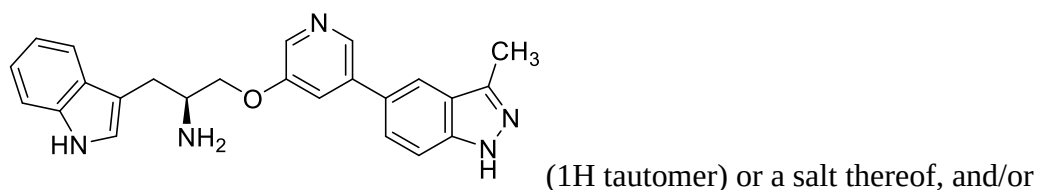


which would indicate Akt is more active in these cells leading to decreased cell death and increased growth and proliferation of benign tumor forming cells.

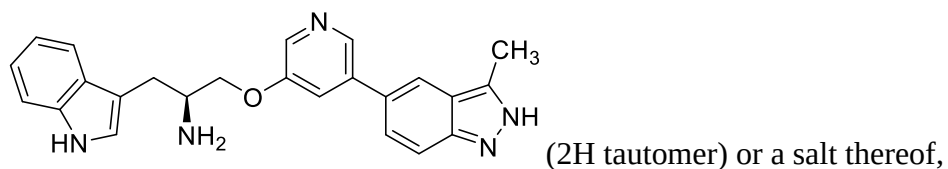
BRIEF SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a use of a composition comprising:

(i) a compound having the structure:



(ii) a compound having the structure:

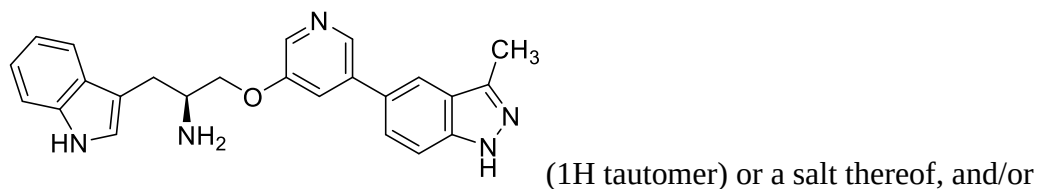


wherein the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.01% to 10%, 0.01% to 5%, or 0.1% to 1% by weight,

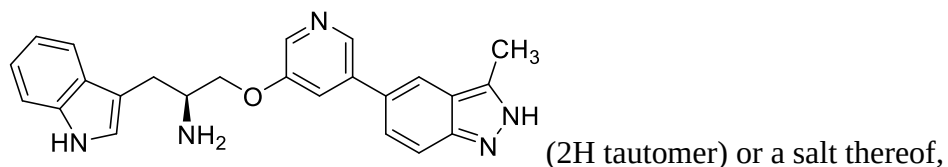
in the manufacture of a medicament for treating a cutaneous lesion, wherein the composition is to be topically administered to the cutaneous lesion.

[0003b] In another aspect of the present disclosure, there is provided a composition comprising:

(i) a compound having the structure:



(ii) a compound having the structure:



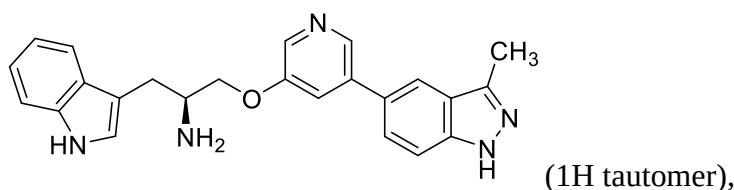
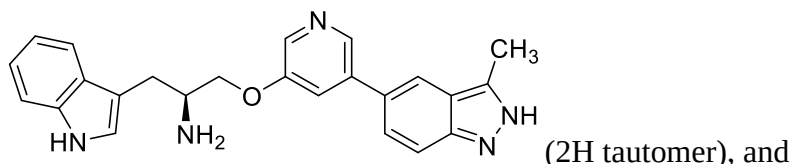
wherein the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.01% to 10%, 0.01% to 5%, or 0.1% to 1% by weight; and wherein the composition further comprises ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol, and hydroxypropyl cellulose.

