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(54) Benævnelse: **FARMACEUTISKE SAMMENSÆTNINGER OMFATTENDE (S)-(+)-7-(1H-IMIDAZOL-4-YLMETHYL)-5,6,7,8-TETRAHYDRO-QUINOLIN TIL BEHANDLING AF HUDSYGDOMME OG -TILSTANDE**

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WO-A2-2009/052073
US-A1- 2005 020 600
US-A1- 2011 118 267
US-B2- 7 323 477
US-B2- 7 439 241
TULANDI T ET AL: "Effect of guanfacine, an alpha-adrenergic agonist, on menopausal flushing", MATURITAS, ELSEVIER SCIENCE PUBLISHERS IRELAND LTD, IR, vol. 8, no. 3, 1 October 1986 (1986-10-01) , pages 197-200, XP002590833, ISSN: 0378-5122
GOTOH Y ET AL: "Clonidine inhibits itch-related response through stimulation of alpha2-adrenoceptors in the spinal cord in mice", EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER SCIENCE, NL, vol. 650, no. 1, 10 January 2011 (2011-01-10), pages 215-219, XP027538840, ISSN: 0014-2999 [retrieved on 2010-10-15]

DESCRIPTION

BACKGROUND OF THE INVENTION

[0001] The present invention relates to a pharmaceutical composition for use in a method for treating skin diseases and skin conditions in a patient in need thereof. The pharmaceutical composition comprises a therapeutically effective amount of (*S*)-(+)-7-(1 H-imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline or the tautomers thereof, or pharmaceutically acceptable salts thereof.

SUMMARY OF THE RELATED ART

[0002] Three alpha 1 and three alpha 2 adrenergic receptors have been characterized by molecular and pharmacological methods. Activation of these alpha receptors evokes physiological responses having useful therapeutic actions. Alpha adrenergic agonists act on the peripheral vasculature to cause vasoconstriction and thereby ameliorate the symptoms of inflammatory skin disorders, including erythema or redness. Alpha adrenergic agonists are useful for ocular mucosal tissue to treat conjunctival redness (hyperemia), for nasal mucosa, as a decongestant for the treatment of allergic rhinitis, and for rectal mucosal administration suitable for treating and curing hemorrhoids.

H. E. Baldwin describes the diagnosis and the actual treatments of rosacea and related skin diseases, in the Journal of Drugs in Dermatology 2012, Vol. 11 (6) pages 725-730.

U.S. Patent No. 6,680,062 discloses topical cosmetic and pharmaceutical compositions for the treatment of the skin.

U.S. Patent Application Publication No. 2012/0035123 describes combinations of compounds for treating skin diseases.

U.S. Patent No. 7,812,049 discloses a method for treating erythema resulting from rosacea comprising oxymetazoline. Oxymetazoline is a selective alpha-1 agonist and partial alpha-2 agonist topical decongestant.

WO 2009/052073 A2 describes a method of treating a sensorimotor disorder comprising administering to a subject in need of such treatment an alpha-2 receptor agonist lacking significant alpha-2A receptor activity.

US 7,439,241 B2 describes a method of treating or preventing rosacea by topically administering an alpha-2 adrenergic receptor agonist to the skin of a patient.

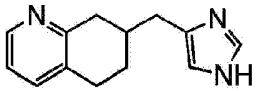
US 2011/118267 A1 describes a method of treating or preventing psoriasis by topically administering an alpha-2 adrenergic receptor agonist to the skin of a patient.

US 2005/020600 A1 also describes a method of treating or preventing psoriasis by topically administering an alpha-2 adrenergic receptor agonist, such as brimonidine, to the skin of a patient.

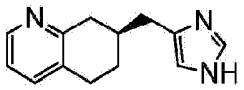
Tulandi et al. have reported the effect of the alpha adrenergic agonist guanfacine on menopausal flushing (Maturitas, 1986, vol. 8(1), pp. 197-200).

Gotoh et al. have reported that clonidine inhibits itch-related response through stimulation of alpha-2 adrenoceptors (Eur. J. Pharmacol., 2011, vol. 650(1), pp. 215-219).

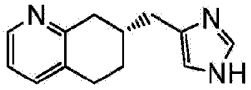
[0003] Compound 7-(1 H-imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline is known as a potent alpha 1 and alpha 2 adrenergic receptor pan agonist. The racemic mixture and the two enantiomers of 7-(1H-imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline are disclosed in U.S. Patent Number 7,323,477 B2. U.S. Patent Number 7,943,641 discloses a composition comprising (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline for the treatment of glaucoma or ocular hypertension.



7-((1*H*-imidazol-4-yl) methyl)-5,6,7,8-tetrahydroquinoline



(*R*)-(-)-7-((1*H*-imidazol-4-yl) methyl)-5,6,7,8-tetrahydroquinoline



(*S*)-(+)-7-((1*H*-imidazol-4-yl) methyl)-5,6,7,8-tetrahydroquinoline

BRIEF SUMMARY OF THE INVENTION

[0004] It has now been discovered that the pharmaceutical compositions of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline are useful for the treatment of skin diseases and skin conditions.

[0005] The present invention relates to pharmaceutical compositions containing as active ingredient (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline for use in the treatment of skin diseases and skin conditions.

