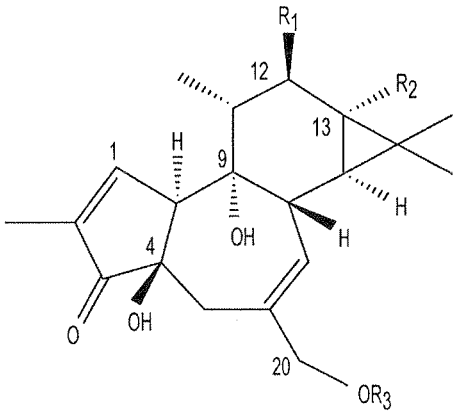
~~80~~29. The use~~method~~ of claim ~~78~~27, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 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~~30. The use~~method~~ of claim ~~78~~27, 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.~~

8331. The usemethod of claim 2782, 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.

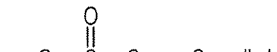
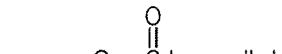
8432. UseA composition for preventing or treating neoplastic disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof




FORMULA I

wherein $R_1$ and $R_2$ are selected from the group consisting of hydrogen, hydroxyl, —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 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

in the manufacture of a medicament for~~to~~ treating or preventing neoplastic disease~~a neoplasm~~ in a mammalian~~said~~ subject.

8533. The use~~composition~~ of claim 8432, wherein $R_1$ or $R_2$ is  the remaining $R_1$ or $R_2$ is  and $R_3$ is hydrogen.

8634. The use~~composition~~ of claim 8432, 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.

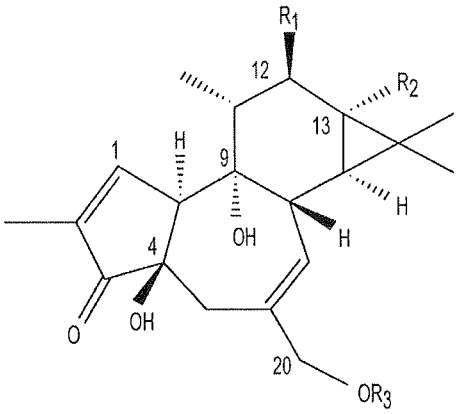
8735. The use~~composition~~ of claim 8432, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

8836. The use~~composition~~ of claim 8432, 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.

8937. The use~~composition~~ of claim 8432, wherein the medicament~~composition~~ contains at least two secondary or adjunctive therapeutic agents.

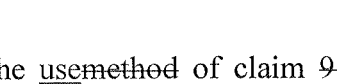
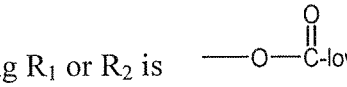
9038. The use~~composition~~ of claim 8937, wherein the at least two secondary or adjunctive therapeutic agents are dexamethasone and choline magnesium trisalicylate.

9139. Use~~A method for preventing or treating one or more side effects of chemotherapy in a mammalian subject comprising administering 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, hydroxyl, —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 and substituted derivatives thereof in the manufacture of a medicament for preventing or treating one or more side effects of chemotherapy in a mammalian subject.

9240. The usemethod of claim 9139, wherein $R_1$ or $R_2$ is  the remaining $R_1$ or $R_2$ is  and $R_3$ is hydrogen.

9341. The usemethod of claim 9139, 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.

9442. The usemethod of claim 9139, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

9543. The usemethod of claim 9139, further comprising the use ofadministering 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 in the manufacture of the medicament to treat or prevent side effects of chemotherapy treatment to said subject.

