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(54) Title: COSMETIC COMPOSITIONS CONTAINING SUBSTITUTED AZOLE AND METHODS FOR IMPROVING THE APPEARANCE OF AGING SKIN

(57) Abstract: Methods of improving the appearance of aging skin that include applying a cosmetic composition to a target skin surface having one or more signs of aging. The cosmetic composition includes a substituted azole. In some instances, the substituted azole compound is 1-phenylimidazole, 4-phenylimidazole, or combinations thereof. An effective amount of the cosmetic composition is applied for a period of time sufficient to improve the appearance of at least one sign of aging skin.

COSMETIC COMPOSITIONS CONTAINING SUBSTITUTED AZOLE AND METHODS FOR IMPROVING THE APPEARANCE OF AGING SKIN

FIELD OF THE INVENTION

Cosmetic compositions and methods for improving the appearance of aging skin using substituted azole compounds, particularly 1-phenylimidazole, 4-phenylimidazole, or combinations thereof.

BACKGROUND OF THE INVENTION

The epidermis, the outermost layer of the skin, comprises a cellular continuum of four layers: the stratum corneum, the granular layer, the spinous layer, and the basal layer. Each cellular layer in the epidermis represents various stages along a process in which basal epidermal keratinocytes undergo a continuous cycle of proliferation, differentiation, and apoptosis, moving upward from the basal layer to finally yield corneocytes. These corneocytes form the cornified layer known as the stratum corneum.

Basal keratinocytes reside at the lower portion of the epidermis. These mitotically active cells undergo a proliferative cycle to generate daughter cells that are physically dislocated upward into the spinous and granular layers and undergo the process of differentiation into corneocytes. On passing through the spinous and granular layers, the cells undergo morphological changes that render them flatter in structure as they lose their cellular viability, undergo alternate keratin expression profiles, and transform into cellular remnants. On average, a younger-aged epidermis turns over in about one month, shedding the older cells and replacing them with newer ones, but this process can increase to over forty days in older skin.

The stratum corneum's corneocytes remain connected to one other via proteins and lipids, creating a protective barrier between the organism and its outside environment. This tightly regulated epidermal permeability barrier functions as a physical and selective barrier against chemical and biological insults. Important functions of this barrier include attenuation of the penetration of free radicals and prevention of penetration of harmful radiation, including UV radiation, into deeper layers. The stratum corneum also acts as a permeability barrier and functions to prevent loss of body moisture to the outside environment. Dysfunction of this barrier can lead to chronic skin conditions, diseases, and in extreme cases can even threaten the viability of the organism.

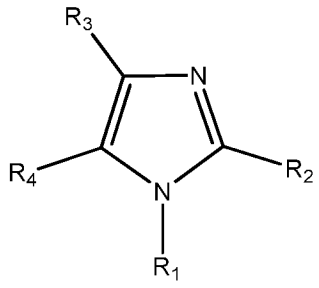
Skin aging is a multifactorial process driven by both intrinsic (chronological aging) and extrinsic (environmental) factors, including ultraviolet (UV) exposure, environmental toxins,

pollutants, and smoking. It is well known in the art that the ability of the stratum corneum to cyclically generate new layers of skin diminishes with age so that the stratum corneum turnover rate is substantially reduced in aged skin, with the cornified layer becoming gradually thinner. This results in a reduction in the functioning capacity of the barrier so that harmful stimuli penetrate the stratum corneum more easily, leading to UV-damage, for example, of the underlying dermal layers, degradation of collagen and elastin, and eventually manifests in appearance as wrinkling and skin atrophy. Thinning of the stratum corneum by the sum of intrinsic and extrinsic aging factors increases the visible appearance of fine lines and wrinkles. Further, the barrier suffers from an age-related increase in permeability to free radicals and a reduction in the amount of lipid in the intercellular matrix, decreasing barrier capacity to diffuse toxins from deeper layers. Recovery capacity of the barrier to environmental insult is also substantially reduced with age.

Thus, the skin's epidermal barrier function is key to the skin's ability to regenerate and protect itself from the appearance of aging signs such as fine lines and wrinkles. Accordingly, it would be desirable to provide compositions and methods of treatment that can improve the skin's epidermal functioning and thus also improve the appearance of aging skin.

SUMMARY OF THE INVENTION

The present invention provides a method of improving the appearance of aging skin comprising: (a) identifying an aging skin surface; and (b) applying to the skin surface a composition comprising an effective amount of a substituted azole compound represented by the structure:



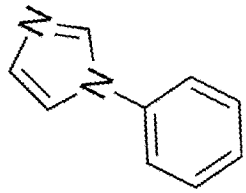
where:

R1: is an alkyl or phenyl electron donating group

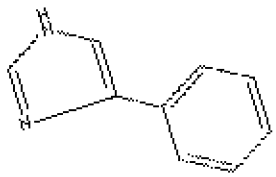
R2: is hydrogen

R3 and R4 (which may be identical or different): do not form a fused ring, and each is independently selected from the monodentate group consisting of H, alkyl, and phenyl.

The substituted azole compound can be one or a combination of more than one substituted azole compound. In some embodiments, the substituted azole compound is 1-phenylimidazole:



In other embodiments, the substsituted azole compound is 4-phenylimidazole:



In some compositions, the substituted azole compound is a combination of 1-phenylimidazole and 4-phenylimidazole.

The composition comprises an effective amount of the substituted azole compound. In some embodiments, the composition comprises up to 20%, 10%, 5%, 3%, or 1%, and alternatively at least 0.001%, 0.01%, 0.1%. 0.2%, or 0.5%, by weight of the total composition, of the substituted azole compound. Suitable ranges can include any combination of the lower and upper limits, for example from 0.001% to 20%; from 0.001% to 1%; or from 0.5% to 10%, by weight of the composition, of the substituted azole compound. The amounts listed herein are only to be used as a guide, as the optimum amount will depend on the specific substituted azole compound selected, since their potency does vary considerably.

The composition also comprises a dermatologically acceptable carrier. The composition can also include optional ingredients as desired, such as a sunscreen active, an anti-inflammatory agent, and/or a skin tone agent. Exemplary skin tone agents can include vitamin B3 compounds, sugar amines, hexamidine compounds, salicylic acid, and/or 1,3-dihydroxy-4-alkylbenzene.

Alternatively, optional ingredients can be delivered in a second composition that is applied contemporaneously as part of a regimen. In such embodiments, a first composition comprises the substituted azole compound and a second composition comprises desired optional ingredients.

The composition is applied for a period of time sufficient to improve the appearance of one or more signs of aging skin. In particular embodiments, the composition is applied to a facial skin surface, which may include the forehead, perioral, chin, periorbital, nose, and/or cheek.

The present invention may take other forms. Further forms of the present invention will be appreciated in the detailed description that follows.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of improving the appearance of aging skin. As used herein, "improving the appearance of aging skin" is broad enough to include not only minimizing and/or preventing and/or delaying at least one sign of aging skin, but also treating aging skin to effect visually and/or tactilely perceptible positive change (i.e., benefit) in appearance and/or feel of at least one sign of aging skin.

"Signs of aging skin" include, but are not limited to, all outwardly visible and/or tactilely perceptible manifestations due to skin aging. These signs may result from processes which include, but are not limited to, the development of textural discontinuities such as wrinkles and coarse deep lines, fine lines, crevices, bumps, large pores, unevenness or roughness; loss of skin elasticity (e.g., due to loss, damage and/or inactivation of functional skin elastin, resulting in such conditions as elastosis, sagging, and/or loss of skin recoil from deformation); thinning of keratinous tissue (e.g., the epidermis and/or dermis and/or sub-dermal layers of the skin); hyperpigmentation (e.g., age spots); decreasing the convolution of the dermal-epidermal border (also known as the rete ridges); skin discoloration (e.g., blotchiness, sallowness); abnormal differentiation; hyperkeratinization; collagen breakdown, and other histological changes in the stratum corneum, dermis, and epidermis.

The method of the present invention comprises: (a) identifying an aging skin surface; and (b) applying to the skin surface a composition comprising an effective amount of a substituted azole compound for a period of time sufficient to improve the appearance of one or more signs of aging skin. Unless otherwise indicated expressly or by context, the term "substituted azole" refers to one or more substituted azole compounds represented by the structure set forth herein. "Aging skin surface" means a skin surface having one or more signs of aging skin. "Applying" means to apply or spread the composition onto a human skin surface (i.e., epidermis).

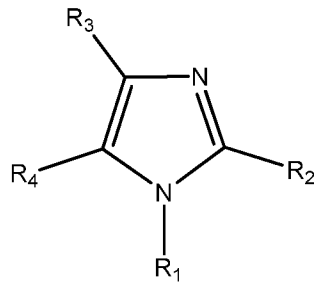
An "effective amount" of a substituted azole compound or of a composition containing such substituted azole compound means an amount of such compound or composition sufficient

to significantly (i.e., statistically significant) improve the appearance of one or more signs of aging skin. The particular amount that is effective depends on the specific substituted azole compound selected, since the potency of these compounds does vary.

