



(51) International Patent Classification:

A61K 31/425 (2006.01) A61K 31/216 (2006.01)
A61K 31/351 (2006.01) A61K 31/166 (2006.01)
A61K 31/522 (2006.01) A61K 31/12 (2006.01)
A61K 31/39 (2006.01) A61K 31/245 (2006.01)
A61K 31/375 (2006.01) A61K 31/194 (2006.01)
A61K 31/4412 (2006.01) A61K 31/616 (2006.01)
A61K 31/536 (2006.01) A61K 31/4035 (2006.01)
A61K 31/192 (2006.01) A61K 31/513 (2006.01)
A61K 31/122 (2006.01) A61Q 19/02 (2006.01)
A61K 31/343 (2006.01) A61Q 19/08 (2006.01)

(21) International Application Number:

PCT/SG2017/050030

(22) International Filing Date:

19 January 2017 (19.01.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10201600391R 19 January 2016 (19.01.2016) SG

(71) Applicant: **NAMZ PTE. LTD.** [SG/SG]; 1 Cleantech Loop, #03-13 CleanTech One, Singapore 637141 (SG).

(72) Inventors: **CHEETHAM, Peter Samuel James**; 3 Chargingworth Drive, Hatton Park, Nr Warwick, Warwickshire, CV35 7SY, United Kingdom (GB). **LANGWALLNER, Christoph**; 73 Jurong West Central 3, The Centris, #05-19, Singapore 648336 (SG). **LANGWALLNER, Margit**; 73 Jurong West Central 3, The Centris, #05-19, Singapore

648336 (SG). **TAN, Wen Jue Amelia**; 426 Clementi Avenue 3, #08-500, Singapore 120426 (SG).

(74) Agent: **ALLEN & GLEDHILL LLP**; One Marina Boulevard #28-00, Singapore 018989 (SG).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: A COSMETIC COMPOSITION AND THE USE THEREOF FOR REGULATING SKIN QUALITY



(I)

(57) Abstract: The present invention relates to cosmetic or personal care compositions comprising two or more compounds, each compound containing an allylic or partially allylic carbonylsubstructure having the following structure I: wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of (i) hydroxyl-based group including -OH or -C(=O)-OH; (ii) carbonyl-based group including -C(=O)-C(=O)-CH₃; (iii) ether group, -O-; (iv) sultam group, -N(H)-S(=O)₂-; (v) lactam group, -N(H)-C(=O)-; (vi) apolar group including cyclic structures based on menthol or carotenoids; (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or -N(H)-C(H)=N-; (viii) amine group, -NH₂; (ix) secondary amine-based group, -N(H)-; and (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-, their derivatives, isomers, salts and/or combination thereof; and a cosmetically acceptable vehicle.



WO 2017/127025 A1

A COSMETIC COMPOSITION AND THE USE THEREOF FOR REGULATING SKIN QUALITY

FIELD OF THE INVENTION

5

The present invention relates to cosmetic compositions and methods for regulating skin quality.

BACKGROUND

10

The following discussion of the background to the invention is intended to facilitate an understanding of the present invention. However, it should be appreciated that the discussion is not an acknowledgment or admission that any of the material referred to was published, known or part of the common general knowledge in any jurisdiction as at
15 the priority date of the application.

Cosmetics and personal care products that lighten the skin are important in many countries worldwide, and especially in Asia. Skin lightening products work by preventing the darkening of the skin due to the action of sunlight and by endogenous hormones. Skin
20 tanning and darkening is due to the formation of melanin in melanocyte cells in the dermis layer of the skin by a metabolic pathway that begins with phenylalanine and then tyrosine, and is transferred in the form of melanosomes into keratinocytes that migrate into the epidermis to provide protection against ultraviolet (UV) light to the cells below them. A range of melanins can be produced which vary in colour from individual to individual
25 depending on their genetics and exposure to sunlight. There are two general types, eumelanins that are black-brown, and then pheomelanins that are brown-red or even lighter in colour that are formed by the incorporation of cysteine and sometimes other compounds such as glutathione and cysteine into the melanin polymer.

30 The melanogenesis metabolic pathway takes place in melanocyte cells and begins with tyrosine that is converted into dopaquinone via L-3, 4-dihydroxyphenylalanine (L-dopa) by the cresolase and then catecholase activities of the enzyme tyrosinase. Dopaquinone then reacts in two ways, either incorporating cysteine or glutathione to form cysteinyl-dopa for example, that lead to the formation of pheomelanins, or dopaquinone is converted into
35 dihydroxyindole carboxylic acid (DHICA or leucodopachrome) by tyrosinase-like protein 2 (TLP2-DHICA isomerase or tautomerase). DHICA then reacts with tyrosinase-like protein 1 (TLP1-DHICA oxidase) to form dopachrome, which then spontaneously decarboxylates

forming dihydroxyindole, and is then oxidised into 5,6-dihydroxyquinolone. These various indoles polymerise to form melanins of various forms depending on the various indole intermediates produced as mentioned above.

5 Skin lighteners can work at various stages in this pathway. One of the most common sites of action of skin lighteners is the inhibition of the tyrosinase enzyme that converts tyrosine into L-dopa. Commonly used skin lightener active ingredients of cosmetics include kojic acid (KA), which inhibits tyrosinase, and possibly other tyrosinase-like proteins that act at
10 subsequent stages in the melanogenesis pathway. Other skin lightener active ingredients have different mechanisms of action, for instance niacinamide inhibits the transfer of melanin from melanosomes to keratinocytes, and alpha- and beta-arbutins that are glycosides of hydroquinone which has a bleaching action on the melanin itself.

Another approach to achieving skin lightening is to use materials that affect the signalling
15 pathways that control melanogenesis. A number of signalling pathways have been identified such as involving compounds such as nitric oxide that activates guanylate kinase to produce cyclic guanosine monophosphate (cGMP) that stimulates melanogenesis, and diacylglycerides that are formed by UV radiation and that activate protein kinase C β (PKC beta) which phosphorylates and thereby activates tyrosinase.

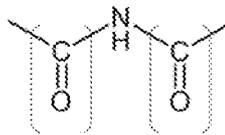
20

The melanogenesis metabolic pathway is initiated in two main ways, either endogenously or UV-initiated. In the former the pituitary gland produces alpha-melanocyte stimulating hormone (α -MSH) by the selective cleavage of the precursor peptides pro-
25 opiomelanocortin (POMC) and then adrenocorticotrophic hormone (ACTH). α -MSH and ACTH bind to the melanocortin receptor 1 (MC1-R), which is located at the surface of the membrane of the melanocyte, which activates adenylyl cyclase to produce cyclic adenosine monophosphate (cAMP) which activates protein kinase A to activate the transcription factor, cAMP response element-binding protein (CREB), and to stimulate the microphthalmia-associated transcription factor (MITF) that in turn stimulates the synthesis
30 of the tyrosinase and other proteins involved in the production of melanin as well as the Rab27a gene and the production of the melanophilin protein that is involved in the transport of melanin in the form of melanosomes along the dendrites of the melanocyte, from which it is transferred into keratinocytes by phagocytosis, a process that is controlled by the G protein coupled receptor (GPCR) protease-activated receptor 2 (PAR-2).

35

The role of MC1-R in melanogenesis is complex. In the absence of stimulation by α -MSH it tends to produce pheomelanins, and there appears to be considerable heterogeneity in the MC1-Rs present in different people also resulting in the formation of different melanins and thus the possession of skins of different tones and degrees of darkness and lightness.

