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(54) Title: SALICYLIC ACID DERIVATIVE AS EFFICACY ENHANCER AND METHOD

(57) Abstract: The present invention relates to compositions containing at least one salicylic acid derivative and at least one cos-
metic, dermatologic, pharmaceutical, etc. active agent, where the salicylic acid derivative increases, enhances, etc., the efficacy of the
active agent, as well as to methods of making and using such compositions. The invention further relates to a method for enhancing
the efficacy of active agents with these salicylic acid derivatives.



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TITLE OF THE INVENTION

SALICYLIC ACID DERIVATIVE AS EFFICACY ENHANCER AND METHOD

5 BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to compositions comprising at least one salicylic acid derivative and at least one cosmetic, dermatologic, pharmaceutical, etc. active agent, where the salicylic acid derivative increases, enhances, etc., the efficacy of the active agent, as well
10 as to methods of making and using such compositions. The invention further relates to a method for enhancing the efficacy of active agents with these salicylic acid derivatives.

BACKGROUND OF THE INVENTION

The intact skin of humans is a very effective barrier to many natural and synthetic
15 substances. Active agents may be pharmacologically effective by systemic administration, but many of them are much less or totally ineffective upon application to the skin. The effectiveness of an active agent can depend on at least two major factors: a) percutaneous absorption and penetration, and b) bioavailability of the penetrated agent to the target site in the skin. To be effective, a pharmaceutical drug must penetrate the stratum corneum into the
20 epidermal layers, and distribute and be bioavailable to the target sites for action. Many active agents may possess inherent characteristics which may prohibit them from effectively penetrating the skin or prohibit them from being bioavailable to the target sites in the skin. Therefore, the efficacy of such agents may be minimal and ineffective.

Accordingly, a need exists for boosters of active agents that provide increased
25 efficacy, improved therapeutic results, etc.

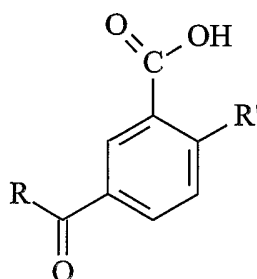
DETAILED DESCRIPTION OF THE PRESENT INVENTION

All publications, patent applications, patents, and other references and documents mentioned herein are incorporated herein by reference in their entirety. Unless specifically
30 defined, all technical and scientific terms used herein have the same meaning as commonly understood by a skilled artisan in biochemistry, chemistry, cosmetology, dermatology, pharmaceutical science, and materials science.

All methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, with suitable methods and materials being described herein. Further, the materials, methods, and examples are illustrative only and are not intended to be limiting.

5 While not bound by a particular theory, the chemical boosters of the invention may be efficacious by acting to enhance the penetration of an active agent into the skin, and/or by increasing the bioavailability of the active agent.

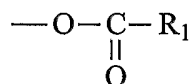
The present invention provides a method for enhancing, increasing, etc. the efficacy of an active agent (e.g., a cosmetic and/or pharmaceutical and/or dermatological active agent)
10 by using, in combination with the active agent, at least one salicylic compound of formula (I):



where

R is a linear, branched or cyclic saturated aliphatic group or an aliphatic unsaturated group containing one or a number of double bonds, which may or may not be conjugated, these groups containing from 2 to 22 carbon atoms and being able to be substituted by at least
15 one substituent selected from (a) halogen atoms, (b) the trifluoromethyl group, (c) hydroxyl groups in the free form or esterified by an acid having from 1 to 6 carbon atoms or (d) a carboxyl functional group which is free or esterified by a lower alcohol having from 1 to 6 carbon atoms;

20 R' is a hydroxyl group or an ester functional group of formula

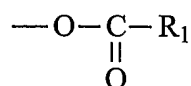


where R₁ is a linear or branched saturated or unsaturated aliphatic group having from 1 to 18 carbon atoms, and salts thereof.

In a preferred embodiment R is a linear, branched or cyclized saturated aliphatic chain
25 containing from 3 to 11 carbon atoms, an unsaturated chain containing from 3 to 17 carbon atoms and containing one or more conjugated or unconjugated double bonds, the abovementioned chains being optionally substituted by one or more halogen atoms or by trifluoromethyl groups, by one or more hydroxyl groups in free form or esterified by an acid

containing from 1 to 6 carbon atoms, or by a carboxyl group, free or esterified by a lower alcohol containing from 1 to 6 carbon atoms, these various groups being optionally simultaneously present in the said substituents; and

R' is a hydroxyl group or an ester group of formula



where R₁ is a saturated or unsaturated aliphatic group containing from 1 to 18 carbon atoms.

