Thus, there exists a need for novel skin brightening agents and formulations that exhibit higher levels of safety and/or efficacy than agents currently on the market.

[0004] *Malassezia* is a genus of lipophilic yeast commonly found in the normal flora of human skin. *Malassezia* is responsible for a number of skin diseases, including tinea versicolor (pityriasis versicolor), seborrheic dermatitis, and atopic dermatitis.

[0005] 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. The indole pigments include malassezin, a tryptophan metabolite of *Malassezia* that may elicit melanocyte apoptosis and contribute to the depigmentation characteristic of *Malassezia* overgrowth.

[0006] The invention disclosed herein utilizes compounds produced by *Malassezia* yeast, including malassezin, and chemical analogs thereof, as the basis for safe and efficacious skin brightening compositions.

SUMMARY

[0007] One embodiment of the present disclosure is a compound for brightening skin. The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0008] Another embodiment of the present disclosure is a compound for inducing melanocyte apoptosis. The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0009] A further embodiment of the present disclosure is a compound for modulating melanocyte activity. The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0010] An additional embodiment of the present disclosure is a compound for agonizing the arylhydrocarbon receptor (AhR). The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0011] Another embodiment of the present disclosure is a compound for improving hyperpigmentation caused by a hyperpigmentation disorder. The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0012] A further embodiment of the present disclosure is a compound for modulating melanin production. The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0013] An additional embodiment of the present disclosure is a compound for modulating melanosome biogenesis. The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0014] Another embodiment of the present disclosure is a compound for modulating melanosome transfer. The compound is a chemical analog of a compound produced by a *Malassezia* yeast, or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0015] A further embodiment of the present disclosure is a composition. The composition comprises a *Malassezia* yeast and a cosmetically or pharmaceutically acceptable vehicle, diluent or carrier.

[0016] An additional embodiment of the present disclosure is a composition. The composition comprises a compound isolated or isolatable from a *Malassezia* yeast and a cosmetically or pharmaceutically acceptable vehicle, diluent or carrier.

[0017] Another embodiment of the present disclosure is a composition. The composition comprises any of the compounds, including analogs, disclosed herein and a cosmetically or pharmaceutically acceptable vehicle, diluent or carrier.

[0018] A further embodiment of the present disclosure is a method of brightening skin in a subject. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

[0019] An additional embodiment of the present disclosure is a method for inducing melanocyte apoptosis in a subject. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

[0020] Another embodiment of the present disclosure is a method for modulating melanocyte activity in a subject. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

[0021] A further embodiment of the present disclosure is a method for agonizing an arylhydrocarbon receptor (AhR) in a subject. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

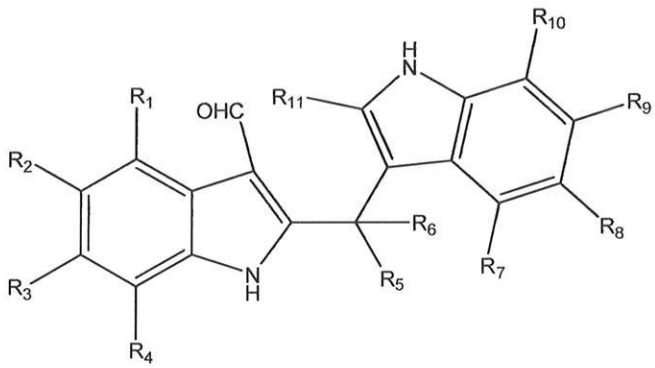
[0022] An additional embodiment of the present disclosure is a method for improving hyperpigmentation caused by a hyperpigmentation disorder in a subject in need thereof. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

[0023] Another embodiment of the present disclosure is a method for modulating melanin production in a subject. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

[0024] A further embodiment of the present disclosure is a method for modulating melanosome biogenesis in a subject. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

[0025] An additional embodiment of the present disclosure is a method for modulating melanosome transfer in a subject. The method comprises contacting the subject with any of the compounds or compositions disclosed herein.

[0026] In one aspect, there is provided a compound having the structure of formula (II):

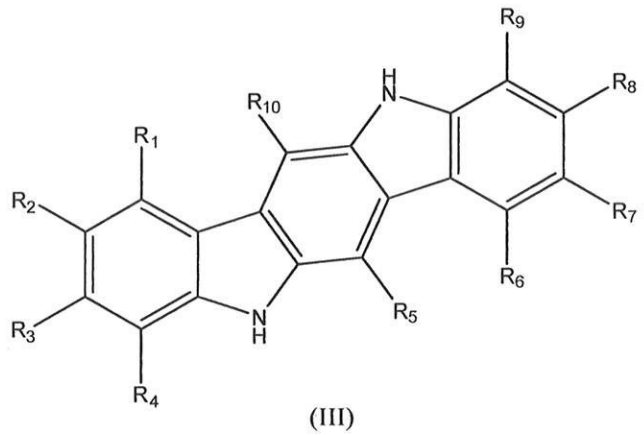


(II)

wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl, and at least one of R1, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 is methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

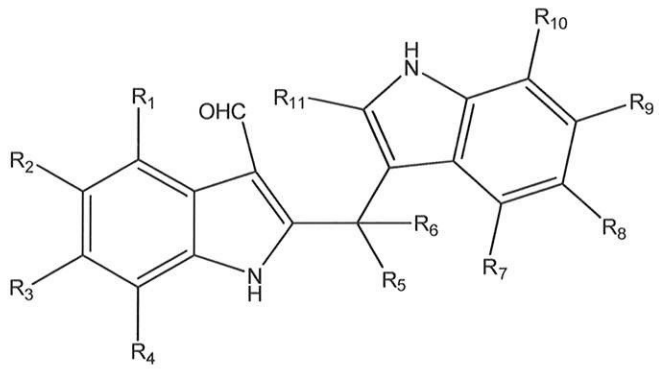
[0027] In one aspect, there is provided a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl, and at least one of R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 is methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

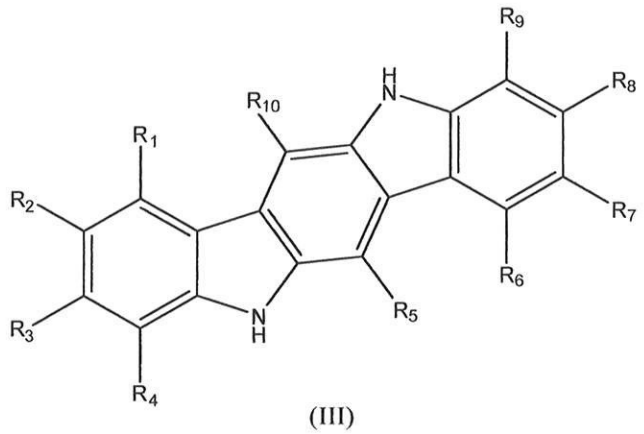
[0028] In one aspect, there is provided a compound for brightening skin, the compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

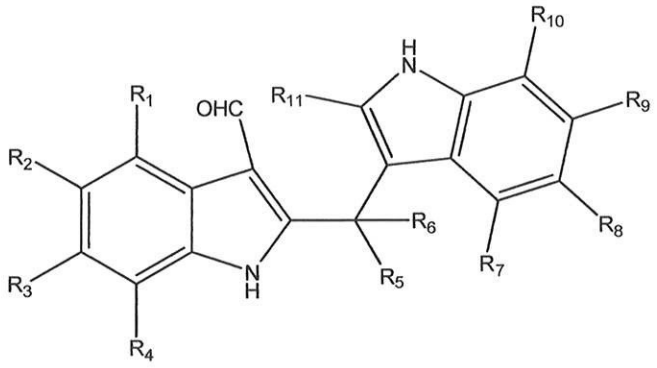
[0029] In one aspect, there is provided a compound for brightening skin, the compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