[0006] In another aspect the present invention relates to a pharmaceutical composition for use in a method for treating skin diseases in a patient in need thereof which comprises administering a pharmaceutical composition comprising a therapeutically effective amount of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline or a pharmaceutically acceptable salt thereof.

[0007] In another aspect the present invention relates to a pharmaceutical composition for use in a method for improving skin diseases in a patient in need thereof which comprises

administering a pharmaceutical composition comprising a therapeutically effective amount of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline or a pharmaceutically acceptable salt thereof.

[0008] The compound may be administered through different routes, including but not limited to, topical dermatological application of an effective dose, direct injection, or formulations that may further enhance the long duration of action such as slow releasing pellets, suspensions, gels, solutions, creams, ointments, foams, emulsions, microemulsions, milks, patches, serums, aerosols, sprays, dispersions, microcapsules, vesicles, microparticles, wet cloths, dry cloths, facial cloths, or sustained delivery devices such as any suitable drug delivery system known in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009]

Figure 1 shows topical (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline inhibits 37°C-induced cutaneous vessel dilation in rat paws for at least 4 hrs post-treatment following a single application and for at least 6 hrs post-treatment following 4 daily applications.

Figure 2 shows the rate of percutaneous absorption as the flux of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline that appears in the receptor solution under the skin in an *ex vivo* human trunk skin preparation

Figure 3 shows the distribution of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline following a 48 hour dose exposure to *ex vivo* human trunk skin as a mass recovered

Figure 4 shows Inhibition of LL-37-induced mouse skin inflammation after topical treatment with (S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline

Figure 5 shows reduction of UVB-induced mouse skin erythema (redness) for at least 48 hrs following treatment with(S)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline.

Figure 6 shows reduction of UVB-induced cutaneous vessel dilation in mouse ears for at least 48 hrs following treatment with(S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline.

Figure 7 shows reduction of tactile hypersensitivity in UVB exposed mouse skin 4 hrs following treatment with(S)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline.

DETAILED DESCRIPTION OF THE INVENTION

[0010] In one aspect of the invention, there is provided a pharmaceutical composition for use

in a method for treating skin diseases and skin conditions in a patient in need thereof which comprises, consists essentially of or consists of administering a therapeutically effective amount of a pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of (*S*)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline, or the tautomers thereof, or pharmaceutically acceptable salts thereof.

[0011] By "skin diseases" it should be understood any condition, complaint or affliction associated with the listed diseases.

[0012] Skin diseases and skin conditions which may be treated with pharmaceutical compositions containing as active ingredient (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline include rosacea, rosacea fulminans, sunburn, psoriasis, menopause-associated hot flashes, flushing and redness associated with hot flashes, erythema associated with hot flashes, hot flashes resulting from orchiectomyatopic dermatitis, treatment of redness and itch from insect bites, photoaging, seborrheic dermatitis, acne, allergic dermatitis, telangiectasia (dilations of previously existing small blood vessels) of the face, angioectasias, rhinophyma (hypertrophy of the nose with follicular dilation), acne-like skin eruptions (may ooze or crust), burning or stinging sensation, erythema of the skin, cutaneous hyperactivity with dilation of blood vessels of the skin, Lyell's syndrome, Stevens-Johnson syndrome, local itching and discomfort associated with hemorrhoids, hemorrhoids, erythema multiforme minor, erythema multiforme major, erythema nodosum, eye puffiness, urticaria, pruritis, purpura, varicose veins, contact dermatitis, atopic dermatitis, nummular dermatitis, generalized exfoliative dermatitis, stasis dermatitis, lichen simplex chronicus, perioral dermatitis, pseudofolliculitis barbae, granuloma annulare, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, eczema.

[0013] Skin conditions which result in rosacea can be induced by intake of spicy food, of alcohol, of chocolate, of hot or alcoholic drinks, temperature variations, heat, exposure to ultraviolet or infrared radiation, exposure to low relative humidity, exposure of the skin to strong winds or currents of air, exposure of the skin to surfactants, irritants, irritant dermatological topical agents, and cosmetics or psychological stress.

[0014] The actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the condition, the age and weight of the patient, the patient's general physical condition, the cause of the condition, and the route of administration.

[0015] In another aspect of the invention, there is provided a pharmaceutical composition for use in a method for treating skin diseases wherein the pharmaceutical composition comprises, consists essentially of or consists of a therapeutically effective amount of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline, and the pharmaceutical composition is administered through topical skin applications comprising suspensions, gels, solutions, creams, lotions, ointments, foams, emulsions, microemulsions, milks, serums, aerosols, sprays, dispersions, microcapsules, vesicles, microparticles, wet cloths, dry cloths, facial cloths,

applications and formulations that may further enhance the long duration of actions such as a slow releasing pellets, direct injection, or sustained delivery devices such as any suitable drug delivery systems known in the art. Pharmaceutical compositions of the present invention can be used for the topical administration including solutions, gels, lotions creams, ointments, foams, mousses, emulsions, microemulsions, milks, serums, aerosols, sprays, dispersions, patches, micelles, liposomes, microcapsules, vesicles and microparticles thereof.

[0016] Emulsions, such as creams and lotions that can be used as topical carriers and their preparation are disclosed in Remington: The Science and Practice of Pharmacy 282-291 (Alfonso R. Gennaro Ed. 19th ed. 1995).