~~96. The method of claim 95, 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.~~

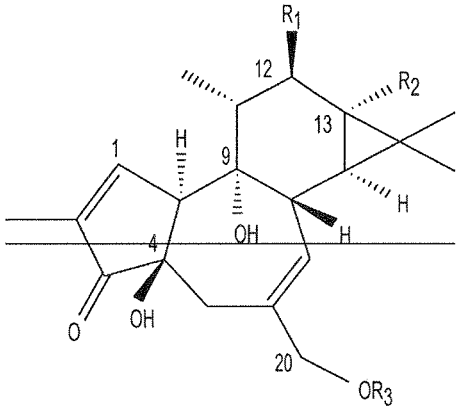
9744. The usemethod of claim 4396, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT3 receptor antagonists, NK1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

9845. The usemethod of claim 9139, wherein the medicamentsaid effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

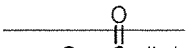
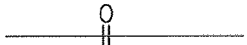
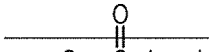
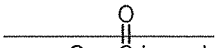
9946. The usemethod of claim 9845, wherein the medicamentsaid effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

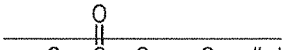
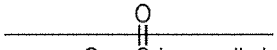
10047. The usemethod of claim 9139, wherein the one or more side effects of chemotherapeutic treatment are alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo or encephalopathy.

101. A composition for preventing or treating one or more side effects of chemotherapy 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,~~  ;  ,  ,  ~~and substituted derivatives thereof, $R_3$ is hydrogen,~~  ~~and substituted derivatives thereof.~~

~~102. The composition of claim 101, wherein $R_1$ or $R_2$ is~~  ~~the remaining $R_1$ or $R_2$ is~~  ~~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.~~

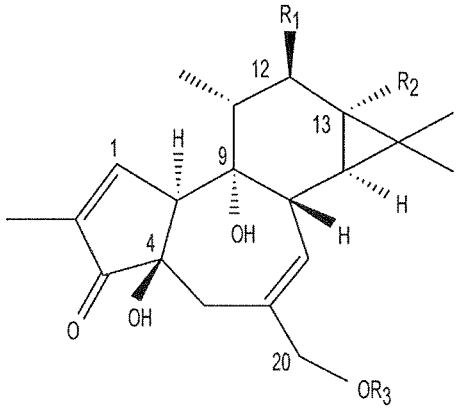
~~104. The composition of claim 101, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.~~

~~105. The composition of claim 101 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 chemotherapy in said subject.~~

~~106. The composition of claim 105, wherein the at least one secondary or adjunctive therapeutic agent is pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT3 receptor antagonists, NK1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, or cannabinoids.~~

~~107. The composition of claim 101, wherein the one or more side effects of chemotherapeutic treatment are alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo or encephalopathy.~~

~~10848~~. Use~~A method for preventing or treating one or more side effects of radiation therapy in a mammalian subject comprising administering 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, hydroxyl, —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 and substituted derivatives thereof in the manufacture of a medicament for preventing or treating one or more side effects of radiation therapy in a mammalian subject.

~~109~~49. The use~~method~~ of claim ~~108~~48, 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.

~~110~~50. The use~~method~~ of claim ~~108~~48, 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~~51. The use~~method~~ of claim ~~108~~48, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~112~~52. The use~~method~~ of claim ~~108~~48, further comprising the use of~~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 in the manufacture of the medicament 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.~~

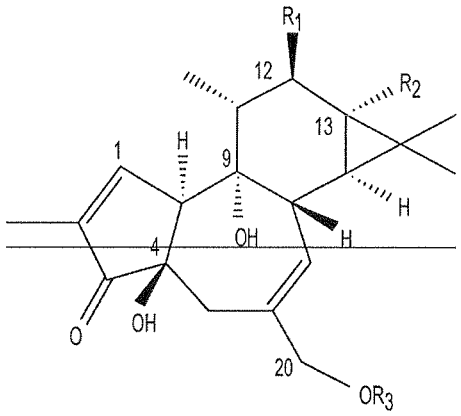
~~114~~53. The use~~method~~ of claim 52~~113~~, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of steroids, amifostine, chlorhexidine, benzydamine, sucralfate, KGF, palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

~~115~~54. The use~~method~~ of claim ~~108~~48, 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.

