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(54) Title: COMPOSITIONS FOR SKIN LIGHTENING COMPRISING BIS-PANTOYL-CYSTAMINE

(57) Abstract: The invention relates to topical compositions which comprise bis-pantoyl cystamine or a derivative thereof, and a vehicle conventionally used in topical compositions.



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COMPOSITIONS FOR SKIN LIGHTENING COMPRISING BIS-PANTOYL-CYSTAMINE

The present invention relates to compositions for skin lightening comprising bis-pantoyl-cystamine or derivatives thereof. More particularly, the present invention relates to topical compositions comprising bis-pantoyl-cystamine or derivatives thereof for lightening of the skin, for the treatment of hyperpigmented skin disorders and for preventing tanning of the skin. In another aspect, the present invention relates to the use of bis-pantoyl-cystamine or a derivative thereof in the manufacture of a topical composition for lightening of the skin, for the treatment of hyperpigmented skin disorders and for preventing tanning of the skin and to a method of lightening the skin, treating hyperpigmented skin disorders and preventing tanning of the skin which comprises topically administering bis-pantoyl-cystamine or a derivative thereof to the afflicted parts of the skin of a person in need of such treatment.

Skin lightening has been of concern to human beings for many years. In particular, the ability to remove hyper pigmentation, such as found in age spots, freckles or aging skin generally, is of interest to individuals to minimize skin blotchiness or desiring a uniform skin tone. Skin lightening in humans is also desired to lighten the natural color of their skin or to prevent of tanning after environmental factors like UV and leads to a more even skin tone.

The understanding of the chemical and enzymatic basis of melanogenesis is heavily documented. The color of human skin is determined by melanin, a biopolymer pigment manufactured by special dendritic cells known as melanocytes residing mostly between the basal cells of the epidermis. The melanocytes produce secretory granules, melanosomes, which produce the desired melanin. Melanogenesis occurs within the melanosome, and

the melanin is later distributed to keratinocytes via the melanocytes dendrites and leads to a more or less pronounced tan or brown skin color.

The biochemical process is a cascade of biosynthesis where the key enzyme is called tyrosinase and triggers several steps in the formation of melanin from tyrosine. Melanin is the end product of an oxidative process in which tyrosine is converted with the aid of the enzyme tyrosinase via 3,4-dihydroxyphenylalanine (dopa), dopaquinone, leucodopacrome, dopacrome, 5,6-dihydroxyindol and indole-5,6-quinone to give, finally, melanin. Although primary regulation of melanin production is via genetic controls, environmental factors may also play an important role in synthesis. Exposure to sunlight or other UV radiation can stimulate the melanocytes to produce more melanin, hence the so-called "tanning" reaction. Melanin production can also increase in response to hormone fluctuations associated with aging, child bearing or the use of birth-control pills. Normal pigmentation of the skin surface is uniform. Localized, excessive pigmentation can occur and such colorization is collectively referred to as hyper pigmentation. Hyper pigmentation encompasses a wide array of afflictions, all of which are accompanied by increased melanin production. Hyper pigmentation of the human skin may include skin blemishes or disorders including freckles, senile lentigo, liver spots, melasma, brown or age spots, sunburn pigmentation, post-inflammatory hyper pigmentation due to abrasion, burns, wounds, insect bites, dermatitis, and other similar small, fixed pigmented lesions.

From a cosmetic and dermatological standpoint, it may often be desirable to decolorize what is considered normally pigmented skin to increase "fairness" or to blend hyper pigmented regions into that of the surrounding normal skin.

The present invention thus comprises topical compositions, i.e. compositions for cosmetic as well as for dermatological, i.e., pharmaceutical, use which contain the active ingredient, bis-pantoyl-cystamine or a derivative thereof, in a vehicle that is conventionally used in cosmetic or topical dermatological compositions. The amount of bis-pantoyl-cystamine or derivative thereof in such compositions is about 0.005 % by weight to about 8.0 % by weight, preferably about 0.05% by weight to about 5.0 % by weight based on bis-pantoyl-cystamine and the total weight of the composition, respectively. . The treatment may extend to a period up to several months. In general, a treatment for the duration of 6-8 weeks will suffice to achieve a substantial lightening effect.

The compound bis-pantoyl-cystamine, (by systematical name : N,N'-(dithio-2,1-ethanediyl)bis(2,4-dihydrox-3,3-dimethyl) butanamide) which has the formula



contains two chiral centers as indicated by an asterisk. Therefore, bis-pantoyl-cystamine may exist in 3 isomeric forms with RR, RS and SS configurations. The isomer with RR configuration is known and has been described in the literature (Boxer et al, J. Biol Chem., 1955, 217,541 Shimizu et al Chem Pharm Bull, 1970, 18, 838 .) The RR/SS diastereomeric pair and the RS (meso) isomer, and mixtures of RR, SS, RR/SS and RS are new and, as such, are also an object of the present invention. While all isomeric forms and their mixtures are intended for use in accordance with the invention, the new isomers and mixtures are preferred. Particularly preferred are the RR/SS diastereomeric pair, and the mixture composed of RR, RS, and SS isomers in a molar ratio of about 25:50:25 to about 30:40:30. They possess unexpected advantageous properties for manufacture, handling, and use.

The substances described are conveniently prepared by reaction of pantolactone with cystamine. When R-pantolactone is used, the RR isomer results which in pure form is found to be a very viscous oil. When S-pantolactone is used, the SS isomer results, which as the pure isomer is also a very viscous oil. These materials are somewhat difficult to handle due to their high viscosity even when warmed. Purification of such materials is normally more difficult than with crystalline solids.

When equal amounts of the RR and SS isomers are mixed there results a new substance, an RR/SS diastereomeric pair, which is a solid easily purified by crystallization.

When racemic pantolactone is used, there results a mixture composed of RR, RS, and SS isomers in a molar ratio of 25:50:25. Unexpectedly, this mixture can easily be crystallized to a white solid which can be further purified by recrystallization, e.g., from ethyl acetate or water. Such purification may result in a change of the RR, RS, and SS isomer molar ratio to about 30:40:30. For the purposes of the present invention, the preferred molar ratio in terms of the RS (meso) to RR/SS ratio is in the range from about 50:50 to about 30:70.

Cosmetic products require the highest standard of purity and safety because of contact to human skin, hair, and mucous membranes. Customers are particularly sensitive to color and odor of such products. Thus purification to the highest quality of this type products is essential. And ease of purification an advantage to manufacturing. Thus the RR or SS

isomers can be used as hair care products provided specialized methods of purification are employed. The mixture of RR/SS and RS meso isomers offer an advantage is being easily purified by conventional chemical process techniques such as crystallization. Accordingly, for the purposes of the present invention the use of the mixture of RR/SS and RS meso isomers, and derivatives thereof, is preferred.