[0017] Suitable gels for use in the invention are disclosed in Remington: The Science and Practice of Pharmacy 1517-1518 (Alfonso R. Gennaro Ed. 19th ed. 1995). Other suitable gels for use within the invention are disclosed in U.S. Pat. No. 6,387,383, U.S. Pat. No. 6,517,847 and U.S. Pat. No. 6,468,989.

[0018] In another aspect of the invention, there is provided a pharmaceutical composition for use in a method for improving skin diseases, by administering to a patient in need thereof a pharmaceutical composition containing as active ingredient (*S*)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline, including rosacea, rosacea fulminans, sunburn, psoriasis, menopause-associated hot flashes, flushing and redness associated with hot flashes, erythema associated with hot flashes, hot flashes resulting from orchiectomyatopic dermatitis, treatment of redness and itch from insect bites, photoaging, seborrheic dermatitis, acne, allergic dermatitis, telangiectasia (dilations of previously existing small blood vessels) of the face, angioectasias, rhinophyma (hypertrophy of the nose with follicular dilation), acne-like skin eruptions (may ooze or crust), burning or stinging sensation, erythema of the skin, cutaneous hyperactivity with dilation of blood vessels of the skin, Lyell's syndrome, Stevens-Johnson syndrome, local itching and discomfort associated with hemorrhoids, hemorrhoids, erythema multiforme minor, erythema multiforme major, erythema nodosum, eye puffiness, urticaria, pruritis, purpura, varicose veins, contact dermatitis, atopic dermatitis, nummular dermatitis, generalized exfoliative dermatitis, stasis dermatitis, lichen simplex chronicus, perioral dermatitis, pseudofolliculitis barbae, granuloma annulare, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, eczema.

[0019] In another aspect of the invention, there is provided a pharmaceutical composition for use in a method of decreasing the irritation of skin associated with rosacea treatment regimen of topically applied a therapeutically effective amount of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline, the method of treating telangiectasia or angioectasias with a therapeutically effective amount of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline, and therefore, it also includes the method of reducing redness associated with the appearance of rosacea.

[0020] In another aspect of the invention, there is provided a pharmaceutical composition comprising (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline for use in a method

for treating skin diseases including rosacea induced by intake of spicy food, chocolate, alcohol, hot or alcoholic drinks, temperature variations, heat, exposure to ultraviolet or infrared radiation, exposure to low relative humidity, exposure of the skin to strong winds or currents of air, exposure of the skin to surfactants, irritants, irritant dermatological topical agents, and cosmetics or psychological stress.

[0021] (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline may be formulated with efficacy enhancing components as disclosed in U.S. Patent Number 7,491,383 B2.

[0022] The (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline compound has physiochemical and pharmacokinetic properties that are beneficial for sustained activity, particularly when the drug is delivered continuously (e.g. to the skin by a dermal patch).

[0023] "Pharmaceutical composition," as used here, means a composition that is suitable for administering to human patients for disease treatment. In one embodiment the compound of the invention is formulated as a pharmaceutically acceptable salt which further includes one or more organic or inorganic carriers or excipients suitable for dermatological applications. The pharmaceutically acceptable excipients may include one or more skin-penetrating agents, moisturizers, preservatives, gelling agents, protective agents, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicon emulsions. The pharmaceutical composition may comprise excipients, binders, lubricants, solvents, disintegrants, or enhancers of cutenous penetration and will be administered preferably topically. The active ingredient is used in an amount of about 0.01 % up to about 20% and preferably about 0.1 % to about 10% by weight based on the total weight of the composition.

[0024] "Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free base and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, or an organic acid such as for example, acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, malonic acid, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, citric acid, methylsulfonic acid, ethanesulfonic acid, benzenesulfonic acid, formic and, salicylic acid and the like (Handbook of Pharmaceutical Salts, P.Heinrich Stahal& Camille G. Wermuth (Eds), Verlag Helvetica Chemica Acta- Zurich, 2002, 329-345).

[0025] In another aspect of the invention, there is provided a pharmaceutical composition for use in a method for treating skin diseases and skin conditions wherein the pharmaceutical composition comprising, consisting essentially of, or consisting of a therapeutically effective amount of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline is selected from topical skin application, direct injection, applications and formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, solution, lotion, cream, ointment, foams, emulsions, microemulsions, milks, serums, aerosols, sprays, dispersions, microcapsules, vesicles, microparticles, wet cloths, soaps, cleansing bars, dry cloths, facial cloths.

[0026] The present invention may be used in conjunction with rosacea treatments of topically applied agents such as macrocyclic lactones of the avermectin family, macrolides known as milbemycins, other alpha 1 or alpha 2 receptor agonists, retinoids, phytosphingosine, green tea extract, azaleic acid.
The present invention may also be used in conjunction with other classes of compounds such as:

Antimicrobials (such as antiparasitic, antibacterial, antifungal, antiviral);

Metronidazole, ivermectin, clindamycin, erythromycin, tetracycline, doxycycline, minocycline;

Steroidal and non-steroidal anti-inflammatory agents (such as corticosteroids, tacrolimus, pimecrolimus, cyclosporine A);

Antiangiogenesis agents;

Antimycobacterial agents (such as dapsone);

Sunscreensor sunblocks or anything that functions like a sunscreen/sunblock (such as titanium dioxide, zinc oxide, avobenzone);

Antioxidants (such as Vitamins C, E, quercetin, resveratrol);

