furfur. It is a stable yellow lipophilic compound showing broad absorption in the UVA, UVB, and UVC spectrum. A similar compound from the genus *Paracoccus* has been isolated and patented as a UV protective agent. (Zhang *et al*., 2018).

[0006] Gambichler *et al*., 2007 investigated the UV protective effect of pityriacitrin in humans using *in vitro* and *in vivo* test methods. Spectrophotometry of pityriacitrin cream and vehicle was performed in the 290-400 nm wavelength range. UV transmission and the sun protection factor ("SPF") were assessed for different cream formulations. Using colorimetry, the authors evaluated erythema and pigmentation following irradiation of cream-protected and non-protected skin of healthy subjects. UVB as well as UVA transmission decreased with increasing pityriacitrin concentrations. An increase of pityriacitrin concentration of 1.25, 2.5, and 5% was associated with slightly increasing SPFs of 1.4, 1.5, and 1.7, respectively. The *in vivo* tests confirmed the validity of the SPF of pityriacitrin 5% cream determined *in vitro*. Overall, the UV protective effect of pityriacitrin was very weak, suggesting that pityriacitrin likely is only an inferior cofactor in the development of hypopigmentation in pityriasis versicolor alba lesions following sun exposure.

[0007] Further studies of the UV filtering effects of pityriacitrin were performed on human skin microflora. (Machowinski *et al*., 2006). The authors determined pityriacitrin has a UV-protective effect on *Candida albicans* and staphylococci with no toxicity in the ranges tested. The UV protective properties of pityrialactone have also been confirmed in a yeast model. (Mayser *et al*., 2003). Pityrialactone appears to be responsible for the yellow fluorescence of Tinea Versicolor under Wood's Light examination.

[0008] Tinea versicolor is a non-contagious skin disease caused by *Malassezia* overgrowth that locally alters pigmentation levels. *Malassezia* yeasts have two metabolic pathways for synthesizing melanin and tryptophan-derived indole pigments. Malassezin and Indirubin are tryptophan metabolites of *Malassezia* that may contribute to the depigmentation characteristic of *Malassezia* overgrowth.

[0009] The invention disclosed herein utilizes compounds produced by or derived from *Malassezia* yeast, including Malassezin, Indirubin, and chemical analogs thereof, as the basis for safe and efficacious skin brightening and skin darkening compositions. Photoprotective compositions comprising Malassezin, Indirubin, and chemical analogs thereof are also disclosed herein.

SUMMARY

[0010] One aspect of the present disclosure is a composition. The composition comprises one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0010a] In another aspect, the present disclosure refers to use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or

cosmetically acceptable salt thereof in the manufacture of a composition for brightening skin in a subject, wherein the subject is to be contacted with the composition. In another aspect, the present disclosure refers to a non-therapeutic method for brightening skin in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0010b] In yet another aspect, the present disclosure refers to use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a medicament for inducing melanocyte apoptosis in a subject, wherein the subject is to be contacted with the composition. In yet another aspect, the present disclosure refers to a non-therapeutic method for inducing melanocyte apoptosis in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0010c] In yet another aspect, the present disclosure refers to use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a composition for modulating arylhydrocarbon receptor (AhR) activity in a subject, comprising that the subject is to be contacted with the composition. In yet another aspect, the present disclosure refers to a non-therapeutic method for modulating arylhydrocarbon receptor (AhR) activity in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0010d] In a further aspect, the present disclosure refers to use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a composition for modulating melanogenesis in a subject, comprising that the subject is to be contacted with the composition. In a further aspect, the present disclosure refers to a non-therapeutic method for modulating melanogenesis in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0010e] In a further aspect, the present disclosure refers to use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a composition for modulating melanin concentration in a subject, comprising that the subject is to be contacted with the composition. In a further aspect, the present disclosure refers to a non-therapeutic method for modulating melanin concentration in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0011] Another example of the present disclosure is a method for brightening skin in a subject. The method comprises contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0012] A further example of the present disclosure is a method for inducing melanocyte apoptosis in a subject. The method comprises contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0013] An additional example of the present disclosure is a method for modulating arylhydrocarbon receptor (AhR) activity in a subject. The method comprises contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0014] Another example of the present disclosure is a method for modulating melanogenesis in a subject. The method comprises contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0015] Another example of the present disclosure is a method for modulating melanin concentration in a subject. The method comprises contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0016] An additional example of the present disclosure is a composition. The composition comprises one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0017] A further example of the present disclosure is a composition for brightening skin. The composition comprises one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0018] Another example of the present disclosure is a composition for inducing melanocyte apoptosis. The composition comprises one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0019] An additional example of the present disclosure is a composition for modulating arylhydrocarbon receptor (AhR) activity. The composition comprises one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0020] A further example of the present disclosure is a composition for modulating melanogenesis. The composition comprises one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0021] Another example of the present disclosure is a composition for modulating melanin concentration. The composition comprises one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0022] An additional example of the present disclosure is a method for brightening skin in a subject. The method comprises contacting the subject with a composition, the composition comprising one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0023] A further example of the present disclosure is a method for inducing melanocyte apoptosis in a subject. The method comprises contacting the subject with a composition, the composition comprising one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