Another way in which melanogenesis is initiated is by the UV photons in sunlight. These have three main effects. UV generates singlet oxygen, a highly reactive form of dioxygen, in the skin, especially via photosensitisers on the skin such as porphyrins. Also UVB in particular damages DNA in skin cells and as a result excision repair produces dimeric degradation products of the pyrimidine base thymine. Two main types are formed, the most common being cyclobutane dimers (CBDs) together with less numerous but reportedly more active 6,4-photoproducts, both of which contain a common amide based substructure -C(=O)-NH-C(=O)-,



15

and with CBD formation and melanogenesis having the same action spectrum so proving that UV does induce melanogenesis. The CBDs stimulate melanogenesis by up-regulating and activating the p53 tumor suppressor system in keratinocytes, with the p53 acting as a transcription factor binding to the POMC promoter stimulating the formation of POMC which is selectively catabolised to form α -MSH, ACTH and endorphins. α -MSH binding to MC1-R also has the effect of activating the MITF system in a similar way to the cytokines as above. In addition, α -MSH also binds to receptors on the melanocyte surface such as MC1-R, which then activates adenylyl cyclase, and eventually MITF as described above resulting in activating the tyrosinase and other enzymes such as the tyrosinase-like proteins 1 and 2 that are essential for melanin formation. Another pathway by which UV stimulates melanogenesis is by it directly stimulating keratinocytes and fibroblasts in the skin, which produce Stem Cell Factor (SCF) in response, which then binds to its cKit receptor (cKitR) which induces mitogen activated protein kinases (MAPKs) that phosphorylate and thus activate MITF which activates the melanogenesis pathway as described above.

30

These processes involving MC1-R are known to be antagonised by agouti signalling peptides, which act as antagonists to the binding of α -MSH to the MC1-R, and has the

effect of reducing melanin formation and of increasing the proportion of pheomelanins that are produced in the absence of α -MSH, and thus the modifying the skin tone of people to a more red tone.

5 Singlet oxygen stimulates keratinocytes and fibroblasts to produce cytokines, especially endothelin receptor type B-1 (ETB1), SCF and hepatocyte growth factor (HGF). These bind to receptors on the melanocytes with ETB1 and SCF binding to the receptors endothelin receptor type B-2 (ETB2) and cKitR respectively. Once activated these receptors stimulate the MITF system in the nucleus of the melanocytes, for instance the
10 binding of SCF to its cKitR induces mitogen activated protein kinase which phosphorylates MITF thereby activating it. Activated MITF up-regulates the production of a number of proteins including tyrosinase, tyrosinase-like protein 1 (TLP1) and tyrosinase-like protein 2 (TLP2) that catalyse essential stages in the melanogenesis metabolic pathway, and melanophilin that is one of the proteins involved in the transfer of
15 melanin in the form of melanosomes to keratinocytes, involving their binding to Rab27a and moving along the dendrites of the melanocytes via myosin filaments. In addition the formation of the prostaglandin PGE2 is stimulated by singlet oxygen, which in addition to causing inflammation also stimulates the production of matrix metalloproteases (MMPs) that play important roles in skin ageing due to their imperfect repair of damaged skin
20 proteins over very many episodes of sun exposure, and also more specifically by degrading collagen IV in the basement membrane of the skin that leads to the formation of sun spots (*senile lentigo*).

While there are many cosmetic and personal-care products available in the market, the
25 development of improved and efficient formulations in cosmetic and personal-care products for skin lightening, skin quality has and continue to receive significant public interest. Along with this has been the desire to establish cosmetic compositions that provide the features of good skin compatibility especially low irritancy potential, enhanced activity, reduced viscosity, enhanced antimicrobial activity without additional preservatives
30 and prolonged shelf-life. In addition, these features and properties need to be provided in a safe, legal and cost-effective way.

Consequently, there is a need to provide alternative compositions and methods for regulating skin quality that seeks to address at least some of the problems described
35 hereinabove, or at least to provide an alternative.

SUMMARY OF THE INVENTION

In accordance with one aspect of the invention, a cosmetic or personal care composition for regulating skin quality or skin lightening is provided. The composition comprises two or more compounds, each compound containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

10

(i) hydroxyl-based group including -OH or -C(=)-(OH);

(ii) carbonyl-based group including -C(=)-C(=O)-CH₃;

(iii) ether group, -O-;

(iv) sultam group, -N(H)-S(=O)₂-;

15

(v) lactam group, -N(H)-C(=O)-;

(vi) apolar group including cyclic structures based on menthol or carotenoids;

(vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or -N(H)-C(H)=N-;

(viii) amine group, -NH₂;

20

(ix) secondary amine-based group, -N(H)-; and

(x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-;

their derivatives, isomers, salts and/or combination thereof; and a cosmetically acceptable vehicle.

25

In accordance with embodiments of the invention, the two or more compounds are selected from one or more of the following groups:

30

(a) gamma-pyrone compound and their salts thereof having the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the hydroxyl or hydroxyl-based group;

- (b) gamma-pyrone compound and their salts thereof having the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the carbonyl or carbonyl-based group;
- 5 (c) sultam compound and their salts thereof containing the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the sulphonamide group forming a sultam ring structure;
- 10 (d) indole-like compound and their salts thereof composed of bicyclic aromatic and heterocyclic five membered rings containing the allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of an amide group and forming a lactam structure;
- 15 (e) cyclohex-2-enone-like compound and their salts thereof having the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y that contains a second unsaturated bond making the compound diallylic or partially diallylic;
- 20 (f) adenine-like compound and their salts thereof with five and six-membered heterobicyclic structures containing the allylic or partially allylic carbonyl substructure adjacent to the second substructure Y consisting of one or more secondary aldimine groups and one or more secondary amine groups; and
- 25 (g) purine-like or xanthine-like compound and their salts thereof containing the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of a secondary amine group or the N(H)-C(=O)-N(H)-group.

30 In accordance with an embodiment of the invention, the two or more compounds each contain different Y substructure. In accordance with other embodiments of the invention, the two or more compounds each contain different Y substructure, with each of the Y substructures selected from different groups (i)-(x).

35 In accordance with yet other embodiments of the invention, the composition comprises two or more compounds containing the same or different Y substructures selected from the same or different groups (i)-(x), and one or more other skin lightening agents.

In accordance with an embodiment of the invention, the two or more compounds are selected from the group consisting of saccharin, maltol, theobromine, their derivatives, isomers, salts and combination thereof.

- 5 In accordance with another aspect of the invention, a method of regulating skin quality of a subject is provided. The method comprises the step of topically applying an effective amount of the cosmetic or personal care composition of the present invention on the skin of a subject.
- 10 In accordance with a further aspect of the invention, a method of skin lightening comprising the step of topically applying an effective amount of the cosmetic or personal care composition of the present invention on the skin of a subject, for lightening of skin is provided.
- 15 In accordance with yet another aspect of the invention, a method of determining a composition for use in regulating or improving skin quality of a subject is provided. The method comprises measuring skin quality of a subject; identifying two or more compounds with melanogenesis inhibiting activities by selecting two or more compounds, each compound containing an allylic or partially allylic carbonyl substructure having the
- 20 following structure I:



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- 25 (i) hydroxyl-based group including -OH or -C(=)-(OH);
 (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
 (iii) ether group, -O-;
 (iv) sultam group, -N(H)-S(=O)₂-;
 (v) lactam group, -N(H)-C(=O)-;
- 30 (vi) apolar group including cyclic structures based on menthol or carotenoids;
 (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or
 -N(H)-C(H)=N-;
 (viii) amine group, -NH₂;
 (ix) secondary amine-based group, -N(H)-; and
- 35 (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-; and

preparing a formulation based on the measured skin quality so as to improve the skin quality using the identified compounds.