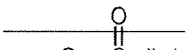
~~116~~55. The use~~method~~ of claim ~~108~~48, wherein the medicament~~said effective amount~~ comprises between about 10 µg and about 1500 µg of said phorbol ester or derivative compound of Formula I ~~every day~~.

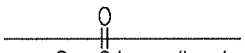
~~117~~56. The use~~method~~ of claim ~~108~~48, wherein the medicament~~said effective amount~~ comprises between about 125 µg to about 500 µg of said phorbol ester or derivative compound of Formula I ~~every day~~.

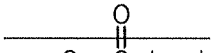
~~118. A composition for preventing or treating one or more side effects of radiation therapy in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof~~

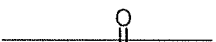



~~FORMULA I~~

~~wherein $R_1$ and $R_2$ are selected from the group consisting of hydrogen,~~ 

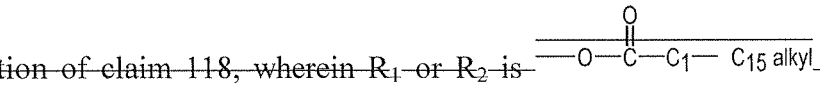
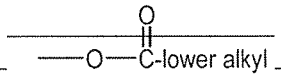
~~,~~ 

~~,~~ 

~~,~~ 

~~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.~~

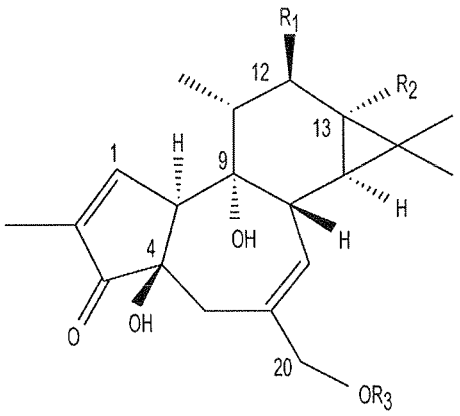
~~121. The composition of claim 118, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.~~

~~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.~~

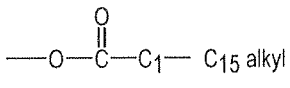
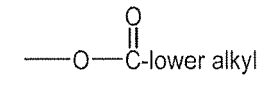
~~124. The composition of claim 118, wherein the one or more side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, or mucosal dryness.~~

~~12~~557. Use~~A method for preventing or treating one or more of the effects of stroke in a mammalian subject comprising administering 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, hydroxyl, —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 and substituted derivatives thereof in the manufacture of a medicament for preventing or treating one or more of the effects of stroke in a mammalian subject.

~~126~~58. The use~~method~~ of claim ~~125~~57, wherein $R_1$ or $R_2$ is  the remaining $R_1$ or $R_2$ is  and $R_3$ is hydrogen.

~~127~~59. The use~~method~~ of claim ~~125~~57, 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.

~~128~~60. The use~~method~~ of claim ~~125~~57, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~129~~61. The use~~method~~ of claim ~~125~~57, further comprising the use of~~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 in the manufacture of the medicament to treat or prevent effects of stroke in said subject.

~~130. The method of claim 129, 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.~~

~~131~~62. The use~~method~~ of claim 61~~129~~, wherein the at least one secondary or adjunctive therapeutic agent is tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

~~132. The method of claim 125, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent effects of stroke in said subject.~~

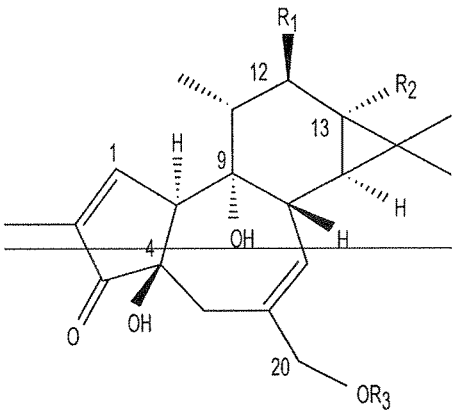
~~133. The method of claim 132, wherein the surgical intervention is a carotid endarterectomy, angioplasty, stent placement, craniotomy, endovascular coil emobilization, or patent foramen ovale closure.~~

~~134~~63. The use~~method~~ of claim ~~125~~57, wherein the one or more effects of stroke are paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia, or impulsivity.