[0003c] In a further aspect of the present disclosure, there is provided a use of a composition disclosed herein, in the manufacture of a medicament for treating a skin disease, condition or disorder in a subject in need thereof.

[0003d] In another aspect of the present disclosure, there is provided a composition disclosed herein, for use in therapy.

[0004] Current methods of treatment for SKs include superficial curettage, freezing, or shave or tangential excision, or chemical ablation of SKs using a high concentration hydrogen peroxide (40% w/w), which can cause skin irritation and damage to healthy keratinocytes. An alternative strategy for treating SKs is targeting and inhibiting Akt, and subsequently the pathway regulating tumor development in SKs.

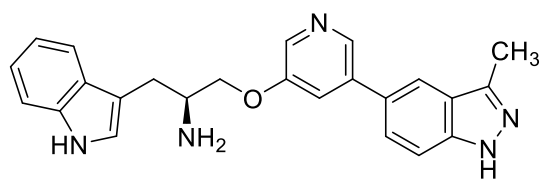
[0005] Akt inhibitors (referred herein as Compound 1), represented by the formulas:



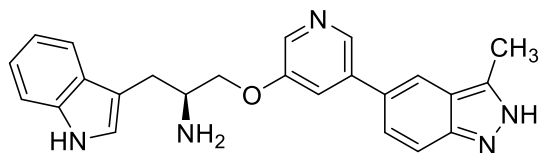
pharmaceutically acceptable salts thereof, are particularly difficult to solubilize into a composition that is easily administered, therapeutically effective, and is not irritating to the skin.

[0006] Common solvents used for formulating other small molecule compounds, such as light mineral oil or water, do not solubilize Compound 1 for use in a clinically acceptable composition. As such, there is urgent need for the development of a topical composition including Compound 1 that can be delivered topically with reduced dermal irritation to treat skin disorders such as seborrheic keratoses.

[0007] In a first example, the present disclosure provides a topical pharmaceutical composition. The topical pharmaceutical composition comprises a compound having the structure:



(Compound 1 1H tautomer) and/or



(Compound 1 2H tautomer) or a

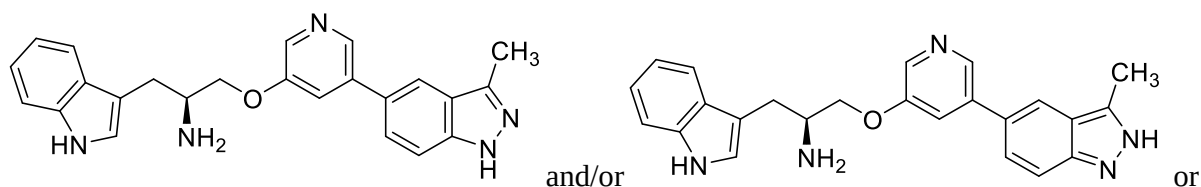
pharmaceutically acceptable salt or tautomer thereof, and one or more excipients selected from (a)-(g):

- a) C₂₋₆ alcohol;
- b) an organic solvent and/or a penetration enhancer;
- c) an antioxidant;
- d) a preservative;
- e) water;
- f) a pH adjuster; and
- g) a gelling agent,

wherein C₂₋₆ alcohol, the organic solvent and/or a penetration enhancer, the antioxidant, the preservative, water, the pH adjuster, and the gelling agent are defined and described herein. In some examples, the composition may be formulated at about 0.01% to about 10%, about 0.01%, or about 10% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.01% to about 5%, about 0.01%, or about 5% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.1% to about 10%, about 0.1%, or about 10% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.1% to about 1%, about 0.1%, or about 1% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. . In some cases, the composition is administered once or twice daily. For example, the composition is administered twice daily. In some cases, the composition is administered for about 2 weeks to about 8 weeks. In some cases, the

composition is administered for about 2 weeks. In some cases, the composition is administered for about 4 weeks.