- 5 In accordance with yet a further aspect of the invention, a method of determining a composition for use as a skin lightening agent is provided. The method comprises determining the skin type of a subject; identifying two or more compounds with melanogenesis inhibiting activities by selecting two or more compounds, each compound containing an allylic or partially allylic carbonyl substructure having the following structure

10 I:



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- 15 (i) hydroxyl-based group including -OH or -C(=)-(OH);
 (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
 (iii) ether group, -O-;
 (iv) sultam group, -N(H)-S(=O)₂-;
 (v) lactam group, -N(H)-C(=O)-;
 20 (vi) apolar group including cyclic structures based on menthol or carotenoids;
 (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or
 -N(H)-C(H)=N-;
 (viii) amine group, -NH₂;
 (ix) secondary amine-based group, -N(H)-; and
 25 (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-; and

preparing a formulation based on the determined skin type of the subject using the identified compounds.

- 30 In accordance with a further aspect of the invention, a method of identifying a compound with melanogenesis inhibiting activities is provided. The method comprises selecting a compound containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- (i) hydroxyl-based group including -OH or -C(=)-(OH);
- 5 (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
- (iii) ether group, -O-;
- (iv) sultam group, -N(H)-S(=O)₂-;
- (v) lactam group, -N(H)-C(=O)-;
- (vi) apolar group including cyclic structures based on menthol or carotenoids;
- 10 (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or -N(H)-C(H)=N-;
- (viii) amine group, -NH₂;
- (ix) secondary amine-based group, -N(H)-; and
- (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-.

15

Other aspects of the invention will become apparent to those of ordinary skill in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

20 BRIEF DESCRIPTION OF THE DRAWINGS

In the figures, which illustrate, by way of example only, embodiments of the present invention, in which:

25 Figure 1 is a chart showing the results obtained in a clinical trial. The chart shows the cost-in-use comparison between a product composition containing niacinamide and a product composition containing maltol and sodium saccharin.

Figure 2 shows the relationship between the improvement of skin tone over time in a trial
30 application of the product composition containing maltol and sodium saccharin.

Figure 3 shows the effect of a product composition containing maltol (1.5%) and sodium saccharin (1.5%) on the dark circles and fine lines around the eyes after 28 days of application.

35

Figure 4 shows the antimicrobial activities of maltol and saccharin together on the shelf-life stability of various compositions over a period of 28 days.

Figure 5 shows the colour and emulsion stability of the various test samples after 30 days of storage at 45°C.

5 Figure 6 shows the effects of maltol and sodium saccharin on the viscosities of various formulutory compositions.

Figure 7 shows the improvement of various compositions on changes in the skin melanin index over 14 and 28 days.

10

Figure 8 is a linear regression graph comparing the degree of skin melanin index (SMI) reduction with the usage of maltol and sodium saccharin (M+SS) versus the mean SMI reduction for those using M or SS alone. The difference in the number of people between M+S versus mean (M or S) was calculated for each SMI reduction category, namely (<0, <5, <10, <15, <20, <25, <30, <35, <40, <45, <50, <55) at the 28-day time point.

15

Figure 9 is a linear regression graph comparing the degree of skin melanin index (SMI) reduction with the usage of maltol and sodium saccharin (M+SS) versus the mean SMI reduction for those using M alone. The difference in the number of people between M+S versus M was calculated for each SMI reduction category, namely (<0, <5, <10, <15, <20, <25, <30, <35, <40, <45, <50, <55) at the 28-day time point.

20

Figure 10 is a linear regression graph comparing the degree of skin melanin index (SMI) reduction with the usage of maltol and sodium saccharin (M+SS) versus the mean SMI reduction for those using SS alone. The difference in the number of people between M+S versus SS was calculated for each SMI reduction category, namely (<0, <5, <10, <15, <20, <25, <30, <35, <40, <45, <50, <55) at the 28-day time point.

25

Figure 11 is a chart showing the results of the cytotoxicity tests carried out on some of the compounds of the present invention, based on fluorescence, at various concentrations of 75µM, 100µM and 300µM.

30

DETAILED DESCRIPTION

35 (A) Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by a skilled person to which the subject matter herein belongs. As used herein, the following definitions are supplied in order to facilitate the understanding of the present invention.

5

As used in the specification, the singular form “a”, “an” and “the” include plural references unless the context clearly dictates otherwise.

As used in the specification, the term “alkyl” refers to a saturated or unsaturated group comprising carbon and hydrogen atom.

10

As used in the specification, the prefix “cyclo” refers to structure in ring form.

Throughout this document, unless otherwise indicated to the contrary, the terms “comprising”, “consisting of”, and the like, are to be construed as non-exhaustive, or in other words, as meaning “including, but not limited to”.

15

(B) Screening Method

Until comparatively recently customers just required products which were as effective as possible at lightening the skin. But now, new needs have arisen. It is no longer enough to just search for more effective skin lightener compounds or materials that produce a fairer skin or act more rapidly, but for compounds or materials that also give significant improvements to the radiant and youthful characteristics of skin, that also have excellent cosmetic benefits such as skin-feel and evenness of application. Other marketing-related advantages such as the use of natural or traditional sources of ingredients and an absence of synthetic preservatives are also desirable. In addition, these benefits and properties need to be provided in a convenient, stable, safe, legal and cost-effective way. The solution to the above needs is therefore not just a more active skin lightener that contains active ingredient such as a compound that inhibits tyrosinase more effectively, but an ingredient that satisfies customers' requirements which are commonly referred to as skin anti-ageing.

20

25

30

Skin ageing occurs as a natural consequence of ageing, the so called chronological ageing. This occurs as a result of exposure to sunlight and in particular, UVA radiation, which is referred to as photo-ageing. A common cause of these types of ageing is that they both occur cumulatively as a result of exposure to reactive oxygen species that

35

possess one or more unpaired electrons. In chronological ageing, the ROSs are produced by metabolism, and in photo-ageing, by the action of UV photons. Visible signs of skin ageing include fine lines and wrinkles, pigmented spots such as 'age spots', and a general loss of elasticity and firmness of the skin. Physiologically, skin ageing is associated with degradation of the extracellular matrix and a flattening of the epidermal-dermal junction. Mechanisms of skin ageing include how UV light stimulates the production of cytokines that in turns stimulates the formation of matrix metalloproteinases such as elastase and collagenase. This degrades the extracellular matrix and damages the epidermal-dermal junction which can result in the formation of age spots.

In response to these multiple requirements, the following approach has been adopted, starting with the understanding that because of the many different physiological processes that contribute to skin appearance and skin ageing, many different active ingredients are required, and because melanogenesis is now known to be a complex process, both as regard the number of steps in the metabolic pathway involved and in the signalling pathways that control it. Therefore, in order to be very effective, a skin lightener needs to inhibit or antagonise as many as possible of the steps in the melanogenesis metabolic and signalling pathways, such as enzymes and receptors. To do this, a number of active ingredients are necessary, but ideally with each active ingredient having multiple different mechanisms of action so as to both inhibit as many of the steps in the melanogenesis metabolic and signalling pathways, as well as to enhance skin quality by lightening skin in a way that enhances the tone of the lightened skin and achieving other skin quality improvements such as improvement in skin smoothness and reduction in wrinkles and fine lines.

Consequentially, multifunctional compounds with a minimum of two or more of the skin lightening and skin quality improving activities, as well as with high specific activities were searched and identified. This is so as to reduce both the number of compounds that need to be co-formulated and the concentrations of active ingredients that have to be formulated so as to reduce the chance of undesirable effects, such as skin irritation, occurring on the skin. Complementary combinations of compounds with different structures and thus different activities were then devised, again to seek further skin quality benefits such as their contribution to fragrance and aroma, skin feel and ease of application of formulated products.

Variations on the combinations of high specific activity and multifunctional compounds can then be made to meet the specific requirements of particular groups of consumers,

and ultimately the requirements of individual customers. The identified compounds can then be packaged or formulated into single or multi-use forms such as capsules or jars; and in different activities appropriate to customers who wish to enhance their skin quality rapidly or more quickly, and to maintain the desired skin quality achieved.