The present invention also provides a method for increasing or enhancing the bioavailability and/or the percutaneous absorption and/or penetration of an active agent by using, in combination with the active agent, at least one of the above-mentioned salicylic compounds having the above-mentioned formula (I).

As used herein, "in combination" includes in the same composition, as well as separate overlapping applications to, e.g., the skin, of each ingredient in any order.

The present invention also provides methods of making compositions by physically combining, blending, contacting, etc. in any order of addition (hereinafter "mixing") at least one salicylic acid derivative of Formula 1 as described above and at least one active agent. The resultant compositions also make up a part of the invention, where the salicylic acid derivative is present in an amount that enhances or increases the efficacy of the active agent.

Preferred salicylic acid derivatives useful herein include those described in U.S. Pat. Nos. 6,159,479 and 5,558,871, FR 2,581,542, U.S. Pat. No. 4,767,750, EP 378,936, U.S. Pat. No. 5,267,407, U.S. Pat. No. 5,667,789, U.S. Pat. No. 5,580,549, and EP-A-570,230, all incorporated herein by reference. Further, particularly preferred salicylic acid derivatives useful herein include 5-n-octanoyl salicylic acid (capryloyl salicylic acid), 5-n-decanoyl salicylic acid, 5-n-dodecanoyl salicylic acid, 5-n-heptyloxy salicylic acid and 4-n-heptyloxy salicylic acid. A highly preferred salicylic acid derivative is capryloyl salicylic acid (Trade name: Mexoryl SAB); see page 139 of the International Cosmetic Ingredient Dictionary, 6th Edition, Volume 1, published by the Cosmetic Toiletries, and Fragrance Association, 1995, incorporated herein by reference.

With regard to formula I above, the R group contains from 2 to 22 carbon atoms, inclusive of each and every carbon atom in between this range, including subranges. Useful carbon numbers include 4, 6, 8, 10, 12, 14, 16, and 18. For the R' group of formula I above, each and every carbon number between 1 and 18 is specifically included, and as are all subranges. Useful carbon numbers include 2, 4, 6, 8, 10, 12, 14, and 16. All odd carbon

numbers between 2 and 22 carbon atoms for R, and all odd numbered carbon numbers between 1 and 18 for R', are also specifically included.

Useful salts of the invention salicylic acid derivative may be obtained by salification with a base. Useful bases include inorganic basis such as alkali and alkaline metal hydroxides (sodium hydroxide, potassium hydroxide, and the like) or ammonia hydroxides. Organic bases may also be used for salification. Also useful are amphoteric bases. See U.S. patent application Ser. No. 08/627,965, incorporated herein by reference, for useful salicylic acid derivatives and useful salts thereof. Quaternium salts such as dimethylhydroxypropyl ammonium salts are also particularly useful.

In the present invention, the compositions comprise the at least one salicylic acid derivative of the invention at a concentration of at least 0.01 wt%, preferably from 1 wt% to 99 wt% including all values and subranges therebetween such as 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, and 95 wt%. In all cases the at least one salicylic acid derivative of the invention is present in an amount that increases, enhances, etc (hereinafter "enhances") the efficacy of the active agent used or present in combination therewith. Where the salicylic acid derivative(s) is applied by itself, either before, after, or simultaneously with a separate overlapping (e.g., to the same site, or applied, at least in part, over one another) application of the active agent, the salicylic acid derivative is applied in an amount sufficient to obtain the desired effect, i.e., enhancement of the efficacy of the active agent, this amount being available to one of skill in the art in view of this disclosure based on his/her knowledge of the active agent's efficacy in the absence of and in the presence of the present invention contribution to the art, the determination of which is easily within the skill of the ordinary artisan in view of this disclosure.

A dermatologically acceptable carrier may also be employed in the compositions of the invention and/or in the application of the invention salicylic acid derivatives and/or active agents. A group of preferred carriers include, for example, dermatologically acceptable liquid solvents in which the salicylic acid derivatives are soluble, preferably at high concentrations. The term "dermatologically acceptable liquid solvents" is intended to mean those solvents which can safely be used on the skin in the topical treatment methods of this invention, i.e., solvents which do not provoke a severe reaction and which are not toxic when contacted with the skin for relatively short periods of time. Examples of preferred solvents include water, alkylene glycols such as propylene glycol, glycolic acid, and aqueous alcohol. Highly preferred solvents include ethanol and isopropanol. Other useful solvents include

acetone, ether (diethyl ether). Mixtures containing one or more of these solvents or other solvents listed above may also be used.