The term "derivative" as used herein denotes any compound that is obtained from bis-pantooyl-cystamine by modification of the hydroxy groups contained therein, particularly the terminal hydroxy groups, and which, while possessing the same or higher degree of lipophilicity than bis-pantooyl-cystamine exerts a similar activity as bis-pantooyl-cystamine. The making of lipophilic derivatives is a well known method by the person skilled in the art to achieve better skin delivery of a topically applied active ingredient. Examples of such derivatives are acylates, particularly acylates formed with aliphatic, aromatic or araliphatic carboxylic acids containing 2-20 carbon atoms, which may be saturated or unsaturated, and may be substituted by, e.g. hydroxy groups, such as the mono- or di-acetate, propionate, butyrate, caproate, caprylate, caprate, laurate, myristate, lactate, 2-hydroxycaprylate, 2-hydroxycaprate, 2-hydroxylaurate, 2-hydroxymyristate, di-2-heptylundecanoate, and salicylate. Examples of acylates derived from unsaturated carboxylic acids are oleates and linoleates.

The compositions of the present invention can, e.g., be provided in the form of a lotion, a thickened lotion, a gel, a cream, a milk, a cleansing composition, an ointment, a powder or a solid tube stick and may optionally be packaged as an aerosol and may be provided in the form of a mousse, foam or a spray. They may be in the form of a suspension or dispersion in solvents or fatty substances, or alternatively in the form of an emulsion or microemulsion (in particular of O/W or W/O type, O/W/O or W/O/W-type), such as a cream or a milk, a vesicular dispersion, in the form of an ointment, a gel, a solid tube stick or an aerosol mousse. The emulsions can also contain anionic, nonionic, cationic or amphoteric surfactants.

The compositions of the invention also contain adjuvants and additives, which are conventionally used in cosmetic or dermatological compositions, such as preservatives/antioxidants, fatty substances/ oils, water, organic solvents, silicones, thickeners, softeners, emulsifiers, additional sunscreens, antifoaming agents, moisturizers, skin penetration enhancers, vitamins, desquamation actives, skin soothing actives, fragrances, surfactants, cleansing agents, fillers, sequestering agents, anionic, cationic, nonionic or amphoteric polymers or mixtures thereof, propellants, acidifying or basifying agents, dyes, colorants, pigments or nanopigments, in particular UV screening agents suitable for providing a

photoprotective effect by physically blocking out ultraviolet radiation, conventional skin lightening agents, or any other ingredients usually formulated into cosmetics, in particular for the production of skin lightening compositions, sunscreen compositions and anti-aging compositions.

According to embodiments of the invention, bis-pantoyl-cystamine or derivatives thereof is used in combination with one or more agents selected from UV screening agents, vitamin A or derivatives thereof, ascorbic acid or ascorbic acid derivatives, vitamin E or derivatives thereof, a vitamin from the B complex, panthenol, phytantriol, bisabolol or derivatives thereof, Kojic acid or derivatives thereof, Arbutin or derivatives thereof, Hydroquinone or derivatives thereof, Genistein or derivatives thereof, Epigallocatechin Gallate or derivatives thereof, and Resveratrol or derivatives thereof, Phyllanthus Emblica fruit extract, Leucocyte extract, Bearberry extract, Licorice extract and Mulberry extract.

The term "UV screening agent" means a compound or composition that absorbs UV radiation in the range of about 320 nm to about 400 nm (UV-A) or in the range of about 280 nm to about 320 nm (UV-B). Such UV filters can be organic or inorganic. Organic sunscreens include dibenzoylmethane derivatives such as butyl methoxydibenzoylmethane (PARSOL 1789), benzylidene-cyanoacetates such as 4-methoxy-benzylidene-cyanoacetic acid n-hexyl ester, triazine derivatives such as 4,4'-(6-(bis(2-ethyl-hexyl)-amino)-s-triazine-2,4-diyl)-diresorcinol, anilinomethylene derivatives such as 2-(4-ethoxy-anilino-methylene)-propanedioic acid diethyl ester, camphor derivatives such as 4-methyl benzylidene camphor (PARSOL 5000) and terephthalylidene-3,3'-dicamphor-10,10'-disulfonic acid, benzimidazol derivatives such as 2,2'-(1,4-phenylene)-bis-1H-benzimidazol-4,6-disulfonic acid Na salt; cinnamates such as ethylhexyl methoxycinnamate (PARSOL MCX); salicylic acid derivatives such as ethylhexyl salicylate and homomenthyl salicylate; p-aminobenzoic acid derivatives such as p-dimethylaminobenzoic acid 2-ethylhexyl ester; benzophenone derivatives such as 2-hydroxy-4-methoxy-benzophenone, and 4-phenyl-benzophenone-2-carboxylic acid 2-ethylhexyl ester; anthranilates such as homomenthyl-N-acetylanthranilate and menthylanthranilate; acrylates such as 2-ethylhexyl-2-cyano-3,3-diphenylacrylate ((PARSOL 340); benzimidazole derivatives such as 2-phenylbenzimidazole-5-sulphonic acid (PARSOL HS); benzoxazole derivatives such as 2-phenyl-5-methyl-benzoxazole, malonate derivatives such as dimethyl diethylbenzalmalonate (PARSOL SLX); triazine derivatives such as 2,4-Bis((4-(ethyl-hexyloxy)-2-hydroxy)-phenyl)-6-(4-methoxyphenyl)-1,3,5-triazine (Tinosorb S - Ciba); benzotriazol derivatives such as 2,2'-Methylene-bis-(6(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) (Tinosorb M - Ciba), Uvinul T-150 (BASF), UVASORB HEB (3V-Sigma). In preferred compositions the UV-A filter is selected from the group consisting of PARSOL 1789, 4,4'-(6-(bis(2-

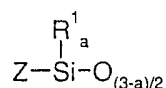
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ethyl-hexyl)-amino)-s-triazine-2,4-diyl)-diresorcinol (Triazin), 2-(4-ethoxy-anilinomethylene)-propanedioic acid diethyl ester, and mixtures thereof, PARSOL MCX or PARSOL SLX.

Further examples of organic UV filters for use in the present invention are :

Compounds as disclosed in European patent application No. 02015849.9 filed 16.7.2002 the contents of which are incorporated herein for reference, and which are characterized by the presence of one each of the structural elements $(\text{H}_3\text{C})_3\text{-Si-}$ (I) and $\text{-O-Si}(\text{CH}_3)_3$ (II), and 2-200 elements in arbitrary order selected from $\text{-O-Si}(\text{CH}_3)[\text{CH}(\text{CH}_3)\text{R}^1]\text{-}$ (IIIa), $\text{-O-Si}(\text{CH}_3)(\text{CH}_2\text{-CH}_2\text{-R}^1)\text{-}$ (IIIb), $\text{-O-Si}(\text{CH}_3)[\text{C}(=\text{CH}_2)\text{R}^1]\text{-}$ (IIIc), and $\text{-O-Si}(\text{CH}_3)(\text{CH}=\text{CH-R}^1)\text{-}$ (IIId) wherein R^1 is a UV light absorbing group; and 2-200 elements in arbitrary order selected from IIIa, IIIb, IIIc and IIId wherein R^1 is hydrogen or a lipophilic group; and, optionally, 1-100 elements in arbitrary order selected from IIIa, IIIb, IIIc and IIId wherein R^1 is a group which is able to form ionogenic or hydrogen bonds, and, further optionally, 1-20 elements in arbitrary order of formula $\text{-O-SiH}(\text{CH}_3)\text{-}$;