~~135~~64. The use~~method~~ of claim ~~125~~57, wherein the medicament~~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~~65. The use~~method~~ of claim ~~135~~64, wherein the medicament~~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 ~~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-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-decanoa.te, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.~~

~~140. The composition of claim 138, wherein the phorbol ester is 12-O-tetradecanoylphorbol 13-acetate.~~

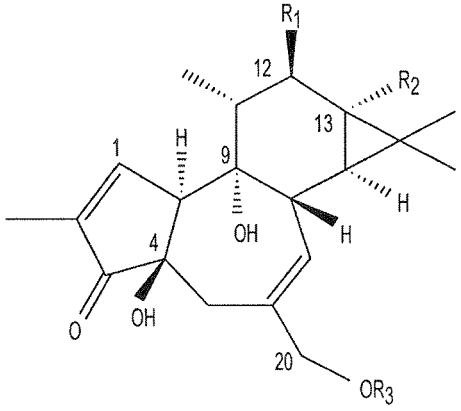
~~141. The composition of claim 138, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent an effect of stroke in said subject.~~

~~142. The composition of claim 138, wherein the at least one secondary or adjunctive therapeutic agent is tissue plasminogen activator, an anticoagulant,, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.~~

~~143. The composition of claim 138, wherein the one or more side effects of stroke is paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia, or impulsivity.~~

~~144~~66. Use~~A method for treating or preventing one or more of the symptoms of Parkinson's disease in a mammalian subject comprising administering 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, hydroxyl, $-O-\overset{O}{\overset{\|}{C}}\text{-alkyl}$, $-O-\overset{O}{\overset{\|}{C}}\text{-lower alkenyl}$, $-O-\overset{O}{\overset{\|}{C}}\text{-phenyl}$, $-O-\overset{O}{\overset{\|}{C}}\text{-benzyl}$ and substituted derivatives thereof, $R_3$ is hydrogen, $-\overset{O}{\overset{\|}{C}}\text{-lower alkyl}$ and substituted derivatives thereof in the manufacture of a medicament for treating or preventing one or more of the symptoms of Parkinson's disease in a mammalian subject.

~~14567~~. The use~~method~~ of claim ~~14466~~, wherein $R_1$ or $R_2$ is $-O-\overset{O}{\overset{\|}{C}}-C_1-\ C_{15}\text{ alkyl}$ the remaining $R_1$ or $R_2$ is $-O-\overset{O}{\overset{\|}{C}}\text{-lower alkyl}$ and $R_3$ is hydrogen.

~~14668~~. The use~~method~~ of claim ~~14466~~, 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~~69. The use~~method~~ of claim ~~144~~66, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~148~~70. The use~~method~~ of claim ~~144~~66, further comprising the use of~~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 in the manufacture of the medicament to treat or prevent one or more of the symptoms of Parkinson's disease.

~~149. The method of claim 148, 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.~~

~~150~~71. The use~~method~~ of claim ~~148~~70, 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.

~~151. The method of claim 144, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent symptoms of Parkinson's disease in said subject.~~

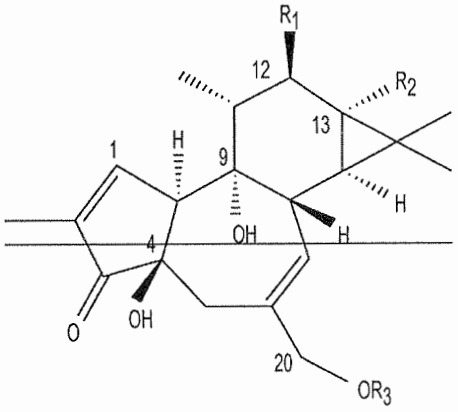
~~152. The method of claim 151, wherein the surgical intervention is deep brain stimulation or lesion formation.~~

~~153~~72. The use~~method~~ of claim ~~144~~66, 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 and postural instability.