In some embodiments, the composition comprises up to 20%, 10%, 5%, 3%, or 1%, and alternatively at least 0.001%, 0.01%, 0.1%. 0.2%, or 0.5%, by weight of the total composition, of the substituted azole compound. Suitable ranges can include any combination of the lower and upper limits, for example from 0.001% to 20%; from 0.001% to 1%; or from 0.5% to 10%, by weight of the composition, of the substituted azole compound. These exemplary amounts are only to be used as a guide, as the optimum amount will depend on the potency of the specific substituted azole compound. Hence, the amount of some compounds useful in the present invention may be outside the ranges set forth herein. Determining the effective amount for the chosen substituted azole compound is within the knowledge of one skilled in the art.

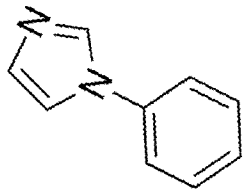
The composition further comprises a dermatologically acceptable carrier. The term "dermatologically acceptable" as used herein means that the compositions or components described are suitable for use in contact with human skin tissue without undue toxicity, incompatibility, instability, allergic response, and the like.

The substituted azole compound of the present invention is represented by the structure:

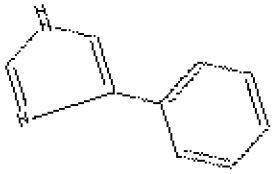


where: R1 is an alkyl or phenyl electron donating group; R2 is hydrogen; R3 and R4 (which may be identical or different) do not form a fused ring and each is independently selected from the monodentate group consisting of H, alkyl, and phenyl. The N-substituted azole compound can be one or a combination of more than one substituted azole compound.

In some embodiments, the substituted azole compound is 1-phenylimidazole:



In other embodiments, the substsituted azole compound is 4-phenylimidazole:



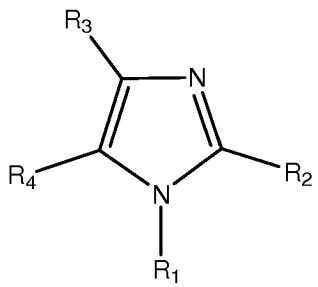
In some compositions, the substituted azole compound is a combination of 1-phenylimidazole and 4-phenylimidazole.

I. Compositions

The present invention relates to various compositions and, more specifically, to compositions for application to a skin surface. The compositions may be in a wide variety of product forms that include, but are not limited to, solutions, suspensions, lotions, creams, gels, toners, sticks, pencil, sprays, aerosols, ointments, cleansing liquid washes and solid bars, shampoos and hair conditioners, pastes, foams, powders, mousses, shaving creams, wipes, strips, patches, electrically-powered patches, wound dressing and adhesive bandages, hydrogels, film-forming products, facial and skin masks (with and without insoluble sheet), make-up such as foundations, eye liners, and eye shadows, and the like. The composition form may follow from the particular dermatologically acceptable carrier chosen, if present in the composition.

A. Substituted Azole Compound

Compositions of the present invention comprise an effective amount of a substituted azole compound represented by the structure:



where: R1 is an alkyl or phenyl electron donating group; R2 is hydrogen; R3, and R4 (which may be identical or different) do not form a fused ring and each is independently selected from the monodentate group consisting of H, alkyl, and phenyl.

Electron donating groups have a lone pair of electrons on the atom directly bonded to the ring. The electron donating group increases the aromatic ring's electron density through a resonance donation effect. This is a very stable resonance form, as the resulting carbocation is stabilized by the electron donating group. More stable intermediates (the carbocation) have lower transition state energies and thus a faster reaction rate, resulting in substituents being preferentially directed to positions where they are in conjugation with the aromatic ring. Electron donating groups on an aromatic ring are said to be "activating", because they increase the rate of the second substitution so that it is higher than that of the standard aromatic molecule.

Applicant has surprisingly discovered that this class of substituted azole compounds can alleviate the signs of aging when applied topically. Not to be limited by theory, it is believed that the effectiveness of these particular substituted azole compounds is due to their ability to inhibit cytochrome P450 ("CYP") enzyme activity, and thus function as retinoic acid metabolism blocking agents ("RAMBA"s).

1. Mechanism of Action

Researchers have long appreciated that vitamin A is a critical regulator of growth and differentiation of developing and adult mammalian skin. Vitamin A deficiency causes disruption of normal cellular homeostatic mechanisms, resulting in impairment of skin barrier function. *All-trans*-retinoic acid ("ATRA"), the biologically most active metabolite of vitamin A, plays a major role in cellular differentiation and proliferation of epithelial tissue.

The main source of retinoic acid ("RA") in humans, excluding therapeutic dosing, is through synthesis from dietary precursors such as beta-carotene and retinyl palmitate. Vitamin A is stored primarily in liver stellate cells as retinyl esters, which are hydrolyzed in hepatocytes by retinyl ester hydrolases to retinol. Retinol, the precursor of RA, is the main circulating retinoid and is obtained from retinol through a two-step synthesis in which the conversion of retinol to retinal is the rate limiting step. Retinol is oxidized intracellularly by retinol dehydrogenases to retinal, and retinal is then metabolized by NAD/NADP-dependent retinal dehydrogenases to RA.

While RA is synthesized endogenously in the body from dietary precursors, it may also be administered exogenously, such as via topical retinoid application. Research has shown that ATRA has the ability to not only prevent but also to repair skin cell damage. With aging, the skin's endogenous ATRA levels are depleted, leading to impaired functioning of the epidermal

barrier. Thus, maintaining elevated levels of ATRA is critical in order to maintain barrier function integrity and thus prevent and/or improve the appearance of aging skin.

Unfortunately, therapeutic administration of exogenous (e.g., topical) retinoids has challenges. Although they can be very effective, retinoids are not well tolerated by many people. Common side effects associated with topically applied retinoids include burning and stinging of the skin, peeling, redness, and heightened photosensitivity. Furthermore, the therapeutic effect decreases over time, necessitating the use of increasingly higher retinoid levels to maintain the same level of benefit. Retinoid side effects are largely dose-dependent. As a result, many individuals with sensitivity to retinoids cannot tolerate levels sufficient to provide the desired positive results. Additionally, retinoids are rapidly metabolized by the body, resulting in the need for higher doses than would otherwise be required to achieve the desired therapeutic effects.

An approach to overcoming the drawbacks associated with exogenous retinoid therapy and/or the rapid elimination of ATRA is to amplify endogenous levels of ATRA by inhibiting the CYP-mediated catabolism of RA using agents known as retinoic acid metabolism blocking agents (RAMBAs). RAMBAs prevent the in vivo catabolism of ATRA by inhibiting the CYP-mediated catabolism enzymes responsible for ATRA elimination. Inhibiting the CYP enzymes blocks their metabolism and prolongs RA residence time at the site of action, thus increasing the level of endogenous ATRA within the cells. This results in higher in vivo ATRA concentrations, thus reducing and/or preferably eliminating the need to apply topical exogenous retinoids to achieve the desired effect.

2. In vitro Cytochrome P450 Inhibition Assay

Cytochrome P450 is a large and diverse group of enzymes that catalyze the oxidation of organic substances. Some members of the CYP family contribute to the elimination of ATRA by catalyzing its 4-hydroxylation in the mammalian liver and skin, including that of humans as well as swine. Applicant evaluated the potential RAMBA activity of several azoles using pig liver microsomes, a rich source of CYP activity, comprising many different CYP 450 isoforms. Therefore, this approach, while a reasonable way to assess CYP inhibitors with broad activities may or may not be the best way to discover RAMBAs with selectivity for the skin, which has a much more narrow complement of CYP expression. As understanding in this area has progressed, a more specific CYP inhibition assay can be used to provide better predictivity of activity in human skin. Nevertheless, this assay may still be used as a general predictor of overall CYP activity.

As shown in Example 2, several compounds were screened through an in vitro CYP assay using pig liver microsomes to determine their effectiveness as CYP inhibitors and correspondingly potential RAMBAs. It is clear from the data in Table 2 that with the exception of the positive control, ketoconazole, none of the tested materials yielded IC_{50} values at concentrations less than 10 μM. This is likely due to the diversity of CYPs in the microsomal sample, which could dilute the inhibitory activity of CYPs most relevant for ATRA metabolism in the skin.