Compounds as disclosed in European patent application No. 02008419.0 filed 12.4.2002 the contents of which are incorporated herein for reference, which comprise a unit of the formula



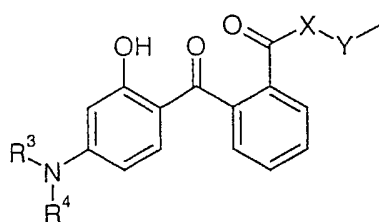
wherein

a is 0, 1 or 2,

R^1 is hydrogen, a saturated or unsaturated $\text{C}_1\text{-C}_{30}$ hydrocarbon group or a trimethylsilyloxy group; and

Z is an amino substituted hydroxybenzophenone of the formula

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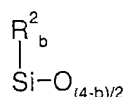
wherein

R^3 and R^4 independently are hydrogen, C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, C_3 - C_{10} cycloalkyl or C_3 - C_{10} cycloalkenyl or R^3 and R^4 , together with the nitrogen atom they are bound to, form a 5 to 6 membered ring;

X is -O- or -NR⁵- wherein R^5 is hydrogen, C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, C_3 - C_{10} cycloalkyl or C_3 - C_{10} cycloalkenyl; and

Y is a divalent C_3 - C_{12} alkylene or alkenylene chain;

and, optionally, a unit of the formula

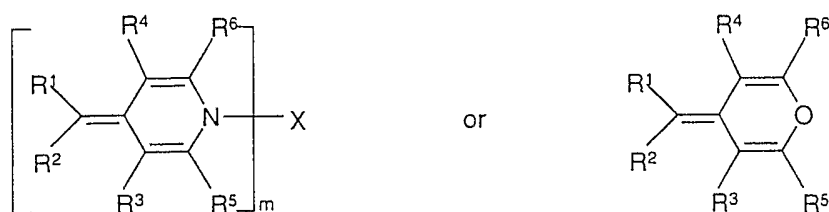


wherein

b is 0, 1, 2, 3; and

R^2 is hydrogen, a saturated or unsaturated C_1 - C_{30} hydrocarbon group or a trimethylsilyloxy group;

Compounds as disclosed in European patent application No. 02002093.9 filed 12.2.2002 the contents of which are incorporated herein for reference, and which are of the general formulas

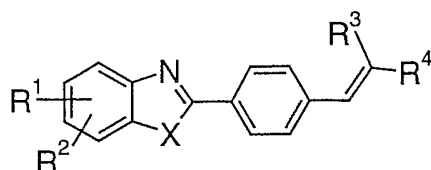


wherein m is 1 or 2; R^1 and R^2 are identical or different electron-withdrawing groups, or one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an electron-withdrawing group; R^3 , R^4 , R^5 , are R^6 are, independently, hydrogen, alkyl or aryl; R^3 and R^5 and/ or R^4 , and R^6 taken together with the carbon atoms to which they are attached, may form a 5 or 6 membered ring which optionally is substituted with one to four alkyl or alkoxy groups; X

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is a moiety R^7 , when m is 1; and is alkylene or poly(oxyalkylene) when m is 2; and R^7 is hydrogen, alkyl, alkoxyalkyl or aryl; and

Compounds as disclosed in European patent application No. 02014158.6 filed 25.6.2002 the contents of which are incorporated herein for reference, and which are of the general formula I



wherein R^1 and R^2 are, independently from each other, hydrogen; halogen; hydroxy; (C_1-C_{20}) -alkyl; (C_2-C_{20}) -alkenyl; or (C_1-C_{20}) -alkoxy; X is oxygen or an imino group, optionally substituted with R^1 ; R^3 and R^4 are, independently from each other, cyano; $-COOR^5$; $-COR^6$; $-CONH_2$; $-CONHR^7$; or $-CONR^8R^9$; R^5 , R^6 , R^7 , R^8 and R^9 are, independently from each other, hydrogen; (C_1-C_{20}) -alkyl, wherein one or more methylene groups are optionally replaced by one or more oxygens; (C_1-C_{20}) -haloalkyl; (C_2-C_{20}) -alkenyl, optionally substituted by tri- (C_1-C_5) -alkylsilyl, triphenylsilyl or a group $-Si[CH_3]_n[OSi(CH_3)_3]_{3-n}$, wherein n is 0, 1, 2 or 3.

A safe and effective amount of the organic sunscreen active is used, typically from about 1 wt.-% to about 20 wt.-%, more typically from about 2 wt.-% to about 10 wt.-%.

Other suitable sunscreen actives may also be inorganic sunscreens. Inorganic sunscreens useful herein include the following metallic oxides; titanium dioxide having an average primary particle size of from about 15 nm to about 100 nm, zinc oxide having an average primary particle size of from about 15 nm to about 150 nm, zirconium oxide having an average primary particle size of from about 15 nm to about 150 nm, iron oxide having an average primary particle size of from about 15 nm to about 500 nm, and mixtures thereof. When used herein, the inorganic sunscreens are present in the amount of from about 0.1 wt.-% to about 20 wt.-%, preferably from about 0.5 wt.-% to about 10 wt.-%, more preferably from about 1 wt.-% to about 5 wt.-%.

Vitamin A acetate or palmitate which may be present in the skin care products in an amount from about 0.01 wt.-% to about 1.00 wt.-%.

The term ascorbic acid derivative for use in accordance with the present invention may be any non-toxic, non skin-irritating water-soluble or oil-soluble ascorbic acid derivative. Example of such oil soluble derivatives are ascorbyl palmitate, ascorbyl tetraisoalmitate, ascorbyl linoleate, ascorbyl octanoate. Preferred are water soluble ascorbyl derivatives such as sodium ascorbyl phosphate, magnesium ascorbyl phosphate and ascorbyl glycoside. The amount of ascorbic acid derivative in the skin care product for use in accordance with the present invention is suitably in the range from about 0.1 wt.-% to about 5 wt.-%.

A vitamin E derivative for use in the present invention is tocopheryl acetate. Tocopheryl acetate may be present in the skin care products in an amount from about 0.05 wt.-% to about 5 wt.-%. Another vitamin E derivative of interest is tocopheryl linoleate. Tocopheryl linoleate may be present in the skin care composition in an amount from about 0.05 wt.-% to about 5 wt.-%.

Examples of vitamins from the B complex for use in the present invention are vitamin B₃, B₆ and biotin. Vitamin B₃ may be present in the skin care products in an amount from about 0.01 wt.-% to about 1.00 wt.-%. Vitamin B₆ may be present in the skin care products in an amount from about 0.01 wt.-% to about 1.00 wt.-%. Biotin may be present in the skin care products in an amount from about 0.001 wt.-% to about 0.5 wt.-%.