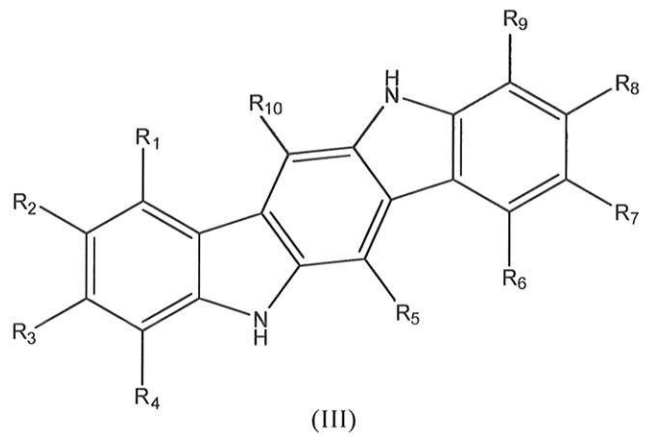
[0030] In one aspect, there is provided a compound for inducing melanocyte apoptosis, the compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

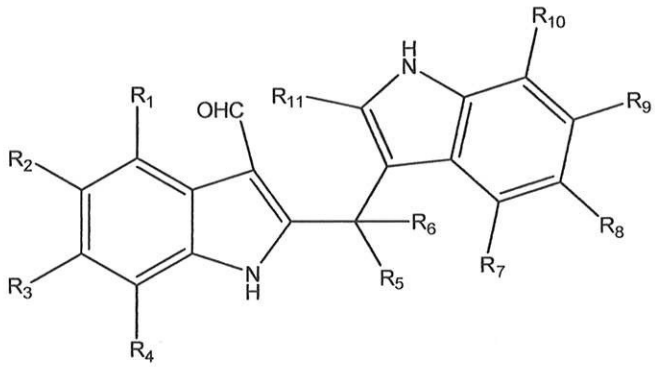
[0031] In one aspect, there is provided a compound for inducing melanocyte apoptosis, the compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

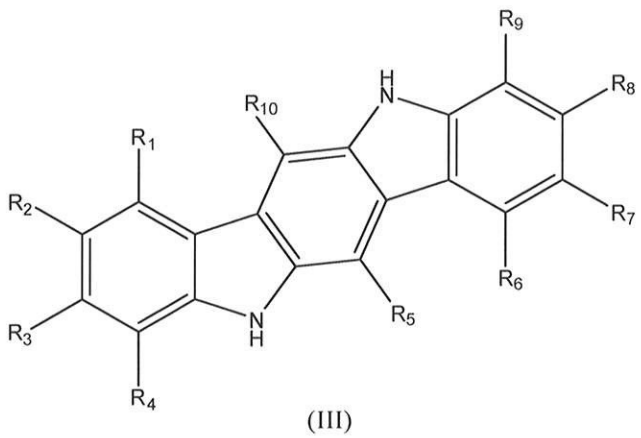
[0032] In one aspect, there is provided a compound for agonizing the arylhydrocarbon receptor (AhR), the compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

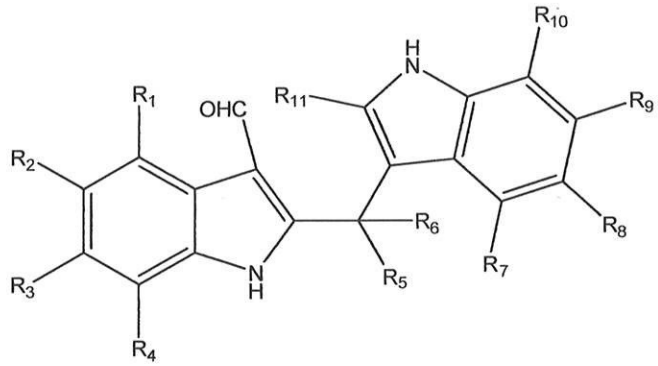
[0033] In one aspect, there is provided a compound for agonizing the arylhydrocarbon receptor (AhR), the compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

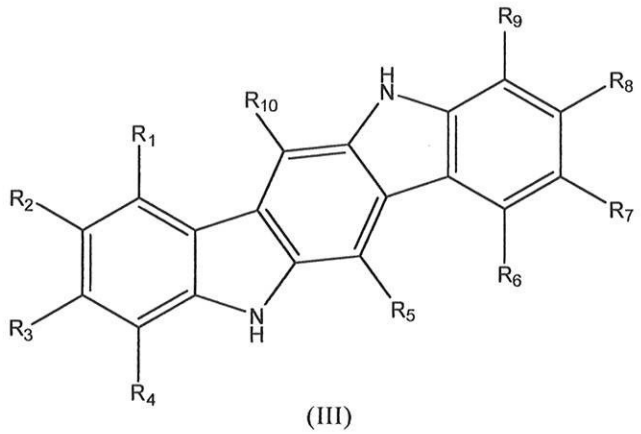
[0034] In one aspect, there is provided a composition comprising a compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof, and a cosmetically or pharmaceutically acceptable vehicle, diluent or carrier.

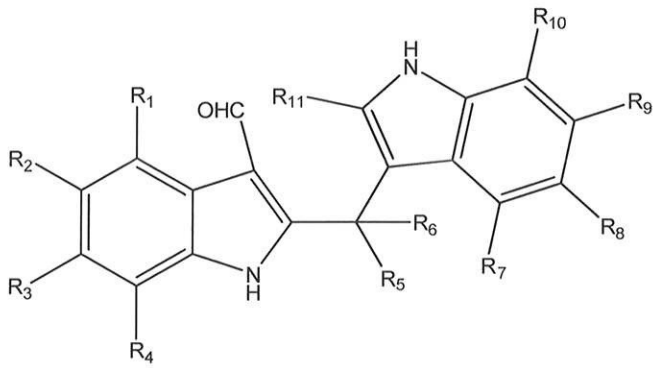
[0035] In one aspect, there is provided a composition comprising a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof, and a cosmetically or pharmaceutically acceptable vehicle, diluent or carrier.

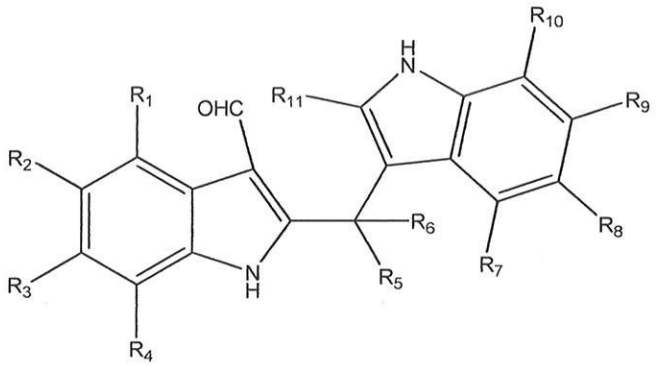
[0036] A further embodiment of the present disclosure is a method for brightening skin in a subject. The method comprises: contacting the subject with a compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

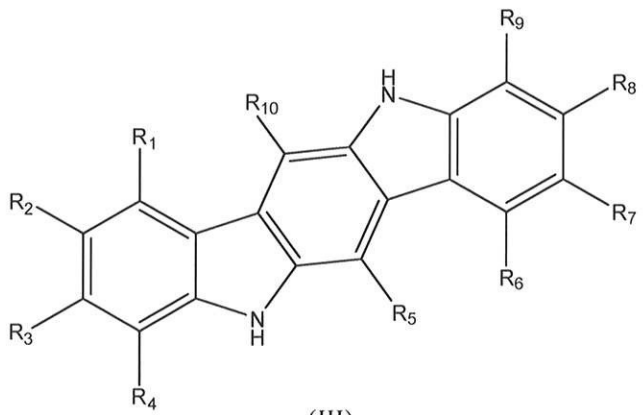
[0036a] In one aspect, there is provided use of a compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for brightening skin in a subject.