As indicated above, invention materials may contain water. It is important to note that the above-mentioned dermatologically acceptable liquid solvents, whether preferred or not, may be utilized alone or in combination with one another.

Other useful carriers herein include the various dermatological and cosmetic carriers such as gels, emulsions, creams, waxes, compacts, etc.

As mentioned above, the present invention provides methods of enhancing the efficacy of an active agent. While not bound by a theory, this enhancement may occur for example by enhancing the bioavailability, the percutaneous absorption, and/or the penetration of the active agent. Further, the invention relates to compositions comprising at least one salicylic acid derivative of formula 1 and at least one active agent, where the at least one salicylic acid derivative of formula 1 is present in an amount effective to enhance the efficacy of at least one active agent present.

Examples of active agents useful herein include, for example, age spot agents, keratose removing agents, analgesic, anesthetic, antiacne agents, antibacterial, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirant, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringent, softener, emollient agents, coal tar, bath oil, sulfur, rinse conditioner, foot care agents, fungicide, hair growth promoter, hair remover, keratolytic agents, moisturizer agents, powder, shampoo, skin bleach, skin protectant, soap, cleanser, antiaging agents, sunscreen agents, wart remover, wet dressing, vitamin, tanning agents, topical antihistamine agents, hormone, vasodilator, retinoid, bronchial dilator, and topical cardiovascular agents.

Preferred active agents include agents (1) to (13) below:

1) Agents which modify cutaneous differentiation and/or proliferation and/or pigmentation such as retinoic acid and isomers thereof, retinol and esters thereof, vitamin D and compounds thereof, estrogens such as estradiol, kojic acid or hydroquinone;

(2) Antibacterial agents such as clindamycin phosphate, erythromycin or antibiotics from the tetracycline family;

(3) Antiparasitic agents, in particular metronidazole, crotamiton or

pyrethroids;

(4) Antifungal agents, in particular compounds of the imidazole family such as econazole, ketoconazole or miconazole or salts thereof, polyene compounds
5 such as amphotericin B, compounds of the allylamine family, such as terbinafine, or alternatively octopirox;

(5) Steroidal anti-inflammatory agents such as hydrocortisone, betamethasone valerate or clobetasol propionate, or nonsteroidal anti-inflammatory agents
10 such as ibuprofen and salts thereof, diclofenac and salts thereof, acetylsalicylic acid, acetaminophen or glycyrrhetinic acid;

(6) Anaesthetic agents such as lidocaine hydrochloride and compounds thereof;

(7) Antipruriginous agents such as thenaldine, trimeprazine or cyproheptadine;

(8) Antiviral agents such as acyclovir;

(9) Keratolytic agents such as alpha- and beta-hydroxycarboxylic acids or
20 beta- ketocarboxylic acids, salts, amides or esters thereof and more particularly hydroxy acids such as glycolic acid, lactic acid, salicylic acid, citric acid and fruit acids in general, and 5-n-octanoylsalicylic acid;

(10) Anti-free-radical agents such as alpha-tocopherol or esters thereof, superoxide dismutases, certain metal-chelating agents or ascorbic acid and
25 esters thereof;

(11) Antiseborrhoeic agents such as progesterone;

(12) Antidandruff agents such as octopirox or zinc pyrithione;

(13) Antiacne agents such as retinoic acid or benzoyl peroxide.

Other useful active agents are found in US patents 5,665,776, 5,561,157, and 5,554, 654, all incorporated herein by reference. Of course, combinations of active agents may be used herein.

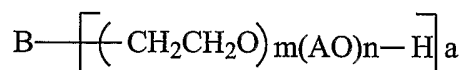
The present invention preferably uses the active agent in concentrations of at least 0.01 wt%, preferably from 1 wt% to 99 wt%, including all values and subranges therebetween, such as 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, and 95 wt%. Where the active agent(s) is applied by itself, either before, after, or simultaneously with a separate application of the salicylic acid derivative, the agent is applied in an amount sufficient to obtain the desired effect, this amount being available to one of skill in the art based on knowledge of the active agent's increased efficacy in view of the present invention contribution to the art, the determination of which is easily within the skill of the ordinary artisan in view of this disclosure.

The compositions of the present invention may be prepared by mixing one or more invention salicylic acid derivatives with the active agent. If used in separate applications the salicylic acid derivative and/or active agent may themselves be formulated with, e.g., a carrier, preferably a dermatologically acceptable liquid solvent.