5

To obtain such multifunctional active ingredients, the compounds that were selected should have natural, traditional, safe, legal and cost-effective characteristics and properties that make the compounds acceptable and affordable to mass-market to customers and making it useable in high-street as well as luxury brands as well. The compounds were then screened for the possession of multiple mechanisms of action, which may be at one or more stages in the melanogenesis pathway itself and/or in the signalling pathways that control the synthesis and distribution of melanin, together with beneficial effects on skin quality factors such as radiance, skin tone, reduced wrinkles and age spots, anti-irritant properties, and improved softness, smoothness, evenness of tone and elasticity that contribute to a skin anti-ageing effect and a glowing and youthful appearance. Reduction of microbial growth on the skin is also desirable so as to reduce damage by UV light due to microorganisms depositing materials on the skin that accentuate the effects of UV radiation, such as porphyrins.

10

15

20

25

30

The screening method used in the present invention is aided by an understanding of the structural characteristics and/or substructures that are associated with, and that at least in part dictate, the mechanisms of action of the compounds they occur in, relatively independently of the complete chemical structures of the compounds. Any single structure or substructure may exert two or more different mechanisms of action. For instance, particular substructures tend to be responsible for one or more mechanisms of action that include the following general types: scavenging reactive oxygen species produced by the action of UV-light on the skin; acting as antagonists in the signalling pathways such as versus agonists, for example, α -MSH at MC1-R receptors; inhibiting enzymes such as tyrosinase or TLP1 and TLP2; or down-regulating the synthesis of proteins such as cytokines and enzymes involved in melanogenesis, especially via transcription factors such as MITF; and the packaging of melanin into the melanosomes and transfer to the keratinocytes. Advantages of this approach are that it selects active compounds that would not be detected in simple screens based on the inhibition of a single enzyme, or that do not allow UV-induced pathways to be tested.

35

The screening method further comprises screening for compounds with additional cosmetic benefits such as the abilities to give stable products that, when formulated, do

not discolour the product, do not separate the product into different phases, do not become microbially contaminated, oxidised, or stain clothes. Other benefits include improving the physical stability of the formulation, reducing the viscosity of the formulation so that additional active ingredients can be added without reducing the ease of application and skin feel of the cosmetic product.

The uses of the identified compounds were then evaluated in combination for ability to achieve fast and effective skin lightening, and a high quality of lightened skin, achieved in a mild and gentle manner that is best carried out by only partially inhibiting several stages in the melanogenesis pathway and/or signalling pathways or other physiological processes, so that the overall cumulative effect on skin lightness and quality is greater than if any single active ingredient with a single mechanism of action is used. Whereas when a combination of different skin lightening active ingredients is used, they act rapidly to produce a high quality visibly lightened skin, together with other benefits as detailed hereinabove.

Using this approach in selecting suitable candidate for use in skin lightening and skin quality enhancement, a range of structurally diverse compounds having skin lightening, skin tone and skin quality improving and/or formulatory benefits has been identified. The compounds possess a number of different but complementary mechanisms of action.

Accordingly, in one aspect of the invention, a method of identifying a compound with melanogenesis inhibiting activities is provided. The method comprises selecting a compound containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- (i) hydroxyl-based group including -OH or -C(=)-(OH);
- (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
- (iii) ether group, -O-;
- (iv) sultam group, -N(H)-S(=O)₂-;
- (v) lactam group, -N(H)-C(=O)-;
- (vi) apolar group including cyclic structures based on menthol or carotenoids;
- (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or

-N(H)-C(H)=N-;

- (viii) amine group, -NH₂;
- (ix) secondary amine-based group, -N(H)-; and
- (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-;

5

It was found that efficacy of skin lightening and skin quality improvements can be maximized by using a combination of compounds, with each compound containing the allylic or partially allylic carbonyl substructure of structure I and a second substructure Y selected from one of the groups (i)-(x) as described hereinabove. It was found that the compounds work best when used in combination with each other, particularly when compounds with different substructure Y are combined, as each of the compounds with the different substructure Y would have different mechanisms of action and the compounds can therefore inhibit multiple melanogenesis pathways.

10 The substructures identified as determining the skin lightening activities of the compounds of the present invention are essential in identifying and designing composition with melanogenesis inhibiting activities. Without these substructures, costly, time- and effort- consuming high throughput screening would be required, while on the contrary, the substructures enable very productive low throughput screenings to be carried out.

15 The compounds of the present invention possess activities that improve skin tone and skin quality, and have formulatory advantages. The compounds can be used to advantage in combination with each other, and especially when formulated into cosmetic and personal care products in combination with complementary compounds and materials that potentiate their skin lightening activities, such as epidermal penetration enhancers, or reduce skin pigmentation such as UV absorbers, UV blockers and with currently used skin lighteners, and that have rejuvenating and anti-ageing activities and/or formulatory advantages such as shelf-life extending activities.

25

30 **(C) Compounds and Composition**

In accordance with an aspect of the invention, a cosmetic or personal care composition for regulating skin quality or skin lightening is provided. The composition comprises two or more compounds, each compound containing an allylic or partially allylic carbonyl substructure having the following structure I:

35



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- 5 (i) hydroxyl-based group including -OH or -C(=)-(OH);
 (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
 (iii) ether group, -O-;
 (iv) sultam group, -N(H)-S(=O)₂-;
 (v) lactam group, -N(H)-C(=O)-;
- 10 (vi) apolar group including cyclic structures based on menthol or carotenoids;
 (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or
 -N(H)-C(H)=N-;
 (viii) amine group, -NH₂;
 (ix) secondary amine-based group, -N(H)-; and
- 15 (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-;

their derivatives, isomers, salts and/or combination thereof; and a cosmetically acceptable vehicle.

- 20 The two or more compounds and/or their derivatives, isomers, salts and/or combination thereof that contain the allylic or partially allylic carbonyl substructure (ACSS) are selected from one or more of the following groups consisting of:

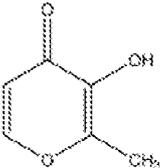
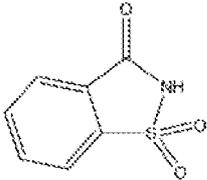
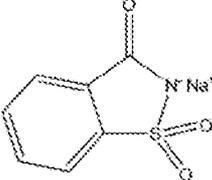
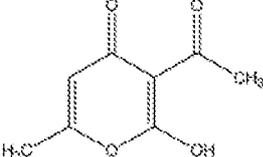
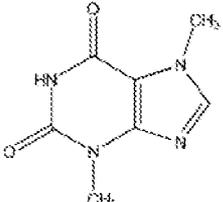
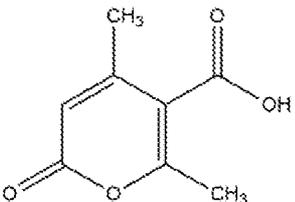
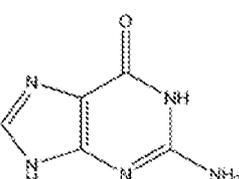
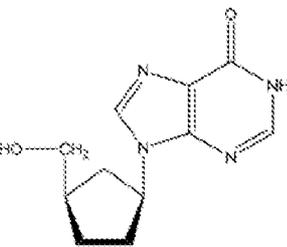
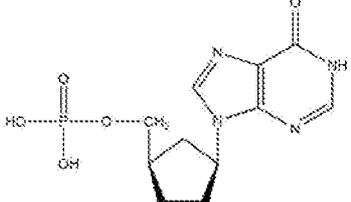
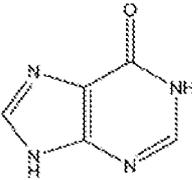
- 25 (a) Gamma-pyrone compounds and their salts thereof that contain the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the hydroxyl or hydroxyl-based group. Compounds belonging to this group act by inhibiting tyrosinase, as antioxidants including as scavengers of reactive oxygen species such as singlet oxygen, and inhibiting the formation of cytokines. Examples of such compounds include, but are not limited to, maltol, ethyl maltol, acetyl salicylic acid, aconitic acid and protocatechuic acid;
- 30 (b) Gamma-pyrone compounds and their salts thereof that contain the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the carbonyl or carbonyl-based group. Example of such compound includes, but is not limited to, dehydroacetic acid;
- 35