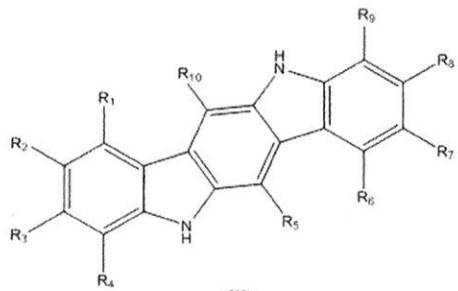
[0037] An additional embodiment of the present disclosure is a method for brightening skin in a subject. The method comprises: contacting the subject with a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

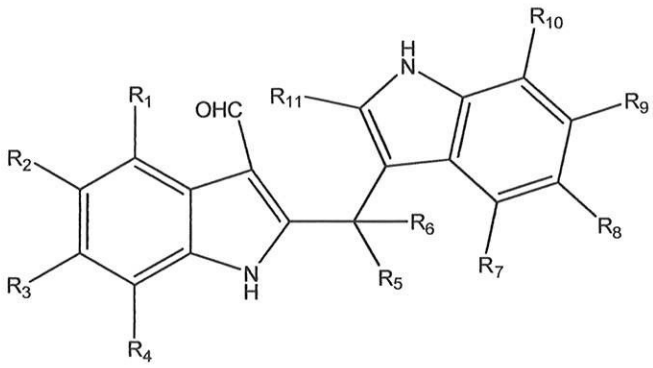
[0037a] In one aspect, there is provided use of a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for brightening skin in a subject.

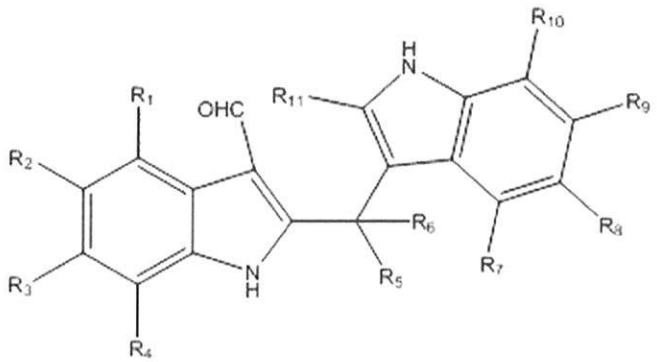
[0038] Another embodiment of the present disclosure is a method for inducing melanocyte apoptosis in a subject. The method comprises: contacting the subject with a compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

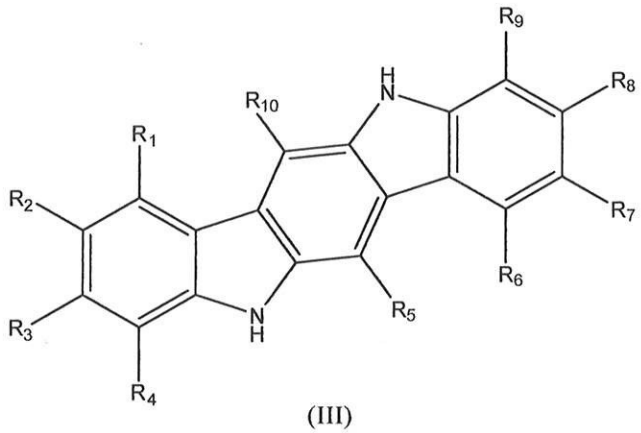
[0038a] In one aspect, there is provided use of a compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing melanocyte apoptosis.

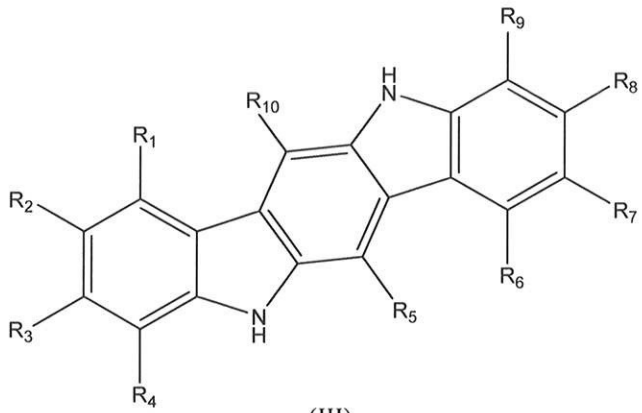
[0039] A further embodiment of the present disclosure is a method for inducing melanocyte apoptosis in a subject. The method comprises: contacting the subject with a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

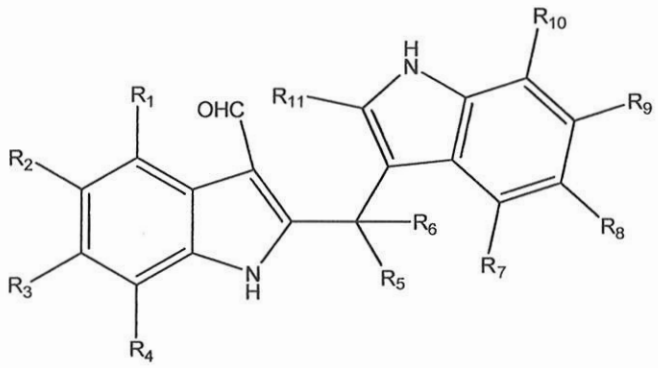
[0039a] In one aspect, there is provided use of a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing melanocyte apoptosis in a subject.

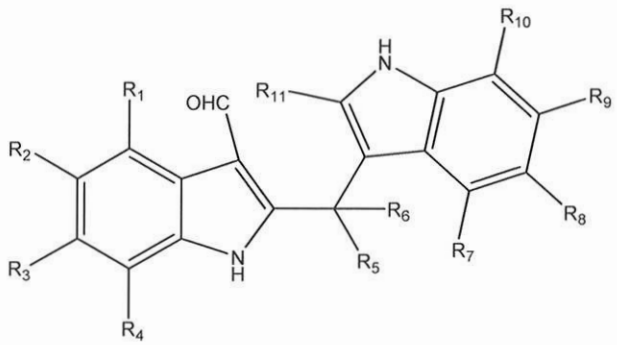
[0040] Another embodiment of the present disclosure is a method for agonizing an arylhydrocarbon receptor (AhR) in a subject. The method comprises: contacting the subject with a compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

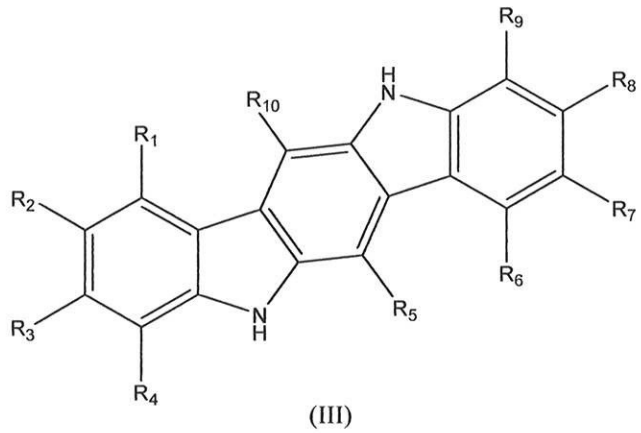
[0040a] In one aspect, there is provided use of a compound having the structure of formula (II):



(II)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for agonizing an arylhydrocarbon receptor (AhR) in a subject.