Other alpha agonists (such as brimonidine, oxymetazoline, clonidine);

Beta blockers (such as nadolol, propanolol, carvedilol);

Antihistamines;

Retinoids (such as tretinoin, adapalene, tazarotene, isotretinoin, retinaldehyde) Benzoyl peroxide;

Menthol and other "cooling" agents;

Sodium sulfacetamide and derivatives;

Antifungal agents (such as imidazole derivatives, ployene compounds, allylamine compounds);

Serine protease (kallikrein) inhibitors (such as aminocaproic acid);

Example 1

Rat blood flow assay

Background

[0027] Rosacea can be triggered by heat exposure. The physiological sympathetic nervous system-mediated response to body cooling is cutaneous vasoconstriction and the response to body warming is cutaneous vasodilation. α-adrenergic agonists that act on the sympathetic nervous system outflow can regulate cutaneous blood flow in response to temperature changes.

Method

[0028] A laser Doppler microvascular perfusion monitor (laser Doppler flowmetry technique, LDP) was used to monitor red blood cell perfusion in the microvasculature of the hind foot pad. The laser doppler flowmetry (LDP) is an OxyFlo Microvascular Perfusion Monitor, from Oxford Optronix LTd. UK.

[0029] Briefly, 15 µL of test articles was applied topically once, or repeatedly (once daily for 4 consecutive days) to one hind foot pad of anaesthetized hairless CD rats and 15 µL of vehicle was applied to the other footpad.

[0030] At various timepoints up to 8 hrs following the last test article administration, dynamic blood flow changes were measured and recorded every 15 seconds for 4 minutes per temperature interval for 5 intervals (22°C→37°C→4°C→37°C→22°C). Rats were placed on a 37°C heat pad to increase their temperature and on an ice pad to decrease their temperature to 4°C. The levels of blood flow in the two paws were compared.

[0031] **Figure 1** shows topical (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline significantly inhibits 37°C induced vessel dilation for up to 4 hrs following single topical dosing to the skin at a concentration of 0.1%. Following 4 days of topical dosing (once per day), the duration of statistically significant inhibition is increased to at least 6 hrs. The % blood flow inhibition is calculated as the % difference in the AUC of peak 1 (first 8 min heating and cooling interval) of the laser doppler recordings between the drug-treated and vehicle-treated paws. Data are the mean % inhibition values from 8-10 rats per group.

[0032] This data demonstrates that topical (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline can inhibit heat-induced cutaneous blood vessel dilation (or overall cutaneous blood flow) in rats, and the effect of one topical application (15 µl of a 0.1 % gel) lasts for at least 4 hours. There is an extended duration of at least 6 hrs following 4-day repeat dosing.

Example 2

***In vitro* human skin permeability assay**

[0033] Human, *ex vivo,* trunk skin was cut into multiple smaller sections large enough to fit on nominal 2 cm^2 static Franz diffusion cells. The dermal receptor compartment was filled to capacity with receptor solution consisting of 0.1 X phosphate buffered solution with 0.1% Oleth-20, and the epidermal chamber (chimney) is left open to ambient laboratory environment. The cells were placed in a diffusion apparatus in which the receptor solution in contact with the underside of the dermis was stirred magnetically at ~600 RPM and its temperature maintained to achieve a skin surface temperature of 32.0 ± 1.0 °C.

[0034] To assure the integrity of each skin section, its permeability to tritiated water was determined before application of the test products. Skin specimens in which absorption of ^3H_2O was less than 1.56 µL- equ/cm^2 were considered acceptable.

[0035] (*S*)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline was applied to three (3) replicate sections of the same donor skin for each donor, evaluating three (3) donors for the designated dose duration. A dose of 5 mg formulation/cm^2/skin section was evenly dispersed and rubbed into the skin surface using a glass rod.

[0036] At designated time points and at the end of the study dose duration, the receptor solution was removed in its entirety, and a predetermined volume aliquot saved for subsequent analysis. After the last receptor sample was collected, the donor compartment (chimney) was removed, and the surface of the skin was cleansed twice to collect any un-absorbed formulation from the skin surface. Following the surface cleanse, the skin was tape stripped to remove the stratum corneum. The tape strips were extracted overnight in acetonitrile and analyzed for content of the compound of interest. The skin was then removed from the diffusion cell, split into epidermis and dermis, and each skin sample extracted overnight in 50%:50% (v/v) ethanol/water or 50%:50% (v/v) methanol water for epidermis and dermis, respectively. The skin section samples were analyzed for content of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline. All samples were stored at ~ -20 °C (± 15 °C) pending analysis. Quantitation of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline was analyzed by liquid chromatography with tandem mass spectrometry (PLC/MS).

[0037] Replicates within donors were averaged and the standard deviation calculated for each key parameter. Within donor averages were then collated and the across donor population mean with standard error of the mean calculated.

[0038] **Figure 2** shows the rate of percutaneous absorption as the flux of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline that appears in the receptor solution under the skin after a 0.58% (w/w) dose.

[0039] **Figure 3** shows the distribution of (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline in each skin layer following a 48 hour dose exposure of a 0.58% (w/w) dose to ex vivo human trunk skin as a mass recovered.

[0040] The data indicate that (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline does penetrate into and through *ex vivo* human trunk skin using the *in vitro* Franz diffusion cell. The increased rate of flux at the 18 and 36 hr timepoints (Figure 2) and the higher concentration in the epidermis (Figure 3) suggests that the drug depots in the skin, which is consistent with a long duration of action and extended duration following repeated dosing.