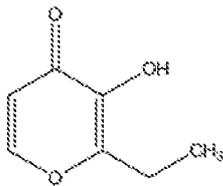
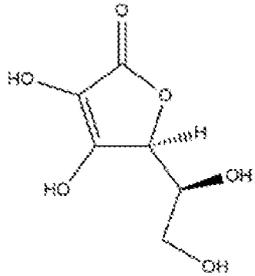
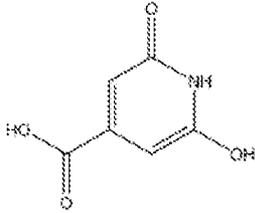
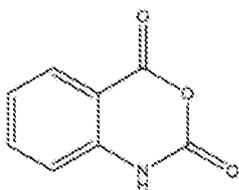
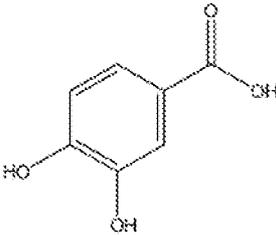
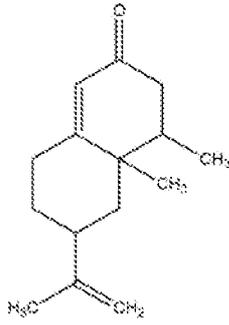
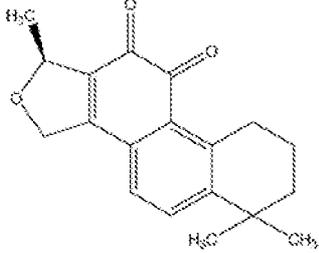
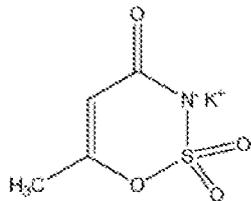
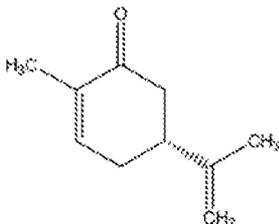
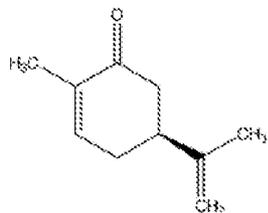
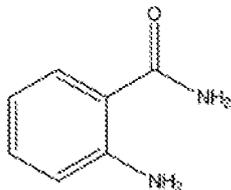
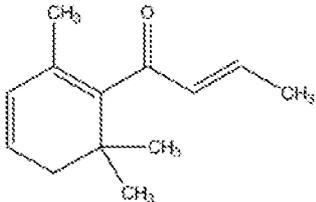
- 5 (c) Sultam compounds and their salts thereof that contain the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the sulphonamide group forming a sultam ring structure. Compounds belonging to this group act as antagonists at the MC1-R receptor. Examples of such compounds include, but are not limited to, saccharin, sodium saccharin and potassium acesulphame;
- 10 (d) Indole-like compounds and their salts thereof composed of bicyclic aromatic and heterocyclic five membered rings containing the allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of an amide group and forming a lactam structure. Compounds belonging to this group inhibits tyrosine-like protein 1 and/or 2. Example of such compound includes, but is not limited to phthalimide;
- 15 (e) Cyclohex-2-enone-like compounds and their salts thereof having the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y that contains a second unsaturated bond making the compound diallylic or partially diallylic. Compounds belonging to this group have mechanisms of action that include scavenging reactive oxygen species such as singlet oxygen and inhibiting the formation of cytokines. Example of such compounds includes, but is not limited to canthaxanthin;
- 20 (f) Adenine-like compounds and their salts thereof with five and six-membered heterobicyclic structures containing the allylic or partially allylic carbonyl substructure adjacent to the second substructure Y consisting of one or more secondary aldimine groups and one or more secondary amine groups. Compounds belonging to this group act by mechanisms that include inhibition of adenylyl cyclase. Examples of such compounds includes, but are not limited to, guanine, guanosine, guanosine monophosphate, inosine, inosine monophosphate; and
- 25 (g) Purine-like or xanthine-like compounds and their salts thereof containing the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of a secondary amine group or the N(H)-C(=O)-N(H)-group. Compounds belonging to this group are known to be antagonists of adenosine binding receptors. The compounds act by mechanisms that include via inhibition of adenylyl cyclase, or that may inhibit adenylyl cyclase and therefore
- 30
35

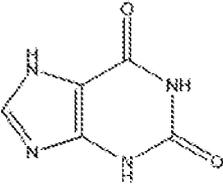
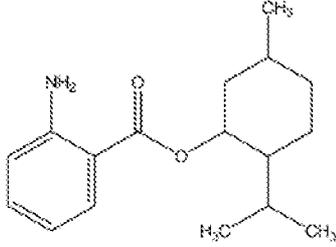
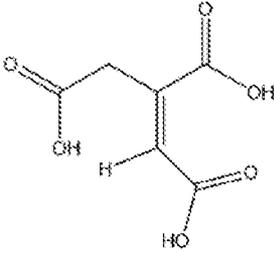
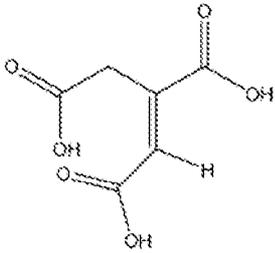
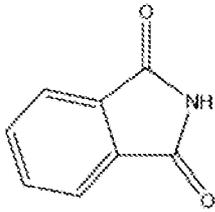
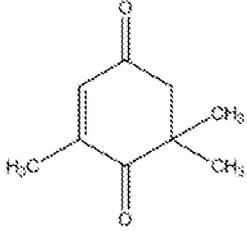
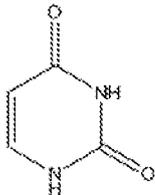
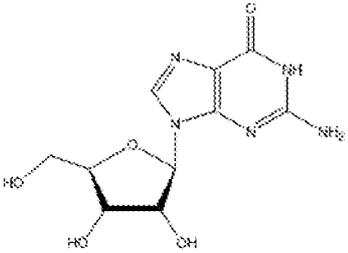
act as indirect inhibitors of protein kinase by depriving them of cyclic AMP, or may complex with thymine dimers and prevent them from binding to their receptors. Examples of such compounds include, but are not limited to, theobromine, hypoxanthine, xanthine and uracil.