[0008] In a second example, the present disclosure provides a topical pharmaceutical composition, the composition comprising a compound having the structure:



a pharmaceutically acceptable salt or tautomer thereof, and five or more excipients comprising ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol, water, hydroxypropyl cellulose, optionally an antioxidant, and optionally a preservative, wherein the antioxidant and preservative are defined and described herein. In some examples, the composition may be formulated at about 0.01% to about 10%, about 0.01%, or about 10% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.01% to about 5%, about 0.01%, or about 5% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.1% to about 10%, about 0.1%, or about 10% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.1% to about 1%, about 0.1%, or about 1% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some cases the composition is administered once or twice daily. For example, the composition is administered twice daily. In some cases, the composition is administered for about 2 weeks to about 8 weeks. In some cases, the composition is administered for about 2 weeks. In some cases, the composition is administered for about 4 weeks.

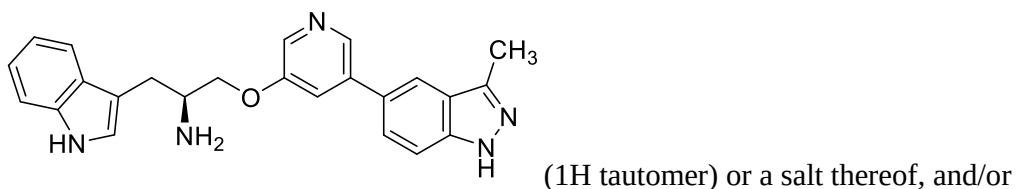
[0009] In a third example, the present disclosure provides a method of treating a skin disease, condition or disorder in a subject in need thereof, the method comprising administering to the subject a composition, as described herein. In some examples, the composition may be formulated at about 0.01% to about 10%, about 0.01%, or about 10% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.01% to about 5%, about 0.01%, or about 5% Compound 1 (e.g., Compound 1 1H tautomer and/or

Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.1% to about 10%, about 0.1%, or about 10% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some examples, the composition may be formulated at about 0.1% to about 1%, about 0.1%, or about 1% Compound 1 (e.g., Compound 1 1H tautomer and/or Compound 1 2H tautomer) or a salt thereof. In some cases, the composition is administered once or twice daily. For example, the composition is administered twice daily. In some cases, the composition is administered for about 2 weeks to about 8 weeks. In some cases, the composition is administered for about 2 weeks. In some cases, the composition is administered for about 4 weeks.

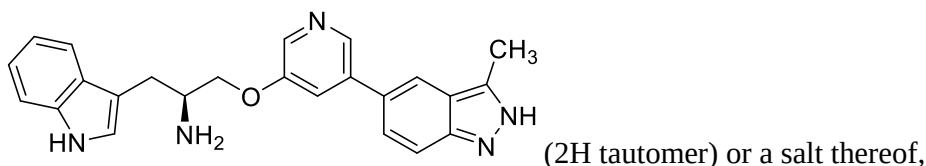
[0010] In a fourth example, the present disclosure provides a kit comprising a topical pharmaceutical composition as described herein, in a tube, flexible aluminum tube or laminated plastic tube, with instructions for use.

[0011] In a further example, the present disclosure provides a method of treating a cutaneous lesion, the method comprising topically administering to the cutaneous lesion a composition comprising:

(i) a compound having the structure:



(ii) a compound having the structure:



wherein the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.1% to 1% by weight. Alternatively, the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.01% to 10% or 0.01% to 5%.

[0012] In some examples, the cutaneous lesion is a keratosis. In some examples, the keratosis is a seborrheic keratosis. In some examples, the composition is administered

one, two, three, or four times a day. In some examples, the composition is administered one, two, three, or four times a day for about 14 days to about 28 days. In some examples, the composition is administered one, two, three, four, or five times a week. In some examples, the composition is administered in a cycle comprising 1-4 daily administration for about 1-7 days, followed by no administration for about 1-7 days. In some examples, the cycle comprises twice daily administration for about 4 days, followed by no administration for about 4 days. In some examples, the cycle is repeated about 2-10 times. In some examples, the cycle is repeated about 7 times. In some examples, the composition is administered at least once daily for about 28 days (e.g., about once or twice a day). In some examples, the composition is administered once daily three times a week. In some examples, the composition is administered for a total duration of about 1, 2, 3, 4, 5, or 6 months.