Panthenol may be present in the skin care products in an amount from about 0.05 wt.-% to about 5.00 wt.-%. Phytantriol may be present in the skin care products in an amount from about 0.01 wt.-% to about 2.5 wt.-%. Bisabolol may be present in the skin care products in an amount from about 0.05 wt.-% to about 5.00 wt.-%.

Further skin lightening agent which may be used in the present invention in combination with bis-pantoyl-cystamine are Kojic acid or derivatives thereof, which may be present in the skin care products of the present invention in an amount from about 0.05 wt.-% to about 5 wt.-%;

Arbutin or derivatives thereof, which may be present in the skin care products of the present invention in an amount from about 0.05 wt.-% to about 5 wt.-%;

Hydroquinone or derivatives thereof, which may be present in the skin care products of the present invention in an amount from about 0.05 wt.-% to about 2 wt.-%;

Phyllanthus Emblica fruit extract (trade name: EmblicaTM), which may be present in the skin care compositions of the present invention in an amount from 0.05 wt.-% to about 3 wt.-%;

Leucocyte extract, which may be present in the skin care compositions of the present invention in an amount from 0.05 wt.-% to about 3 wt.-%;

Bearberry extract, which may be present in the skin care compositions of the present invention in an amount from 0.05 wt.-% to about 3 wt.-%;

Licorice extract, which may be present in the skin care compositions of the present invention in an amount from 0.05 wt.-% to about 3 wt.-%; and

Mulberry extract, which may be present in the skin care compositions of the present invention in an amount from 0.05 wt.-% to about 3 wt.-%.

A safe and effective amount of a desquamation active may be added to the compositions of the present invention, more preferably from about 0.1% to about 10%, even more preferably from about 0.2% to about 5%, by weight of the composition. Desquamation actives enhance the skin appearance benefits of the present invention. One desquamation system that is suitable for use herein contains sulfhydryl compounds and zwitterionic surfactants and is described in U.S. Pat. No. 5,681,852, to Bissett, incorporated herein by reference. Another desquamation system that is suitable for use herein contains salicylic acid and zwitterionic surfactants and is described in U.S. Pat. No. 5,652,228 to Bissett, incorporated herein by reference. Zwitterionic surfactants such as described in these applications are also useful as desquamatory agents herein, with cetyl betaine being particularly preferred.

The necessary amounts of the cosmetic and dermatological adjuvants and additives can, based on the desired product, easily be determined by the skilled person.

The efficiency of bis-pantoyl-cystamine for use in accordance with the present invention can, e.g., be shown by its ability to inhibit melanin production in human primary melanocytes using the methods described below. In these tests, a mixture of bis-pantoyl-cystamine diastereomers as obtainable by the process described below in paragraph D. was used.

1. Human melanocyte based assay for melanogenesis

Normal human melanocytes were obtained from freshly excised foreskin of skin type II/III or IV-VI. Human melanocytes were maintained in 75cm² culture flasks in melanocyte growth medium M2 supplemented with 1% Pen/Step at 37°C in a water-saturated, 5% CO₂ in air atmosphere. Cultured melanocytes were placed in a 6-well plate at a density of 120.000 cells/well, 2-3 days precultivated and over 5 days treated with daily renewed agents at designated concentrations. In the case of stimulation we irradiated the melanocytes once

per day over a period of 5 days with $2.5\text{J}/\text{cm}^2$ from a Philips Sunmobile as UV-A source in DMEM without phenolred, plus 0.2% Glucose and 50mM HEPES. Cells from one well were harvested and dissolved in 1N NaOH with vigorous vortexing and 30min incubation in an ultra sound bath. Melanin contents were determined in the supernatant by measuring the absorption of cell lysates at 475nm and by adopting it to a standard curve made with the use of synthetic melanin.

2. Cell-Pellet assay

For this assay human melanocytes were cultured with the agents in designated concentrations in a 6-well plate as mentioned above. Following the lapse of given experimental periods, the cells were harvested and then collected by centrifugation.

3. Melanin content in media

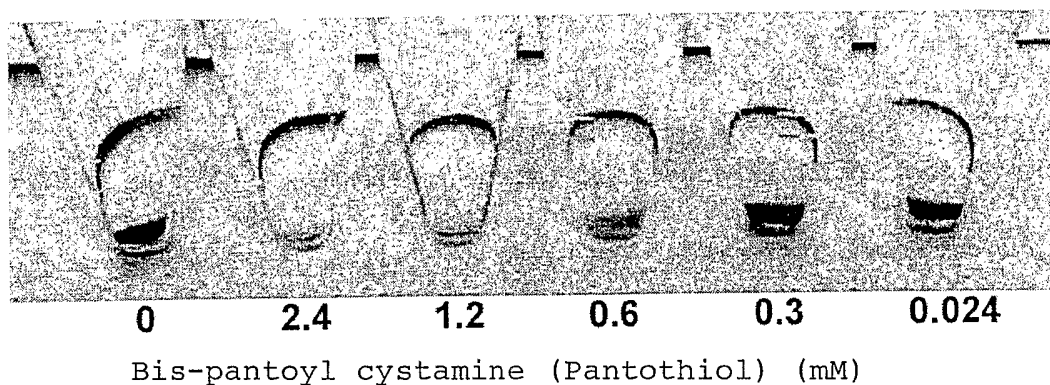
The amount of melanin produced for each well was quantified by assessing melanin released into the culture media. The human melanocyte based assay for melanogenesis were done in a defined volume of colorless growth medium over 5 days. The media from each well were transferred and the amount of melanin were quantified by reading the absorbance spectrum, esp. at 475nm or 530nm.

4. Tyrosinase assay

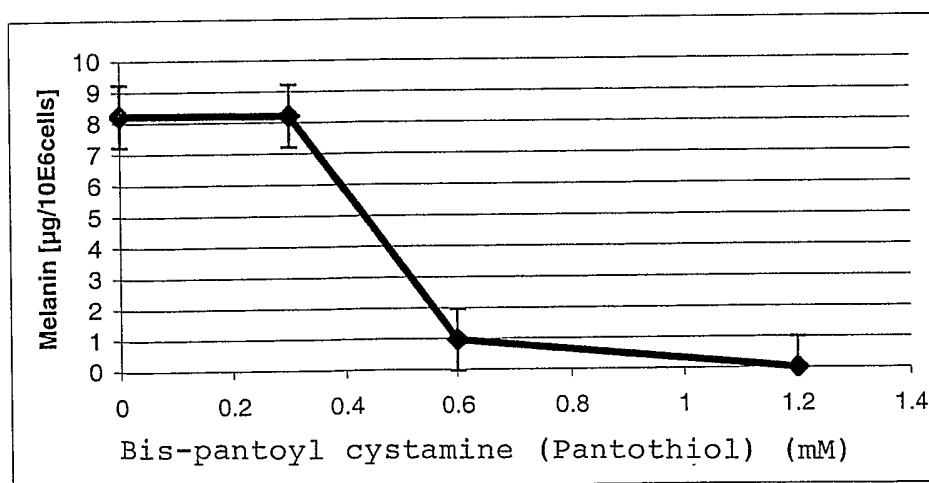
Tyrosinase activity using L-dopa as the substrate was assayed spectrophotometrically. Tyrosinase reaction were performed with 0.1M Sodium phosphate buffer (pH 6.4) containing 5U commercial available mushroom tyrosinase, designated concentrations of L-dopa as the substrate in the presence or absence of agents like bis-pantoyl-cystamine or standard tyrosinase inhibitors as control. The plates were incubated at 37°C for 10, 20 or 30min, respectively, and the absorbance was measured at 465nm in a microplate reader.