The metabolism of retinoic acid and vitamin D in the skin is incompletely understood, but there is evidence for the involvement of CYP26A1, CYP3A4 and CYP2C8 in catalyzing the 4-hydroxylation of *all-trans* RA to 4-hydroxy-RA. It is believed, without being limited by theory, that CYP3A4 may be particularly important for ATRA metabolism in the skin. This is because CYP3A4 is expressed in skin, involved in RA metabolism, a CYP with one of the broadest substrate specificities of all of the known CYPs and available as a human recombinant protein in a commercial kit. Thus, a commercially available CYP3A4 assay was used as a surrogate to predict RAMBA potential in the skin. The method is described in more detail below in Example 3, and the results are illustrated in Table 3. As illustrated in Table 3, the IC_{50} values of several compounds indicate strong inhibition of CYP3A4 when the IC_{50} value is $\leq$ 10μM and weak or no inhibition when the IC_{50} value is > 10μM.

Several simple imidazole structures showed a remarkably high level of inhibitory activity relative to the positive control, ketoconazole. Of particular note are the results for 1-, 2-, and 4-phenylimidazole. These materials are positional isomers, differing from one another only in the location of the phenyl group relative to the imidazole ring. The 1- and 4-phenylimidazole had IC_{50} values in the same range as climbazole, a known 4-hydroxylase inhibitor that is marketed as an antifungal active. However, the 2-phenyimidazole analogue lacked any significant inhibitory activity, indicating that positioning of the imidazole ring relative to the phenyl group seems to play an important structural component for CYP enzyme interaction. Thus, 1- and 4-phenylimidazole elicit CYP inhibitory activity, while 2-phenylimidazole does not. Accordingly, 1- and 4- can serve as effective RAMBAs, boosting the endogenous ATRA concentration. These results demonstrate that substituted azole compounds having the particular structure set forth herein function differently from other compounds, even when those compounds are positional isomers. (The chemical structures of the materials tested in Example 2 can be found in Table 3 of Example 3. For brevity, the structures are not duplicated by inclusion in both tables.)

3. In vitro CYP / CYP3A4 Inhibition Assay

The commercially available P450-GLO™ Assay kit (Promega Corporation, Madison WI) was used to screen various compounds for potential CYP activity, specifically CYP3A4A inhibition activity. CYP3A4A is thought to be among the primary CYP isoforms responsible for retinoic acid metabolism in the skin.

Three benchmark agents, liarozole, climbazole, and ketoconazole, were assessed for CYP3A4 inhibition to confirm that the inhibition activity (the IC_{50} for CYP inhibition) measured by the assay corresponded to the activity reported by the published literature.

The results set forth in Table 3 show that the substituted azole compounds having the specific structure set forth herein are CYP inhibitors, and thus function as RAMBAs. Of particular note, once again, are the results for the positional isomers 1-, 2-, and 4-phenylimidazole. Consistent with the results from Example 2's CYP in vitro assay, the R1 substituted 1-phenylimidazole and the R3 substituted 4-phenylimidazole showed inhibitory activity in the CYP3A4 assay, but the R2 substituted 2-phenylimidazole analogue did not. This underscores the importance of the substituted azole structure to the CYP enzyme interaction.

As used in Table 3, "hit" or "no hit" mean, respectively, strong inhibition (IC_{50} value < 10μM) or weak/ no inhibition (IC_{50} value > 10μM) of CYP3A4.

B. Dermatologically Acceptable Carrier

The compositions of the present invention may also comprise a dermatologically acceptable carrier (which may be referred to as "carrier") for the composition. The phrase "dermatologically acceptable carrier", as used herein, means that the carrier is suitable for topical application to the skin surface, has good aesthetic properties, is compatible with the actives in the composition, and will not cause any unreasonable safety or toxicity concerns. In one embodiment, the carrier is present at a level of from 50% to 99%, or from 60% to 98%, or from 70% to 98%, or, alternatively, from 80% to 95%, by weight of the composition.

The carrier can be in a wide variety of forms. Non-limiting examples include simple solutions (*e.g.*, aqueous, organic solvent, or oil based), emulsions, and solid forms (*e.g.*, gels, sticks, flowable solids, or amorphous materials). In certain embodiments, the dermatologically acceptable carrier is in the form of an emulsion. Emulsion may be generally classified as having a continuous aqueous phase (*e.g.*, oil-in-water and water-in-oil-in-water) or a continuous oil phase (*e.g.*, water-in-oil and oil-in-water-in-oil). The oil phase of the present invention may comprise silicone oils, non-silicone oils such as hydrocarbon oils, esters, ethers, and the like, and mixtures thereof.

The aqueous phase typically comprises water. However, in other embodiments, the aqueous phase may comprise components other than water, including but not limited to water-soluble moisturizing agents, conditioning agents, anti-microbials, humectants and/or other water-soluble skin care actives. In one embodiment, the non-water component of the composition comprises a humectant such as glycerin and/or other polyols. However, it should be recognized that the composition may be substantially (*i.e.*, less than 1% water) or fully anhydrous.

A suitable carrier is selected to yield a desired product form. Furthermore, the solubility or dispersibility of the components (*e.g.*, extracts, sunscreen active, additional components) may dictate the form and character of the carrier. In one embodiment, an oil-in-water or water-in-oil emulsion is preferred.

Emulsions may further comprise an emulsifier. The composition may comprise any suitable percentage of emulsifier to sufficiently emulsify the carrier. Suitable weight ranges include from 0.1% to 10%, or 0.2% to 5% of an emulsifier, based on the weight of the composition. Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Patent 3,755,560, U.S. Patent 4,421,769, and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324 (1986). Suitable emulsions may have a wide range of viscosities, depending on the desired product form.

The carrier may further comprise a thickening agent as are well known in the art to provide compositions having a suitable viscosity and rheological character.

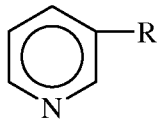
C. Skin Tone Agent

In some embodiments, it may be desirable to include a skin tone agent in the composition. The skin tone agents can be included to further improve overall skin tone. When present, the compositions of the present invention can contain up to 50%, 40%, 30%, 20%, 10%, 5%, or 3%, by weight of the composition, of the skin tone agent. When present, the compositions of the present invention can contain at least 0.001%, 0.01%, 0.1%, 0.2%, 0.5%, or 1%, by weight of the composition, of the skin tone agent. Suitable ranges include any combination of the lower and upper limits including suitable ranges from 0.1% to 50%; from 0.2% to 20%; or from 1% to 10%, by weight of the composition, of the skin tone agent. The amounts listed herein are only to be used as a guide, as the optimum amount of the skin tone agent will depend on the specific active selected since their potency does vary considerably.

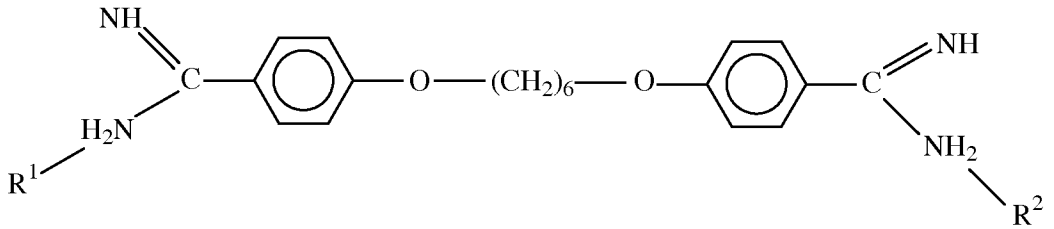
Suitable skin tone agents include, but are not limited to, sugar amines, vitamin B3 compounds, arbutin, deoxyarbutin, 1,3-dihydroxy-4-alkylbenzene such as hexylresorcinol, sucrose dilaurante, bakuchoil (4-[(1E, 3S)-3-ethenyl-3,7-dimethyl – 1,6 octadienyl] phenol or

monterpene phenol), pyrenoine (available from Biotech Marine, France), panicum miliaceum seed extract, arlatone dioic acid, cinnamic acid, ferulic acid, achromaxyl, methyl nicotinamide, oil soluble licorice extract, folic acid, undecylenic acid (i.e., undecenoic acid), zinc undecylenate, thiamine (Vitamin B1) and its hydrochloride, L-tryptophan, helianthus annuus (sunflower) and vitis vinifera (grape) leaf extract, carnosine (i.e., dragosine), methyl gentisate, 1,2-hexandiol and 1,2-octandiol (i.e., combination sold as Symdiol 68 by Symrise AG, Germany), inositol, decylenoylphenylalanine (e.g., sold under the tradename Sepiwhite by Seppic, France), kojic acid, hexamidine compounds, and salicylic acid.