~~154~~73. The use~~method~~ of claim ~~144~~66, wherein the medicament~~said effective amount~~ comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~155~~74. The use~~method~~ of claim ~~144~~66, wherein the medicament~~said effective amount~~ comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~156. A composition for the prevention or treatment of one or more symptoms of Parkinson's 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 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.~~

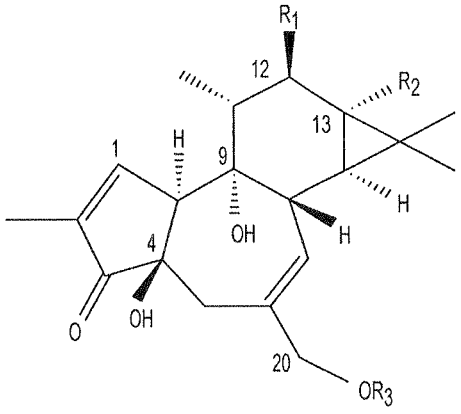
~~159. The composition of claim 156, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.~~

~~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~~75. Use~~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 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, hydroxyl, —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 and substituted derivatives thereof in the manufacture of a medicament for treating or preventing one or more of the symptoms of prostate hypertrophy in a mammalian subject.

~~164~~76. The use~~method~~ of claim ~~163~~75, 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.

~~165~~77. The use~~method~~ of claim ~~163~~75, 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.

~~166~~78. The use~~method~~ of claim ~~163~~75, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~167~~79. The use~~method~~ of claim ~~163~~75, further comprising the use of~~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 in the manufacture of the medicament to treat or prevent one or more of the symptoms of prostate hypertrophy.

~~168. The method of claim 167, 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.~~

~~169~~80. The use~~method~~ of claim 79~~167~~, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.

~~170. The method of claim 163, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent symptoms of prostate hypertrophy disease in said subject.~~

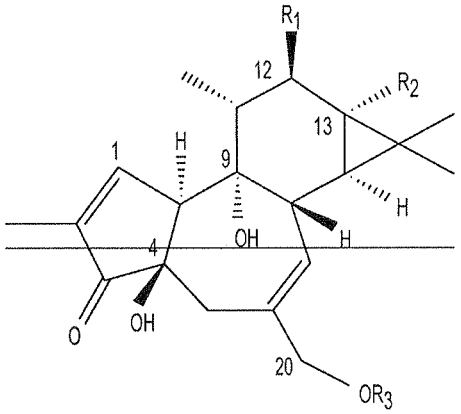
~~171. The method of claim 170, wherein the surgical intervention is transurethral resection of the prostate, transurethral incision of the prostate, laser surgery, or prostatectomy.~~

~~172~~81. The use~~method~~ of claim ~~163~~75, wherein the medicament~~said effective amount~~ comprises between about 10 µg and about 1500 µg of said phorbol ester or derivative compound of Formula I ~~every day~~.

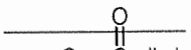
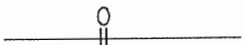
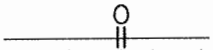
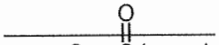
~~173~~82. The use~~method~~ of claim ~~163~~75, wherein the medicament~~said effective amount~~ comprises between about 125 µg to about 500 µg of said phorbol ester or derivative compound of Formula I ~~every day~~.

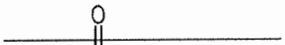
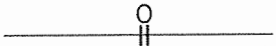
~~174~~83. The use~~method~~ of claim ~~163~~75, wherein the one or more symptoms of prostate hypertrophy are dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, stopping and starting of urine stream, straining to urinate, weak urine stream, or strong and sudden urge to urinate.

~~175. A composition for the prevention or treatment of one or more symptoms of prostate hypertrophy 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, ; , ,  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.