The salicylic acid derivative and active agent used may be in any form.

The compositions of the invention may of course comprise other components, such as preservatives, stabilizers, antioxidants, thickening agents, surfactants, pigments, colorants, fragrances and other adjuvants. Such components are preferably dermatologically acceptable. Preferably, the additional components do not interfere with the efficacy or impose any negative influence upon the efficacy of the active agent. Such additives may further include, for example, an aromatic, a surfactant, a preservative, an anti-oxidant, a moisturizing agent, and so on. Of course the additional components may be present individually or in combination, and their concentrations are not limited.

Other useful additives may include compounds having formula (II)



wherein B is an alcohol residue,

AO is an alkylene-oxy group having from 3 to 18 carbon atoms

a in an integer that is greater than or equal to 1,

m is an integer that is greater than or equal to 4,

n is an integer that is greater than or equal to 0,

provided that a molar amount m of the ethylene oxide to be added is a value that amounts to at least 40% or the entire molecular weight of the ethylene oxide chain moiety.

In the above general formula II, the alcohol to be represented by reference symbol B is intended to mean a monovalent alcohol including, for example, an alkyl alcohol such as ethanol, butanol, lauryl alcohol, myristyl alcohol, palmityl alcohol, stearyl alcohol, cetyl alcohol, etc., and an alkenyl alcohol such as linoleyl alcohol, palmitoyl alcohol, oleyl alcohol, etc., a divalent alcohol such as ethylene glycol, propylene glycol, etc., a trivalent alcohol such as glycerin, trimethylol propane, triethanol amine, etc., a tetravalent alcohol such as pentaerythritol, diglycerin, etc. There may also be used other polyvalent alcohols such as sorbitol, polyglycerin and so on.

The alkyleneoxy group having 3 to 18 carbon atoms, as referred to by reference symbol AO, may include, for example, propyleneoxy, butyleneoxy, tetrahydrofuran, α -olefinoxy, and so on. The alkyleneoxy groups having 3 and 4 carbon atoms, such as oxidopropylene, oxidobutylene and tetrahydrofuran, are preferred.

In the above general formula, reference symbol "a" is an integer of 1 or more. When the alcohol to be used for the present invention is a monovalent alcohol, the reference symbol "a" is 1. When the alcohol to be used therefore is a divalent alcohol, the reference symbol "a" is 2. Likewise, when the alcohol to be used therefore is a trivalent alcohol, the reference symbol "a" is 3. Further, when the alcohol to be used therefore is a polyvalent alcohol, the reference symbol "a" is the integer corresponding to the valence of the alcohol used.

In the above general formula, reference symbol "m" is intended to mean an average molar amount of ethylene oxide to be added. The number of a polymerization chain of the ethylene oxide has to be at least 4.

Reference symbol "n" is intended to mean an average molar amount of an oxidized alkylene to be added. The number of a polymerization chain of the oxidized alkylene is zero or 1 or more.

The manner of polymerization of the ethylene oxide and the alkylene oxide is random or block polymerization.

The molar amount m of the ethylene oxide to be added is set to amount to 40% or more of the entire molecular weight of the ethylene oxide chain. This setting is based on the fact that, if the molar amount m of the ethylene oxide to be added would be less than the above molar amount, the phenol compound such as salicylic acid derivative would become unlikely to be sustained in the polyethylene glycol compound.

The additive compounds having formula II may be synthesized in a conventional manner, for example, by reacting the ethylene oxide and the alkylene oxide with the alkyl alcohol or the alkenyl alcohol under an inert gas such as nitrogen or the like in the presence of a basic catalyst such as sodium hydroxide, potassium hydroxide or the like or an acidic catalyst such as boron tetrafluoride, tin tetrachloride or the like.

Specific examples of the additive compounds having formula II are discussed in EP 1 214 925 A1, incorporated herein by reference.

The combination of active agent and salicylic acid derivative is applied to the skin, body, eyes, etc, where the active agent is expected to have its effect, including the hair, lips, mucuous membranes, inteugments, scalp, eyes, etc. (hereinafter 'the body") and allowed to remain there for action in or on the body.

The composition of the present invention may be in cream or ointment form containing at least one of salicylic acid derivative and at least one active agent. These components may be initially dissolved in a solvent such as water, ethanol, acetone, propylene glycol or polysorbate 80. The solution may then be mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum.

