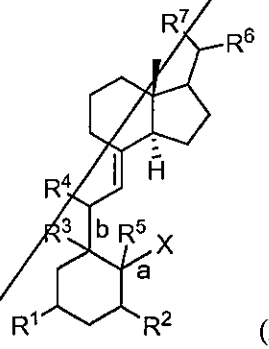
Claims

1. A method of preventing or treating alopecia in an individual, comprising topically administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a vitamin D compound formulated to be delivered to epidermis while substantially avoiding dermis delivery.

2. The method of claim 1, wherein the pharmaceutical composition comprises about 40% (w/w) propylene glycol and about 60% (w/w) anhydrous absolute ethanol (200 proof, U.S.); or about 30% (w/w) propylene glycol, about 10% (w/w) ethoxydiglycol or transcutol, and about 60% (w/w) anhydrous absolute ethanol (200 proof, U.S.).

3. The method of claim 1, wherein the vitamin D compound is represented by Formula (I):



(I)

wherein

a and b are each independently a single or double bond

X is -CH_2 when a is a double bond, or X is hydrogen or a hydroxyl substituted alkyl when a is a single bond;

R^1 is hydrogen, hydroxyl, alkoxyl, tri-alkyl silyl or alkyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^2 is hydrogen, hydroxyl, -O-trialkyl silyl, or alkyl, alkoxyl or alkenyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^3 is absent when b is a double bond or R^3 is hydrogen, hydroxyl or alkyl, or R^3 and R^1 together with the carbon atoms to which they are attached may be linked to form 5-7 membered carbocyclic ring when b is a single bond;

R^4 is absent when b is a double bond orhydrogen, halogen or hydroxyl when b is a single bond;

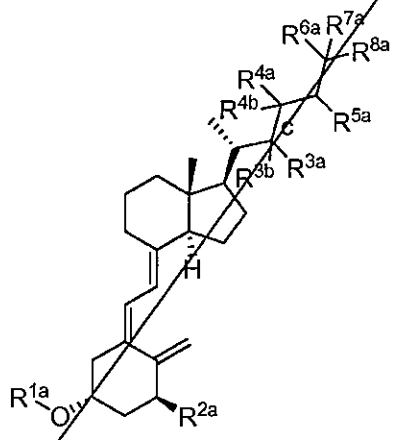
R^5 is absent when a is a double bond or R^5 is hydrogen, halogen or hydroxyl when a is a single bond;

R^6 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclicyl, alkyl-O-alkyl, alkyl-CO_2-alkyl optionally substituted with one to five, hydroxyl, oxo, halogen, alkoxyl, aryl, heteroaryl, cyano, nitro or -NR'R" moieties;

R^7 is alkyl optionally substituted with one to three hydroxyl, halogen, alkoxyl, aryl, heteroaryl, cyano, nitro or -NR'R" moieties; and,

R' and R" are each, independently, hydrogen, hydroxyl, halogen, alkyl or alkoxyl, and pharmaceutically acceptable salts thereof.

4. The method of claim 1, wherein the vitamin D compound is represented by Formula (II):



(II)

wherein

c is a single or double bond;

R^{1a} is hydrogen, tri-alkyl silyl or alkyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^{2a} is hydrogen, hydroxyl, -O-trialkyl silyl, or alkyl, alkoxyl or alkenyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^{3a}, R^{4a} are absent when c is a double bond, or are each independently hydrogen, hydroxyl, halogen, alkoxyl or alkyl optionally substituted with one to three hydroxyl or halogen moieties when c is a single bond

R^{3b}, R^{4b}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are each, independently, hydrogen, hydroxyl, halogen, alkoxyl or alkyl optionally substituted with one to three hydroxyl or halogen moieties, or any two of R^{6a}, R^{7a} and R^{8a} may be linked to form a 3-7 membered carbocyclic ring, and pharmaceutically acceptable salts thereof.

5. The method of claim 1, wherein the vitamin D compound is 1,25-dihydroxyvitamin D3; 1,25-dihydroxy-16-ene-23-yne-cholecalciferol; 1,25-dihydroxy-16-ene-yne-cholecalciferol; 1α-hydroxyvitamin D3; 1α,24-dihydroxyvitamin D3, or MC 903.