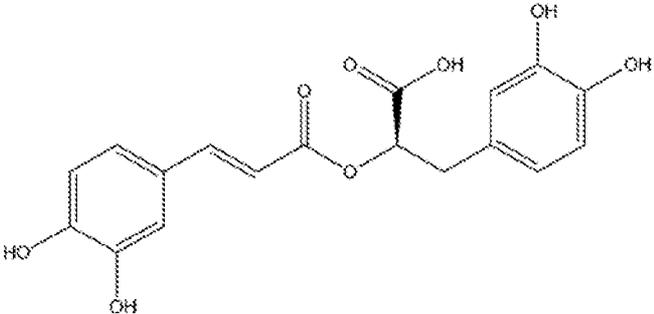
5

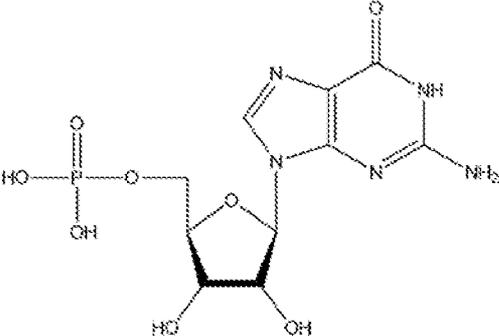
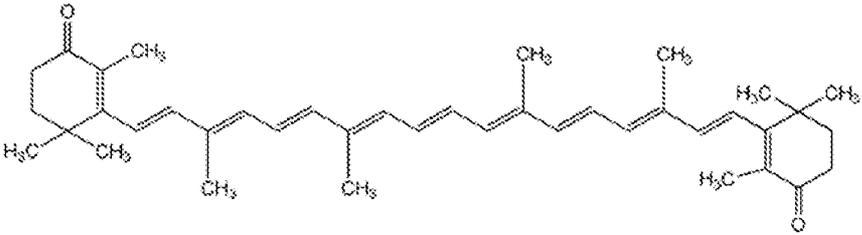
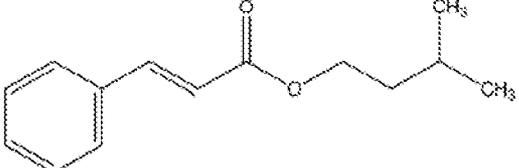
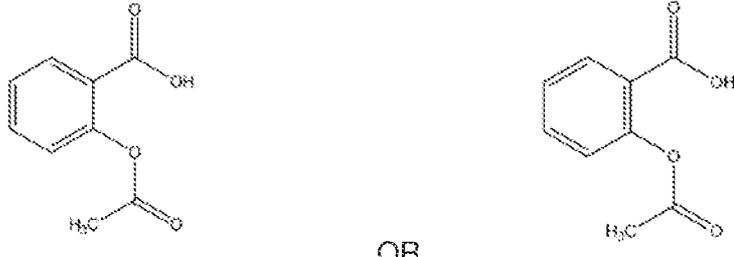
In some embodiments, the two or more compounds are selected from the group consisting of:

Compound Name	Chemical Structure	Compound Name	Chemical Structure
Maltol		Saccharin	
Sodium Saccharin		Dehydroacetic Acid (DHAA)	
Theobromine		Isodehydroacetic acid	
Guanine		Inosine	
Inosine Monophosphate (IMP)		Hypoxanthine	

<p>Ethyl Maltol</p>		<p>Erythorbic Acid</p>	
<p>Citrazinic Acid</p>		<p>Isatoic Anhydride</p>	
<p>Protocatechuic Acid (PCA)</p>		<p>Nootkatone</p>	
<p>Cryptotanshinone</p>		<p>Acesulphame K (Potassium Acesulphame)</p>	
<p>S-carvone</p>		<p>R-carvone</p>	
<p>Anthranilamide</p>		<p>Beta-damascenone</p>	

<p>Xanthine</p>		<p>Menthyl-anthranilate</p>	
<p>Trans-Aconitic Acid</p>		<p>Cis-Aconitic Acid</p>	
<p>Phthalimide</p>		<p>4-ketoisophorone</p>	
<p>Uracil</p>		<p>Guanosine</p>	

<p>Rosmarinic Acid</p>	
------------------------	--

Guanosine Monophosphate	
Canthaxanthine	
Isoamyl Cinnamate	
Acetyl Salicylic Acid	

and their derivatives, isomers, salts and/or combination thereof.

The compounds of the present invention may be provided in the form of an extract
 5 derived from a plant material or yeast. Examples of such compounds include, but are not
 limited to, maltol, theobromine, hop extracts and yeast extracts containing inosine,
 guanosine monophosphates and/or purines.

In some embodiments, the two or more compounds each contain different Y
 10 substructures. In other embodiments, the two or more compounds each contain different
 Y substructures, with each of the Y substructures selected from different groups (i)-(x).

In further embodiments of the invention, the composition comprises two or more compounds containing the same or different Y substructure, with each of the Y substructures selected from the same or different groups (i)-(x), and one or more other skin lightening agents.

5

The compounds as described hereinabove include compounds in which UV-induced melanogenesis is reduced by some combination of inactivating initiators of melanogenesis signalling pathways produced by the action of sunlight such as UV radiation and in particular UVB radiation on the skin, by inhibiting one or more of the stages in a melanogenesis pathway or one or more melanogenesis signalling pathways, and by inhibiting one or more stages in the melanogenesis pathway from precursor amino acid to melanin transferred into keratinocytes.

The compounds as described hereinabove include compounds that possess some combination of melanogenesis inhibiting, skin tone improving, enhancing effects on one or more aspects of skin quality such as enhancing the smoothness of skin or reducing wrinkles or dark circles around the eyes, and one or more formulatory benefits such as extending the shelf-life of cosmetic products by preventing the growth of microbial contaminants.

15
20

The two or more compounds of the present invention may possess different combination of two or more different skin quality improving activities and with different useful mechanisms of action because of the complexity of the melanogenesis process and the range of desirable skin quality effects and properties. The desirable skin quality effects and properties include skin lightening, improving the skin tone and other desirable skin features such as smoothness, reducing wrinkles and dark circles around the eyes, and formulatory advantages for the cosmetic products they are used in such as to extend the shelf-lives or by reducing the viscosity of the creams and so improve their ease of spreading on the skin so that each compound has different multifunctional skin quality improving properties.

25
30

The composition of the present invention comprising the two or more compounds as described hereinabove has two or more skin lightening and skin quality improving effects such as by improving the skin tone by increasing a^* (rosy-red tone) and/or reducing b^* (yellow skin tone) components respectively, and/or by reducing fine lines and wrinkles, the intensity of pigmented spots or microbial damage; and/or improving skin radiance, anti-irritant properties, softness, smoothness, elasticity, skin cell regeneration and

35

evenness of appearance, and other characteristics of youthful skin. The effects are proven and illustrated in Examples 5, 6 and 7 below.

5 The composition of the present invention comprising the two or more compounds as described hereinabove possess one or more characteristics or properties that give quality benefits in the form of formulatory advantages when the compounds are used in cosmetic or personal care products. The composition possess shelf-life extending properties, a positive aroma, a reduced viscosity of creams on the products the composition is added to and so improve the ease of spreading of the creams on the skin, or resistance to colour
10 formation on storage. These characteristics or properties are illustrated in Examples 8, 9 and 10 below.

The composition of the present invention has high specific activities such that the composition can produce visibly improved skin within just one to two weeks of use even
15 when used at low concentrations and without any additional ingredients to improve the activities such as epidermal penetration enhancers, and to improve the consumer products they are used in, such as being able to make preservative-free claims, thereby minimising any skin irritancy due to chemicals preservatives used or other undesirable effects. These characteristics or properties are illustrated in Example 1 and 17.

20 The composition of the present invention can visibly reduce the degree of pigmentation of human skin within 14 days when applied twice daily dissolved in a cream or some other similar form at a dose of less than 1% w/w but without any other active materials such as penetration enhancer ingredients being present in the cream that can enhance the activity
25 of the compounds, or that can reduce UV-induced skin pigmentation such as UV-absorbers, that are generally less available and so more expensive than the compounds of this invention so that easy to formulate and low cost end-products can be made. This effect is illustrated in Example 1 below.