[0013] In some examples, the method further comprises occlusion of the cutaneous lesion.

[0014] In some examples, the cutaneous lesion is present on a human subject. In some examples, the cutaneous lesion is present on the face, trunk, or an extremity, or a combination thereof, of the human subject. In some examples, treating comprises an improvement of one grade or more in Physician's Lesion Assessment (PLA) score as compared to before administering the composition. In some examples, the PLA score prior to administering is at least 2.

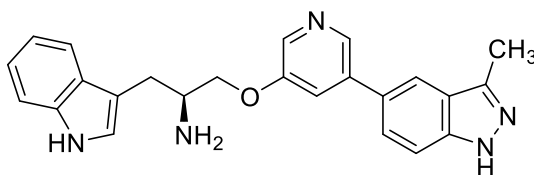
[0015] In some examples, treating comprises reducing the thickness of the cutaneous lesion to less than 1 mm. In some examples, the thickness of the cutaneous lesion prior administering is greater than or equal to 1 mm. In some examples, the length of the cutaneous lesion prior to administering is from 1 mm to 15 mm, and the width of the cutaneous lesion prior to administering is from 1 mm to 15 mm.

[0016] In some examples, treating comprises inducing apoptosis of a keratinocyte in the cutaneous lesion.

[0017] In some examples, apoptosis is measured by TUNEL assay.

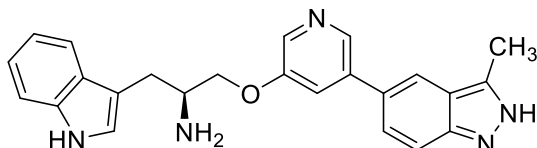
[0018] In some examples, the composition is a gel formulation. In some examples, the composition comprises an alcohol, a gelling agent, or an antioxidant, or a combination of two or more thereof.

[0019] In a further example, the present disclosure provides a composition comprising:



(i) a compound having the structure:

(1H tautomer) or a salt thereof, and/or



(ii) a compound having the structure:

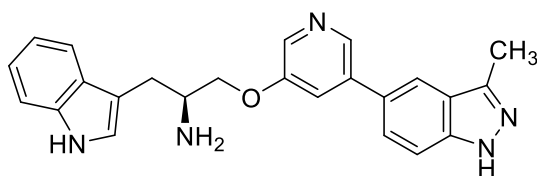
(2H tautomer) or a salt thereof,

wherein the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.1% to 1% by weight. Alternatively, the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.01% to 10% or 0.01% to 5%.

[0020] In some examples, the composition is a gel formulation. In some examples, the composition comprises an alcohol, a gelling agent, or an antioxidant, or a combination of two or more thereof. In some examples, the composition further comprises a preservative. In some examples, the composition further comprises a gelling agent.

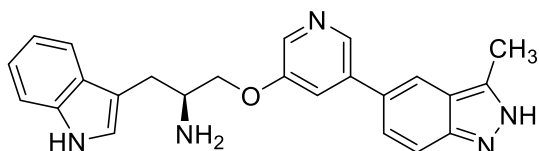
[0021] In a further example, the present disclosure provides a composition comprising:

(i) a compound having the structure:



(1H tautomer) or a salt thereof, and/or

(ii) a compound having the structure:



(2H tautomer) or a salt thereof;

and one or more excipients selected from (a)-(e):

- a) alcohol;
- b) an organic solvent and/or a penetration enhancer;
- c) an antioxidant;
- d) a preservative; and
- e) a gelling agent.

[0022] In any of the foregoing and forthcoming examples and examples, the composition may comprise an alcohol, organic solvent and/or penetration enhancer, an antioxidant, a preservative, or a gelling agent, or a combination of two or more thereof. The composition may be administered in the methods described herein.