Compositions of the instant invention may also be formulated in gel, lotion, shampoo, spray, stick or powder. An example of one gel composition of the instant invention utilizes at least one of salicylic acid derivative and at least one active agent dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose or ammoniated glycyrrhizinate may then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

The present invention is explained in more detail with the aid of the following embodiment examples. Percents are weight percents based on total weight unless otherwise specified. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limited. Of course, any of the aforementioned salicylic acid derivatives and active agents may be substituted according to the teachings of this invention in the following examples.

EXAMPLES

Example 1 : Lotion with Kojic Acid

Kojic Acid 1% / Capryloyl salicylic acid 2% / EDTA 0.1% / Ethanol 40% / Water Qs
100%

Example 2 : Cream with Hydroquinone

5	Phase A	water	QS 100%
		Preservative, sequestrant, anti-oxidant	0.4%
		Glycerin	23%
		Hydroquinone	4%
		Capryloyl salicylic acid	1%
10		Propylene glycol	6%
	Phase B	Cyclopentasiloxane (and) PEG/PPG-18/18	
		Dimethicone	20%
		Dimethicone (and) dimethicone/vinyl dimethicone	
		Crosspolymer	5%
15		Preservative	0.1%

Example 3 : Lotion with Hydrocortisone

20	Caprolactame	46%
	Ethanol	46%
	Hydrocortisone	2%
	Capryloyl salicylic acid	3%
	Glycerine	3%

25

Example 4 : Cream with Vitamin C

	Phase A	water	QS 100%
		Preservative, sequestrant, anti-oxidant	0.4%
		Glycerin	23%
30		Magnesium ascorbyl phosphate	5%
		Capryloyl salicylic acid	1%
		Propylene glycol	6%
	Phase B	Cyclopentasiloxane (and) PEG/PPG-18/18	
		Dimethicone	20%

Dimethicone (and) dimethicone/vinyl dimethicone

Crosspolymer 5%

Preservative 0.1%

5

Example 5 : Cream with Retinol

Phase A water QS 100%

Preservative, sequestrant, anti-oxidant 0.4%

Glycerin 23%

10 Retinol 0.25%

Capryloyl salicylic acid 1%

Propylene glycol 6%

Phase B Cyclopentasiloxane (and) PEG/PPG-18/18

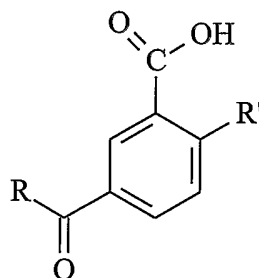
Dimethicone 20%

15 Dimethicone (and) dimethicone/vinyl dimethicone

Crosspolymer 5%

Preservative 0.1%

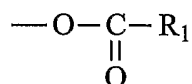
20 The above specification provides a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in this art to make and use the same, this description and enablement including that for a method of enhancing the efficacy of an active agent in or on the body, comprising applying to the body a combination of an active agent and at least one
25 salicylic acid derivative of formula (I) in an amount effective to enhance the efficacy of the active agent:



wherein

R is a linear, branched or cyclic saturated aliphatic group or an aliphatic unsaturated group containing one or a number of double bonds, which may or may not be conjugated, these groups containing from 2 to 22 carbon atoms and being able to be substituted by at least one substituent selected from the group consisting of (a) halogen atoms, (b) a trifluoromethyl group, (c) hydroxyl groups in the free form or esterified by an acid having from 1 to 6 carbon atoms and (d) a carboxyl functional group which is free or esterified by a lower alcohol having from 1 to 6 carbon atoms;