30 In some embodiments, the composition of the present invention includes compounds with skin lightening activities that reduce endogenous and/or UV-induced melanogenesis, together with some combination of additional skin tone, skin quality improving, and/or cosmetic and formulatory advantages. An exemplary embodiment of this invention includes a composition comprising two or more compounds selected from the group
35 consisting of saccharin, maltol, theobromine, their derivatives, isomers, salts and/or combination thereof. In one embodiment, the composition comprises saccharin and/or its salts thereof and maltol, preferably sodium saccharin and maltol. In another embodiment,

the composition comprises maltol and theobromine. In yet another embodiment, the composition comprises saccharin and/or its salts thereof, maltol and theobromine.

5 Maltol has also been proven to be an in-vivo skin lightener, and with an ex-vivo melanogenesis reducing activity, together with antioxidant activity, skin tone and skin quality improving activities.

10 In Example 3 below, it is shown that maltol (3-hydroxy-2-methyl-4H-pyran-4-one) can effectively reduce melanogenesis activity as a result of testing the lightening effect of maltol on cultured melanocytes (see Table X in Example 3) with an IC50 of 0.065 g/l in B16 cultured melanocyte assays

The composition comprising maltol has no significant tendency to decolourise when formulated in a concentration of less than 2% into cosmetic or personal care products.
15 The composition possesses antimicrobial and antioxidant activities sufficient to extend the shelf-lives of the formulated cosmetic or personal care products without the need for any other preservative ingredients. The activities of maltol as described hereinabove are described in Tables I, II, III, V, VI and X, and Examples 1 and 3 below.

20 Sodium saccharin has been proven to have skin tone and skin quality improving activities including skin radiance-brightness imparting properties, together with viscosity reducing properties when formulated into products, antimicrobial activity sufficient to extend the shelf-lives of formulated products without the need for any other preservative ingredients, and ability to form zinc saccharide when saccharin is formulated with a source of zinc
25 such as zinc hydroxide or oxides, together with in-vivo skin lightener activity, with an ex-vivo melanogenesis reducing activity of IC50 of 0.055 g/l in B16 cultured melanocyte assays (see Table X and Example 3). The activities of sodium saccharin as described hereinabove are described in Tables I, II, III, V, VI, X, and Examples 1, 3 and 16 below.

30 Sodium saccharin when used in combination with maltol, forms a cosmetic composition that yields better antimicrobial activity based on the weight of the composition as opposed to sodium saccharin or maltol being used individually, thereby the combination extends the shelf-life of the formulated cosmetic or personal care product. In Example 3 below, it is shown that sodium saccharin when used in combination with maltol can effectively
35 reduce melanogenesis activity as a result of testing the lightening effect of the combination on cultured melanocytes (see Table X in Example 3). with an IC50 of 0.046 g/l in B16 cultured melanocyte assays, lower than if maltol or sodium saccharin were to

be used on its own. The activities of sodium saccharin when used in combination with maltol as described hereinabove are described in the relevant Tables and Examples below.

5 Both maltol and saccharin (and sodium saccharin) have good antimicrobial activities, but when used in B16 assays or on human skin (in clinical studies), both are exposed to mammalian cells that one would expect to be more sensitive than microbial cells. However, the mammalian cells are hardly affected. Both maltol and saccharin or the combination of maltol and saccharin show no real cytotoxic activities on either the B16
10 cells or on intact human skin.

As regards its melanogenesis inhibiting activities, maltol is a tyrosinase inhibitor and also an antioxidant, including scavenging the singlet oxygen generated by the action of
15 sunlight on skin. By contrast, saccharin (2H-1lamda 6, 2-benzothiazol-1,1,3-trione) does not have either tyrosinase inhibiting or antioxidant activities; but it contains a lipophilic group in the form of its aromatic ring combined with its amide and sulphonamide groups giving it an analogous structure to the 'pharmacophore' of Agouti signalling peptides (ASPs) that contains a phenylalanine and its associated amide bonds. Since ASPs have been identified as endogenous antagonists of α -MSH binding to MC1-R, and so act as a
20 physiological inhibitor of melanin synthesis, it is likely that saccharin has a similar antagonist and melanogenesis inhibiting activities, particularly as combinations of its lipophilic and both its amide or its sulphonamide groups, could mimic the antagonist activity of the ASP pharmacophore. The complementary skin quality enhancing activities of maltol and saccharin can be similarly explained. Singlet oxygen stimulates cytokines
25 that activate not just melanogenesis, but also the formation of MMPs, such as collagenases and elastases that play key roles in skin ageing and in age spot formation. Likewise the antagonism of α -MSH binding to MC1-R not only inhibits melanogenesis but also increases the proportion of pheomelanins produced, rather than eumelanins, giving the skin a rosier and more youthful appearance.

30

The use of active compounds with different but complementary mechanisms of action and characteristics extends to the formulatory benefits of combinations of the compounds of the present invention. While maltol has bactericidal activity, saccharin is bacteriostatic interfering with folic acid synthesis. Saccharin and maltol have different water solubility,
35 and therefore they tend to protect different phases of emulsified products and have different epidermal penetration properties. It has been shown that the use of sodium saccharin or saccharin in conjunction with maltol significantly reduces the viscosity of the

cosmetic and personal care products. This is advantageous as a reduced viscosity allows for the addition of other compounds (for example, potassium acesulphame including particulates such as titanium dioxide or zinc oxide), thus providing more flexibility to formulators, without reducing the ease of application and skin feel of the product.

5 Furthermore, sodium saccharin used in combination with maltol also provides a more pleasant fragrance, as opposed to either active ingredient being used individually.

In various embodiments, the two or more compounds present in the cosmetic or personal care composition include maltol in an amount ranging from 0.01 to 10 wt% based on the total weight of the composition. In other embodiments, maltol is present in an amount of

10 0.02 to 5 wt% based on the total weight of the composition. In further embodiments, maltol is present in an amount of 0.01 to 1 wt% or about 0.25 wt% based on the total weight of the composition.

In various embodiments, the two or more compounds present in the cosmetic or personal care composition include saccharin and/or its derivative, including its cosmetically acceptable salt such as sodium saccharin. In various embodiments, saccharin or sodium saccharin is present in an amount ranging from 0.01 to 70 wt% based on the total weight of the composition. In other embodiments, saccharin or sodium saccharin is present in an amount of 0.01 to 60 wt% based on the total weight of the composition. In other

20 embodiments, saccharin or sodium saccharin is present in an amount of 0.01 to 50 wt% based on the total weight of the composition. In yet other embodiments, saccharin or sodium saccharin is present in an amount of 0.01 to 40 wt% based on the total weight of the composition. In further embodiments, saccharin or sodium saccharin is present in the composition in an amount 0.01 to 30 wt% based on the total weight of the composition. In further embodiments, saccharin or sodium saccharin is present in the composition in an amount of 0.01 to 20 wt% based on the total weight of the composition. In yet further

25 embodiments, saccharin or sodium saccharin is present in the composition in an amount of 0.01 to 10 wt% based on the total weight of the composition. In yet further

30 embodiments, saccharin or sodium saccharin is present in an amount of 0.02 to 5 wt% based on the total weight of the composition. In various embodiments, saccharin or sodium saccharin is present in the composition in an amount of 0.01 to 1 wt% or about 0.25 wt% based on the total weight of the composition.

Theobromine has a melanogenesis reducing activity of IC₅₀ of 0.037 g/l in B16 cultured melanocyte assays, as described in Table X and Example 3. It can also be used in the form of cocoa extracts.

35

Other compounds with similar structures to maltol include ethyl maltol, acetyl salicylic acid, citrazinic acid and dehydroacetic acid. The IC50 values of these compounds range from of 0.059 to 0.262 g/l in B16 cultured melanocyte cell melanogenesis inhibition
5 assays (see Table VI, Example 2). These compounds also tend to have bactericidal and fungicidal activities, and so can extend the shelf-life of the formulated products containing the said compounds. Further compounds include canthaxanthin, aconitic acid, protocatechuic acid, cryptotanshinone, ubiquinone, ubisemiquinone, the alpha-acids humulone, cohumulone and adhumulone, the beta-acids lupulone, colupulone and
10 adlupulone, and hop extracts containing them, including boiled extracts containing isohumulone, humulinic acid and isohumulonic acid, and which can also contain xanthohumol and which is an inhibitor of the MMPs elastase and collagenase.