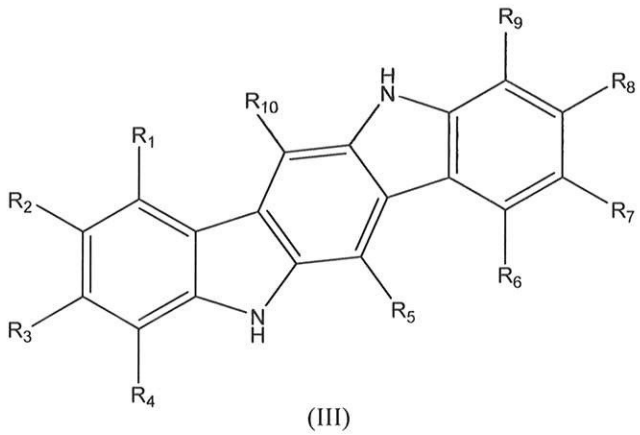
[0041] A further embodiment of the present disclosure is a method for agonizing an arylhydrocarbon receptor (AhR) in a subject. The method comprises: contacting the subject with a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof.

[0041a] In one aspect, there is provided use of a compound having the structure of formula (III):



(III)

wherein: R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl; or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the

manufacture of a medicament for agonizing an arylhydrocarbon receptor (AhR) in a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

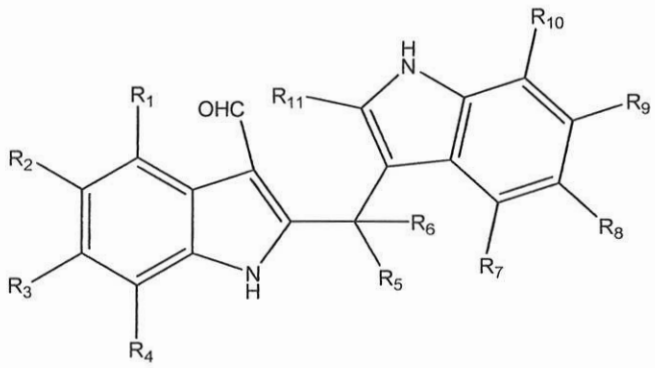
[0042] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

[0043] Fig. 1A is a schematic diagram of the skin's component layers. The inset diagram shows the cellular makeup of the epidermis and dermis. Fig. 1B is a schematic diagram showing potential mechanisms of action of hypopigmentation-causing agents.

[0044] Fig. 2 is a set of synthetic schemes for malassezin and malassezin derivatives: Fig. 2A: malassezin and indolo[3,2-b] carbazole; Fig. 2B: compounds I and IV; Fig. 2C: compound II.

WHAT IS CLAIMED IS:

1. A compound having the structure of formula (II):



(II)

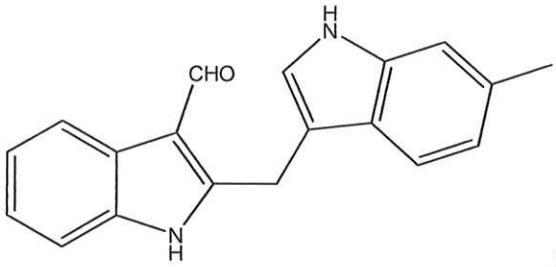
wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl, and

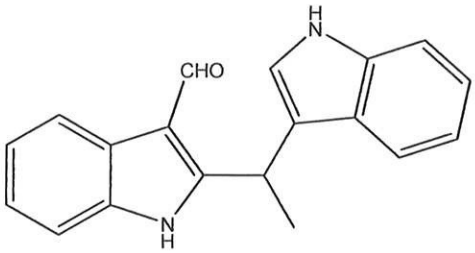
at least one of R1, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 is methyl;

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

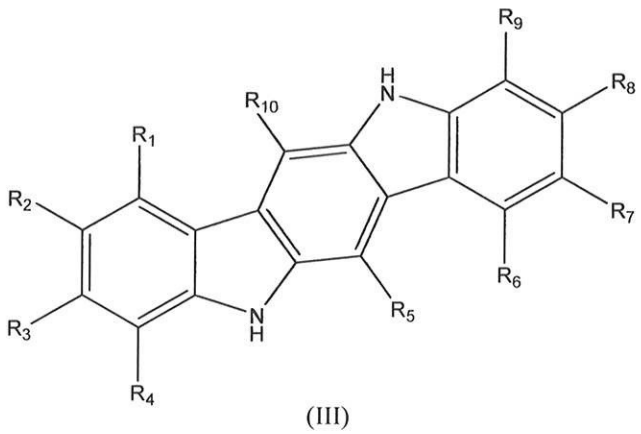
2. A compound according to claim 1, wherein the compound is selected from the group consisting of:



and



3. A compound having the structure of formula (III):



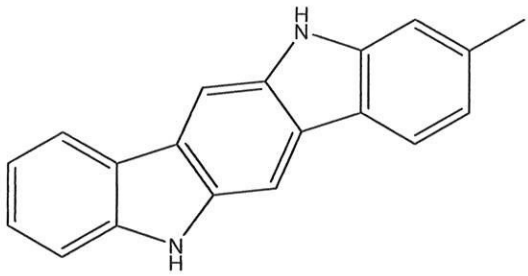
(III)

wherein:

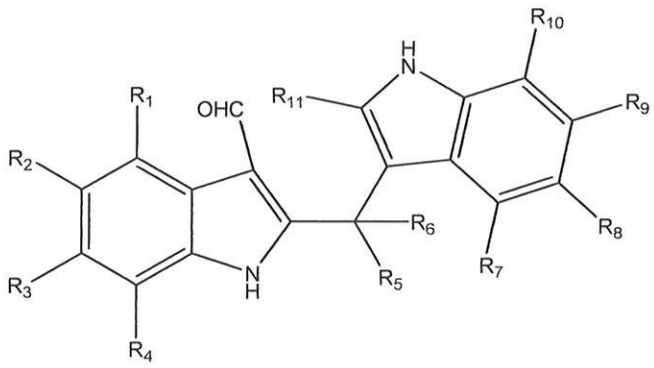
R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl, and at least one of R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 is methyl;

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

4. A compound according to claim 3, wherein the compound is:



5. A compound for brightening skin, the compound having the structure of formula (II):



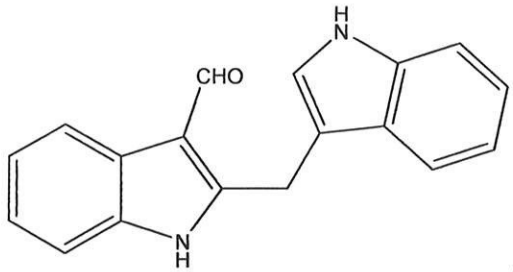
(II)

wherein:

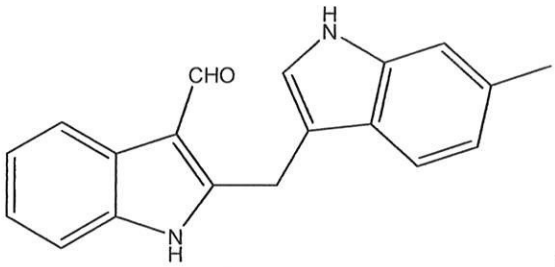
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl;