R' is a hydroxyl group or an ester functional group of formula



wherein R₁ is a linear or branched saturated or unsaturated aliphatic group having from 1 to 18 carbon atoms, and salts thereof, where in a preferred embodiment, the salicylic acid derivative is 5-n-octanoyl-salicylic acid, where the active agent may be selected from, for example, the group consisting of an age spot agents, keratose removing agents, analgesic, anesthetic, antiacne agents, antibacterial, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirant, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringent, softener, emollient agents, coal tar, bath oil, sulfur, rinse conditioner, foot care agents, fungicide, hair growth promoter, hair remover, keratolytic agents, moisturizer agents, powder, shampoo, skin bleach, skin protectant, soap, cleanser, antiaging agents, sunscreen agents, wart remover, wet dressing, vitamin, tanning agents, topical antihistamine agents, hormone, vasodilator, retinoid, bronchial dilator, and topical cardiovascular agents. Further active agents described and enabled herein include retinoic acid, retinoic acid compounds, retinol, retinol ester, vitamin D, vitamin D compounds, estrogen, estradiol, kojic acid, hydroquinone, clindamycin phosphate, erythromycin, erythromycin compound, tetracycline compound, metronidazole, crotamiton, pyrethroids, econazole, ketoconazole miconazole, polyene compound, amphotericin B, allylamine compound, terbinafine, octopirox, steroid, hydrocortisone, betamethasone valerate, clobetasol propionate, nonsteroidal anti-inflammatory agents, ibuprofen, diclofenac, acetylsalicylic acid, acetaminophen, glycyrrhetic acid, lidocaine hydrochloride, lidocaine hydrochloride compound, thenaldine, trimeprazine, cyproheptadine, acyclovir, keratolytic agents, alpha-hydroxycarboxylic acid, beta-hydroxycarboxylic acid, beta-ketocarboxylic acid, alpha-hydroxycarboxylic acid amide, beta-hydroxycarboxylic acid amide, beta-ketocarboxylic acid

amide, alpha-hydroxycarboxylic acid ester, beta-hydroxycarboxylic acid ester, beta-ketocarboxylic acid ester, hydroxy acid, glycolic acid, lactic acid, salicylic acid, citric acid, fruit acid, 5-n-octanoylsalicylic acid, salicylic acid, alpha-tocopherol, alpha-tocopherol ester, superoxide dismutases, metal-chelating agents, ascorbic acid, ascorbic acid ester,

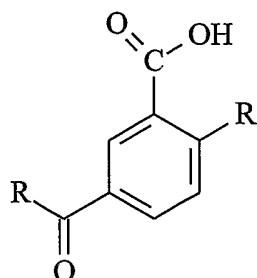
5 progesterone, octopirox, zinc pyrithione, and benzoyl peroxide.

Similarly fully described and enabled is a composition comprising at least one active agent and at least one salicylic acid derivative of formula (I) above in an amount effective to enhance the efficacy of the active agent in or on the body, and a method of making such a composition comprising mixing the at least one salicylic acid derivative with the at least one

10 active agent, as well as a method of using such a composition.

CLAIMS:

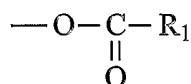
1. A method of enhancing the efficacy of an active agent in or on the body, comprising applying to the body a combination of an active agent and at least one salicylic acid derivative of formula (I) in an amount effective to enhance the efficacy of the active agent:



wherein

R is a linear, branched or cyclic saturated aliphatic group or an aliphatic unsaturated group containing one or a number of double bonds, which may or may not be conjugated, these groups containing from 2 to 22 carbon atoms and being able to be substituted by at least one substituent selected from the group consisting of (a) halogen atoms, (b) a trifluoromethyl group, (c) hydroxyl groups in the free form or esterified by an acid having from 1 to 6 carbon atoms and (d) a carboxyl functional group which is free or esterified by a lower alcohol having from 1 to 6 carbon atoms;

R' is a hydroxyl group or an ester functional group of formula



wherein R₁ is a linear or branched saturated or unsaturated aliphatic group having from 1 to 18 carbon atoms, and salts thereof.

2. The method according to Claim 1, wherein the salicylic acid derivative is 5-n-octanoyl-salicylic acid.

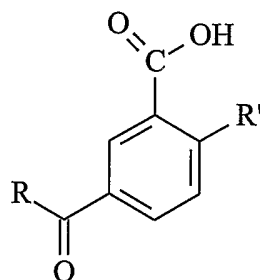
3. The method according to Claim 1, wherein the active agent is selected from the group consisting of an age spot agents, keratose removing agents, analgesic, anesthetic, antiacne agents, antibacterial, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirant,

antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringent, softener, emollient agents, coal tar, bath oil, sulfur, rinse conditioner, foot care agents, fungicide, hair growth promoter, hair remover, keratolytic agents, moisturizer agents, powder, shampoo, skin bleach, skin protectant, soap, cleanser, antiaging agents, sunscreen agents, wart remover, wet dressing, vitamin, tanning agents, topical antihistamine agents, hormone, vasodilator, retinoid, bronchial dilator, and topical cardiovascular agents.