Example 3

LL-37-Induced Skin Inflammation Mouse Model

Background

[0041] Rosacea skin is associated with increased levels of LL-37 cathelicidin compared to normal skin. Intradermal injection of LL-37 into mice induces skin inflammation that is similar to that seen in rosacea skin (Yamasaki 2007).

Method

[0042] (S)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline gel or its corresponding vehicle was applied to the dorsal surface of the ears of BALB/c mice. One hour following application, the left ear was intradermally injected with LL-37 peptide and the right ear was injected with phosphate-buffered saline (PBS). Ear thickness measurements were made with a digital caliper (Mitutoyo) at various timepoints up to 8 hrs post-injection with LL-37. Ear swelling is an indicator of inflammation.

[0043] **Figure 4** shows statistically significant inhibition of LL-37-induced skin inflammation at 6 and 9 hrs after topical treatment with (S)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline. The data are the mean values from 9-10 mice per group.

[0044] The data indicates that topical administration of (S)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline has an anti-inflammatory effect that is relevant to the treatment of rosacea.

Example 4

Ultraviolet B-Induced Mouse Sunburn Model

Background

[0045] Rosacea can be triggered by exposure to ultraviolet (UV) light. Exposure of hairless mice to UVB irradiation results in a sunburn-like response characterized by erythema, cutaneous blood vessel dilation, tactile hypersensitivity and inflammation that persists for at least 48 hrs.

Method

[0046] SKH1 hairless mice, lying on their stomachs with their left sides covered, were exposed to UVB at an intensity of 120 mJ/cm2 for 91 sec. Approximately 30 min after irradiation, (S)-(+)-7-(1 H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline gel or its corresponding vehicle was applied topically to a region of the back and the dorsal surface of the ears. At various timepoints up to 48 hrs post UVB-irradiation, the following assessments were made:

1. 1. Vasculature area in the exposed and unexposed ears by image analysis of digital photos using ImagePro Premier (Media Cybernetics) software. Images are converted to gray-scale, expanded and thresholding, based on each ear's baseline pixel values, is applied to the images. Thresholding differentiates the desired "object" features (i.e. vasculature network) from the background (i.e. skin tissue). The "object" pixels are then quantified and reported as the vasculature area.
2. 2. Erythema on the exposed and unexposed back using a Chromameter (Konica Minolta).
3. 3. Tactile hypersensitivity assessment using a paint brush test. The hypersensitivity is assessed by light stroking of the flank of the mice with a small paint brush every 5 min over 35 min. The behavioral response is scored as follows: 0, no response; 1, mild squeaking with attempts to move away from the brush; 2, vigorous squeaking evoked by the brush, biting at the brush and strong efforts to escape. The scores at the eight time points are summed so the maximum hypersensitivity score for each mouse can be 16. The exposed (right) and unexposed (left) flanks were scored independently.

[0047] **Figure 5** shows that topical dosing of (S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline to the back 30 min following UVB exposure results in a statistically significant reduction of erythema (measured with a chromameter) to nearly baseline levels that lasts for at least 48 hrs. Data are the mean of values from 6 mice per group.

[0048] **Figure 6** shows that topical dosing of (S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline to the ear 30 min following UVB exposure results in statistically significant cutaneous vasoconstriction (measured as a reduction of cutaneous vasculature area) to nearly baseline levels that lasts for at least 48 hrs. Data are the mean of values from 6 mice per group.

[0049] **Figure 7** shows that topical dosing of (S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline to the back 30 min following UVB exposure results in a statistically significant reduction of tactile hypersensitivity (scored by the response to stroking with a paint brush) assessed 4 hrs following UVB irradiation. There was a reduction in hypersensitivity on both the UV-exposed and control sides. Data are the mean of values from 6 mice per group.

[0050] The data indicate that topical administration of (S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline has a long-lasting beneficial effect on inflammation, erythema (redness) and hypersensitivity, which are signs and symptoms of many skin diseases and conditions. The findings have particular relevance to the treatment of sunburn, rosacea and psoriasis.

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. Farmaceutisk sammensætning til anvendelse i en fremgangsmåde til behandling af hudtilstande hos en patient, der lider deraf, hvor den farmaceutiske sammensætning omfatter en terapeutisk effektiv mængde af (*S*)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinolin, eller de individuelle tautomerer deraf, eller et farmaceutisk acceptabelt salt deraf.

2. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor den behandlede tilstand er valgt fra: rosacea, rosacea fulminans, solskoldning, psoriasis, menopause-associerede hedeture, rødmen og rødhed associeret med hedeture, erytem associeret med hedeture, hedeture som resultat af orchiektomyatopisk dermatitis, behandling af rødhed og kløe fra insektbid, fotoaldring, seboroisk dermatitis, akne, allergisk dermatitis, ansigtstelangiektasi (udvidelser af allerede eksisterende små blodkar), angioektasi, rhinophyma (hypertrofi af næsen med follikulær udvidelse), akne-lignende hududslæt (kan sive ud eller danne skorpe), brændende eller sviende fornemmelse, huderytem, kutan hyperaktivitet med udvidelse af blodkar i huden, Lyells syndrom, Stevens-Johnson syndrom, lokal kløe og ubehag associeret med hæmorroider, hæmorroider, erytem multiform minor, erytem multiform major, erytem nodosum, hævede øjne, urticaria, pruritis, purpura, åreknuder, kontaktdermatitis, atopisk dermatitis, nummulat dermatitis, generaliseret exfoliativ dermatitis, stasedermatitis, lichen simplex chronicus, perioral dermatitis, pseudofolliculitis barbae, granuloma annulare, aktinisk keratose, basal celle karcinom, pladeepithelkarcinomer, og eksem.

3. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor tilstanden er rosacea.

4. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor tilstanden er psoriasis.

5. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor tilstanden er rosacea fulminans.

6. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor tilstanden er ansigtstelangiektasi.

7. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor tilstanden er huderytem.

8. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor tilstanden er solskoldning.

9. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor tilstanden er kutan hyperaktivitet med udvidelse af blodkar i huden.

10. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor den farmaceutiske sammensætning er i en formulering egnet til topikal dermatologisk administration.

11. Den farmaceutiske sammensætning til anvendelse i en fremgangsmåde ifølge krav 1, hvor den farmaceutiske sammensætning administreres som en form valgt fra suspensioner, geler, opløsninger, cremer, lotions, salver, skum, emulsioner, mikroemulsioner, mælk, serummer, aerosoler, sprays, dispersioner, mikrokapsler, vesikler, mikropartikler, våde klude, tørre klude, ansigtsklude eller direkte injektion.

DRAWINGS

Figure 1

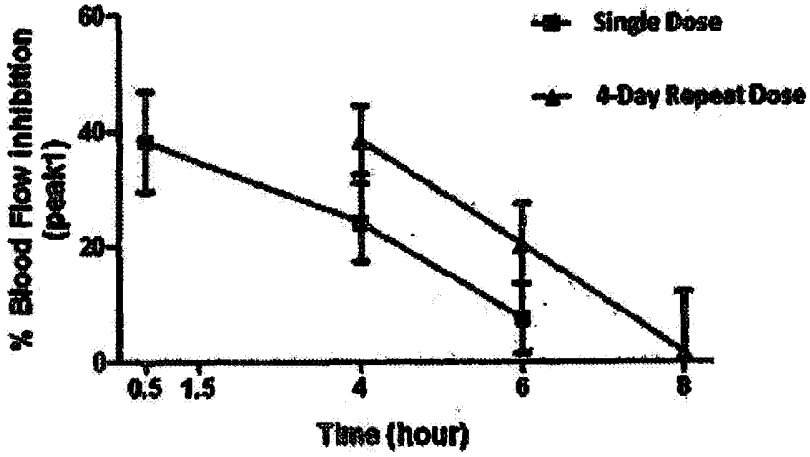


FIGURE 2

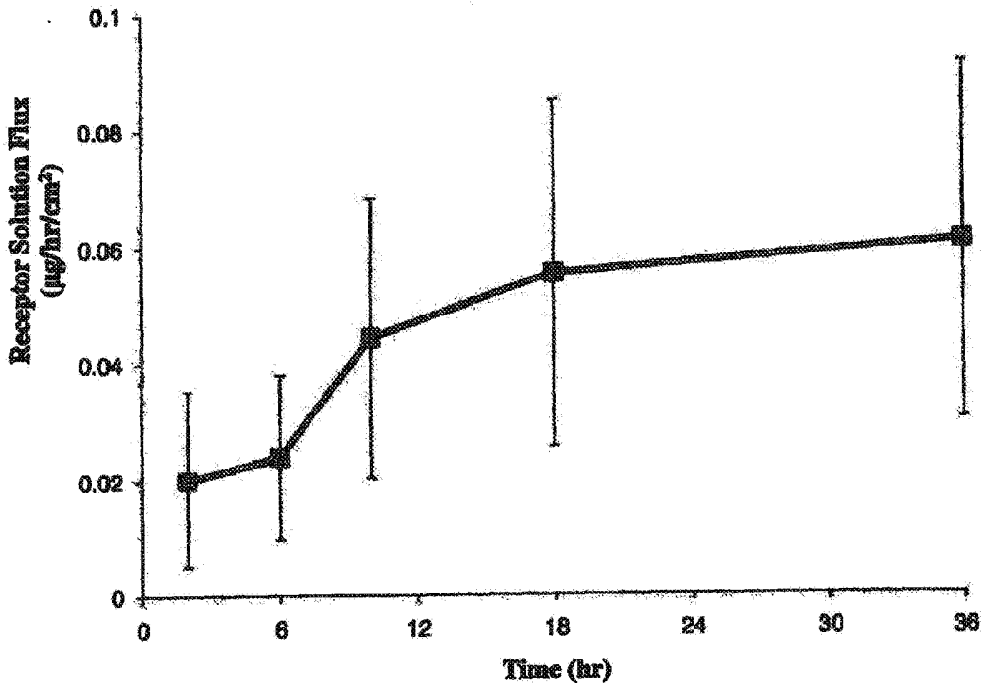

Receptor Solution Flux
(µg/hr/cm²)
0.1
0.08
0.06
0.04
0.02
0
0
6
12
18
24
30
36
Time (hr)