6. The method of claim 1, wherein the vitamin D compound is not 1,25-dihydroxyvitamin D3; 1,25-dihydroxy-16-ene-23-yne-cholecalciferol; 1,25-dihydroxy-16-ene-yne-cholecalciferol; 1α-hydroxyvitamin D3; 1α,24-dihydroxyvitamin D3, or MC 903.

7. The method of claim 1, wherein the vitamin D compound exhibits similar or identical gene regulation profile as equivalent amount of calcitriol in normal keratinocytes.

8. The method of claim 1, wherein the vitamin D compound promotes the expression of one or more genes whose expression levels are promoted by an equivalent amount of calcitriol.

9. The method of claim 1, wherein the vitamin D compound inhibits the expression of one or more genes whose expression levels are inhibited by an equivalent amount of calcitriol.

10. The method of claim 1, wherein the vitamin D compound modulates the expression of HSPA2 or HSF4 mRNA, HSPB1 or DNAJC6 mRNA in normal keratinocytes.

11. The method of claim 1, wherein the vitamin D compound modulates the expression of SLC1A1, KCNB2, oKCNN4 protein or SLC1A3 protein in normal keratinocytes.

12. The method of claim 1, wherein the vitamin D compound modulates the expression of one or more proteins in Table 3-1 and Table 3-2 by at least about 2-fold.

13. The method of claim 1, wherein the vitamin D compound induces overexpression of one or more proteins in Tables 3-3, 3-4, 3-5 or 3-6 after about 24-hour exposure of normal keratinocytes to said vitamin D compound.

14. The method of claim 1, wherein the vitamin D compound induces overexpression in normal keratinocytes of one or more of: GST, Keratin 1, Keratin 17, Galectin 1, S100 A9 (Calprotectin), or S100 A13.

15. The method of claim 1, wherein the alopecia is alopecia areata (AA), alopecia totalis (AT), alopecia universalis (AU), or chemotherapy-induced alopecia (CIA).

16. The method of claim 15, wherein alopecia areata includes diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, and alopecia areata barbae.

17. The method of claim 1, wherein the alopecia excludes androgenetic alopecia (alopecia androgenetica) or post-chemotherapy alopecia (PCA).

18. The method of claim 1, wherein the individual is a primate.

19. The method of claim 1, wherein the individual is a human.

20. The method of claim 1, wherein alopecia has not commenced in the individual.

21. The method of claim 1, wherein the individual is undergoing or about to undergo chemotherapy.

22. The method of claim 21, wherein the pharmaceutical composition is administered to the individual prior to chemotherapy or concurrent with chemotherapy.

23. The method of claim 21, wherein the pharmaceutical composition is administered to the individual after the commencement of chemotherapy, but prior to the commencement of alopecia.

24. The method of claim 21, wherein the pharmaceutical composition does not substantially reduce the efficacy of chemotherapy.

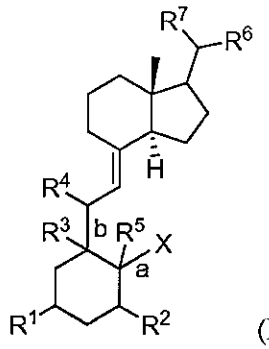
25. The method of claim 21, wherein chemotherapy is systemic chemotherapy.

26. The method of claim 21, wherein chemotherapy includes one or more of: Anthracyclines (Adriamycin/Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Valrubicin), 5-FU, Tamoxifen, Irinotecan, Paclitaxel (Taxol), Carboplatin, Etoposide, Cytoxan/Cyclophosphamide, Cisplatin, Erlotinib (Tarceva), Gemcitabine, Staurosporin, Vincristine, Imatinib (Gleevec), Gefitinib (Iressa), Sorafenib, Dasatinib, Dactinomycin, Hexamethamelamine (HMM, altretamine), Ifosfamide, bleomycin, methotrexate, Docetaxel (Taxotere), Vindesine, Vinorelbine, Topotecan, Amsacrine, Cytarabine, Busulphan, Melphalan, Vinblastine, Lomustine(CCNU), Thiotepa, Gemcitabine, Carmustine(BCNU), Mitroxantrone, Mitomycin C, Procarbazine, 6-Mercaptopurine, Sreptozotocin, Fludarabine, Raltitrexate (Tomudex), Capecitabine, and equivalents thereof.