4. The method according to Claim 1, wherein the active agent is selected from the group consisting of retinoic acid, retinoic acid compounds, retinol, retinol ester, vitamin D, vitamin D compounds, estrogen, estradiol, kojic acid, hydroquinone, clindamycin phosphate, erythromycin, erythromycin compounds, tetracycline compounds, metronidazole, crotamiton, pyrethroids, econazole, ketoconazole miconazole, polyene compounds, amphotericin B, allylamine compounds, terbinafine, octopirox, steroid, hydrocortisone, betamethasone valerate, clobetasol propionate, nonsteroidal anti-inflammatory agents, ibuprofen, diclofenac, acetylsalicylic acid, acetaminophen, glycyrrhetic acid, lidocaine hydrochloride, lidocaine hydrochloride compound, thenaldine, trimeprazine, cyproheptadine, acyclovir, keratolytic agents, alpha-hydroxycarboxylic acid, beta-hydroxycarboxylic acid, beta-ketocarboxylic acid, alpha- hydroxycarboxylic acid amide, beta-hydroxycarboxylic acid amide, beta-ketocarboxylic acid amide, alpha-hydroxycarboxylic acid ester, beta-hydroxycarboxylic acid ester, beta- ketocarboxylic acid ester, hydroxy acid, glycolic acid, lactic acid, salicylic acid, citric acid, salicylic acid, alpha-tocopherol, alpha-tocopherol ester, superoxide dismutases, metal-chelating agents, ascorbic acid, ascorbic acid ester, progesterone, octopirox, zinc pyrithione, and benzoyl peroxide.

5. The method according to Claim 1, wherein the salicylic acid derivative and active agent are present in a composition which further comprises a dermatologically acceptable carrier.

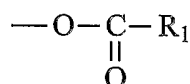
6. A composition comprising an active agent and a salicylic acid derivative of formula (I) in an amount effective to enhance the efficacy of the active agent in or on the body:



wherein

R is a linear, branched or cyclic saturated aliphatic group or an aliphatic unsaturated group containing one or a number of double bonds, which may or may not be conjugated, these groups containing from 2 to 22 carbon atoms and being able to be substituted by at least one substituent selected from the group consisting of (a) halogen atoms, (b) a trifluoromethyl group, (c) hydroxyl groups in the free form or esterified by an acid having from 1 to 6 carbon atoms and (d) a carboxyl functional group which is free or esterified by a lower alcohol having from 1 to 6 carbon atoms;

R' is a hydroxyl group or an ester functional group of formula



wherein R₁ is a linear or branched saturated or unsaturated aliphatic group having from 1 to 18 carbon atoms, and salts thereof.

7. The composition according to Claim 6, wherein the salicylic acid derivative is 5-n-octanoyl-salicylic acid.

8. The composition according to Claim 6, wherein the active agent is selected from the group consisting of an age spot agents, keratose removing agents, analgesic, anesthetic, antiacne agents, antibacterial, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirant, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringent, softener, emollient agents, coal tar, bath oil, sulfur, rinse conditioner, foot care agents, fungicide, hair growth promoter, hair remover, keratolytic agents, moisturizer agents, powder, shampoo, skin bleach, skin protectant, soap, cleanser, antiaging agents, sunscreen agents, wart remover, wet dressing, vitamin, tanning agents, topical antihistamine agents, hormone, vasodilator, retinoid, bronchial dilator, and topical cardiovascular agents.

9. The composition according to Claim 6, wherein the active agent is selected from the group consisting of retinoic acid, retinoic acid compounds, retinol, retinol ester, vitamin D, vitamin D compounds, estrogen, estradiol, kojic acid, hydroquinone, clindamycin phosphate, erythromycin, erythromycin compounds, tetracycline compounds, metronidazole, crotamiton, pyrethroids, econazole, ketoconazole miconazole, polyene compounds, amphotericin B, allylamine compounds, terbinafine, octopirox, steroid, hydrocortisone, betamethasone valerate, clobetasol propionate, nonsteroidal anti-inflammatory agents, ibuprofen, diclofenac, acetylsalicylic acid, acetaminophen, glycyrrhetic acid, lidocaine hydrochloride, lidocaine hydrochloride compound, thenaldine, trimeprazine, cyproheptadine, acyclovir, keratolytic agents, alpha-hydroxycarboxylic acid, beta-hydroxycarboxylic acid, beta-ketocarboxylic acid, alpha- hydroxycarboxylic acid amide, beta-hydroxycarboxylic acid amide, beta-ketocarboxylic acid amide, alpha-hydroxycarboxylic acid ester, beta-hydroxycarboxylic acid ester, beta- ketocarboxylic acid ester, hydroxy acid, glycolic acid, lactic acid, salicylic acid, citric acid, salicylic acid, alpha-tocopherol, alpha-tocopherol ester, superoxide dismutases, metal-chelating agents, ascorbic acid, ascorbic acid ester, progesterone, octopirox, zinc pyrithione, and benzoyl peroxide.