In certain embodiments, the skin tone agent is selected from vitamin B3 compounds, sugar amines, hexamidine compounds, salicylic acid, and a 1,3-dihydroxy-4-alkylbenzene such as hexylresorcinol. As used herein, "vitamin B_3 compound" means a compound having the formula:



wherein R is - $CONH_2$ (*i.e.*, niacinamide), - COOH (*i.e.*, nicotinic acid) or - CH_2OH (*i.e.*, nicotinyl alcohol); derivatives thereof; and salts of any of the foregoing. As used herein, "sugar amine" includes isomers and tautomers of such and its salts (*e.g.*, HCl salt) and its derivatives. Examples of sugar amines include glucosamine, N-acetyl glucosamine, mannosamine, N-acetyl mannosamine, galactosamine, N-acetyl galactosamine, their isomers (*e.g.*, stereoisomers), and their salts (*e.g.*, HCl salt). As used herein, "hexaminide compound" means a compound having the formula:



wherein R^1 and R^2 are optional or are organic acids (*e.g.*, sulfonic acids, etc.). In one embodiment, the hexamidine compound is hexamidine diisethionate.

Furthermore, the skin tone agent of the present invention can include a xanthine compound. As used herein, "xanthine compound" means one or more xanthines, derivatives therof, and mixtures thereof. Xanthine compounds that can be useful herein include, but are not limited to, caffeine, xanthine, 1-methyl xanthine, theophylline, theobromine, derivatives thereof,

and mixtures thereof. In one embodiment, the composition comprises from about 0.1% to about 10% of a xanthine compound, in another embodiment from about 0.5% to about 5% of a xanthine compound, and in yet another embodiment from about 1% to about 2% of a xanthine compound.

D. Anti-Inflammatory Agents

Hyperpigmentation may result from skin inflammation. Transient inflammatory events triggering hyperpigmentation and, more specifically, post-inflammatory hyperpigmentation include, but are not limited to, acne lesions, ingrown hairs, scratches, insect bites, surfactant damage, allergens, and short-term UV exposure. Inflammation induced hyperpigmentation including post-inflammatory hyperpigmentation may be managed by incorporating into the compositions of the present invention an anti-inflammatory agent. When present, the compositions of the present invention can contain up to 20%, 10%, 5%, 3%, or 1% by weight of the composition, of the anti-inflammatory agent. When present, the compositions of the present invention can contain at least 0.001%, 0.01%, 0.1%, 0.2%, 0.3%, 0.5%, or 1%, by weight of the composition, of the anti-inflammatory agent. Suitable ranges include any combination of the lower and upper limits. Exact amounts will vary depending upon the chosen anti-inflammatory agent; determining the appropriate amount is within the knowledge of one of skilled in the art.

Suitable anti-inflammatory agents include, but are not limited to nonsteroidal anti-inflammatory agents ("NSAIDS" including but not limited to ibuprofen, naproxen, flufenamic acid, etofenamate, aspirin, mefenamic acid, meclofenamic acid, piroxicam and felbinac), glycyrrhizic acid (also known as glycyrrhizin, glycyrrhixinic acid, and glycyrrhetinic acid glycoside) and salts such as dipotassium glycyrrhizate, glycyrrhetenic acid, licorice extracts, bisabolol (*e.g.*, alpha bisabolol), manjistha (extracted from plants in the genus *Rubia*, particularly *Rubia cordifolia*), and guggal (extracted from plants in the genus *Commiphora*, particularly *Commiphora mukul*), kola extract, chamomile, and sea whip extract (extracts from plant in the order *Gorgonacea*), derivatives of any of the foregoing, and mixtures thereof.

E. Sunscreen Actives

The compositions of the subject invention may comprise one or more sunscreen actives (or sunscreen agents) and/or ultraviolet light absorbers. As used herein, "sunscreen active" collectively includes sunscreen actives, sunscreen agents, and/or ultraviolet light absorbers. Sunscreen actives include both sunscreen agents and physical sunblocks. Sunscreen actives may be organic or inorganic. Examples of suitable sunscreen actives are disclosed in Personal Care

Product Council's *International Cosmetic Ingredient Dictionary and Handbook*, Thirteenth Edition, as "sunscreen agents."

Suitable sunscreen actives include 2-ethylhexyl-p-methoxycinnamate (commercially available as PARSOL™ MCX), 4,4′-t-butyl methoxydibenzoyl-methane (commercially available as PARSOL™ 1789), 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid, digalloyltrioleate, 2,2-dihydroxy-4-methoxybenzophenone, ethyl-4-(bis(hydroxypropyl))aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, 2-ethylhexyl-salicylate, glyceryl-p-aminobenzoate, 3,3,5-tri-methylcyclohexylsalicylate, menthyl anthranilate, p-dimethyl-aminobenzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethyl-amino-benzoate, 2-phenylbenzimidazole-5-sulfonic acid, 2-(p-dimethylaminophenyl)-5-sulfonicbenzoxazoic acid, octocrylene, zinc oxide, benzylidene camphor and derivatives thereof, titanium dioxide, and mixtures thereof.

When present, the compositions of the present invention can contain up to 20%, 10%, 5%, 3%, or 1% by weight of the composition, of the sunscreen active. When present, the compositions of the present invention can contain at least 0.001%, 0.01%, 0.1%, 0.2%, 0.3%, 0.5%, or 1%, by weight of the composition, of the sunscreen active. Suitable ranges include any combination of the lower and upper limits. Exact amounts will vary depending upon the chosen sunscreen active and the desired Sun Protection Factor (SPF), which is within the knowledge of one of skilled in the art.

F. Other Optional Components

The compositions of the present invention may optionally contain a variety of other ingredients provided that they do not unacceptably alter the benefits of the invention. When present, compositions of the present invention may contain from 0.0001% to 50%; from 0.001% to 20%; or, alternately, from 0.01% to 10%, by weight of the composition, of the optional components. The amounts listed herein are only to be used as a guide, as the optimum amount of the optional components used in a composition will depend on the specific active selected since their potency does vary considerably. Hence, the amount of some optional components useful in the present invention may be outside the ranges listed herein.

The optional components, when incorporated into the composition, should be suitable for use in contact with human skin tissue without undue toxicity, incompatibility, instability, allergic response, and the like. The compositions of the present invention may include optional components such as anti-acne actives, desquamation actives, anti-cellulite agents, chelating agents, flavonoids, tanning active, non-vitamin antioxidants and radical scavengers, hair growth

regulators, anti-wrinkle actives, anti-atrophy actives, minerals, phytosterols and/or plant hormones, N-acyl amino acid compounds, antimicrobial or antifungal actives, and other useful skin care actives, which are described in further detail in U.S. application publication No. US2006/0275237A1 and US2004/0175347A1.

The Personal Care Product Council's *International Cosmetic Ingredient Dictionary and Handbook*, Thirteenth Edition, describes a wide variety of non-limiting cosmetic and pharmaceutical ingredients commonly used in the skin care industry, which are suitable optional components for use in the compositions of the present invention. Examples of these ingredient classes include: abrasives, absorbents, aesthetic components such as fragrances, pigments, colorings/colorants, essential oils, anti-caking agents, antifoaming agents, antimicrobials, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, emollients, external analgesics, film formers or materials, opacifying agents, pH adjusters, preservatives, propellants, reducing agents, sequestrants, skin cooling agents, skin protectants, thickeners viscosity modifiers, vitamins, and combinations thereof.

II. Methods of Treatment

Various methods of treatment, application, regulation, or improvement may utilize the aforementioned compositions. Identification of a region of skin subject to the signs of aging may occur on any skin surface of the body. Skin surfaces of the most concern tend to be those not typically covered by clothing, such as facial skin surfaces, hand and arm skin surfaces, foot and leg skin surfaces, and neck and chest skin surfaces (e.g., décolletage). In particular, identification of the region of aging skin may be on a facial skin surface including the forehead, perioral, chin, periorbital, nose, and/or cheek skin surfaces.

One suitable method of improving the appearance of aging skin includes the step of topically applying a composition comprising an effective amount of substituted azole to the skin surface, wherein the composition is applied for a period of time sufficient to improve the appearance of the aging skin.

The method may comprise the step of applying the composition to the previously identified area of aging skin, and/or an area where one seeks to prevent the appearance of aging skin. Many regimens exist for the application of the composition. The composition may be applied at least once a day, twice a day, or on a more frequent daily basis, during a treatment period. When applied twice daily, the first and second applications are separated by at least 1 to

12 hours. Typically, the composition may be applied in the morning and/or in the evening before bed.

The treatment period is ideally of sufficient time to provide an improvement in the appearance of aging skin. The treatment period may be at least 1 week, and in some embodiments the treatment period may last 4 weeks or 8 weeks. In certain embodiments, the treatment period will extend over multiple months (*i.e.*, 3-12 months) or multiple years. In one embodiment the composition is applied at least once a day during a treatment period of at least 4 weeks or at least 8 weeks. In one embodiment the composition is applied twice a day during a treatment period of at least 4 weeks or 8 weeks.