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

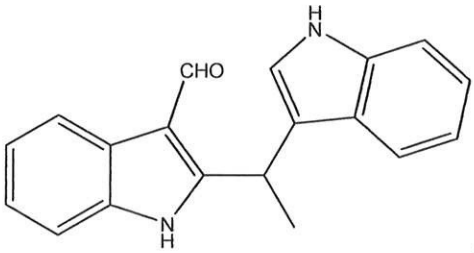
6. A compound according to claim 5, wherein the compound is selected from the group consisting of:



,

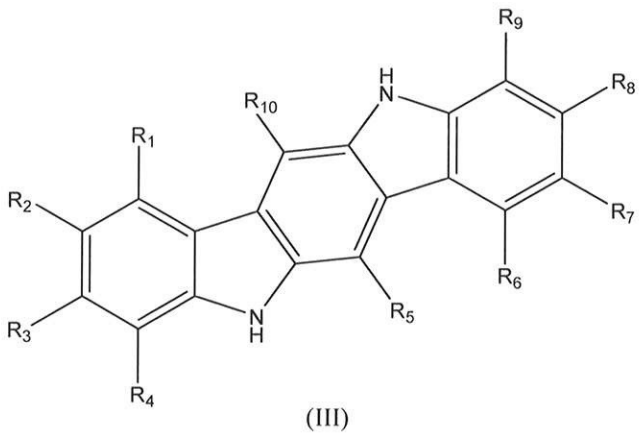


and



.

7. A compound for brightening skin, the compound having the structure of formula (III):



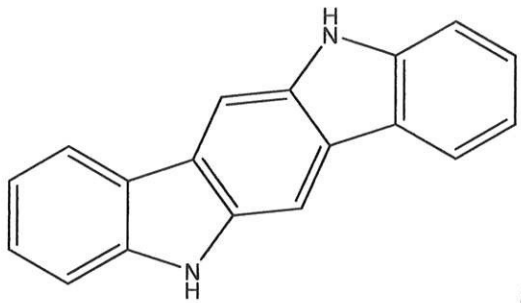
(III)

wherein:

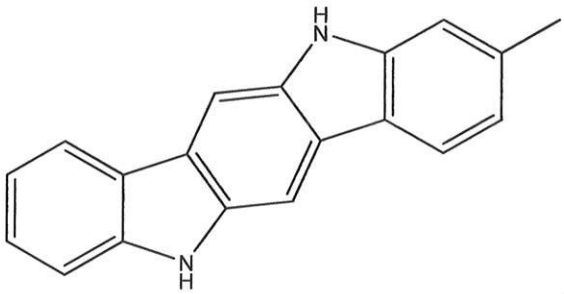
R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl;

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

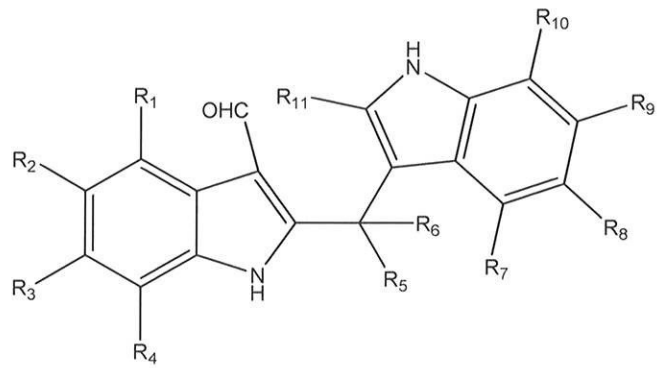
8. A compound according to claim 7, wherein the compound is selected from the group consisting of:



and



9. A compound for inducing melanocyte apoptosis, the compound having the structure of formula (II):



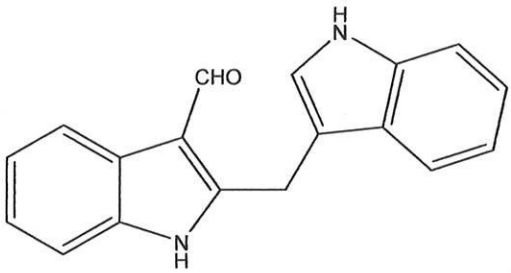
(II)

wherein:

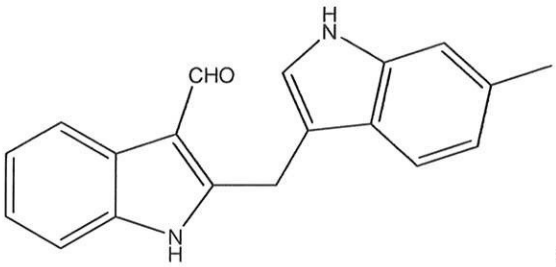
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl;

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

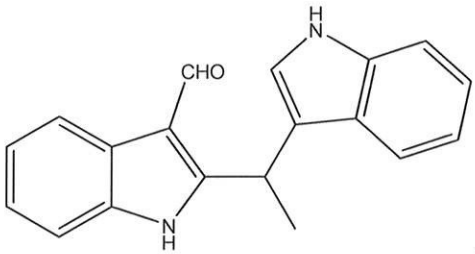
10. A compound according to claim 9, wherein the compound is selected from the group consisting of:



,

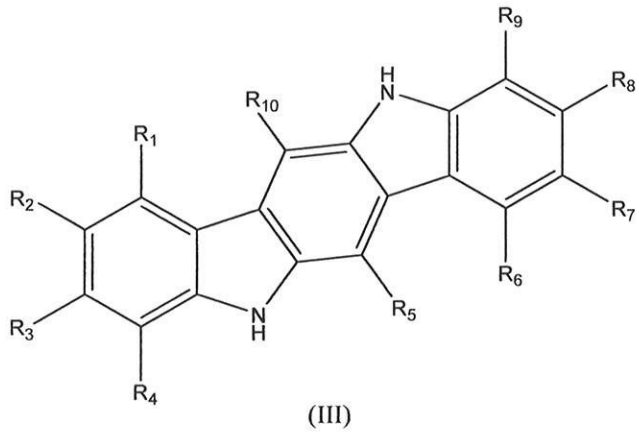


and



.

11. A compound for inducing melanocyte apoptosis, the compound having the structure of formula (III):



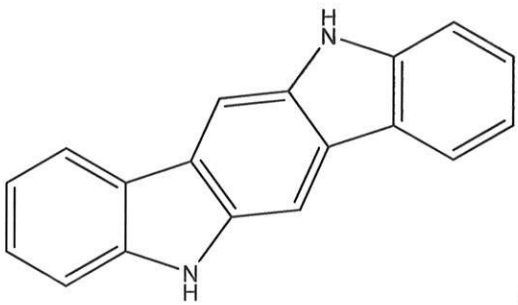
(III)

wherein:

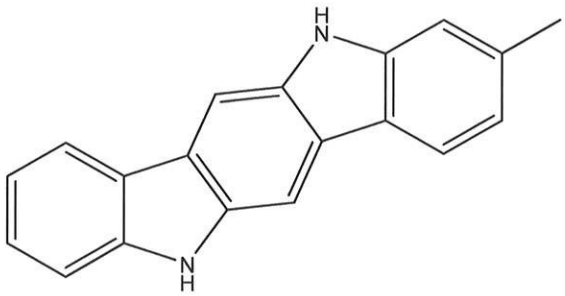
R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl;

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

12. A compound according to claim 11, wherein the compound is selected from the group consisting of:

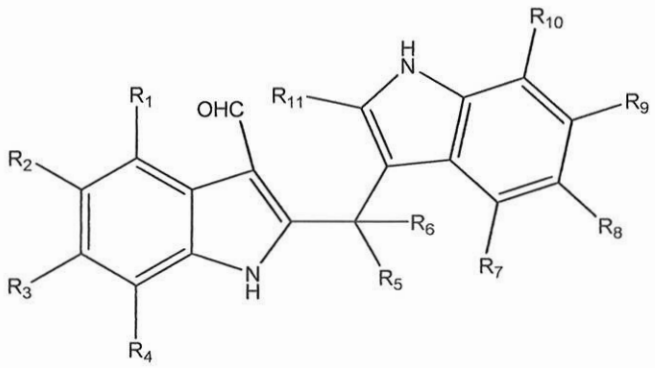


and



.