FIGURE 3

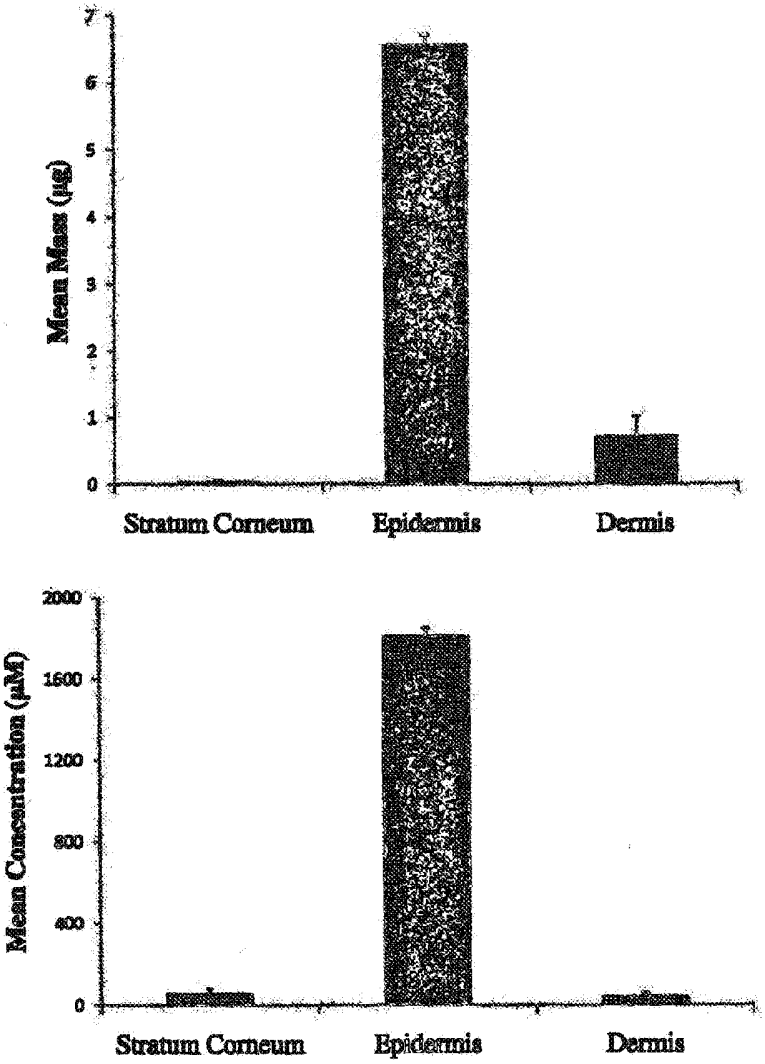

Mean Mass (µg)
0
1
2
3
4
5
6
7
Stratum Corneum
Epidermis
Dermis
Mean Concentration (µM)
0
400
800
1200
1600
2000
Stratum Corneum
Epidermis
Dermis

FIGURE 4

Inhibition of LL-37-induced skin inflammation after topical treatment with (S)-(+)-7-(1H-Imidazol-4-yimethyl)-5,6,7,8-tetrahydro-quinoline

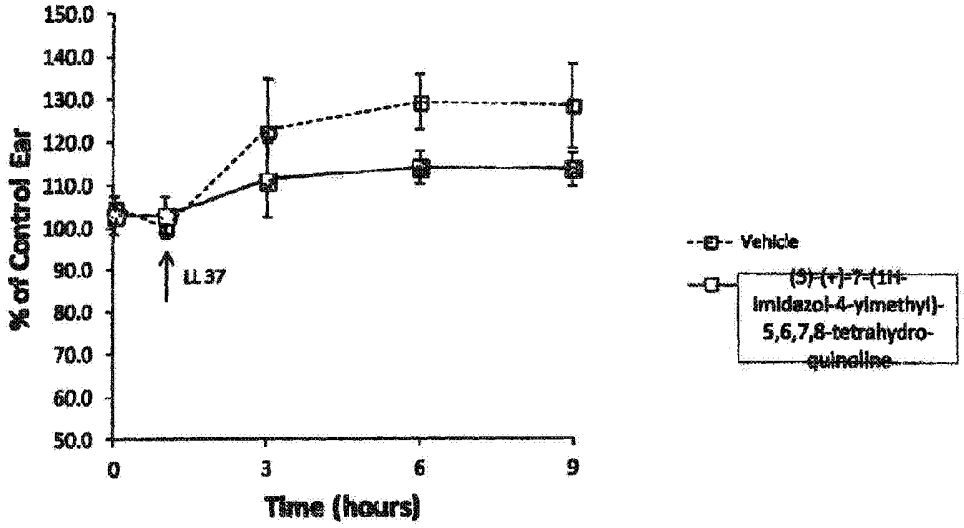
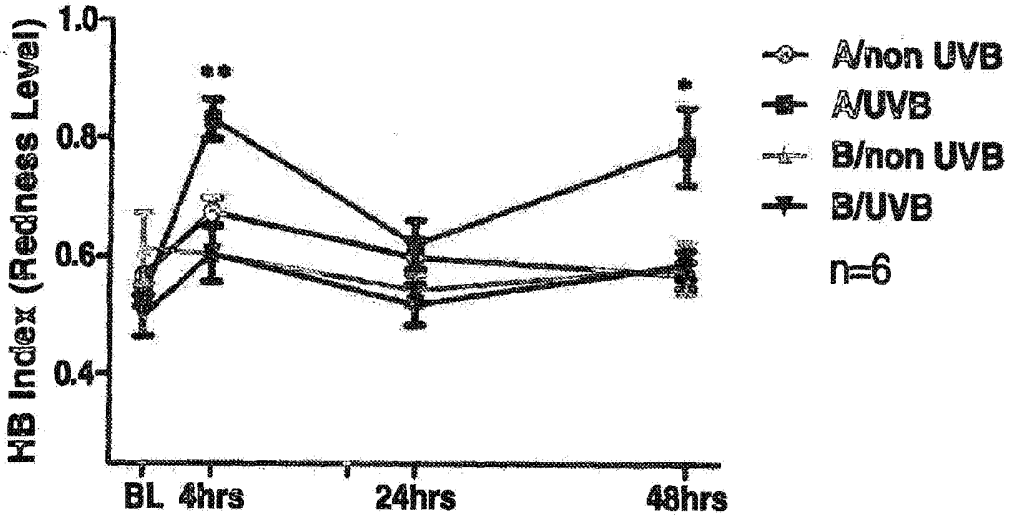


