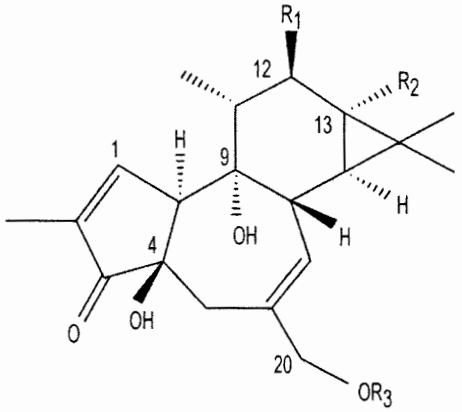
We claim:

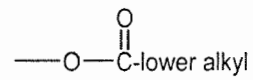
1. Use of a phorbol ester ~~or derivative~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or polymorph ~~or prodrug~~ thereof



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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is selected from hydrogen~~,~~ and —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 treating or preventing neoplasms in a mammalian subject;

wherein the medicament comprises between about 10 µg to about 1500 µg of said phorbol ester of Formula I, and the medicament is administered to the mammalian subject every other day.

2. The use of claim 1, wherein R_1 or R_2 is the remaining R_1 or R_2 is  and R_3 is hydrogen.

3. The use of claim 1, 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.

4. The use of claim 1, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

5. The use of claim 1, 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.

6. The use of claim 1, wherein two secondary or adjunctive therapeutic agents are used in the manufacture of the medicament.

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

~~8. The use of claim 1, wherein the medicament comprises between about 10 and 1500 µg of said phorbol ester or derivative compound of Formula I.~~

~~9~~8. The use of claim 1, wherein the medicament comprises between about 150 to 500 µg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~10~~9. The use of claim 1 wherein the neoplasm is caused by a haematological malignancy/bone marrow disorder.

~~11~~10. The use of claim ~~10~~9, wherein the hematological malignancy/bone marrow disorder is leukemia.

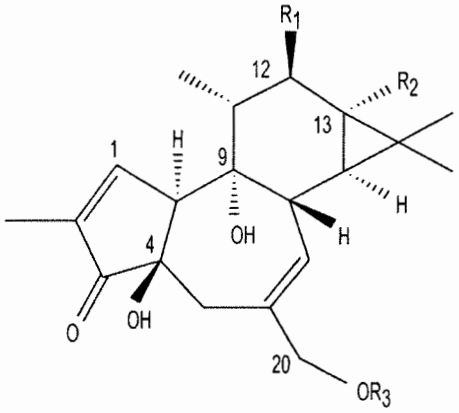
~~12~~11. The use of claim ~~11~~10, wherein the leukemia is acute myeloid leukemia.

~~13~~12. The use of claim 1, wherein the neoplasm is a solid tumor.

~~14~~13. The use of claim 1, wherein the neoplasm is a relapsing neoplasm.

~~15~~14. The use of claim 1, wherein the neoplasm is refractory.

~~16~~15. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen; and —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 treating or preventing one or more symptoms or conditions of neoplastic disease in a mammalian subject;

wherein the medicament comprises between about 10 µg to about 1500 µg of said phorbol ester of Formula I, and the medicament is administered to the mammalian subject every other day.

~~17~~16. The use of claim ~~16~~15, 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.

~~18~~17. The use of claim ~~16~~15, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate,

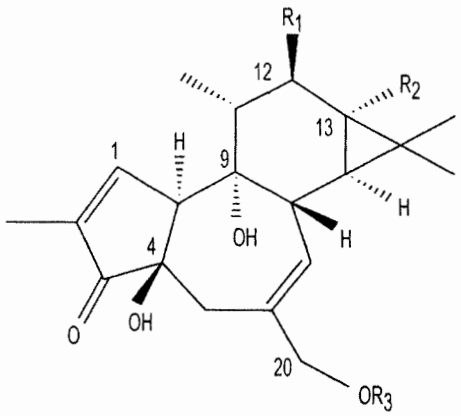
phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionatc, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 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.