27. The method of claim 1, wherein the vitamin D compound is topically administered to the individual at a dosage volume equivalent to about 0.1 μg of calcitriol/cm^2.

28. The method of claim 27, wherein the total dose is equivalent to about 2-100 μg of calcitriol/75 kg body weight.

29. A method of preventing or treating alopecia in an individual, comprising topically administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a vitamin D compound represented by Formula (I):



(I)

wherein

a and b are each independently a single or double bond

X is $-CH_2$ when a is a double bond, or X is hydrogen or a hydroxyl substituted alkyl when a is a single bond;

R^1 is hydrogen, hydroxyl, alkoxyl, tri-alkyl silyl or alkyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^2 is hydrogen, hydroxyl, -O-trialkyl silyl, or alkyl, alkoxyl or alkenyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^3 is absent when b is a double bond or R^3 is hydrogen, hydroxyl or alkyl, or R^3 and R^1 together with the carbon atoms to which they are attached may be linked to form 5-7 membered carbocyclic ring when b is a single bond;

R^4 is absent when b is a double bond orhydrogen, halogen or hydroxyl when b is a single bond;

R^5 is absent when a is a double bond or R^5 is hydrogen, halogen or hydroxyl when a is a single bond;

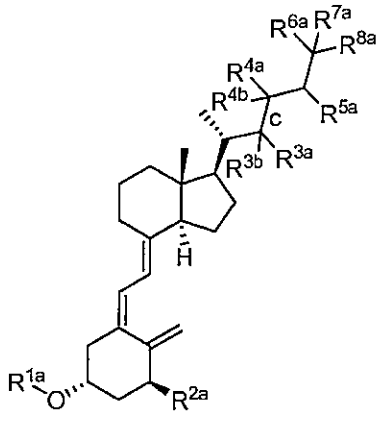
R^6 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclicyl, alkyl-O-alkyl, alkyl-CO_2-alkyl optionally substituted with one to five, hydroxyl, oxo, halogen, alkoxyl, aryl, heteroaryl, cyano, nitro or -NR'R" moieties;

R^7 is alkyl optionally substituted with one to three hydroxyl, halogen, alkoxyl, aryl, heteroaryl, cyano, nitro or -NR'R" moieties; and,

R' and R" are each, independently, hydrogen, hydroxyl, halogen, alkyl or alkoxyl, and pharmaceutically acceptable salts thereof;

wherein the vitamin D compound is not 1,25-dihydroxyvitamin D3; 1,25-dihydroxy-16-ene-23-yne-cholecalciferol; 1,25-dihydroxy-16-ene-yne-cholecalciferol; 1α-hydroxyvitamin D3; 1α,24-dihydroxyvitamin D3, or MC 903.

30. The method of claim 29, wherein the vitamin D compound is represented by Formula (II):



(II)

wherein

c is a single or double bond;

R^{1a} is hydrogen, tri-alkyl silyl or alkyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^{2a} is hydrogen, hydroxyl, -O-trialkyl silyl, or alkyl, alkoxyl or alkenyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^{3a}, R^{4a} are absent when c is a double bond, or are each independently hydrogen, hydroxyl, halogen, alkoxyl or alkyl optionally substituted with one to three hydroxyl or halogen moieties when c is a single bond

R^{3b}, R^{4b}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are each, independently, hydrogen, hydroxyl, halogen, alkoxyl or alkyl optionally substituted with one to three hydroxyl or halogen moieties, or any two of R^{6a}, R^{7a} and R^{8a} may be linked to form a 3-7 membered carbocyclic ring, and pharmaceutically acceptable salts thereof.

31. A method of preventing or treating alopecia in an individual, comprising topically administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a vitamin D compound, wherein said vitamin D compound, when topically administered to the individual at an effective concentration of:

(1) about 50 μg/mL, does not cause toxicity after at least about 25 consecutive days of drug administration; or

(2) about 100 μg/mL, does not cause toxicity after at least about 7 consecutive days of drug administration.