[0023] In some examples, the composition comprises the alcohol. In some examples, the alcohol comprises ethanol, propanol, isopropanol, n-butanol, isobutanol, 2-butanol, or tert-butanol, propylene glycol, (2-(2-ethoxyethoxy)ethanol), phenoxyethanol, or a combination of two or more thereof. In some examples, the alcohol comprises a C₂₋₆ alcohol. In some examples, the C₂₋₆ alcohol comprises ethanol, propanol, isopropanol, n-butanol, isobutanol, 2-butanol, or tert-butanol, or a combination of two or more thereof. In some examples, the C₂₋₆ alcohol comprises ethanol. In some examples, the C₂₋₆ alcohol is present in an amount of 1% to 30%, from 5% to 30%, from 10% to 30%, from 5% to 20%, from 10% to 20%, or about 15% by weight of the composition. In some examples, the total amount of alcohol present in the composition is about 1% to about 80% by weight of the composition.

[0024] In some examples, the alcohol comprises an organic solvent and/or penetration enhancer.

[0025] In some examples, the composition comprises the organic solvent and/or penetration enhancer. In some examples, the organic solvent and/or penetration enhancer comprises a C₂₋₆ alkylene glycol, C₁₋₃ alkyl-(OCH₂CH₂)₁₋₅-OH, a polyethylene glycol, glycerol, a fatty alcohol, a fatty ester, or a fatty ether, or a combination of two or more thereof. In some examples, the C₂₋₆ alkylene glycol is propylene glycol; the C₁₋₃ alkyl-(OCH₂CH₂)₁₋₅-OH is 2-(2-ethoxyethoxy)ethanol; and the polyethylene glycol is PEG200, PEG400, or a combination thereof. In some examples, the organic solvent and/or penetration enhancer comprises propylene glycol and/or 2-(2-ethoxyethoxy)ethanol. In some

examples, the organic solvent and/or penetration enhancer is present in an amount of from 50% to 99%, from 50% to 80%, from 50% to 70%, or about 60% by weight of the composition.

[0026] In some examples, the composition comprises the antioxidant. In some examples, the antioxidant comprises butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, or a combination of two or more thereof. In some examples, the antioxidant comprises butylated hydroxytoluene. In some examples, the antioxidant is present in an amount of from 0.01% to 5%, from 0.01% to 0.2%, from 0.01% to 0.1%, or about 0.05% by weight of the composition.

[0027] In some examples, the composition comprises the preservative. In some examples, the preservative comprises phenoxyethanol. In some examples, the preservative is present in an amount of from 0.5% to 5.0%, from 0.5% to 2%, or about 1% by weight of the composition. In some examples, the composition further comprises water in an amount of from 0% to 25%, from 5% to 25%, from 10% to 25%, from 15% to 25%, or about 20% by weight of the composition.

[0028] In some examples, the composition comprises the gelling agent. In some examples, the gelling agent comprises hydroxypropyl cellulose. In some examples, the hydroxypropyl cellulose has an average molecular weight of from 700,000 Da to 1,150,000 Da. In some examples, the gelling agent is present in an amount of from 0.5% to 5%, or about 2% by weight of the composition.

[0029] In some examples, the composition comprises ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol, and hydroxypropyl cellulose. In some examples, ethanol is present in an amount of from 10% to 30%, from 10% to 20%, or about 15% by weight; propylene glycol is present in an amount of from 10% to 30%, from 10% to 20%, or about 15% by weight; 2-(2-ethoxyethoxy)ethanol is present in an amount of from 30% to 70%, from 40% to 60%, or about 47% by weight; and hydroxypropyl cellulose having an average molecular weight of from 700,000 Da to 1,150,000 Da is present in an amount of from 1% to 3% or about 2% by weight of the composition. In some examples, ethanol is present in an amount of about 15% by weight; propylene glycol is present in an amount of about 15% by weight; 2-(2-ethoxyethoxy)ethanol is present in an amount of about 47% by weight; and hydroxypropyl cellulose having an average molecular weight of about 850,000 Da is present in an amount of about 2% by weight of the composition.