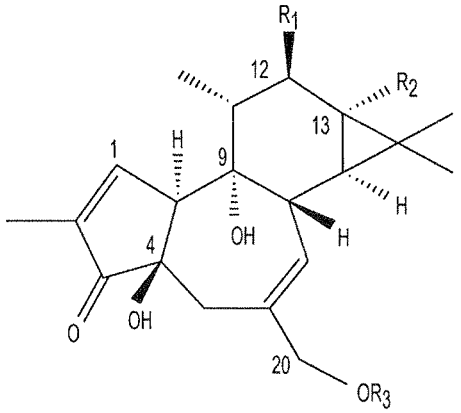
179. The composition of claim 175, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said

~~phorbol ester or derivative compound of Formula I to treat or prevent a symptom of prostate hypertrophy.~~

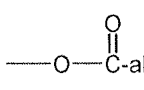
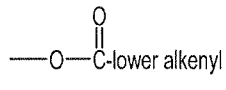
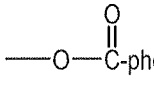
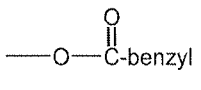
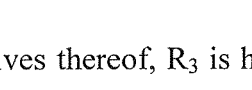
~~180. The composition of claim 179, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.~~

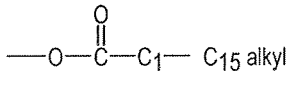
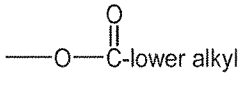
~~181. The composition of claim 179, wherein the one or more symptoms of prostate hypertrophy are dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, stopping and starting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

~~182~~84. Use~~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 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, hydroxyl,  ,  ,  ,  and substituted derivatives thereof, $R_3$ is hydrogen,  and substituted derivatives thereof in the manufacture of a medicament for treating or preventing one or more of the symptoms of rheumatoid arthritis in a mammalian subject.

~~183~~85. The use~~method~~ of claim ~~182~~84, wherein $R_1$ or $R_2$ is  the remaining $R_1$ or $R_2$ is  and $R_3$ is hydrogen.

~~184~~86. The use~~method~~ of claim ~~182~~84, 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.

~~185~~87. The use~~method~~ of claim ~~182~~84, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~186~~88. The use~~method~~ of claim ~~182~~84, further comprising the use of~~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 in the manufacture of the medicament to treat or prevent one or more of the symptoms of rheumatoid arthritis.

~~187. The method of claim 186, 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.~~

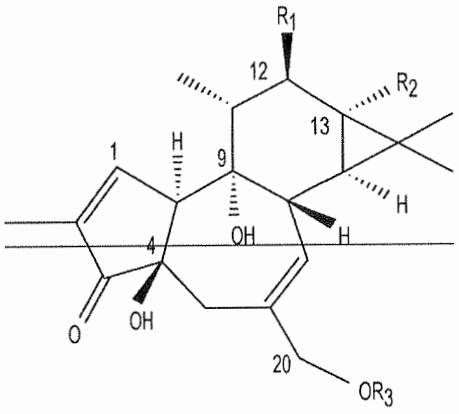
~~188~~89. The use~~method~~ of claim 88~~187~~, wherein the at least one secondary or adjunctive therapeutic agent is a non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine anakinra, abatacept, rituximab, or tocilizumab.

~~189~~90. The use~~method~~ of claim ~~182~~84, wherein the one or more symptoms of rheumatoid arthritis are sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever, or muscle and joint aches.