13. A compound for agonizing the arylhydrocarbon receptor (AhR), the compound having the structure of formula (II):



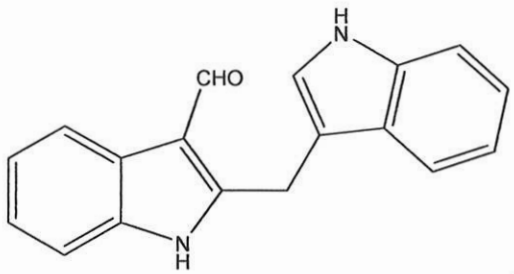
(II)

wherein:

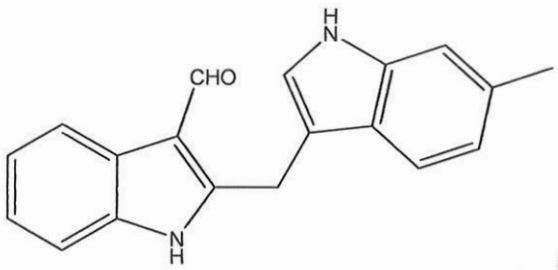
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl;

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

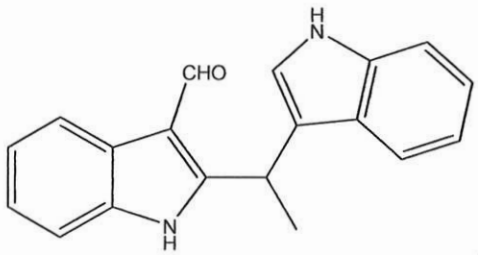
14. A compound according to claim 13, wherein the compound is selected from the group consisting of:



,

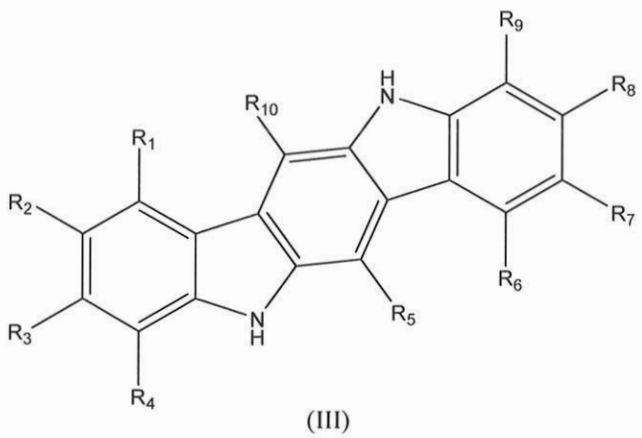


and



.

15. A compound for agonizing the arylhydrocarbon receptor (AhR), the compound having the structure of formula (III):



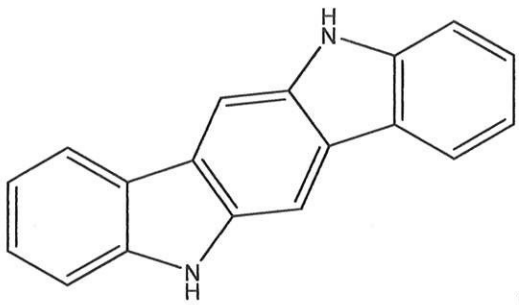
(III)

wherein:

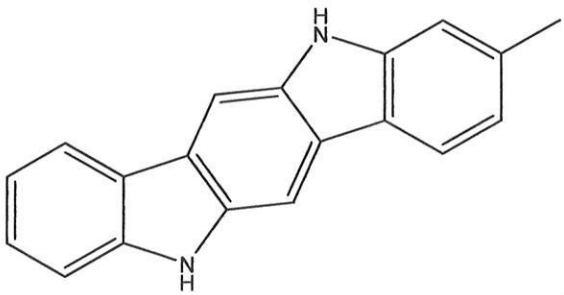
R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl;

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

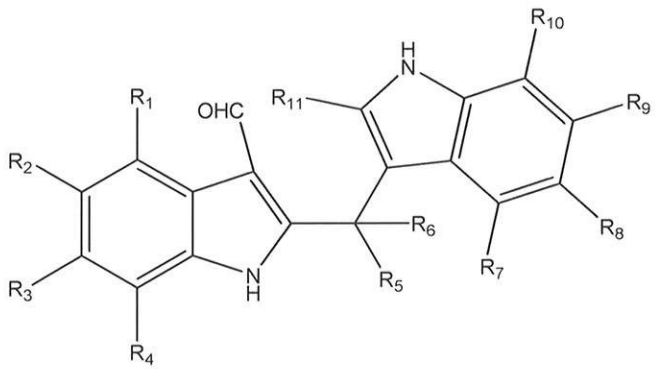
16. A compound according to claim 15, wherein the compound is selected from the group consisting of:



and



17. A composition comprising a compound having the structure of formula (II)



(II)

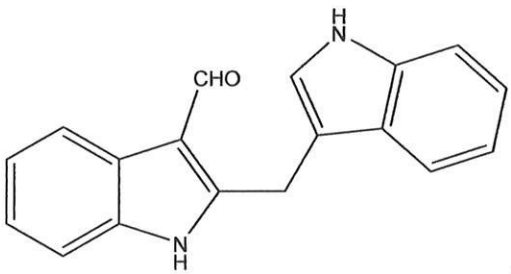
wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl;

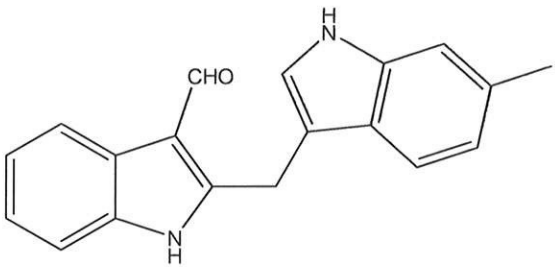
or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof,

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

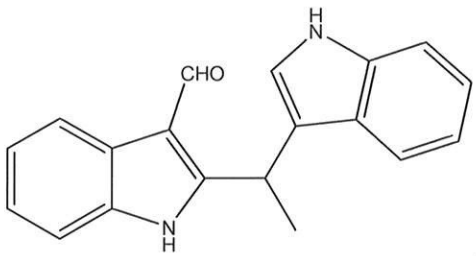
18. A composition according to claim 17, wherein the compound is selected from the group consisting of:



,

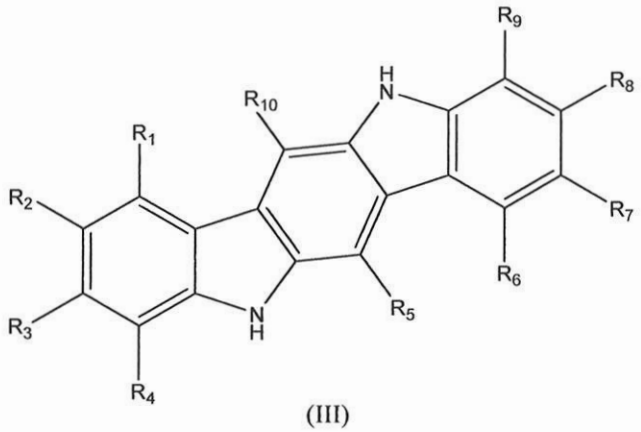


and



.