[0030] In some examples, the composition further comprises an antioxidant and/or a preservative. In some examples, the antioxidant comprises butylated hydroxytoluene, butylated hydroxyanisole, or propyl gallate, or a combination of two or more thereof; and the preservative comprises phenoxyethanol. In some examples, the antioxidant comprises butylated hydroxytoluene in an amount of from 0.01% to 0.1% or about 0.05% by weight; and the preservative comprises phenoxyethanol in an amount of from 0.5% to 2%, or about 1% by weight. In some examples, the antioxidant comprises butylated hydroxytoluene in an amount of about 0.05% by weight; and the preservative comprises phenoxyethanol in an amount of about 1% by weight of the composition.

[0031] In some examples, the composition comprises a pH adjuster, optionally an acid, and further optionally a citric acid.

[0032] In some examples, propylene glycol is a super refined propylene glycol.

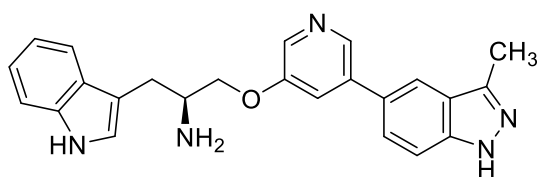
[0033] In some examples, 2-(2-ethoxyethoxy)ethanol is Transcutol HP having a purity of > 99.90%.

[0034] In some examples, the total amount of (i), (ii), or (i) and (ii) present in the composition is from 0.01% to 10%, 0.1% to 10.0%, from 0.5% to 5%, from 0.5% to 2%, from 0.1% to 1%, or about 1% by weight or about 0.1% by weight of the composition.

[0035] In some examples, the total amount of (i), (ii), or (i) and (ii) is about 1% by weight of the composition.

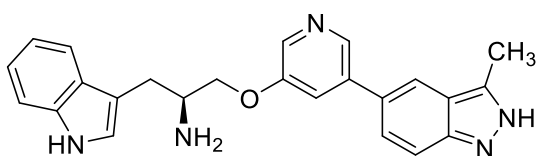
[0036] In a further example, the present disclosure provides a composition comprising:

(i) a compound having the structure:



(1H tautomer) or a salt thereof, and/or

(ii) a compound having the structure:



(2H tautomer) or a salt thereof; and

ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol, hydroxypropyl cellulose, and optionally an antioxidant, and optionally a preservative.

[0037] In some examples, the antioxidant, when present, comprises butylated hydroxytoluene; and the preservative, when present, comprises phenoxyethanol.

[0038] In some examples, the composition has a viscosity of about 10000 cp to about 30000 cp.

[0039] In some examples, the composition is a pharmaceutical composition. In some examples, the composition is a topical composition. In some examples, the composition is in the form of a gel, ointment, lotion, foam or emollient. In some examples, the composition is a component of a patch, tape, film, wafer, or bandage.

[0040] In one example, the present disclosure provides a method of treating a skin disease, condition or disorder in a subject in need thereof, comprising administering to the subject the composition described herein.

[0041] In some examples, the skin disease, condition or disorder is seborrheic keratosis, benign tumor, malignant tumor, parasite, virus of the skin, immune disease or disorder, or a bacterial, fungal or microbial infection. In some examples, the skin disease, condition or disorder is seborrheic keratosis. In some examples, the skin disease, condition or disorder is the benign tumor, wherein the benign tumor is a benign vascular tumor, benign fibrotic tumor, benign adipocyte tumor, benign sebaceous tumor, benign epidermal tumor, benign melanocytic lesion, or benign neural tumor; the skin disease, condition or disorder is the malignant tumor, wherein the malignant tumor is a malignant melanocytic tumor, malignant epidermal tumor, malignant vascular tumor, malignant metastatic tumor, malignant adipocyte tumor, malignant sebaceous tumor, or malignant fibrotic tumor; the skin disease, condition or disorder is the parasite, wherein the parasite is of the genus Trypanasoma or Lishmania; the skin disease, condition or disorder is the virus, wherein the virus is molluscum contagiosum virus or human papilloma virus; or the skin disease, condition or disorder is the bacterial, fungal or microbial infection, wherein the bacterial, fungal or microbial infection is otitis media, Staphylococcus aureus infection, Mycobacterium infection, Porphyromonas infection, Salmonella infection, Chlamydia infection, tuberculosis, gingivitis or periodontal disease.