~~190~~91. The use~~method~~ of claim ~~182~~84, wherein the medicament~~said effective amount~~ comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~191~~92. The use~~method~~ of claim ~~182~~84, wherein the medicament~~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 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-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.~~

~~195. The composition of claim 192, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.~~

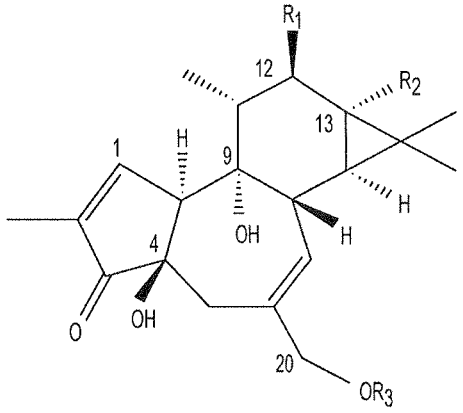
~~196. The composition of claim 192, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of rheumatoid arthritis.~~

~~197. The composition of claim 196, wherein the at least one secondary or adjunctive therapeutic agent is a non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.~~

~~198. The composition of claim 192, wherein the one or more symptoms of rheumatoid arthritis are sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever, or muscle and joint aches.~~

~~199~~93. Use~~A method for treating or preventing one or more of the symptoms of myasthenia gravis in a mammalian subject comprising administering 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, hydroxyl, —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 and substituted derivatives thereof in the manufacture of a medicament for treating or preventing one or more of the symptoms of myasthenia gravis in a mammalian subject.

~~2009~~4. The ~~use~~method of claim ~~1999~~3, 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.

~~2019~~5. The ~~use~~method of claim ~~1999~~3, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~202~~96. The use~~method~~ of claim ~~199~~93 further comprising the use of~~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 in the manufacture of the medicament 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~~97. The use~~method~~ of claim ~~202~~96, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.

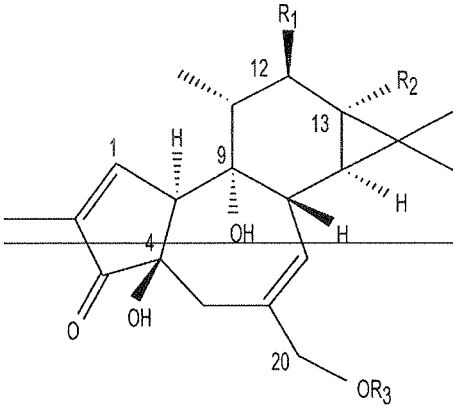
~~205~~98. The use~~method~~ of claim ~~199~~93, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

~~206~~99. The use~~method~~ of claim ~~199~~93, wherein the medicament~~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~~100. The use~~method~~ of claim ~~199~~93, wherein the medicament~~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 and substituted derivatives thereof.

209. The composition of claim 208, 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.

210. The composition of claim 208, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

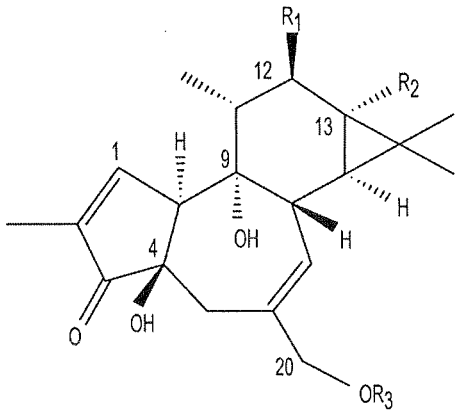
211. The composition of claim 208, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said

~~phorbol ester or derivative compound of Formula I to treat or prevent a symptom of myasthenia gravis.~~

~~212. The composition of claim 211, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.~~

~~213. The composition of claim 208, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.~~

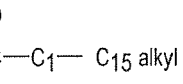
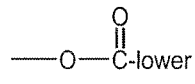
~~214~~101. Use~~A method for treating or preventing symptoms of kidney disease in a mammalian subject comprising administering an effective amount~~ of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof ~~to said subject~~




FORMULA I

wherein $R_1$ and $R_2$ are selected from the group consisting of hydrogen, hydroxyl, —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 and substituted derivatives thereof in

the manufacture of a medicament for treating or preventing symptoms of kidney disease in a mammalian subject.

~~215~~102. The use~~method~~ of claim ~~214~~101, wherein $R_1$ or $R_2$ is  the remaining $R_1$ or $R_2$ is  and $R_3$ is hydrogen.