32. A method of preventing or treating alopecia in an individual, comprising topically administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a vitamin D compound for preventing or treating alopecia in said individual, without substantially interfere with the efficacy of a co-administered chemotherapeutic agent.

33. A method of preventing or treating alopecia in an individual, comprising topically administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a vitamin D compound that:

(1) exhibits similar or identical gene regulation profile as equivalent amount of calcitriol in normal keratinocyte;

(2) modulates the expression of one or more genes whose expression levels are modulated by an equivalent amount of calcitriol;

(3) modulatess the expression of HSPA2 or HSF4 mRNA, HSPB1 or DNAJC6 mRNA in normal keratinocytes;

(4) modulates the expression of SLC1A1, KCNB2, or KCNN4 protein or SLC1A3 protein in normal keratinocytes;

(5) modulates the expression of one or more proteins in Table 3-1 and Table 3-2 by at least about 2-fold;

(6) induces overexpression of one or more proteins in Tables 3-3, 3-4, 3-5 or 3-6 after about 24-hour exposure of normal keratinocytes to said vitamin D compound; or,

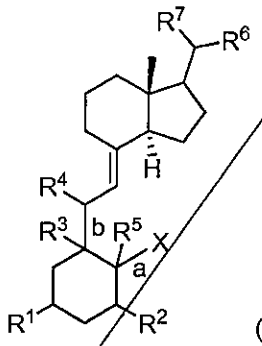
(7) induces overexpression in normal keratinocytes of one or more of: GST, Keratin 1, Keratin 17, Galectin 1, S100 A9 (Calprotectin), or S100 A13;

wherein the vitamin D compound is not 1,25-dihydroxyvitamin D3; 1,25-dihydroxy-16-ene-23-yne-cholecalciferol; 1,25-dihydroxy-16-ene-yne-cholecalciferol; 1α-hydroxyvitamin D3; 1α,24-dihydroxyvitamin D3, or MC 903.

34. A pharmaceutical composition for topical administration, comprising a therapeutically effective amount of a vitamin D compound for preventing or treating alopecia, wherein said vitamin D compound is formulated to be delivered to epidermis while substantially avoiding dermis delivery.

35. The pharmaceutical composition of claim 34, comprising about 40% (w/w) propylene glycol and about 60% (w/w) anhydrous absolute ethanol (200 proof, US), undenatured; or about 30% (w/w) propylene glycol, about 10% (w/w) ethoxydiglycol or transcutol, and about 60% (w/w) anhydrous absolute ethanol (200 proof, US), undenatured.

36. A pharmaceutical composition for topical administration, comprising a therapeutically effective amount of a vitamin D compound for preventing or treating alopecia, wherein said vitamin D compound is represented by Formula (I):



(I)

wherein

a and b are each independently a single or double bond

X is $-CH_2$ when a is a double bond, or X is hydrogen or a hydroxyl substituted alkyl when a is a single bond;

R^1 is hydrogen, hydroxyl, alkoxyl, tri-alkyl silyl or alkyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^2 is hydrogen, hydroxyl, -O-trialkyl silyl, or alkyl, alkoxyl or alkenyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^3 is absent when b is a double bond or R^3 is hydrogen, hydroxyl or alkyl, or R^3 and R^1 together with the carbon atoms to which they are attached may be linked to form 5-7 membered carbocyclic ring when b is a single bond;

R^4 is absent when b is a double bond orhydrogen, halogen or hydroxyl when b is a single bond;

R^5 is absent when a is a double bond or R^5 is hydrogen, halogen or hydroxyl when a is a single bond;

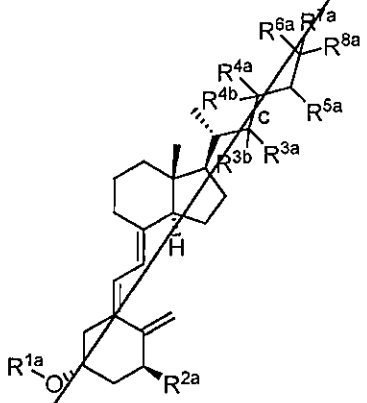
R^6 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclicyl, alkyl-O-alkyl, alkyl-CO_2-alkyl optionally substituted with one to five, hydroxyl, oxo, halogen, alkoxyl, aryl, heteroaryl, cyano, nitro or -NR'R" moieties;