The step of applying the composition may be accomplished by localized application. In reference to application of the composition, the terms "localized", "local", or "locally" mean that the composition is delivered to the targeted area (such as age spots) while minimizing delivery to skin surface not requiring treatment. The composition may be applied and lightly massaged into an area of aging skin. The form of the composition or the dermatologically acceptable carrier should be selected to facilitate localized application. While certain embodiments of the present invention contemplate applying a composition locally to an area, it will be appreciated that compositions of the present invention can be applied more generally or broadly to one or more skin surfaces.

In some embodiments, the composition may be delivered by a variety of applicators appropriate for localized and general application. Such applicators can include droppers, applicator wands, cotton swabs, or any other suitable device. Other suitable applicators include SH-0127 pen applicator available from Shya Hsin Plastic Works, Inc., Taiwan and either the Xpress Tip or liquid filled swab available from SwabPlus, Inc., China. The applicator may be configured to easily apply the composition to a sign of aging skin, for example, age spots having an approximate diameter between about 2 mm and about 10 mm and allowing for a dosed amount of the composition of between about 1 to about 50 $\mu L/cm^2$ or between about 1 to about $5\mu L/cm^2$. In another embodiment, the composition is applied to the one or more signs of aging (e.g., age spots) and more generally to one or more facial skin surfaces contemporaneously (*i.e.*, over a period of less than 30 minutes or, more typically, less than 5 minutes).

While some methods described herein contemplate applying the compositions of the present invention with an applicator, it will be appreciated that applicators are not required and the compositions of the present invention can also be applied directly by using one's finger or in other conventional manners.

In one embodiment, the method comprises the steps of applying a first composition comprising an effective amount of substituted azole to a skin surface and of applying a second composition to the skin surface, before or after the first composition. The first and second compositions may be any compositions described herein; however, the second composition may optionally comprise an effective amount of the substituted azole compound present in the first composition. The second composition may comprise one or more skin tone agents, sunscreen actives, anti-inflammatory agents, or other optional components. The first composition may be generally or locally applied, while the second composition may be generally or locally applied to the skin surface including the aging skin to which the first composition is applied. In certain embodiments, the skin surface is facial skin surface which includes one or more of the forehead, perioral, chin, periorbital, nose, and cheek skin surfaces. In another embodiment, the first and second compositions are applied contemporaneously to at least the cheek, forehead, and chin/perioral skin surfaces. For general application to a skin surface and, particularly a facial skin surface, the dosed amount of the first or second composition may be between about 1 to about 50 $\mu L/cm^2$ per application (*i.e.*, per single application to the skin surfaces).

Suitable methods may comprise any one or more of the abovementioned steps. All of the aforementioned steps are applicable to application, treatment, regulation, and/or improvement of aging skin appearance.

EXAMPLES

Example 1 – Exemplary Compositions

Table 1 sets forth non-limiting examples of the compositions of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention, which would be recognized by one of ordinary skill in the art. In the examples, all concentrations are listed as weight percent, unless otherwise specified and may exclude minor materials such as diluents, filler, and so forth. The listed formulations, therefore, comprise the listed components and any minor materials associated with such components. As is apparent to one of ordinary skill in the art, the selection of these minor materials will vary depending on the physical and chemical characteristics of the particular ingredients selected to make the present invention as described herein.

All examples may be used to improve the appearance of aging skin. The present invention may further relate to a regimen involving the localized treatment for one or more signs

of aging by a first composition (e.g., Examples A or B) and a more broad or general facial skin treatment by a second composition (e.g., Examples C or D), which can be applied before or after the localized treatment to improve a particular sign of aging skin (*e.g.*, across the entire face).

TABLE 1

Exemplary Compositions

Component / % by wt.	Example A	Example B	Example C	Example D
1-phenylimidazole	0.50	1.5	0.00	1.00
4-phenylimidazole	0.50	0.00	1.50	0.75
N-Acetylglucosamine	0.00	0.00	2.00	0.00
Hexamidine Diisethionate	0.00	0.00	0.09	0.09
Sepiwhite™ (Undecylenoyl-phenylalanine, neutralized) (available from SEPPIC)	0.00	0.00	0.50	0.50
Sepigel 305™ (Polyacrylamide + C13-14 isoparaffin + laureth-7) (available from SEPPIC)	0.00	0.00	2.00	2.00
Dipotassium Glycyrrhizate	0.00	0.10	0.10	0.30
Hexamidine Diisethionate	0.00	0.00	0.09	0.09
Homosalate	0.00	0.00	0.00	9.00
Avobenzone	0.00	0.00	0.00	3.00
Octocrylene	0.00	0.00	0.00	2.60
Oxybenzone	0.00	0.00	0.00	1.00
Octisalate	0.00	0.00	0.00	4.50
Butylene Glycol (CAS No. 107-88-0)	5.50	5.50	5.50	5.50
Niacinamide (CAS No. 98-92-0)	5.00	5.00	5.00	5.00
Glycerin (CAS No. 56-81-5)	2.50	2.50	2.50	2.50
DC 1503 Fluid™ (available from DowCorning)	2.50	2.50	2.50	2.50
Lubrajel Oil™ (available from Sederma)	1.44	1.44	1.44	1.44
Phenonip XB™ (available from Clariant)	1.25	1.25	1.25	1.25
D-panthenol (CAS No. 81-13-0)	1.00	1.00	1.00	1.00
Tospearl 2000™ (Polymethylsils esquioxane) (CAS No. 68554-70-1) (available from GE Silicones/Momentive)	1.00	1.00	1.00	1.00
DL-Alpha Tocopheryl Acetate (CAS No. 7695-91-	0.50	0.50	0.50	0.50

2)				
Prodew 400™ (available from Ajinomoto)	0.50	0.50	0.50	0.50
Pemulen TR-2™ (Acrylates/C10-30 Alkyl Acrylate Crosspolymer) (available from Noveon)	0.25	0.25	0.25	0.25
Polysorbate 20 (CAS No. 9005-64-5)	0.25	0.25	0.25	0.25
Sodium Metabisulfite (CAS No. 7681-57-4)	0.25	0.25	0.25	0.25
Allantoin (CAS No. 97-59-6)	0.20	0.20	0.20	0.20
Sodium Hydroxide (CAS No. 1310-73-2) (50% solution by weight in water)	0.17	0.17	0.17	0.17
Disodium EDTA (CAS No. 139-33-3)	0.10	0.10	0.10	0.10
Xanthan Gum (CAS No. 11138-66-2)	0.05	0.05	0.05	0.05
Sodium Hyaluronate (CAS No. 9067-32-7)	0.01	0.01	0.01	0.01
Water (CAS No. 7732-18-5)	QS	QS	QS	QS
TOTAL (% by weight of total composition)	100.00	100.00	100.00	100.00

The compositions of the present invention are generally prepared by conventional methods such as are known in the art of making topical compositions. Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like. Typically, emulsions are prepared by first mixing the aqueous phase materials separately from the fatty phase materials and then combining the two phases as appropriate to yield the desired continuous phase. The compositions are preferably prepared such as to optimize stability (e.g., physical stability, chemical stability, photostability) and/or delivery of the active materials. This optimization may include appropriate pH (e.g., less than 7), exclusion of materials that can complex with the active agent and thus negatively impact stability or delivery (e.g., exclusion of contaminating iron), use of approaches to prevent complex formation (e.g., appropriate dispersing agents or dual compartment packaging), use of appropriate photostability approaches (e.g., incorporation of sunscreen/sunblock, use of opaque packaging), etc.

Example 2 – In vitro ATRA 4-hydroxylase activity assay to determine CYP inhibition.

All procedures were carried out under minimal light in order to prevent degradation of the retinoid samples.

Microsomal preparation: One lobe of fresh pig liver is obtained (e.g., at about the time of slaughter from a food-processing company) and immediately placed in ice cold 15mM KH2PO4/250mM sucrose (pH 7.4) and kept on ice during transportation. A 10g sample of liver is minced and homogenized in 30 mL of homogenization buffer (15mM KH2PO4/250mM sucrose) using a Tekmar homoginizer or equivalent by pulsing 3 times with 20 second pulses. This procedure is repeated for a total of 8 x 10 g samples of pig liver. The remaining pig liver may be stored at -80 °C. The homogenates from the 8 samples are pooled and centrifuged at 13,000xg for 20 minutes at 4 °C to remove crude debris. The supernatant is further centrifuged at 100,000xg for 70 minutes at 4 °C. The microsomal pellets are re-suspended into 50 mL of 150mM KH2PO4/1mM DTT (pH 7.4) and 1 mL aliquots are stored at -80° C.