~~19~~18. The use of claim ~~16~~15, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~20~~19. The use of claim ~~16~~15, 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.

~~21~~20. The use of claim ~~19~~18, 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.

~~22~~21. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~; R_3 is hydrogen; and —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 inducing remission in a mammalian subject suffering from neoplastic disease;

wherein the medicament comprises between about 10 µg to about 1500 µg of said phorbol ester of Formula I, and the medicament is administered to the mammalian subject every other day.

~~23~~22. The use of claim ~~22~~21, 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

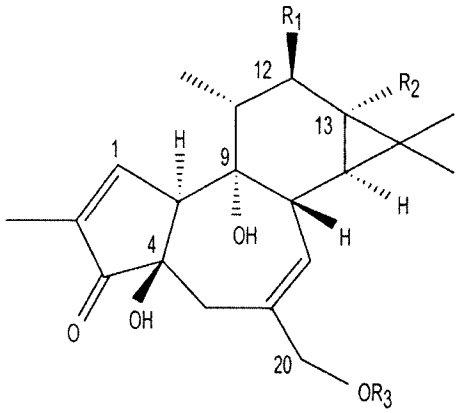
adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester ~~or derivative compound~~ of Formula I to induce remission in said subject.

~~24~~23. The use of claim ~~22~~21, 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.

~~25~~24. The use of claim ~~22~~21, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

~~26~~25. The use of claim ~~22~~21, 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.

~~27~~26. Use a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen; and —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 inducing apoptosis in a neoplasm in a mammalian subject suffering from neoplastic disease;

wherein the medicament comprises between about 10 µg to about 1500 µg of said phorbol ester of Formula I, and the medicament is administered to the mammalian subject every other day.

~~28~~27. The use of claim ~~27~~26, 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

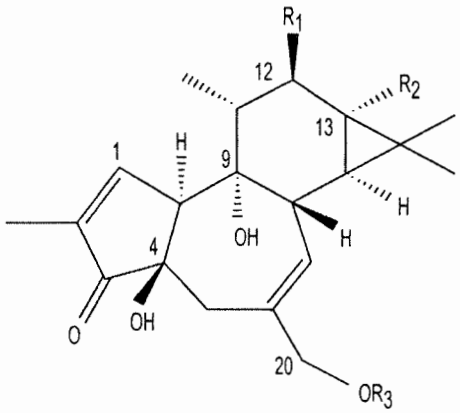
coordinate treatment regimen with said phorbol ester ~~or derivative compound~~ of Formula I to treat or prevent malignancy in said subject.

~~29~~28. The use of claim ~~27~~26, 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.

~~30~~29. The use of claim ~~27~~26, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

~~31~~30. The use of claim ~~27~~26, 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.

~~32~~31. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen; and —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 treating or preventing neoplastic disease in a mammalian subject;

wherein the medicament comprises between about 10 µg to about 1500 µg of said phorbol ester of Formula I, and the medicament is administered to the mammalian subject every other day.

~~33~~32. The use of claim ~~32~~31, 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.

~~34~~33. The use of claim ~~32~~31, 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.

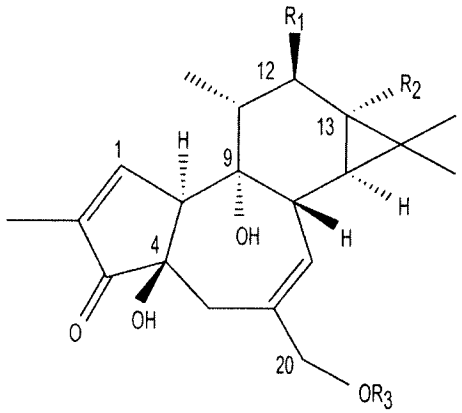
~~35~~34. The use of claim ~~32~~31, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

~~36~~35. The use of claim ~~32~~31, 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.

~~37~~36. The use of claim ~~32~~31, wherein the medicament contains at least two secondary or adjunctive therapeutic agents.