19. A composition comprising a compound having the structure of formula (III):



(III)

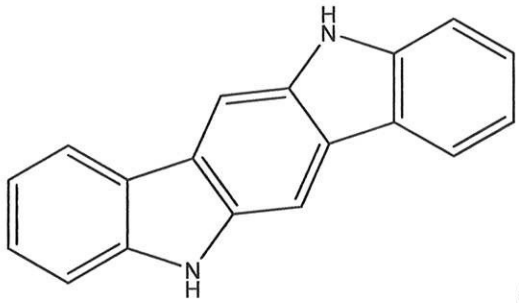
wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl;

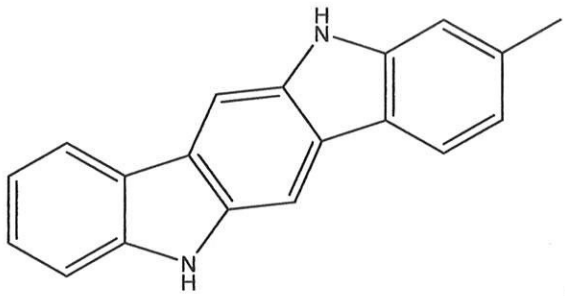
or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof,

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

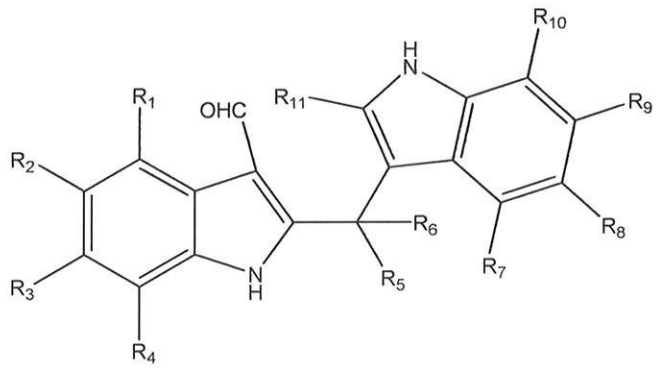
20. A composition according to claim 19, wherein the compound is selected from the group consisting of:



and



21. Use of a compound having the structure of formula (II):



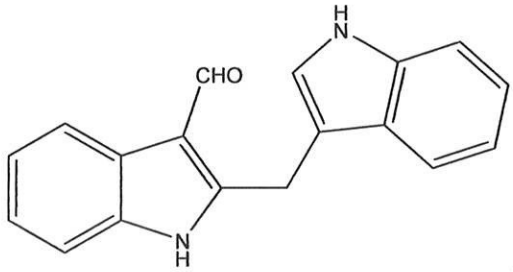
(II)

wherein:

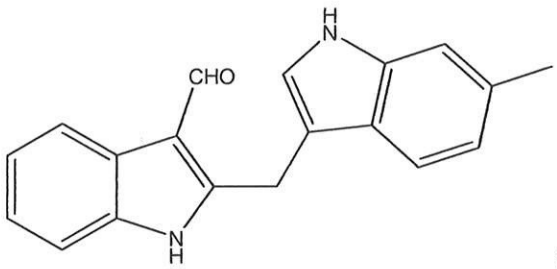
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl;

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for brightening skin in a subject.

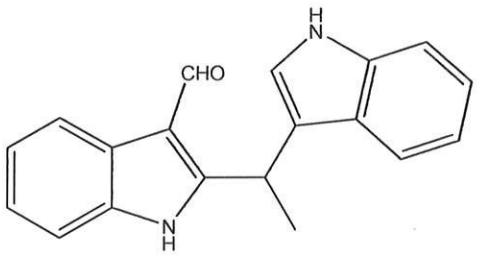
22. The use of claim 21, wherein the compound is selected from the group consisting of:



,

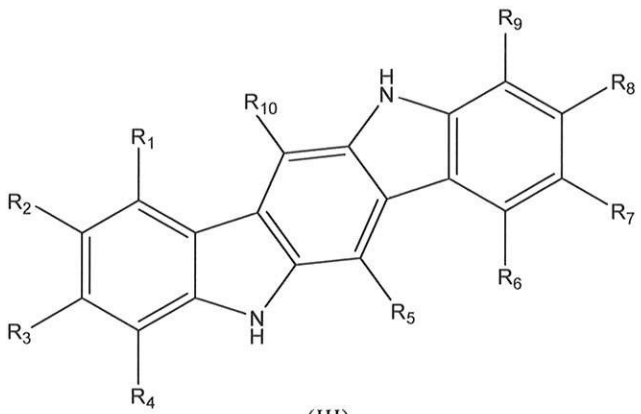


and



.

23. Use of a compound having the structure of formula (III):



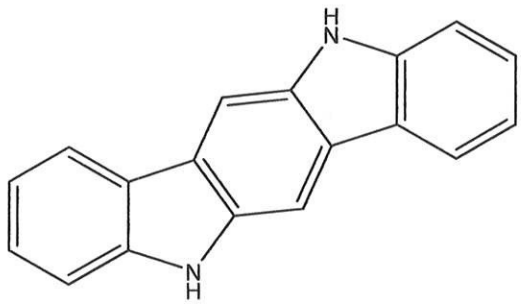
(III)

wherein:

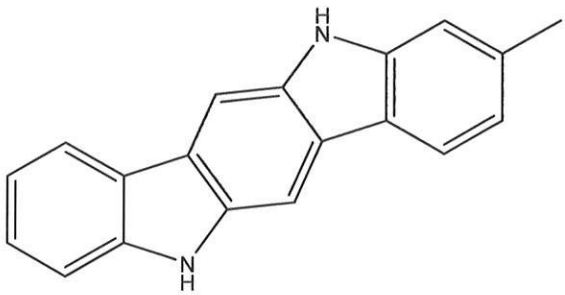
R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl;

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for brightening skin in a subject.

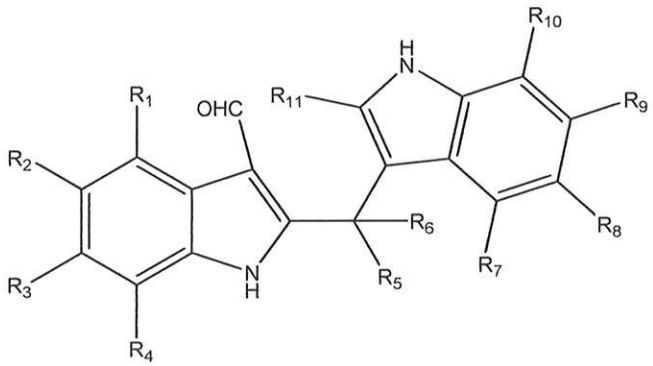
24. The use of claim 23, wherein the compound is selected from the group consisting of:



and



25. Use of a compound having the structure of formula (II):



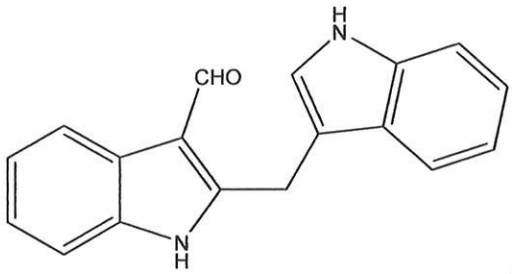
(II)

wherein:

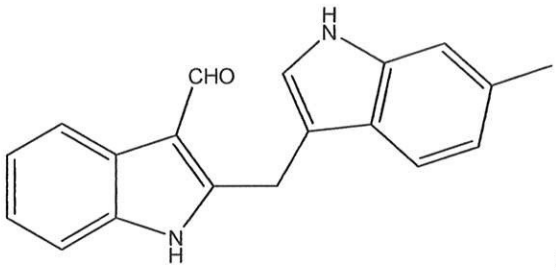
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl;

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing melanocyte apoptosis.