100-150 µg of pig liver microsomal protein in 150 mM KH2PO4 is incubated at 37 °C in the presence of radiolabeled ATRA and 5 mM NADPH for 90 min. The final ATRA concentration is 1 µM, as a combination of [20-Methyl-^{3}H]ATRA and unlabeled ATRA. Initially, radiolabeled ATRA may be used to assist in validating the method. Once retention times of retinoid metabolites are identified, unlabeled ATRA is used for screening. Compounds tested as possible competitive substrates are added to the assay 10 min prior to the addition of ATRA. Ethanol, containing 0.1% butylated hydroxytoluene (BHT) as an antioxidant, is used to stop the reactions. For recovery of ATRA the pH of reactions are adjusted to 3.0 before extraction with 0.1N HCl. Retinoids are extracted from the protein aqueous phase with 4 mL hexane, 1 ml 100µg/ml BHT in water (pH 3). An additional 4 mlL of hexane (pH 3) is used for a second extraction. The organic extractions are pooled, evaporated to dryness using a speed vac, and resuspended in 62.5 µl acetonitrile containing 1mg/ml BHT. Samples are analyzed by HPLC.HPLC separation of retinoids. A suitable HPLC system (e.g., Waters Corp., Milford MA) containing a Vydac 201 TP54 column (15cm X 46mm), multi-wavelength detector (Waters 490) set at 350nm, and a β-RAM detector (IN/US Systems, Tampa, FL) is used to separate retinoids. Mobile phases used for gradient elution of retinoids are those of Duell et al., J. Clin. Invest. 1992 October; 90(4): 1269–1274. Mobile phase A is acetonitrile:0.02 M ammonium acetate:acetic acid (1:1:0.01) and mobile phase B is acetonitrile:0.2M ammonium acetate:acetic acid (19:1:0.008). At the start of the HPLC run, solvent A is run 100% followed by a linear gradient to solvent B at 3 minutes, a shallow gradient to 81% solvent B at 38 minutes, and 100% solvent B at 40 minutes. The flow rate is 0.5mL/min and the total time for separation is 60 minutes. Effluent from the HPLC column flows directly into a flow-through scintillation spectrometer (β-RAM). Because of the sensitivity limitations of the β-RAM spectrometer, it is not used to

quantitate peak areas but rather to confirm ATRA and ATRA 4-hydroxylase activity. Calculated peaks areas (using Millenium software - Waters Corp.) of ATRA and ATRA metabolites are used to quantify relative activity levels. Table 2 shows the compounds screened through the in vitro 4-hydroxylase assay. Ketoconazole was used as a positive control, while climbazole is a known 4-hydroxylase inhibitor marketed as an antifungal active.

TABLE 2

Screening results from in vitro 4-hydroxylase inhibition assay

Compound	IC_{50} (μM)
Ketoconazole	8.8
Climbazole	47.5
1-phenylimidazole	52.5
4-phenylimidazole	58.8
1-benzylimidazole	77.5
4,5-diphenylimidazole	100.0
1-benzyl-2-methylimidazole	307.5
Clotrimazole	>500
2-phenylimidazole	>500

Example 3 - In vitro CYP3A4 Inhibition Assay

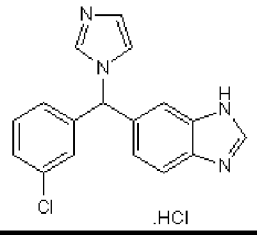
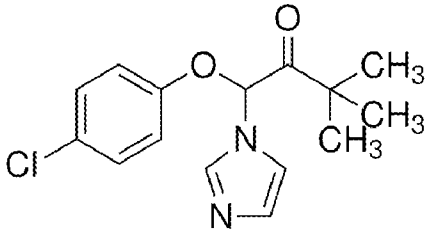
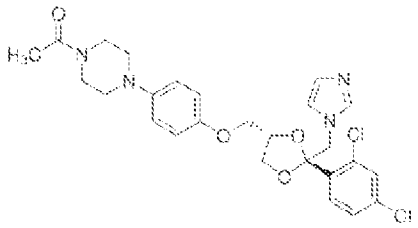
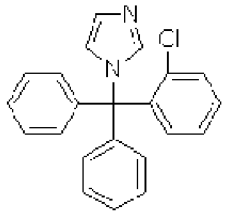
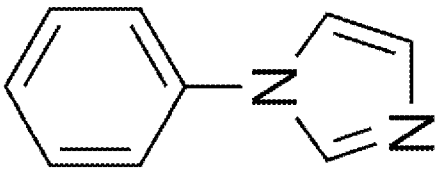
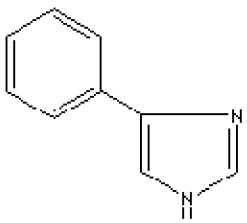
A commercially available P450-GLO™ Assay kit (Promega Corporation, Madison WI) is used to screen various compounds for CYP3A4A inhibition activity. CYP3A4A is thought to be one of the primary CYP isoforms responsible for retinoic acid metabolism in the skin. Three benchmark agents, liarozole, climbazole, and ketoconazole, were assessed for CYP3A4 inhibition to confirm that the inhibition activity (the IC_{50} for CYP3A4 inhibition) measured by the assay corresponds to the activity reported by the published literature.

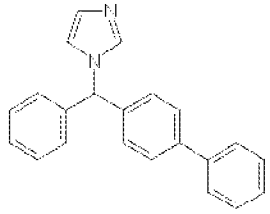
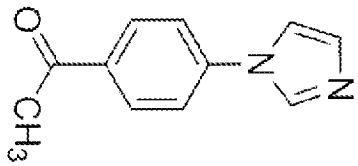
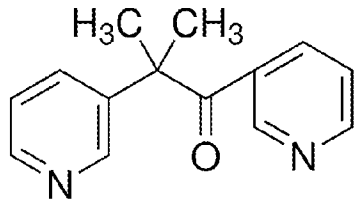
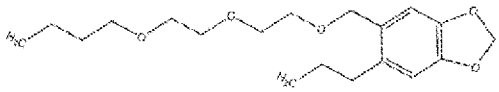
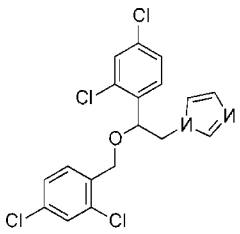
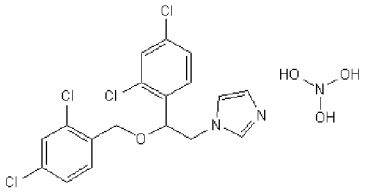
The results set forth in Table 3 show that the substituted azole compounds having the specific structure set forth herein are CYP inhibitors, and thus function as RAMBAs.

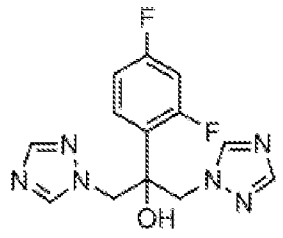
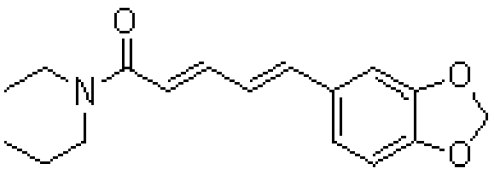
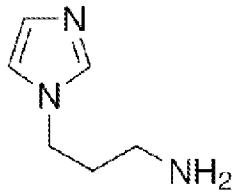
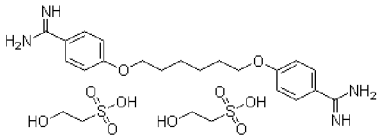
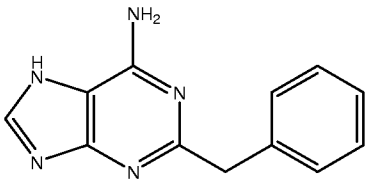
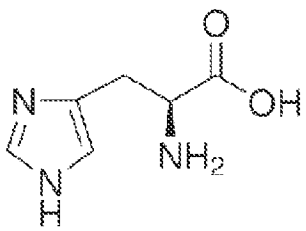
TABLE 3

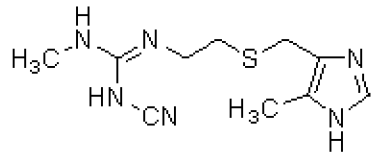
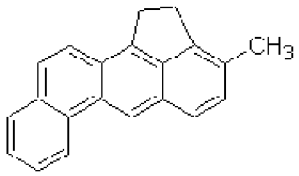
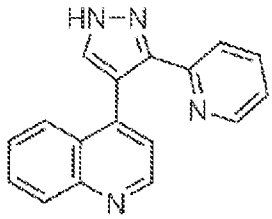
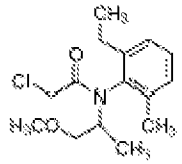
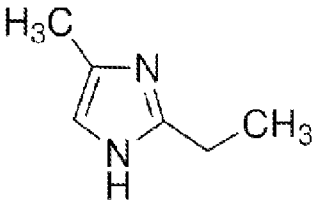
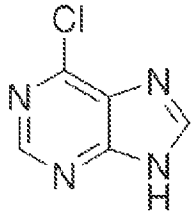
Screening results from in vitro CYP3A4 Inhibition Assay