Results :

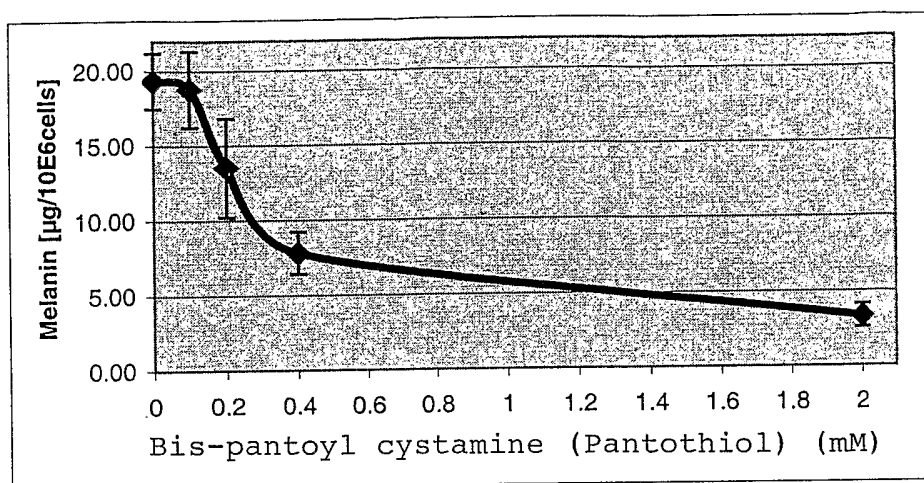
1. Human melanocytes were following treatment collected by centrifugation and photographed. Appearance of the pellets in the absence and presence after 5d treatment with different Bis-pantoyl cystamine concentrations is shown in the figure below.



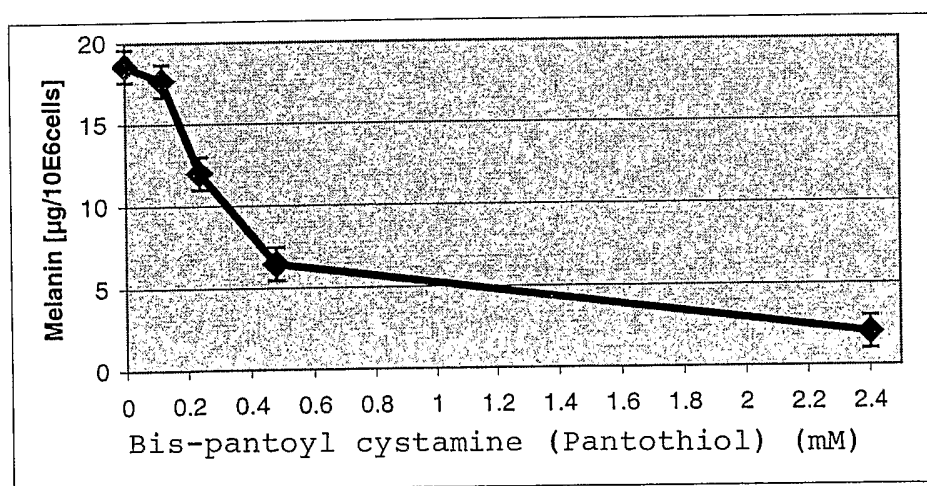
2. As in the methodology described melanin content in human melanocyte culture was calculated in the absence or presence of different Bis-pantoyl cystamine concentrations.
- 2.1. Depigmentation of Bis-pantoyl cystamine in melanocytes from skin type II/III without stimulation via UV-A irradiation.



- 2.2. Depigmentation of Bis-pantoyl cystamine in melanocytes from skin type V without stimulation via UV-A irradiation.



- 2.3. Depigmentation of Bis-pantoyl cystamine in melanocytes from skin type IV after $2.5\text{J}/\text{cm}^2$ UV-A irradiation.



3. The amount of melanin in the cell culture medium were quantified by reading the absorbance spectrum. We were not able to detect any melanin in the media after 8 days cultivation of melanocytes.

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Bis-pantoyl-cystamine as a diastereomeric mixture or enantiomeric pair can be obtained as follows:

A. Preparation of RR-bis-pantoyl-cystamine

36.8 g of R-pantolactone was melted in a 500 mL round bottom flask at 95 °C inner temperature using an oil bath. To the stirred colorless liquid there was added dropwise 21.2 g of cystamin base and 0.94 ml of butanol . After 24 hours of heating the brown sirupy solution was allowed to cool to below 80 °C, then 225 ml of ethylacetate was added dropwise over 20 min. After the addition of 0.6 g of activated charcaol the hot suspension filtered over diatomaceous earth and filter paper. The light yellow clear solution was allowed to cool over the course of 2 hours during which time an oil settled out. The solvent was removed by rotovacuum distillation at 75 °C and 40 mm to yield a yellowish brown oil of 32.0 g crude product. This was chromatographed on 500 g of silica gel using a 9:2 mixture of ethylacetate and ethanol The homogeneous fractions were evaporated, then dried by heating in vacuo at 70 °C and 0.25 mm for 40 hours to yield 18.4 g of RR-bis-pantoyl-cystamine as a glassy orange-coloured oil. HPLC analysis showed a purity of 95% with a diastereomer ratio of 3:96 of RS meso and RR/SS isomers. (The small amount of products of the S isomer results from S isomer in the R-pantolactone.) This sample remained a glass on storage at room temperature for over 2 months. NMR data were consistent with the structure assigned.

B. Preparation of SS-bis-pantoyl-cystamine

2 g of S-pantolactone was melted at 95 C internal temperature in a round bottom flask 1.16 g of cystamin base was added dropwise followed by 0.05 ml of butanol and the mixture was stirred for 22 hours. The were added to the brown sirupy mixture

12 ml of ethyl acetate and 0.03 g of activated charcoal, the mixture filtered through diatomaceous earth and paper, and the filtrate evaporated in vacuo. The resulting yellow oil was chromatographed on silica and the recovered product dried by heating at 70 °C at 0.25mm to constant weight. There was obtained 0.74 g of orange glass comprised of 94 % of SS-bis-pantoyl-cystamine along with 2 % of its RS meso isomer (by HPLC analysis). This substance did not crystallize on storage at room temperature for 2 months.