[0042] In some examples, the composition is applied topically to the head, scalp, face, ear(s), neck, chest, back, inframammary region(s), arm(s), leg(s), intertriginous zone(s), hand(s), foot or feet, or groin. In some examples, the composition is administered twice daily. In some examples, the composition is administered for about 2 weeks to about 8 weeks. In some examples, the composition is administered for about 4 weeks.

[0043] In some examples, the composition is administered in a pulsed cycle. In some examples, the composition is administered under occlusion.

[0044] In some examples, the skin disease, condition or disorder is skin pigmentation disorder. In some examples, the skin pigmentation disorder is Acanthosis nigricans.

[0045] In another example, the present disclosure provides a kit comprising a topical pharmaceutical composition in a tube, flexible aluminum tube or laminated plastic tube, with instructions for use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0046] **FIG. 1A-FIG. 1D** show local skin tolerability of four (4) compositions of Example 2 including Compound 1 and the respective placebos following once daily or every other day dermal administration for 14 days to Göttingen Minipigs, measured by scores of Erythema and Edema.

[0047] **FIG. 2** shows explant TUNEL assay images. TUNEL (brown) demonstrates increased apoptosis in the keratinocytes of human seborrheic keratosis treated with the composition of Example 5 including 1% Compound 1 as compared with untreated and vehicle treated explants. Top row: 4X magnification, Bottom row 10X magnification.

[0048] **FIG. 3A.** Time-to-event KM plot of when lesions have 1 point drop in PLA scores, during the first 8 weeks post treatment, stratified by cohorts. For cohort 1, median response time of 1 point PLA drop is 42 days (28 to 42 days, 95% CI). For cohort 2 and 3, median response time of 1 point PLA drop is 21 days (cohort 2 95% CI: 21 to 35 days; cohort 3 95% CI: 21 to 56 days). Censoring time is set to be the last visit.

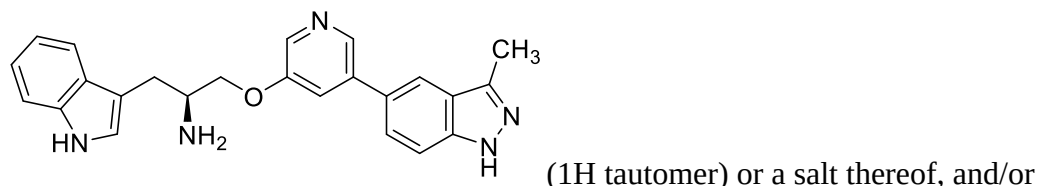
[0049] **FIG. 3B.** Time-to-event KM plot of when lesions have 1 point drop in PLA scores, during the first 8 weeks post treatment, in all cohorts. For all cohorts combined, median response time of 1 point PLA drop is 21 days (21 to 35 days, 95% CI).

CLAIMS

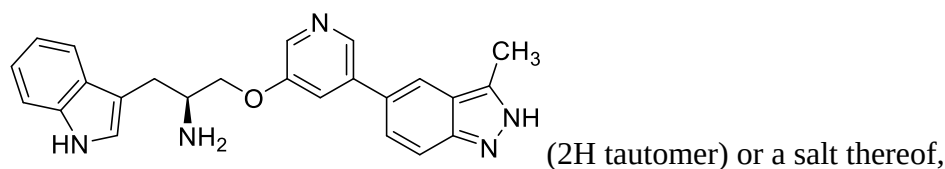
What is claimed is:

1. Use of a composition comprising:

(i) a compound having the structure:



(ii) a compound having the structure:



wherein the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.01% to 10%, 0.01% to 5%, or 0.1% to 1% by weight,

in the manufacture of a medicament for treating a cutaneous lesion, wherein the composition is to be topically administered to the cutaneous lesion.