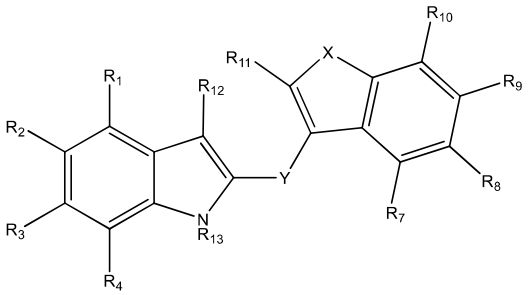
[0024] Another example of the present disclosure is a method for modulating arylhydrocarbon receptor (AhR) activity in a subject. The method comprises contacting the subject with a composition, the composition comprising one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0025] An additional example of the present disclosure is a method for modulating melanogenesis in a subject. The method comprises contacting the subject with a composition, the composition comprising one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0026] A further example of the present disclosure is a method for modulating melanin concentration in a subject. The method comprises contacting the subject with a composition, the composition comprising one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

[0027] Another example of the present disclosure is a composition. The composition comprises a *Malassezia* yeast and a cosmetically or pharmaceutically acceptable vehicle, diluent, or carrier.

[0028] An additional example of the present disclosure is a composition. The composition comprises a compound having the structure of the following formula:



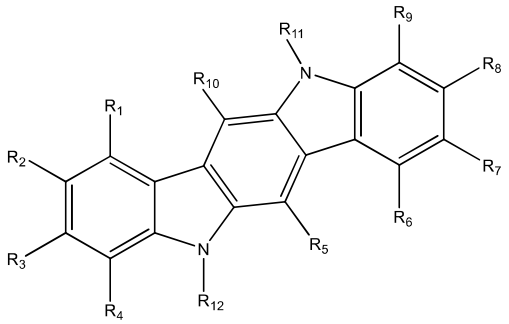
wherein:

X is selected from the group consisting of NR_{14} and O; Y is a covalent bond, CR_5R_6, O, or NR_{15}; R_1, R_2, R_3, R_4, R_7, R_8, R_9, R_{10}, and R_{11} are independently selected from the group consisting of hydrogen, halogen, CN, hydroxyl, R_{16}, or OR_{16}; R_{13}, R_{14}, and R_{15} are independently hydrogen or R_{16}; R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxyl, OR_{16}, R_{16}, and C_{3-6} cycloalkyl, or R_5 and R_6 combine to form an oxo (=O) group or a C_{3-6} cycloalkyl; R_{12} is selected from the group consisting of hydrogen, –COR^a, and R_{16}; each R_{16} is independently formyl, C_{1-9} alkyl, C_{2-9} alkenyl, or C_{2-9} alkynyl; and, R^a is selected from the group consisting of hydrogen, hydroxyl, and OR_{16};

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof,

and a cosmetically or pharmaceutically acceptable vehicle, diluent, or carrier.

[0029] A further example of the present disclosure is a composition. The composition comprises a compound having the structure of the following formula:



wherein:

R_1, R_4, R_5, R_6, R_9, and R_{10} are independently selected from the group consisting of hydrogen, hydroxyl, halogen, CN, R_{13}, OR_{13}, $OCOR_{13}$ and -CHO; R_2 and R_3 are independently selected from the group consisting of hydrogen, hydroxyl, halogen, CN, R_{13}, OR_{13}, $OCOR_{13}$ and -CHO, or R_2 and R_3 combine to form a 5- or 6-membered heterocyclyl; R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxyl, halogen, CN, R_{13}, OR_{13}, $OCOR_{13}$ and -CHO, or R_7 and R_8 combine to form a 5- or 6-membered heterocyclyl; R_{11} and R_{12} are independently hydrogen or R_{13}; and, each R_{13} is independently C_{1-9} alkyl, C_{2-9} alkenyl, or C_{2-9} alkynyl;

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof,

and a cosmetically or pharmaceutically acceptable vehicle, diluent, or carrier.

[0030] Another example of the present disclosure is a composition. The composition comprises a compound listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof,

and a cosmetically or pharmaceutically acceptable vehicle, diluent, or carrier.