C. Preparation of the RR/SS bis-pantoyl-cystamine (enantiomeric pair)

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208 mg of the RR isomer and 208 mg of the SS isomer were mixed and kept at room temperature under argon overnight during which the mixture crystallized. 170 mg of the mixture was recrystallized from 8 mL of methanol-ethyl acetate (3:5) to give 134 mg of beige crystals of RR/SS bis-pantoyl-cystamine (enantiomeric pair) melting point ca. 145 °C.

D. Preparation of mixture of RR/SS- and RS-bis-pantoyl-cystamine.

121.5 g of DL-pantolactone was melted in a 2.5 L round bottom flask at an inner temperature of 95 °C. To this there was added dropwise 73.7 of cystamin base and 1.0 g of n-butanol. The mixture was stirred and heated for 16 hours, then the resulting sirupy brown solution was cooled to below 80 °C and was added over 20 minutes 744 ml of ethyl acetate and 2.0 g of activated charcoal, then the mixture was filtered over a teflon membrane filter. The clear filtrate was allowed to cool over the course of 2 hours to room temperature during which at about 50 °C crystallization occurred. The mixture was allowed to stir at room temperature for 3 hours, cooled to 10°C, held for 30 minutes, then filtered, and the solids rinsed with 150 ml of ethyl acetate (10 °C) After 12 hours drying at 50 °C at 4mm there were obtained 165.8 g of beige solids consisting of 96 % by weight of a mixture of diastereomers of bis-pantoyl-cystamine. HPLC analysis showed this to be composed of a mixture of 41 % RS- isomer with 56% of the RR/SS-enantiomeric pair.

The following examples, which are to construed in a non-limitative manner, illustrate the preparation of a number of effective formulations of the invention.

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Example 1Skin Lightening Cream (O/W)

<u>Ingredients</u>	<u>% (w/w)</u>
A) Estol 3650 (Glyceryl Myristate)	5.00
Lanette 16 (Cetyl Alcohol)	2.00
Amphisol A (Cetyl Phosphate)	2.00
Tegosoft M (Isopropyl Myristate)	10.00
Vitamine E Acetate (Tocopheryl Acetate)	0.50
Almond Oil	2.00
BHT	0.05
Phenonip (Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben & Isopropylparaben)	0.60
B) Tris (Tromethamine)	0.90
C) Water	Ad 100
EDETA BD (Disodium EDTA)	0.10
Propylene Glycol	5.00
Transcutol (Ethoxydiglycol)	10.00
Bis-pantoyl-cystamine	2.00
D) Sepigel 305 (Polyacrylamide & C13-14 Isoparaffin & Laureth-7)	2.00
E) Triethanolamine	q.s.

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Example 2Skin Lightening Cream (O/W)

<u>Ingredients</u>	<u>% (w/w)</u>
A) Estol 3650 (Glyceryl Myristate)	5.00
Lanette 16 (Cetyl Alcohol)	2.00
Brij 72 (Steareth-2)	2.00
Brij 721 (Steareth-21)	2.00
Tegosoft M (Isopropyl Myristate)	10.00
Bisabolol	0.20
Vitamine E Acetate (Tocopheryl Acetate)	1.00
Almond Oil	2.00
BHT	0.05
Phenonip (Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben & Isopropylparaben)	0.60
B) Water	Ad 100
EDETA BD (Disodium EDTA)	0.10
Propylene Glycol	10.00
Sodium Ascorbyl Phosphate	1.00
Arbutin	1.00
D-Panthenol	0.50
Niacinamide	0.20
Salicylic acid	0.50
Bis-pantoyl-cystamine	1.00
C) Sepigel 305 (Polyacrylamide & C13-14 Isoparaffin & Laureth-7)	2.00
D) Triethanolamine	q.s.

Example 3Skin lightening cream with UV protection (indicativeSPF: 8, O/W)

<u>Ingredients</u>	<u>% (w/w)</u>
A) Estol 3650 (Glyceryl Myristate)	5.00

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Lanette 16 (Cetyl Alcohol)	2.00
Brij 72 (steareth-2)	2.00
Brij 721 (steareth-21)	2.00
Tegosoft M (Isopropyl Myristate)	10.00
BHT	0.05
Ascorbyl Palmitate	0.50
Parsol 1789 (Butyl Methoxydibenzoylmethane)	1.00
Parsol MCX (Ethyl Hexylmethoxycinnamate)	2.00
Eusolex OS (Octyl Salicylate)	2.00
Phenonip (Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben & Isopropylparaben)	0.60
B) Water	Ad 100
EDETA BD (Disodium EDETA)	0.10
Bis-pantoyl-cystamine	2.00
Propyleneglycol	8.00
C) Sepigel	2.00
D) Triethanolamine	q.s.

Example 4Skin Lightening Cream(W/O)

<u>Ingredients</u>	<u>% (w/w)</u>
A) Cremophor WO7 (PEG-7 Hydrogenated Castor Oil)	6.00
Elfacos ST 9 (PEG-45/Dodecyl Glycol Copolymer)	2.00
Myritol 318 (Caprylic/Capric Triglyceride)	5.00
Lunacera M (Micro wax)	2.00
Paraffin Oil	10.00
Resveratrol	0.50
Phytantriol	0.10
Vitamine E Acetate (Tocopheryl Acetate)	1.00
Jojoba Oil	5.00
BHT	0.05
Phenonip (Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben &	0.60

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	Isopropylparaben)	
B)	Water	Ad 100
	EDETA BD (Disodium EDTA)	0.10
	D-Panthenol	0.50
	Propylene Glycol	5.00
	Kojic Acid	1.00
	Bis-pantoyl-cystamine	1.00

Example 5Skin Lightening Gel

	<u>Ingredients</u>	<u>% (w/w)</u>
A)	Pemulen TR-1 (Acrylate/C10-30 Alkyl Acrylate Crosspolymer)	0.80
	Biotin	0.01
	Water	Ad 100
B)	EDETA BD (Disodium EDTA)	0.10
	D- Panthenol	0.20
	Hyasol BT (Sodium Hyaluronate)	1.00
	Euxyl K 400 (Methyldibromo Glutaronitrile & Phenoxyethanol)	0.20
C)	NaOH (30%)	1.00
D	Water	12.00
	Transcutol (Ethoxydiglycol)	10.00
	Propylene Glycol	5.00
	Epigallocatechin Gallate	0.50
	Genistein	0.10
	Niacinamide	0.50
	Emblica (Phyllanthus Emblica fruit extract)	0.50
	Hydroquinone	0.20
	Bis-pantoyl-cystamine	2.00
E)	Citric Acid (10%)	q.s.

Example 6Skin Lightening Lotion

	<u>Ingredients</u>	<u>% (w/w)</u>
A)	Water	Ad 100

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Propylene Glycol	5.00
Bis-pantoyl-cystamine	1.00
D-Panthenol	0.50
Sodium PCA	0.25
Ethanol	10.00
B) Citric Acid (10%)	q.s.