FIGURE 5



A = Vehicle

B = (S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline

$^{*}p< 0.05$, $^{**}p<0.01$ vs treated

FIGURE 6

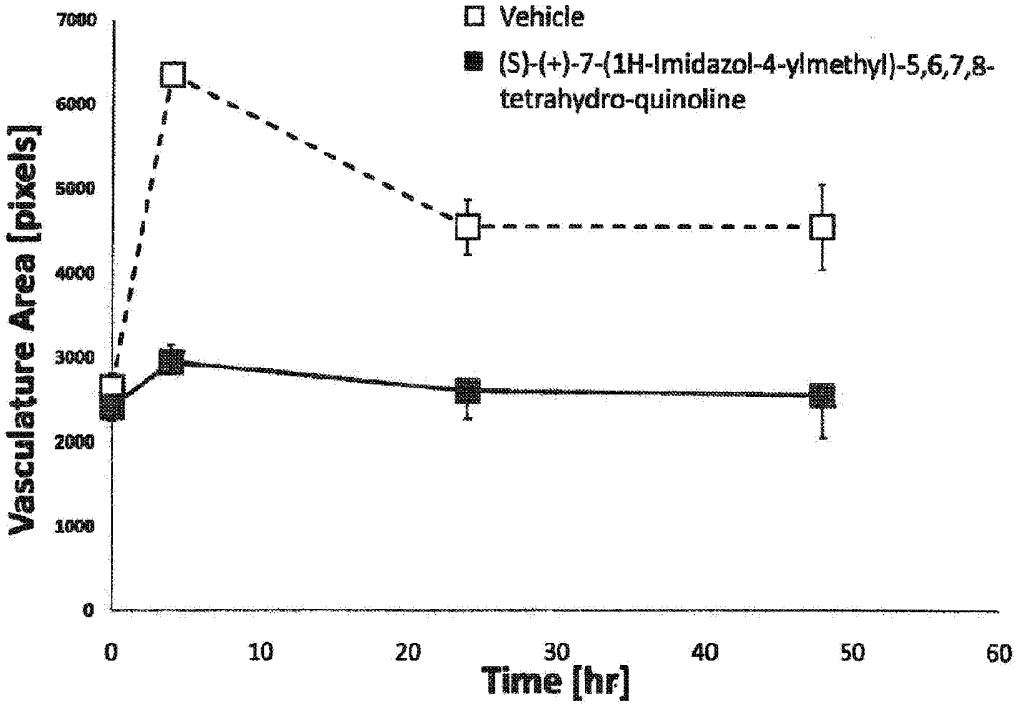
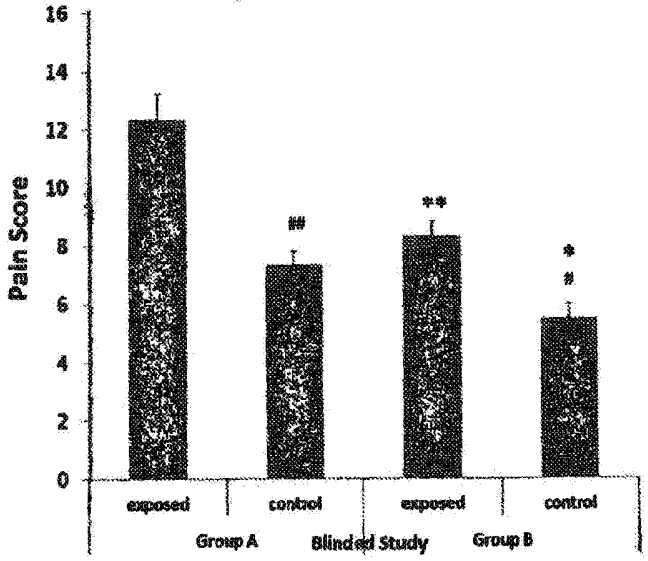

Vehicle
(S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline
Vasculature Area [pixels]
7000
6000
5000
4000
3000
2000
1000
0
0
10
20
30
40
50
60
Time [hr]

FIGURE 7



Group A = Vehicle

Group B = (S)-(+)-7-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydro-quinoline

 # p< 0.05, ## p<0.01 vs Exposed Control

** p< 0.05, ** p<0.01 vs Group A*