[0031] An additional example of the present disclosure is a method of treating or preventing UV-induced skin damage in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0032] A further example of the present disclosure is a method of treating or preventing UV-induced erythema in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0033] Another example of the present disclosure is a method of treating or preventing UV-induced aging of the skin in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0034] An additional example of the present disclosure is a method of treating or preventing sunburn in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0035] A further example of the present disclosure is a method of treating or preventing UV-induced hyperpigmentation in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0036] Another example of the present disclosure is a method for brightening skin in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0037] An additional example of the present disclosure is a method for inducing melanocyte apoptosis in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0038] A further example of the present disclosure is a method for modulating arylhydrocarbon receptor (AhR) activity in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0039] Another example of the present disclosure is a method for modulating melanogenesis in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

[0040] An additional example of the present disclosure is a method for modulating melanin concentration in a subject. The method comprises contacting the subject with any of the compositions disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] Figs. 1-2 are tables showing mean tissue viability and melanin concentration data ascertained from separate experiments with MelanoDerm™ substrates treated with varying concentrations of the test articles shown.

[0042] Fig. 3 shows compounds produced by *Malassezia*.

[0043] Figs. 4-5 are tables showing mean tissue viability and melanin concentration data ascertained from separate experiments with MelanoDerm™ substrates treated with varying concentrations of the test articles / test compositions shown.

[0044] Figs. 6A-6B show synthesis schemes for AB17590 (Fig. 6A) and AB17653, AB17654, AB17655, AB17656, AB17657, and AB17658 (Fig. 6B).

[0045] Fig. 7 is a schematic showing a skin treatment template for Skin Type IV patients. Values indicate UV dose for a given area in mJ/cm^2.

[0046] Fig. 8 is a table showing a Dualight scale for Skin Types I-VI.

[0047] Fig. 9 is a table showing Mexameter MX 16 measurements of melanin and erythema at Day 8 after Day 7 irradiation.

[0048] Fig. 10 is a table showing Mexameter MX 16 measurements of melanin and erythema at Day 15 after Day 14 irradiation.

[0049] Fig. 11 is a table showing an erythema scale of numerical values associated with various degrees of erythema.

[0050] Fig. 12 is a photograph showing a subject's skin 24 hours after irradiation with various levels of UV according to the skin treatment template shown in Fig. 7. The minimal erythema dose ("MED") was 120 mJ UVB 24 hours after irradiation.

[0051] Fig. 13 is a photograph showing test sites on a subject's skin at Day 7.

[0052] Fig. 14 is a photograph showing test sites on a subject's skin at Day 8, 24 hours post-irradiation with 120 mJ UVB.

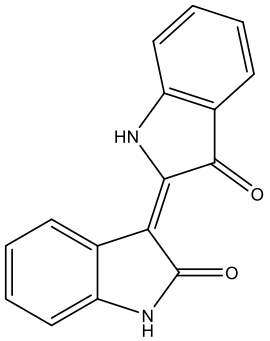
[0053] Fig. 15 is a photograph showing test sites on a subject's skin at Day 14 after an additional week of Malassezin therapy. Treatment areas were dosed with 120 mJ UVB.

WHAT IS CLAIMED IS:

1. A composition comprising one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

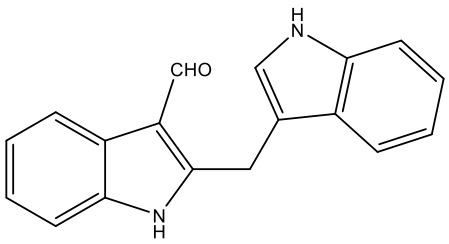
2. The composition of claim 1, wherein the composition comprises:

a first compound having the structure of the following formula:



or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof; and,

a second compound having the structure of the following formula:



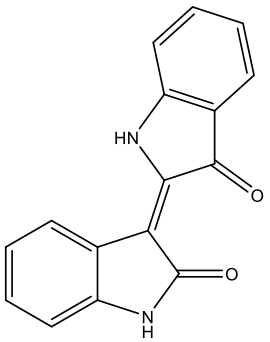
or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

3. Use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a composition for brightening skin in a subject, wherein the subject is to be contacted with the composition.

4. A non-therapeutic method for brightening skin in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

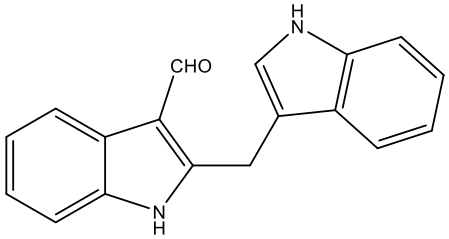
5. The use of claim 3 or the method of claim 4, wherein the subject is to be contacted with:

a first compound having the structure of the following formula:



or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof; and,

a second compound having the structure of the following formula:



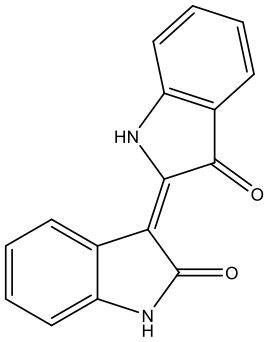
or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

6. Use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a medicament for inducing melanocyte apoptosis in a subject, wherein the subject is to be contacted with the composition.