Example 7

Skin lightening cream with UV protection
(indicative SPF: 8, O/W)

<u>Ingredients</u>	% (w/w)
A) PARSOL SLX (Dimethico Diethylbenzalmalonate)	8.00
Uvinul Titanium Dioxide (Titanium Dioxide)	2.00
Tegosoft TN (C12-15 Alkyl Benzoate)	5.00
Silicone 2503 Cosmetic Wax (Stearyl Dimethicone)	2.00
Cetyl Alcohol	1.00
Butylated Hydroxytoluene (BHT)	0.05
Estol GMM 3650 (Glyceryl Myristate)	4.00
Edeta BD (Disodium EDTA)	0.10
Phenonip (Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben)	0.60
AMPHISOL K (Potassium Cetyl Phosphate)	2.00
B) Water deionized	Ad 100
Carbopol 980 (Carbomer)	10.00
Bis-pantoyl-cystamine	1.00
Propylene Glycol	5.00
C) KOH sol. 10%	0.50

Example 8

Skin Lightening Gel

<u>Ingredients</u>	% (w/w)
A) Pemulen TR-1 (Acrylate/C10-30 Alkyl Acrylate Crosspolymer)	0.80
Water	Ad 100
B) EDETA BD (Disodium EDTA)	0.10
D- Panthenol	0.10

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	Hyasol BT (Sodium Hyaluronate)	1.00
	Euxyl K 400 (Methyldibromo Glutaronitrile & Phenoxyethanol)	0.20
C)	NaOH (30%)	1.00
D	Water	12.00
	Transcutol (Ethoxydiglycol)	10.00
	Propylene Glycol	5.00
	Melawhite (Water and Leucocyte extract)	1.00
	Kojic Acid	0.50
	Niacinamide	0.50
	Hydroquinone	0.50
	Bis-pantoyl-cystamine	1.00
E)	Citric Acid (10%)	q.s.

Example 9Skin Lightening Gel

	<u>Ingredients</u>	% (w/w)
A)	Pemulen TR-1 (Acrylate/C10-30 Alkyl Acrylate Crosspolymer)	0.80
	Biotin	0.01
	Water	Ad 100
B)	EDETA BD (Disodium EDTA)	0.10
	D- Panthenol	0.10
	Hyasol BT (Sodium Hyaluronate)	1.00
	Euxyl K 400 (Methyldibromo Glutaronitrile & Phenoxyethanol)	0.20
C)	NaOH (30%)	1.00
D	Water	12.00
	Transcutol (Ethoxydiglycol)	10.00
	Propylene Glycol	5.00
	Melfade (Water and Glycerin and Bearberry extract)	1.00
	Kojic Acid	0.50
	Niacinamide	0.50
	Bis-pantoyl-cystamine	1.00
E)	Citric Acid (10%)	q.s.

Example 10Skin Lightening Gel

<u>Ingredients</u>	<u>% (w/w)</u>
A) Pemulen TR-1 (Acrylate/C10-30 Alkyl Acrylate Crosspolymer)	0.80
Water	Ad 100
B) EDETA BD (Disodium EDTA)	0.10
D- Panthenol	0.10
Hyasol BT (Sodium Hyaluronate)	1.00
Euxyl K 400 (Methyldibromo Glutaronitrile & Phenoxyethanol)	0.20
C) NaOH (30%)	1.00
D Water	12.00
Transcutol (Ethoxydiglycol)	5.00
Propylene Glycol	10.00
Licorice extract	0.50
Mulberry extract	0.50
Kojic Acid	0.50
Niacinamide	0.50
Bis-pantoyl-cystamine	0.50
E) Citric Acid (10%)	q.s.

Example 11Skin Lightening Gel

<u>Ingredients</u>	<u>% (w/w)</u>
A) Carbopol ETD 2020 (Carbomer)	0.80
Water	Ad 100
Panthenol	0.50
Niacinamide	0.10
B) NaOH (30%)	0.50
C) Ethanol	35.00
Propylene Glycol	8.00
Bis-pantoyl-cystamine diacetate	2.00

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Example 12

Skin lightening cream with UV protection
(indicative SPF: 8, O/W)

	<u>Ingredients</u>	<u>% w / w</u>
A)	Parsol 1789 (Butyl Methoxydibenzoylmethane)	1.50
	Uvinul Titanium Dioxide (Titanium Dioxide)	3.00
	Parsol MCX (Ethyl Hexylmethoxycinnamate)	4.00
	Tegosoft TN (C12-15 Alkyl Benzoate)	8.00
	Silicone 2503 Cosmetic Wax (Stearyl Dimethicone)	2.00
	Cetyl Alcohol	1.00
	Butylated Hydroxytoluene (BHT)	0.05
	Estol GMM 3650 (Glyceryl Myristate)	4.00
	Edeta BD (Disodium EDTA)	0.10
	Phenonip (Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben)	0.60
	AMPHISOL K (Potassium Cetyl Phosphate)	2.00
B)	Water deionized	Ad 100
	Carbopol 980 (Carbomer)	10.00
	Bis-pantoyl-cystamine	2.00
	Propylene Glycol	5.00
C)	KOH sol. 10%	0.50

Example 13

Skin lightening cream with UV protection
(indicative SPF: 10, O/W)

	<u>Ingredients</u>	<u>% w / w</u>
A)	PARSOL SLX (Polysilicone 15)	6.00
	PARSOL 1789 (Butyl Methoxydibenzoylmethane)	2.00
	Parsol MCX (Ethyl Hexylmethoxycinnamate)	4.00
	Softisan 100 (Hydrogenated Coco-Glycerides)	2.00
	Glyceryl Myristate	4.00
	Myritol 318 (Caprylic/Capric Triglyceride)	7.00
	Cosmacol ESI (Tridecyl Salicylate)	8.00
	VITAMIN E ACETATE (Tocopheryl Acetate)	0.50
	Phenonip (Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben)	0.80

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	AMPHISOL K (Potassium Cetyl Phosphate)	2.00
B)	Deionized water	ad 100
	1,2-Propylene Glycol (Propylene Glycol)	5.00
	Carbopol ETD 2020 (Acrylate/C10-30 Alkyl Acrylate Crosspolymer)	0.30
	Edeta BD (Disodium EDTA)	0.10
C)	KOH 10% sol.(Potassium Hydroxide)	1.60
D)	STAY-C 50 (Sodium Ascorbyl Phosphate)	1.00
	Bis-pantoyl-cystamine	2.00
	Deionized water	3.00
E)	Retinyl Palmitate	0.50
	VITAMIN E (Tocopherol)	0.10

Example 14Skin lightening liquid soap

	<u>Ingredients</u>	<u>% w / w</u>
A)	Texapon NSO (Sodium Laureth Sulfate)	40.00
	Tego Betain L7 (Cocamidopropyl Betaine)	10.00
	Lamepon S (Potassium Cocoyl Hydrolysed Collagen)	5.00
	Plantaren 1200 (Lauryl Glucoside)	5.00
	Cetiol HE (PEG-7 Glyceryl Cocoate)	3.00
	Preservative	q.s.
B)	Polymer JR 400 (Polyquaternium-10)	0.20
	Water (Aqua)	Ad 100
	Panthenol 75 L (Panthenol)	0.40
	Bis-pantoyl-cystamine	1.00
	EDETA BD (Disodium EDTA)	0.10
C)	Vitamine E Acetate (Tocopheryl Acetate)	0.30
	Cremophor RH 40 (PEG-40 Hydrogenated Castor Oil)	2.00
D)	Sodium Chloride	1.00