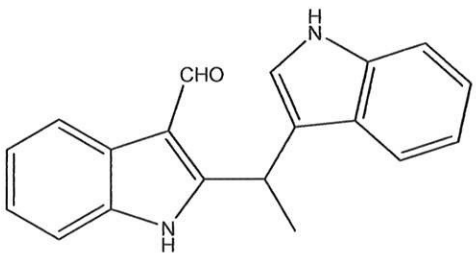
26. The use of claim 25, wherein the compound is selected from the group consisting of:



,

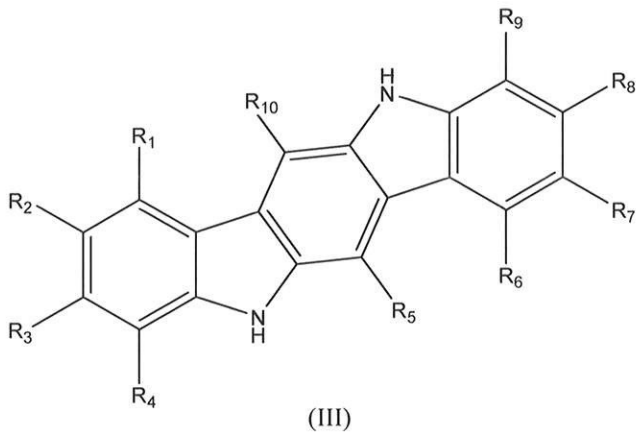


and



.

27. Use of a compound having the structure of formula (III):



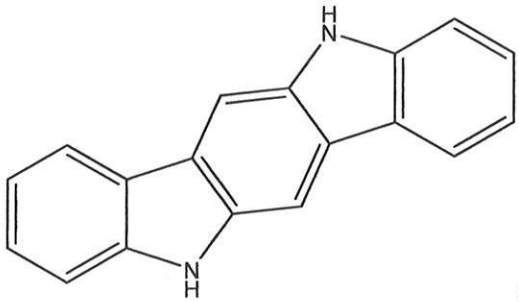
(III)

wherein:

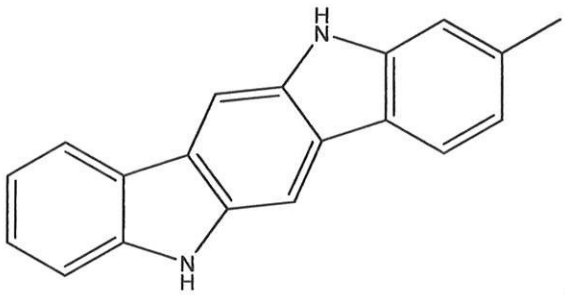
R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl;

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for inducing melanocyte apoptosis in a subject.

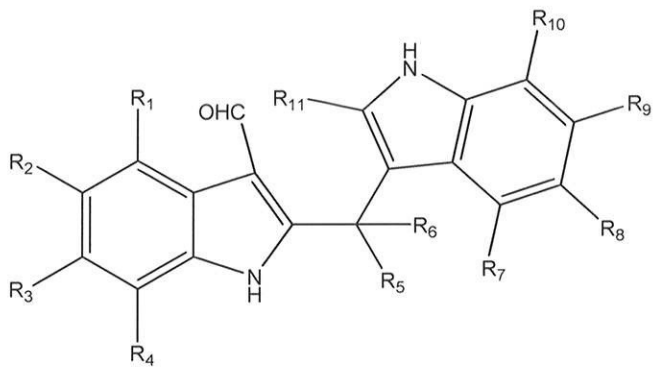
28. The use of claim 27, wherein the compound is selected from the group consisting of:



and



29. Use of a compound having the structure of formula (II):



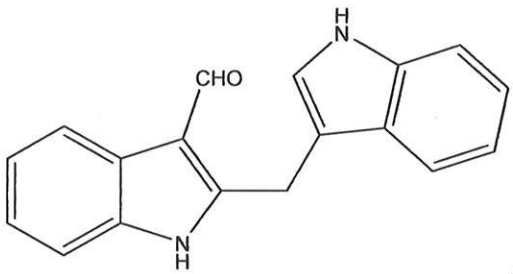
(II)

wherein:

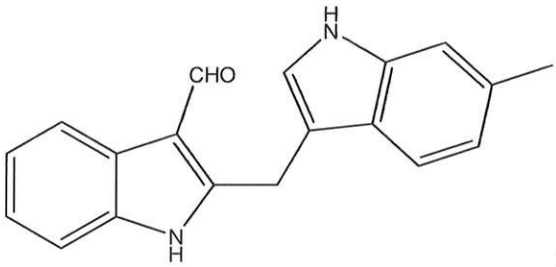
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, and R11 are independently selected from the group consisting of hydrogen and methyl;

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for agonizing an arylhydrocarbon receptor (AhR) in a subject.

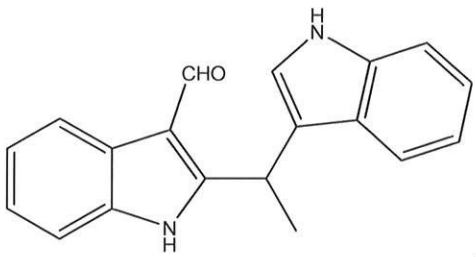
30. The use of claim 29, wherein the compound is selected from the group consisting of:



,

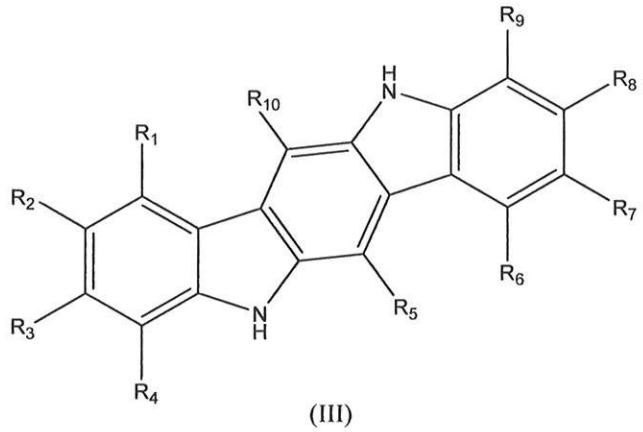


and



.

31. Use of a compound having the structure of formula (III):



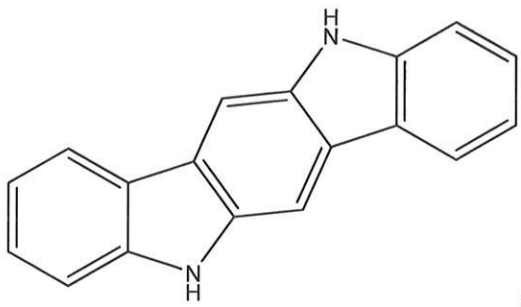
(III)

wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of hydrogen and methyl;

or a crystalline form, hydrate, or cosmetically or pharmaceutically acceptable salt thereof in the manufacture of a medicament for agonizing an arylhydrocarbon receptor (AhR) in a subject.

32. The use of claim 31, wherein the compound is selected from the group consisting of:



and