2. The use of claim 1, wherein the cutaneous lesion is a keratosis.

3. The use of claim 2, wherein the keratosis is a seborrheic keratosis.

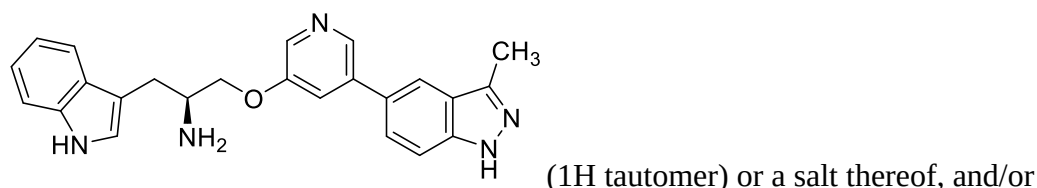
4. The use of any one of claims 1-3, wherein the composition is administered one, two, three, or four times a day.

5. The use of any one of claims 1-3, wherein the composition is administered one, two, three, or four times a day for about 14 days to about 28 days, or for about 2 weeks to about 8 weeks.

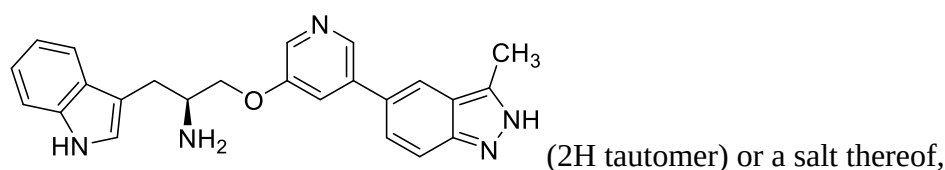
6. The use of any one of claims 1-3, wherein the composition is to be administered in a cycle comprising twice daily administration for about 4 days, followed by no administration for about 4 days.

7. The use of any one of claims 1-6, the cutaneous lesion is to be further occluded.
8. The use of any one of claims 1-7, wherein the cutaneous lesion is present on a human subject.
9. The use of any one of claims 1-8, wherein use comprises an improvement of one grade or more in Physician's Lesion Assessment (PLA) score as compared to before the composition is to be administered.
10. The use of any one of claims 1-9, wherein use comprises inducing apoptosis of a keratinocyte in the cutaneous lesion.
11. The use of any one of claims 1-10, wherein the composition is a gel formulation.
12. A composition comprising:

(i) a compound having the structure:



(ii) a compound having the structure:



wherein the total amount of (i), (ii), or (i) and (ii) present in the composition is 0.01% to 10%, 0.01% to 5%, or 0.1% to 1% by weight; and wherein the composition further comprises ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol, and hydroxypropyl cellulose.

13. The composition of claim 12, wherein the composition is a gel formulation.
14. The composition of claim 12, wherein the propylene glycol is present in an amount of 10% to 20% by weight of the composition.

15. The composition of claim 12, wherein the 2-(2-ethoxyethoxy)ethanol is present in an amount of 40% to 60% by weight of the composition.
16. The composition of claim 12, wherein the hydroxypropyl cellulose is present in an amount of from 0.5% to 5% by weight of the composition.
17. The composition of claim 12, wherein ethanol is present in an amount of 10% to 20% by weight; propylene glycol is present in an amount of from 10% to 20% by weight; 2-(2-ethoxyethoxy)ethanol is present in an amount of from 40% to 60% by weight; and hydroxypropyl cellulose is present in an amount of 1% to 3% by weight.
18. The composition of claim 12, wherein the composition is a topical composition.
19. Use of a composition of any one of claims 12-18, in the manufacture of a medicament for treating a skin disease, condition or disorder in a subject in need thereof.
20. The use of claim 18, wherein the skin disease, condition or disorder is seborrheic keratosis.
21. A composition of any one of claims 12-18, for use in therapy.