~~38~~37. The use of claim ~~37~~36, wherein the at least two secondary or adjunctive therapeutic agents are dexamethasone and choline magnesium trisalicylate.

~~39~~38. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen; and —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.

~~40~~39. The use of claim ~~39~~38, 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.

~~41~~40. The use of claim ~~39~~38, 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.

~~42~~41. The use of claim ~~39~~38, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~43~~42. The use of claim ~~39~~38, further comprising the use of 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.

~~44~~43. The use of claim ~~43~~42, 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.

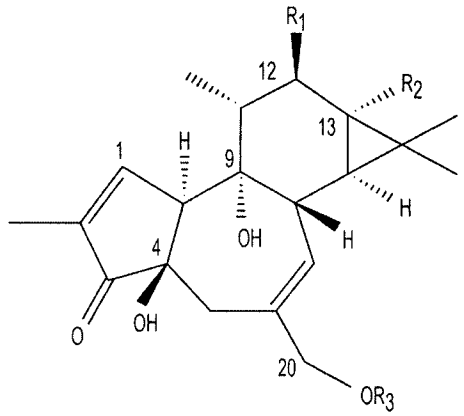
~~45~~44. The use of claim ~~39~~38, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~46~~45. The use of claim ~~45~~44, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~47~~46. The use of claim ~~39~~38, 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.

4847. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen; and —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.

4948. The use of claim 4847, 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.

~~50~~49. The use of claim ~~48~~47, 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.

~~51~~50. The use of claim ~~48~~47, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~52~~51. The use of claim ~~48~~47, further comprising the use of 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.

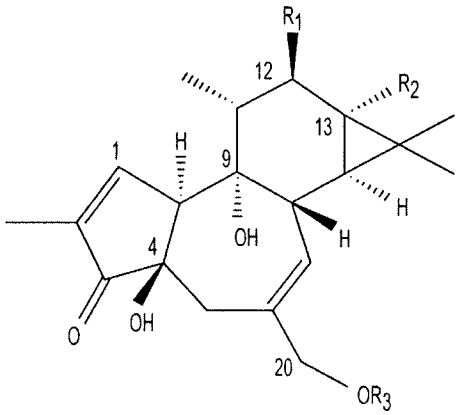
~~53~~52. The use of claim ~~52~~51, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of steroids, amifostine, chlorhexidine, benzydamine, sucralfate, KGF, palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

~~54~~53. The use of claim ~~48~~47, 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.

~~55~~54. The use of claim ~~48~~47, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

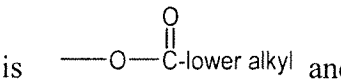
~~56~~55. The use of claim ~~48~~47, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~57~~56. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen, and —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.

5857. The use of claim 5756, wherein R_1 or R_2 is the remaining R_1 or R_2 is  and R_3 is hydrogen.

5958. The use of claim 5756, 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.

6059. The use of claim 5756, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

6160. The use of claim 5756, further comprising the use of 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.

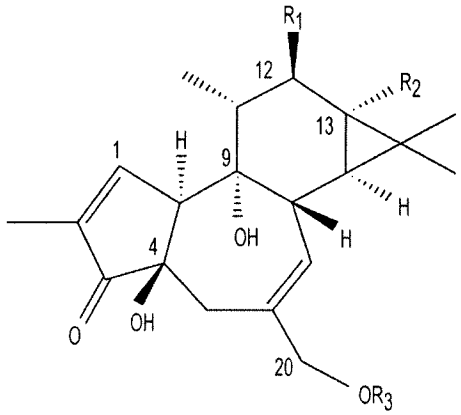
6261. The use of claim 6160, wherein the at least one secondary or adjunctive therapeutic agent is tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

6362. The use of claim 5756, 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.

6463. The use of claim 5756, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

6564. The use of claim 6463, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

6665. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and~~

~~substituted derivatives thereof~~, R_3 is hydrogen~~,~~ and $-\overset{O}{\overset{\|}{C}}$-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.