R^7 is alkyl optionally substituted with one to three hydroxyl, halogen, alkoxyl, aryl, heteroaryl, cyano, nitro or -NR'R" moieties; and,

R' and R" are each, independently, hydrogen, hydroxyl, halogen, alkyl or alkoxyl, and pharmaceutically acceptable salts thereof;

wherein the vitamin D compound is not 1,25-dihydroxyvitamin D3; 1,25-dihydroxy-16-ene-23-yne-cholecalciferol; 1,25-dihydroxy-16-ene-yne-cholecalciferol; 1α-hydroxyvitamin D3; 1α,24-dihydroxyvitamin D3, or MC 903.

37. The pharmaceutical composition of claim 36, wherein the vitamin D compound is represented by Formula (II):



(II)

wherein

c is a single or double bond;

R^{1a} is hydrogen, tri-alkyl silyl or alkyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^{2a} is hydrogen, hydroxyl, -O-trialkyl silyl, or alkyl, alkoxyl or alkenyl, optionally substituted with one to three halogen, hydroxyl, cyano or -NR'R" moieties;

R^{3a}, R^{4a} are absent when c is a double bond, or are each independently hydrogen, hydroxyl, halogen, alkoxyl or alkyl optionally substituted with one to three hydroxyl or halogen moieties when c is a single bond

R^{3b}, R^{4b}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are each, independently, hydrogen, hydroxyl, halogen, alkoxyl or alkyl optionally substituted with one to three hydroxyl or halogen moieties, or

any two of R^{6a}, R^{7a} and R^{8a} may be linked to form a 3-7 membered carbocyclic ring, and pharmaceutically acceptable salts thereof.

38. A pharmaceutical composition for topical administration, comprising a therapeutically effective amount of a vitamin D compound for preventing or treating alopecia, wherein said vitamin D compound, when topically administered to the individual at an effective concentration of:

(1) about 50 μg/mL, does not cause toxicity after at least about 25 consecutive days of drug administration; or

(2) about 100 μg/mL, does not cause toxicity after at least about 7 consecutive days of drug administration.

39. A pharmaceutical composition for topical administration, comprising a therapeutically effective amount of a vitamin D compound for preventing or treating alopecia, wherein said therapeutically effective amount of the vitamin D compound, when co-administered with a chemotherapeutic agent, does not substantially interfere with the efficacy of the chemotherapeutic agent.

40. A pharmaceutical composition for topical administration, comprising a therapeutically effective amount of a vitamin D compound for preventing or treating alopecia, wherein said therapeutically effective amount of the vitamin D compound:

(1) exhibits similar or identical gene regulation profile as equivalent amount of calcitriol in normal keratinocytes;

(2) modulates the expression of one or more genes whose expression levels are modulated by an equivalent amount of calcitriol;

(3) modulates the expression of HSPA2 or HSF4 mRNA, HSPB1 or DNAJC6 mRNA in normal keratinocytes;

(4) modulates the expression of SLC1A1, KCNB2, or KCNN4 protein, SLC1A3 protein in normal keratinocytes;

(5) modulates the expression of one or more proteins in Table 3-1 and Table 3-2 by at least about 2-fold;

(6) induces overexpression of one or more proteins in Tables 3-3, 3-4, 3-5 or 3-6 after about 24-hour exposure of normal keratinocytes to said vitamin D compound; or,

(7) induces overexpression in normal keratinocytes of one or more of: GST, Keratin 1, Keratin 17, Galectin 1, S100 A9 (Calprotectin), or S100 A13;

wherein the vitamin D compound is not 1,25-dihydroxyvitamin D3; 1,25-dihydroxy-16-ene-23-yne-cholecalciferol; 1,25-dihydroxy-16-ene-yne-cholecalciferol; 1α-hydroxyvitamin D3; 1α,24-dihydroxyvitamin D3, or MC 903.

Claims:

1. An invention not claimed in any divisional application.