What is claimed is:

1. Topical compositions which comprise bis-pantoyl-cystamine or a derivative thereof, and a vehicle conventionally used in topical compositions.
2. A composition as in claim 1 wherein the bis-pantoyl-cystamine is selected from at least one of RR-, SS-, RS (meso)- and RR/SS- bis-pantoyl-cystamine.
3. A composition as in claim 1 wherein the bis-pantoyl-cystamine is the enantiomeric pair, RR/SS-bis-pantoyl-cystamine, or R,S- (meso-) bis-pantoyl-cystamine, or mixtures thereof.
4. A composition as in claim 1 wherein the bis-pantoyl-cystamine is the diastereomeric mixture of RR/SS-bis-pantoyl-cystamine and R,S- (meso-) bis-pantoyl-cystamine wherein the molar ratio of RS(meso) : RR/SS is within the range from about 50:50 to about 30:70.
5. A composition as in any one of claims 1-4, wherein bis-pantoyl-cystamine is present in amount from 0.05 to 5.00 wt.-%
6. A composition as in any one of claims 1-4, wherein bis-pantoyl-cystamine-diacetate is present in amount from 0.05 to 5.00 wt.-%
7. A composition as in any one of claims 1-6 for cosmetic and pharmaceutical use, for lightening of the skin, for the treatment of hyperpigmented skin disorders and for preventing tanning of the skin.
8. A composition as in claim 7 which is a cream, a gel, an ointment, a lotion, a tincture, a spray, a mousse, a cleansing composition or a foam.
9. A composition according to any one of claims 1-8 comprising bis-pantoyl-cystamine or a derivative thereof in combination with one or more agents selected from UV screening agents, vitamin A or derivatives thereof, ascorbic acid or ascorbic acid derivatives, vitamin E or derivatives thereof, a vitamin from the B complex, panthenol, phytantriol, bisabolol or derivatives thereof, Kojic acid or derivatives thereof, Arbutin or derivatives thereof, hydroquinone or derivatives thereof, Genistein or derivatives thereof, Epigallocatechin gallate or derivatives thereof, Resveratrol or derivatives thereof, Phyllanthus Emblica fruit extract, Leucocyte extract, Bearberry extract, Licorice extract and Mulberry extract .

10. A composition according to claim 9 wherein the organic sunscreen is selected from the group consisting of butylmethoxydibenzoylmethane, 2-(4-ethoxy-anilinomethylene)-propanedioic acid diethyl ester, ethylhexylmethoxycinnamate, ethylhexyl salicylate, octocrylene, 2-phenylbenzimidazole-5-sulphonic acid, dimethico diethylbenzalmalonate, 2,4-bis((4-(ethyl-hexyloxy)-2-hydroxy)-phenyl)-6-(4-methoxyphenyl)-1,3,5-triazine, and 2,2'-methylene-bis-(6(2H-benzotriazol-2-yl)-4-(1,1,3,3,-tetramethylbutyl)phenol)
11. A composition according to claim 9 wherein the inorganic sunscreen is selected from the group consisting of titanium dioxide and zinc oxide.
12. The use of bis-pantoyl-cystamine or a derivative thereof in the manufacture of a topical composition for lightening of the skin, for the treatment of hyperpigmented skin disorders and for preventing tanning of the skin.
13. The use in accordance with claim 12 wherein the bis-pantoyl-cystamine is selected from at least one of RR-, SS-, RS (meso)- and RR/SS- bis-pantoyl-cystamine.
14. The use in accordance with claim 12 wherein the bis-pantoyl-cystamine is the enantiomeric pair, RR/SS-bis-pantoyl-cystamine, or R,S- (meso-) bis-pantoyl-cystamine, or mixtures thereof.
15. The use in accordance with claim 12 wherein the bis-pantoyl-cystamine is the diastereomeric mixture of RR/SS-bis-pantoyl-cystamine and R,S- (meso-) bis-pantoyl-cystamine wherein the molar ratio of RS(meso) : RR/SS is within the range from about 50:50 to about 30:70.
16. The use in accordance with any one of claims 12-15, wherein bis-pantoyl-cystamine is present in amount from 0.05 to 5.00 wt.-%
17. The use in accordance with any one of claims 12-15, wherein bis-pantoyl-cystamine-diacetate is present in amount from 0.05 to 5.00 wt.-%.
18. A method of lightening the skin, treatment of hyperpigmented skin disorders, and preventing tanning of the skin, which comprises topically administering to a person in need of such treatment an effective amount of bis-pantoyl-cystamine or a derivative thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/10702

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WITTMER, CARL.T. ET AL.: "Purification and Properties of a Pantethein-hydrolyzing Enzyme from Pig Kidney"</p> <p>THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 258, no. 16, 25 August 1983 (1983-08-25), pages 9733-9738, XP002264940</p> <p>page 9735, right-hand column, paragraph 2; table III</p> <p>& DATABASE CAPLUS; AN 1983:554225</p> <p>'Online!</p> <p>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 12 May 1984 (1984-05-12)</p> <p>* see IT *</p> <p>abstract</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1,2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

15 December 2003

Date of mailing of the international search report

05/01/2004

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Minas, S

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/10702

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIMUZU, MASAO ET AL.: "Investigations on panthothenic acid and its related compounds" CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 18, no. 4, 1970, pages 838-841, XP008025764 cited in the application * Chart 2 on page 840 *	1-3
X	--- DATABASE CAPLUS; ; AN: 1960:129522 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 April 2001 (2001-04-22) ARIYAMA, H., KIMURA, S.: "Pantothenic acid antagonist" XP002264999 * see IT * abstract & JOURNAL OF VITAMINOLOGY, vol. 6, 1960, pages 52-61, ISSN: 0022-5398	1-3
A	--- US 5 523 077 A (BOLOGNIA JEAN L ET AL) 4 June 1996 (1996-06-04) claim 5	1-18
A	--- US 4 749 719 A (TAKI TOSHIO ET AL) 7 June 1988 (1988-06-07) the whole document	1-18
A	--- QIU, LING ET AL.: "Inhibition of melanin synthesis by cystamine in human melanoma cells" THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 114, no. 1, January 2000 (2000-01), pages 21-27, XP002264941 the whole document	1-18
A	--- FRANCHI, JOCELYNE ET AL.: "Depigmenting effects of calcium D-pantetheine-S-sulfonate on human melanocytes" PIGMENT CELL RESEARCH, vol. 13, 2000, pages 165-171, XP002264942 the whole document -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/10702

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

Although claim 18 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds and compositions.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/10702

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5523077	A	04-06-1996	NONE	
US 4749719	A	07-06-1988	JP 60064922 A IT 1179435 B KR 9109995 B1	13-04-1985 16-09-1987 10-12-1991