~~67~~66. The use of claim ~~66~~65, wherein R_1 or R_2 is $-O-\overset{O}{\overset{\|}{C}}-C_1-$ C_{15} alkyl the remaining R_1 or R_2 is $-O-\overset{O}{\overset{\|}{C}}$-lower alkyl and R_3 is hydrogen.

~~68~~67. The use of claim ~~66~~65, 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.

~~69~~68. The use of claim ~~66~~65, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~70~~69. The use of claim ~~66~~65, further comprising the use of 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.

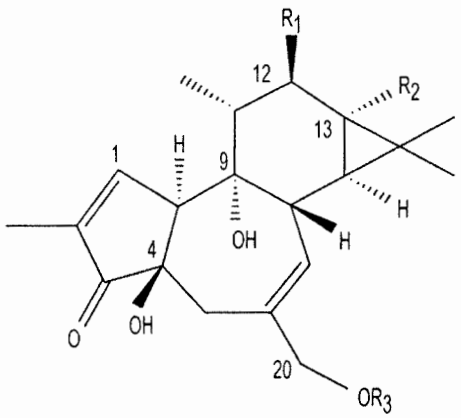
~~71~~70. The use of claim ~~70~~69, wherein the at least one secondary or adjunctive therapeutic agent is levodopa, carbidopa, pyridoxine, seleyiline, rasagiline, tolcapone, dopamine agonist, MAO-B inhibitors, amantidine, or anticholinergics.

~~72~~71. The use of claim ~~66~~65, 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.

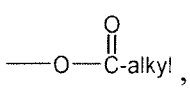
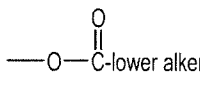
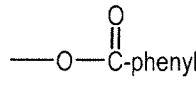
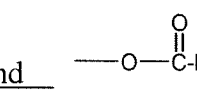
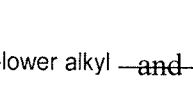
~~73~~72. The use of claim ~~66~~65, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

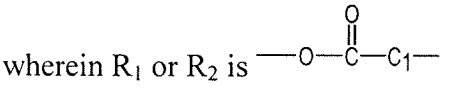
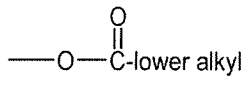
~~74~~73. The use of claim ~~66~~65, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~75~~74. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or polymorph ~~or prodrug~~ thereof



FORMULA I

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

~~76~~75. The use of claim ~~75~~74, wherein R_1 or R_2 is  the remaining R_1 or R_2 is  and R_3 is hydrogen.

~~77~~76. The use of claim ~~75~~74, 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.

~~78~~77. The use of claim ~~75~~74, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~79~~78. The use of claim ~~75~~74, further comprising the use of 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.

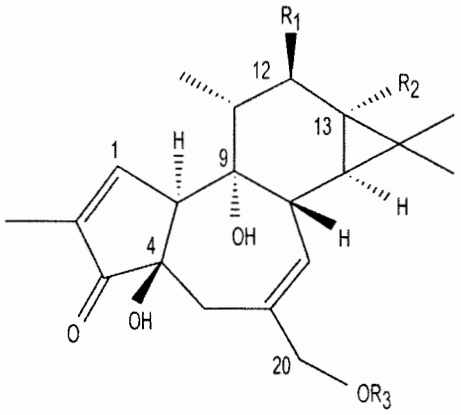
~~80~~79. The use of claim ~~79~~78, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.

~~81~~80. The use of claim ~~75~~74, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~82~~81. The use of claim ~~75~~74, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~83~~82. The use of claim ~~75~~74, 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.

~~84~~83. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen~~,~~ and —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 rheumatoid arthritis in a mammalian subject.

~~85~~84. The use of claim ~~84~~83, 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.

~~86~~85. The use of claim ~~84~~83, 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.

~~87~~86. The use of claim ~~84~~83, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~88~~87. The use of claim ~~84~~83, further comprising the use of 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.