10. The composition according to Claim 6, further comprising a dermatologically acceptable carrier.

11. A method of making the composition according to Claim 6, comprising mixing the salicylic acid derivative and the active agent.

INTERNATIONAL SEARCH REPORT

PCT/EP2004/001169

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K47/14 A61K7/48 A61K7/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 443 823 A (ROSENBAUM GEORGES ET AL) 22 August 1995 (1995-08-22) column 1, line 37 - column 2, line 8 column 6 - column 7; examples 1-7 claims 1-11	1-11
X	US 6 267 972 B1 (BRETON LIONEL ET AL) 31 July 2001 (2001-07-31) column 2, line 31 - line 43 column 3, line 10 - line 15 column 7, line 45 - column 8, line 67 column 12; example 7	1-11
X	EP 0 679 388 A (OREAL) 2 November 1995 (1995-11-02) page 6 - page 7; examples 1-3	1-11
-/--		
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search 24 June 2004		Date of mailing of the international search report 06/07/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Muller, S

INTERNATIONAL SEARCH REPORT

PCT/EP2004/001169

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 164 185 A (MILLECAMPS FRANCOIS ET AL) 17 November 1992 (1992-11-17) column 4 - column 5; example 1 -----	1-11
X	EP 0 909 556 A (OREAL) 21 April 1999 (1999-04-21) page 4, line 34 - line 41 page 6, line 7 - line 28 page 8, line 25 - line 40 -----	1-11

INTERNATIONAL SEARCH REPORT

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/EP2004/001169

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5443823	A	22-08-1995	LU 87187 A1	26-10-1989
			AT 79742 T	15-09-1992
			CA 1341267 C	26-06-2001
			DE 68902565 D1	01-10-1992
			DE 68902565 T2	11-03-1993
			EP 0336812 A2	11-10-1989
			JP 1308216 A	12-12-1989
			JP 2744057 B2	28-04-1998
US 6267972	B1	31-07-2001	FR 2740040 A1	25-04-1997
			BR 9611302 A	30-03-1999
			CA 2222311 A1	01-05-1997
			DE 69603681 D1	16-09-1999
			DE 69603681 T2	25-11-1999
			DK 769293 T3	06-12-1999
			EP 0769293 A2	23-04-1997
			WO 9715281 A1	01-05-1997
			HU 9900511 A2	28-07-1999
			JP 2000503628 T	28-03-2000
			NO 976143 A	03-06-1998
			PL 324924 A1	22-06-1998
			RU 2169552 C2	27-06-2001
			US 5958432 A	28-09-1999
EP 0679388	A	02-11-1995	FR 2718640 A1	20-10-1995
			DE 69505177 D1	12-11-1998
			DE 69505177 T2	04-03-1999
			EP 0679388 A1	02-11-1995
			ES 2125569 T3	01-03-1999
			JP 2651367 B2	10-09-1997
			JP 7300404 A	14-11-1995
US 5164185	A	17-11-1992	FR 2653336 A1	26-04-1991
			AT 200977 T	15-05-2001
			AU 638768 B2	08-07-1993
			AU 6628890 A	16-05-1991
			BE 1003833 A3	23-06-1992
			BR 9006960 A	12-11-1991
			CA 2044269 A1	21-04-1991
			CH 682129 A5	30-07-1993
			DE 69033731 D1	13-06-2001
			DE 69033731 T2	07-02-2002
			EP 0450040 A1	09-10-1991
			ES 2085192 A1	16-05-1996
			WO 9105543 A1	02-05-1991
			GB 2244005 A , B	20-11-1991
			IT 1251741 B	23-05-1995
			JP 2659618 B2	30-09-1997
			JP 4502476 T	07-05-1992
			MX 173203 B	08-02-1994
			ZA 9008398 A	28-08-1991
EP 0909556	A	21-04-1999	FR 2768622 A1	26-03-1999
			AT 251888 T	15-11-2003
			CA 2245123 A1	22-03-1999
			DE 69818939 D1	20-11-2003
			DK 909556 T3	02-02-2004
			EP 0909556 A1	21-04-1999

INTERNATIONAL SEARCH REPORT

PCT/EP2004/001169

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0909556	A	JP 3128215 B2	29-01-2001
		JP 11180880 A	06-07-1999
		US 6586020 B1	01-07-2003