7. A non-therapeutic method for inducing melanocyte apoptosis in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

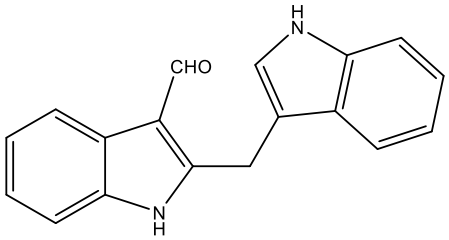
8. The use of claim 6 or the method of claim 7, wherein the subject is to be contacted with:

a first compound having the structure of the following formula:



or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof; and,

a second compound having the structure of the following formula:



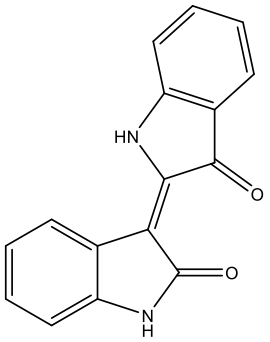
or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

9. Use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a composition for modulating arylhydrocarbon receptor (AhR) activity in a subject, comprising that the subject is to be contacted with the composition.

10. A non-therapeutic method for modulating arylhydrocarbon receptor (AhR) activity in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

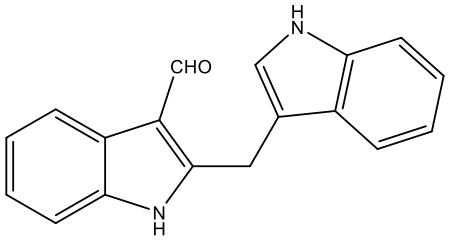
11. The use of claim 9 or the method of claim 10, wherein the subject is to be contacted with:

a first compound having the structure of the following formula:



or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof; and,

a second compound having the structure of the following formula:



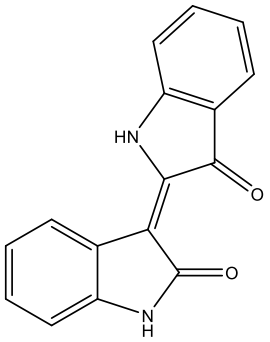
or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

12. Use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a composition for modulating melanogenesis in a subject, comprising that the subject is to be contacted with the composition.

13. A non-therapeutic method for modulating melanogenesis in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

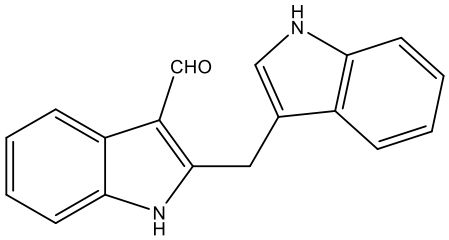
14. The use of claim 12 or the method of claim 13, wherein the subject is to be contacted with:

a first compound having the structure of the following formula:



or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof; and,

a second compound having the structure of the following formula:



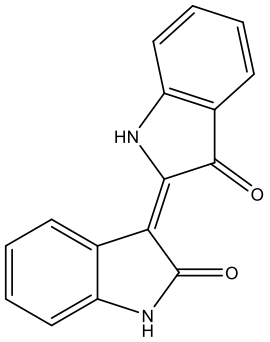
or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

15. Use of one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof in the manufacture of a composition for modulating melanin concentration in a subject, comprising that the subject is to be contacted with the composition.

16. A non-therapeutic method for modulating melanin concentration in a subject, the method comprising contacting the subject with one or more of the compounds listed in Table 1 or Fig. 3, or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.

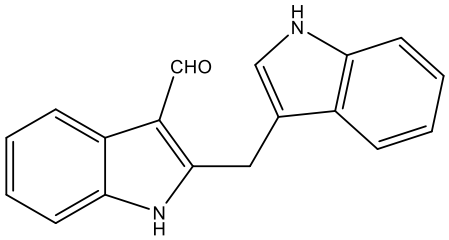
17. The use of claim 15 or the method of claim 16, wherein the subject is to be contacted with:

a first compound having the structure of the following formula:



or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof; and,

a second compound having the structure of the following formula:



or a chemical analog, crystalline form, hydrate, or pharmaceutically or cosmetically acceptable salt thereof.