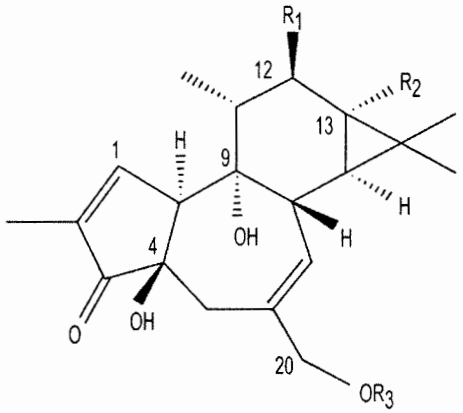
~~89~~88. The use of claim ~~88~~87, wherein the at least one secondary or adjunctive therapeutic agent is a non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine anakinra, abatacept, rituximab, or tocilizumab.

~~90~~89. The use of claim ~~84~~83, 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.

~~91~~90. The use of claim ~~84~~83, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

9291. The use of claim 8483, wherein the medicament comprises between about 125 µg to about 500 µg of said phorbol ester ~~or derivative compound~~ of Formula I.

9392. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen, and —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.

9493. The use of claim 9392, 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.

~~95~~94. The use of claim ~~93~~92, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~96~~95. The use of claim ~~93~~92 further comprising the use of 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.

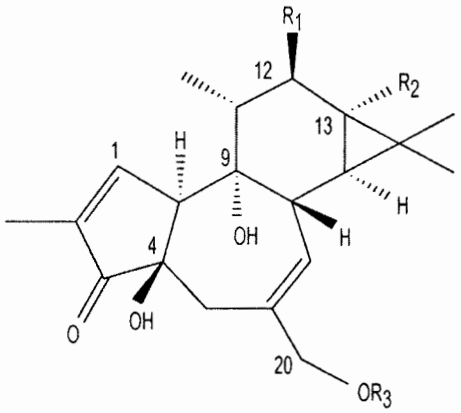
~~97~~96. The use of claim ~~96~~95, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.

~~98~~97. The use of claim ~~93~~92, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

~~99~~98. The use of claim ~~93~~92, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~100~~99. The use of claim ~~93~~92, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~101~~100. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen, and —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.

~~102~~101. The use of claim ~~101~~100, 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~~102. The use of claim ~~101~~100, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~104~~103. The use of claim ~~101~~100, further comprising the use of 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.

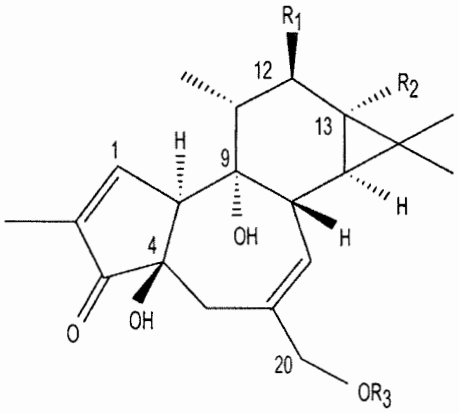
~~105~~104. The use of claim ~~104~~103, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

~~106~~105. The use of claim ~~101~~100, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

~~107~~106. The use of claim ~~101~~100, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~108~~107. The use of claim ~~101~~100, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~109~~108. Use of a phorbol ester ~~or derivative compound~~ of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, or 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, and —O—C(=O)-benzyl ~~and substituted derivatives thereof~~, R_3 is hydrogen; and —C(=O)-lower alkyl ~~and substituted derivatives thereof~~ in the manufacture of a medicament for treating or preventing urinary incontinence in a mammalian subject.

~~110~~109. The use of claim ~~109~~108, 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.

~~111~~110. The use of claim ~~109~~108, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

~~112~~111. The use of claim ~~109~~108, further comprising the use of 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.

~~113~~112. The use of claim ~~112~~111, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

~~114~~113. The use of claim ~~109~~108, wherein the medicament comprises between about 10 μg and about 1500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.

~~115~~114. The use of claim ~~109~~108, wherein the medicament comprises between about 125 μg to about 500 μg of said phorbol ester ~~or derivative compound~~ of Formula I.