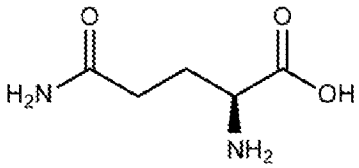
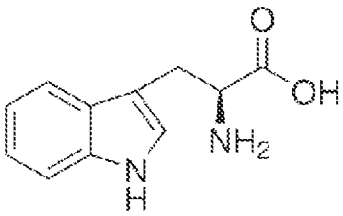
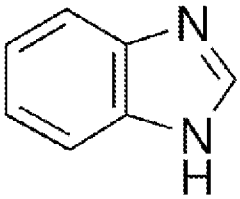
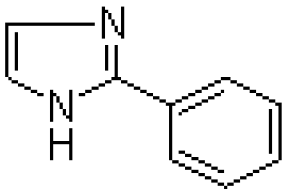
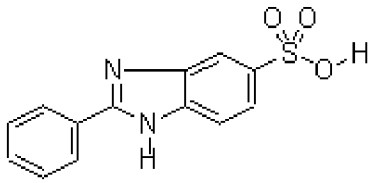
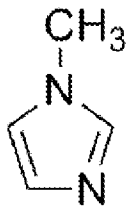
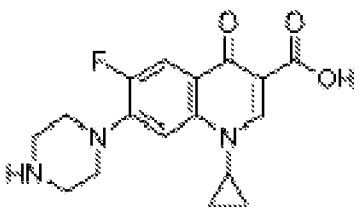
Structure	Compound	CAS No.	IC_{50} (uM)

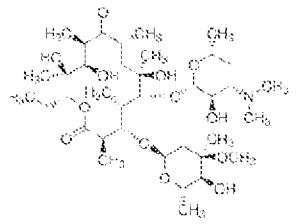
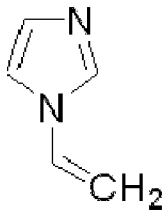
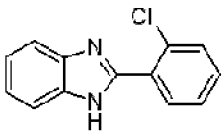
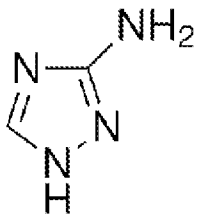
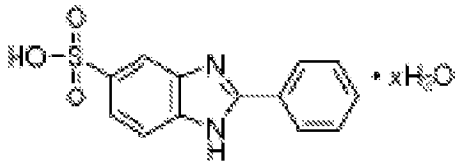
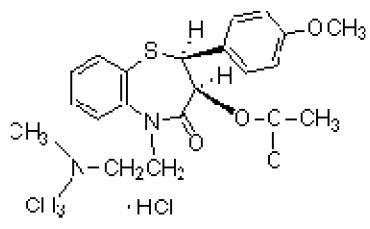
	Liarizole hydrochloride	145858-50-0	Hit <0.1uM (0.08-0.1uM)
	Climbazole	38083-17-9	Hit 0.1uM
	Ketoconozole	65277-42-1	Hit 0.5uM
	Clotrimazole	23593-75-1	Hit 0.3uM
	1-Phenylimidazole	7164-98-9	Hit 1uM
	4-Phenylimidazole	670-95-1	Hit 1.5uM

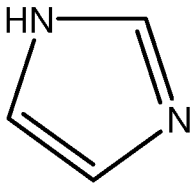
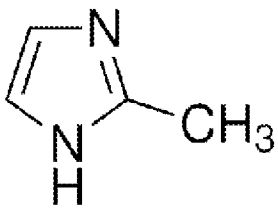
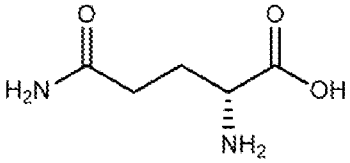
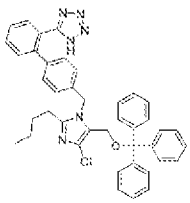
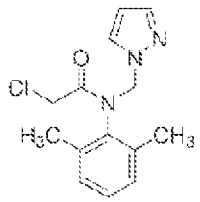
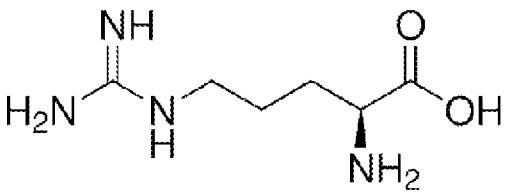
	Bifonazole	60628-96-8	Hit 0.8uM
	4'-(Imidazol-1yl) acetophenome	10041-06-2	Hit 0.8uM
	Metyrapone	54-36-4	Hit 3uM
	Piperonyl butoxide	51-03-6	Hit 3uM
	Miconazole	22916-47-8	Hit 5uM
	Miconazole Nitrate	75319-48-1	Hit 5uM

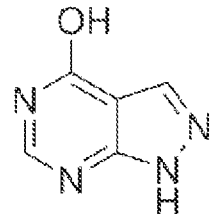
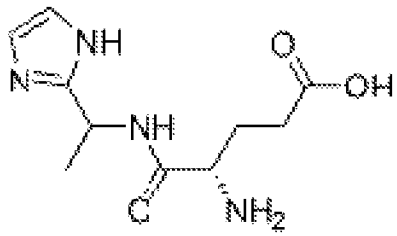
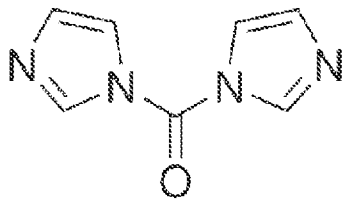
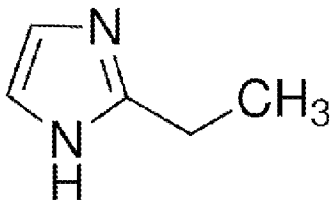
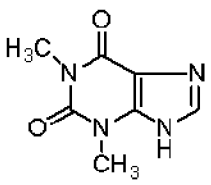
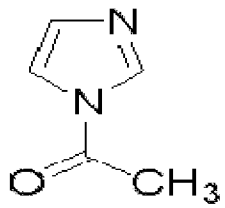
	Fluconazole	86386-73-4	Hit ~10uM
	Piperine	94-62-2	Hit ~10uM
	N-(3-Aminopropyl) imidazole	5036-48-6	no hit >10uM
	Hexamidine diisethionate	659-40-5	no hit >10uM
	3-Benzyladenine	7280-81-1	no hit >10uM
	Histidine	71-00-1	no hit >10uM

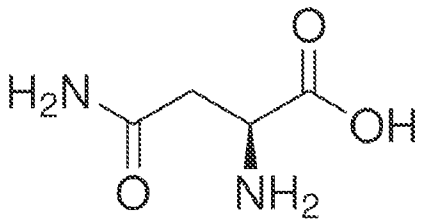
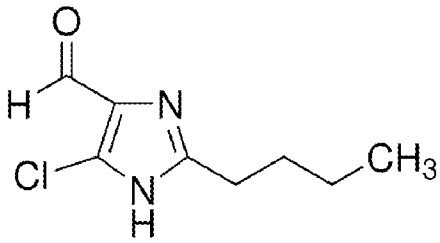
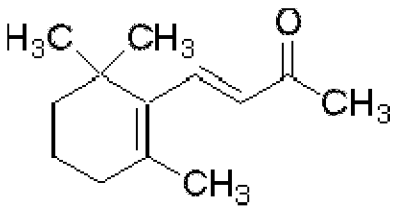
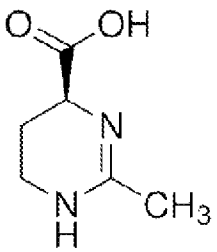
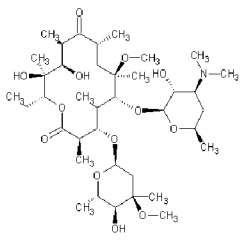
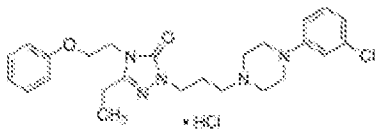
	Cimetidine	51481-61-9	Near Hit IC50 > 10uM
	Methylcholanthrene	56-49-5	Near Hit > 10uM
	LY-364947	396129-53-6	no hit >10uM
	Metolachlor	52118-45-2	no hit >10uM
	2-Ethyl-4-methylimidazole	931-36-2	no hit >10uM
	6-Chloropurine	87-42-3	no hit >10uM