~~216~~103. The use~~method~~ of claim ~~214~~101, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~217~~104. The use~~method~~ of claim ~~214~~101, further comprising the use of~~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 in the manufacture of the medicament 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.~~

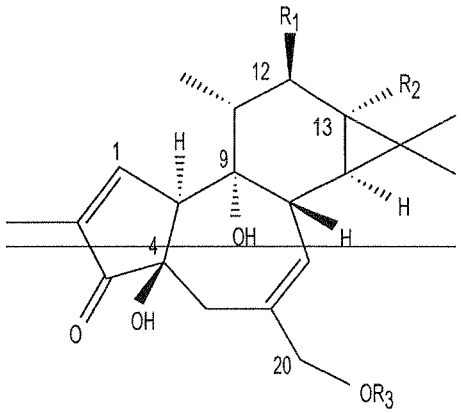
~~219~~105. The use~~method~~ of claim ~~217~~104, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

~~220~~106. The use~~method~~ of claim ~~214~~101, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

~~221~~107. The use~~method~~ of claim ~~214~~101, wherein the medicament~~said effective amount~~ comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

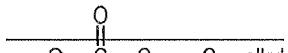
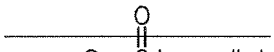
~~222~~108. The use~~method~~ of claim ~~214~~101, wherein the medicament~~said effective amount~~ comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~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 ~~and substituted derivatives thereof.~~

~~224. The composition of claim 223, wherein $R_1$ or $R_2$ is~~  ~~the remaining $R_1$ or $R_2$ is~~  ~~and $R_3$ is hydrogen.~~

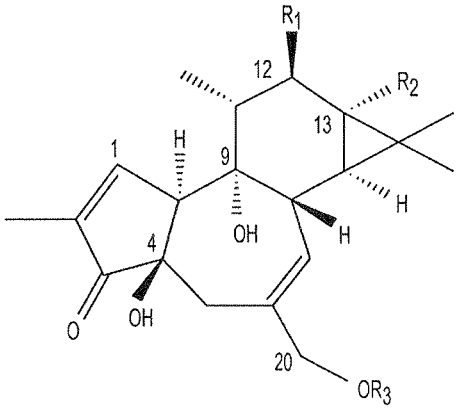
~~225. The composition of claim 223, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.~~

~~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 I 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~~109. Use~~A method for treating or preventing urinary incontinence in a mammalian subject comprising administering 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, hydroxyl, —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 and substituted derivatives thereof in the manufacture of a medicament for treating or preventing urinary incontinence in a mammalian subject.

~~230~~110. The use~~method~~ of claim ~~229~~109, 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~~111. The use~~method~~ of claim ~~229~~109, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~232~~112. The use~~method~~ of claim ~~229~~109, further comprising the use of~~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 in the manufacture of the medicament to treat or prevent symptoms of urinary incontinence.

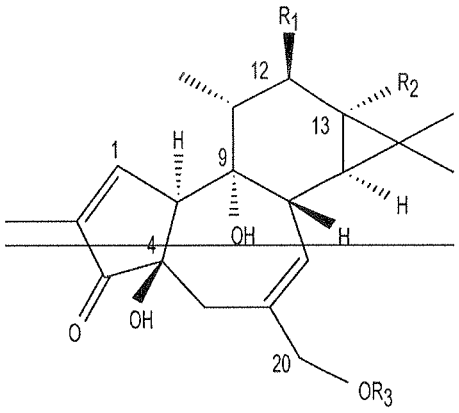
~~233. The method of claim 232, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.~~

~~234~~113. The use~~method~~ of claim ~~232~~112, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

~~235~~114. The use~~method~~ of claim ~~229~~109, wherein the medicament~~said effective amount~~ comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~236~~115. The use~~method~~ of claim ~~229~~109, wherein the medicament~~said effective amount~~ comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I ~~every day~~.

~~237. A composition for the prevention or treatment of urinary incontinence 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 ~~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.~~