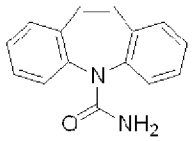
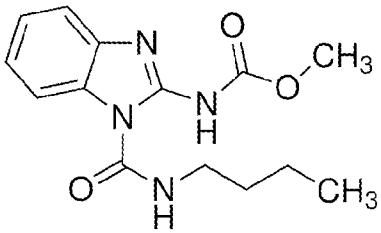
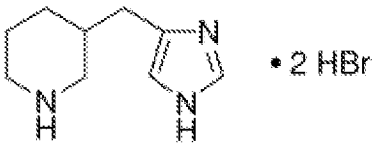
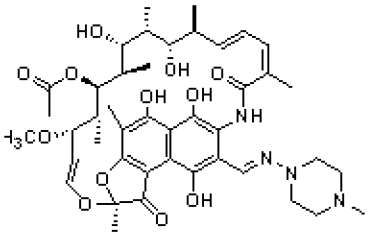
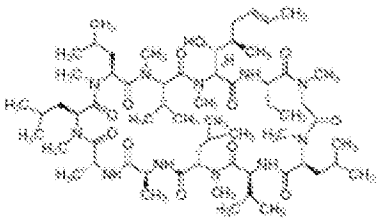
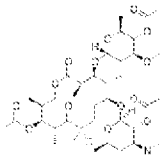
	L-Glutamine	56-85-9	no hit >10uM
	L-Tryptophan	73-22-3	no hit >10uM
	Benzimidazole	51-17-2	no hit >10uM
	2-Phenylimidazole	670-96-2	no hit >10uM
	2-Phenyl benzimidazole	716-79-0	no hit >10uM
	1-Methylimidazole	616-47-7	no hit >10uM
	Ciprofloxacin HCl	85721-33-1	no hit >10uM

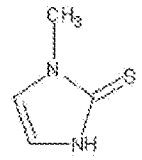
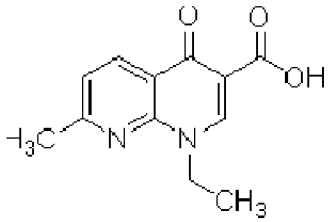
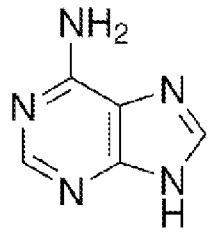
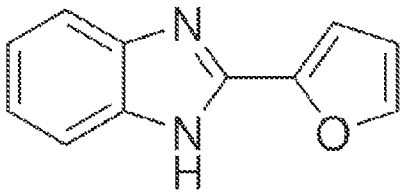
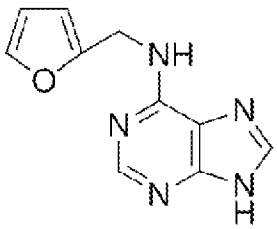
	Erythromycin	114-07-8	no hit >10uM
	1-Vinylimidazole	1072-63-5	no hit >10uM
	2-(2-Chlorophenyl) benzimidazole	3674-96-7	no hit >10uM
	Amitrol	61-82-5	no hit >10uM
	2-Phenyl-5-benzimidazole sulfonic acid	27503-81-7	no hit >10uM
	Diltiazem	42399-41-7	no hit >10uM

	Imidazole	288-32-4	no hit >10uM
	2-Methylimidazole	693-98-1	no hit >10uM
	D-Glutamine	5959-95-5	no hit >10uM
	2-Butyl-4-chloro-5-(hydroxymethyl) imidazole	79047-41-9	no hit >10uM
	Metazachlor	67129-08-2	no hit >10uM
	L-Arginine	74-79-3	no hit >10uM

	Allopurinol	315-30-0	no hit >10uM
	Glutamylamidoethyl imidazole	169283-81-2	no hit >10uM
	1'-1-Carbonylimidazole	530-62-1	no hit >10uM
	2-Ethylimidazole	1072-62-4	no hit >10uM
	Theophylline	58-55-9	no hit >10uM
	1-Acetylimidazole	2466-76-4	no hit >10uM

	L-Asparigine	70-47-3	no hit >10uM
	2-Butyl-4-chloro-5-formylimidazole	83857-96-9	no hit >10uM
	β-Ionone	79-77-6	no hit >10uM
	Ectoine	96702-03-3	no hit >10uM
	Clarithromycin	81103-11-9	no hit >10uM
	Nefazodone HCl	83366-9	no hit >10uM

	Carbamazepine	298-46-4	no hit >10uM
	Benomyl	17804-35-2	no hit >10uM
	Immepip dihydrobromide	164391-47-3	no hit >10uM
	Rifampicin	13292-46-1	no hit >10uM
	Cyclosporin A	59865-13-3	no hit >10uM
	Troleandomycin	2751-09-9	no hit >10uM

	Methimazole	60-56-0	no hit >10uM
	Nalidixic acid	389-08-2	no hit >10uM
	Adenine	73-24-5	no hit >10uM
	Fuberidazole	3878-19-1	no hit >10uM
	Kinetin	525-79-1	no hit >10uM

Example 4 – Method of Treatment

A test subject topically applies a composition comprising 0.55% 1-phenylimidazole, by weight in a vehicle, to the entire face one to two times a day for 8 weeks. After treatment, the subject's facial skin feels and appears less aged, and the subject notices an improvement in the appearance of age spots, overall skin tone, and fine lines and wrinkles.

The dimensions and values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such dimension is intended to mean both the recited value and a functionally equivalent range

surrounding that value. For example, a dimension disclosed as "40 mm" is intended to mean "about 40 mm."

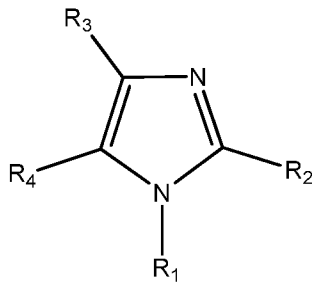
Every document cited herein, including any cross referenced or related patent or application, is hereby incorporated herein by reference in its entirety unless expressly excluded or otherwise limited. In particular, U.S. Provisional Application Ser. No. 61/762,546 is incorporated herein by reference in its entirety. The citation of any document is not an admission that it is prior art with respect to any invention disclosed or claimed herein or that it alone, or in any combination with any other reference or references, teaches, suggests or discloses any such invention. Further, to the extent that any meaning or definition of a term in this document conflicts with any meaning or definition of the same term in a document incorporated by reference, the meaning or definition assigned to that term in this document shall govern.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

CLAIMS

What Is Claimed Is:

1. A method of cosmetically improving the appearance of aging skin comprising:
   a. identifying a target skin surface in need of improvement;
   b. applying to said target skin surface a cosmetic composition comprising:
      i. an effective amount of a substituted azole compound represented by the structure:



where:

R1 is an alkyl or phenyl electron donating group,

R2 is hydrogen,

R3 and R4 do not form a fused ring and are each independently selected from the monodentate group consisting of H, alkyl, and phenyl; and

      ii. a dermatologically acceptable carrier;

   wherein said composition is applied for a period of time sufficient to improve the appearance of one or more signs of aging.

2. The method of claim 1, wherein said substituted azole compound is 1-phenylimidazole, 4-phenylimidazole, or a combination thereof.

3. The method of claim 1 or 2, wherein said skin surface is a facial skin surface.

4. The method of claim 3, wherein said facial skin surface is a forehead, perioral, chin, periorbital, nose, or cheek skin surface.

5. The method of any preceding claim, wherein said composition additionally comprises a sunscreen active.

6. The method of any preceding claim, wherein said composition additionally comprises an anti-inflammatory agent.

7. The method of any preceding claim, wherein said composition further comprises a skin tone agent.

8. The method of claim 7, wherein said skin tone agent is selected from the group consisting of vitamin B3 compounds, sugar amines, hexamidine compounds, salicylic acid, 1,3-dihydroxy-4-alkylbenzene, xanthenes, and combinations thereof.

9. The method of any preceding claim, additionally comprising a step of applying a second composition to the skin surface.

10. The method of any preceding claim, wherein the second composition comprises a sunscreen active, an anti-inflammatory agent, a skin tone agent, or a combination thereof.

11. The method of claim 10, wherein said second composition comprises a skin tone agent selected from the group consisting of vitamin B3 compounds, sugar amines, hexamidine compounds, salicylic acid, 1,3-dihydroxy-4-alkylbenzene, xanthenes, and combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/015206

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K8/49 A61Q19/08 A61P17/00
ADD.

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)
A61K C07D A61Q

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	DE 10 2005 026355 A1 (HENKEL KGAA [DE]) 14 December 2006 (2006-12-14) claims 5,6,12	1

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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 application or patent 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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2014	14/07/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Skulj, Primoz

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Form PCT/ISA/210 (second sheet) (April 2005)

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T	MOBASHER AHMAD: "Study on Cytochrome P-450 Dependent Retinoic Acid Metabolism and its Inhibitors As Potential Agents for Cancer Therapy", SCIENTIA PHARMACEUTICA, vol. 79, no. 4, 1 January 2011 (2011-01-01), pages 921-935, XP055122121, ISSN: 0036-8709, DOI: 10.3797/scipharm.1106-18 the whole document	
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/015206

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/015206

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