In one embodiment, the composition comprises a combination of compounds including
15 saccharin, maltol, theobromine, potassium acesulphame and dehydroacetic acid.

Cyclic sulphamides/oxathiazolinone dioxides such as acesulphame and its salts, in particular, potassium acesulphame has a melanogenesis inhibiting activity with an IC50 of 0.058 g/l in B16 cultured melanocyte assays, as shown in Table X and Example 3 below.

20 The compounds of the present also include phthalimide and its salts, particularly, potassium phthalate that has indole-like structures. In particular, phthalimide has a melanogenesis inhibiting activity with an IC50 of 0.089 g/l in B16 cultured melanocyte assays, as shown in Table X and Example 3 below.

25 The compounds with similar purine structures include hypoxanthine (IC50 of 0.07 g/l, Table X, Example 3), xanthine, purine nucleosides and nucleotide derivatives such as Inosine monophosphate (IMP) (IC50 of 0.227 g/l, Table X, Example 3) and guanosine monophosphate (GMP) (IC50 of 0.07 g/l, Table X, Example 3) and their metabolites such
30 as guanine (IC50 of 0.056 g/l, Table X, Example 3), hypoxanthine and xanthine, which can also be used in the form of yeast extracts. Also, compounds with similar substructures include citrazinic acid (IC50 of 0.077 g/l, Table X, Example 3) and isatoic anhydride (IC50 of 0.132 g/l, Table X, Example 3), and its hydrated product anthranilic acid N-carboxylic acid.

35 The skin quality enhancing activities of the compounds of the present invention can also be enhanced by their use as salts with cations with proven topical health and quality

benefits such as zinc and copper in the form of homo-dimeric or hetero-dimeric salts. Examples of the homo-dimeric and hetero-dimeric zinc salts of the compounds of the present invention, in particular, maltol, dehydroacetic acid, saccharin, theobromine and acesulphame, include the homo-dimers $Zn(saccharin)_2$, $Zn(maltol)_2$, $Zn(theobromine)_2$, $Zn(dehydroacetic\ acid)_2$, $Zn(acesulphame)_2$; and the hetero-dimers saccharin-Zn-maltol, saccharin-Zn-acesulphame, saccharin-Zn-dehydroacetic acid, saccharin-Zn-theobromine; maltol-Zn-dehydroacetic acid, maltol-Zn-theobromine, maltol-Zn-acesulphame; dehydroacetic acid-Zn-theobromine, dehydroacetic acid-Zn-acesulphame and theobromine-Zn-acesulphame. The zinc salts are obtained when the said compounds are formulated with zinc compounds such as zinc oxide, zinc hydroxide or zinc gluconate so that their zinc salts are formed once the compounds are formulated (see Example 16).

Homo-dimeric and hetero-dimeric copper salts of the compounds of the present invention, in particular, maltol, dehydroacetic acid, saccharin, theobromine and acesulphame, include the homo-dimers $Cu(saccharin)_2$, $Cu(maltol)_2$, $Cu(theobromine)_2$, $Cu(dehydroacetic\ acid)_2$, $Cu(acesulphame)_2$; and the hetero-dimers saccharin-Cu-maltol, saccharin-Cu-acesulphame, saccharin-Cu-dehydroacetic acid, saccharin-Cu-theobromine; maltol-Cu-dehydroacetic acid, maltol-Cu-theobromine, maltol-Cu-acesulphame; dehydroacetic acid-Cu-theobromine, dehydroacetic acid-Cu-acesulphame and theobromine-Cu-acesulphame.

The compounds of the present invention include combinations of the above zinc and copper salts of the compounds of the present invention, and also the hetero-dimeric salts composed of one anion selected from the compounds described herein, for example, saccharin and a second anion selected from compounds known to have skin lightening and/or skin quality improving activities such as kojic acid to form hetero-dimeric salts such as saccharin-Zn/Cu-kojic acid, zinc/copper hetero-dimers that consist of one anion such as saccharin or maltol, etc, and a second anion that is a known anti-ageing or skin quality improving active such as ascorbic acid, or alpha-hydroxy acids, such as glycolic and lactic acids with desquamation activity, and zinc/copper hetero-dimers consisting of one anion that is a known skin lightening active as above together with a second anion that is a known anti-ageing active ingredient. In various embodiments, the salt comprises homo-dimeric and/or hetero-dimeric salts in which a zinc cation bridges the two identical or different anions. In other embodiments, the salt comprises homo-dimeric and/or hetero-dimeric salts in which a copper cation bridges the two identical or different anions.

The compounds of the present invention further include compounds in which their skin lightening mechanism or mechanisms of action include one or more of inactivating the products of UV damage to the skin that initiate melanogenesis such as reactive oxygen species, or the generation of cytokines and other signalling compounds, acting as
5 antagonists or reverse agonists in the signalling pathways, inhibiting enzymes, affecting the activity of transcription factors, or by down-regulating the synthesis of proteins involved in melanogenesis.

The compounds of the present invention further include compounds that possess a
10 structure or a substructure or substructures, that give them a mechanism or mechanisms of action for skin lightening, involving inhibition of the melanogenesis metabolic pathway and/or inhibition of one or more melanogenesis signalling pathways, and in addition, one or more mechanisms of action for improving the quality of skin tone and/or skin quality by inhibiting undesirable processes and/or by stimulating desirable processes, and involving
15 one or more formulatory benefits.

The compounds of the present invention further include compounds that act as antagonists or reverse agonists at the MC1-R receptor and in doing so, inhibiting melanogenesis and modifying the colour of the melanins produced. This in turns modifies
20 the skin tone to a more pink-red tone, thus showing how a single mechanism of action can produce quite distinct improvements in skin lightness and skin quality.

The compounds of the present invention include compounds that reduce the formation of cytokines known to stimulate the formation of fine lines and wrinkles, age spots and
25 inflammation by reducing UV-induced MMP formation thus improving the quality of skin as well as inhibiting melanogenesis, again showing how a single mechanism of action can produce two distinct improvements in skin lightness and skin quality.

The compounds of the present invention include compounds that inactivate reactive
30 oxygen species, such as singlet oxygen, and so inhibit the skin ageing effects; such as by antagonising the singlet oxygen stimulated production of cytokines and so reducing prostaglandin-stimulated inflammation and irritancy, matrix metalloproteinase formation, and thus wrinkle formation and the development of age spots for instance via preventing collagen 4 catabolism.

35

The compounds of the present invention include compounds that antagonise or inactivate thymine dimer photodegradation products and so reduce their initiation of melanogenesis.

(D) Cosmetic Composition

5 In various embodiments, the cosmetic or personal care composition of the present invention comprises complementary combinations of two or more compounds, all of the compounds possess the common allylic or partially allylic carbonyl substructure (ACSS) of structure I. The combination of compounds possesses skin lightening activities together with one or more of skin tone improving, skin quality enhancing, and formulatory advantages, and with different physicochemical characteristics. With each of the
10 compounds containing the common allylic or partially allylic carbonyl substructure of structure I, together with the different second substructure Y, the compounds possess different mechanisms of action. This enables each combination of two or more compounds to inhibit multiple different steps in melanogenesis, thus maximising their efficacy and the range of beneficial effects achieved as compared to using just one
15 compound. The combination enables good effects even when the compounds are used in low concentrations and without requiring the use of any additional ingredients to improve the effects of the composition, thereby minimising any undesirable effects. Example 15 below illustrates these effects.

20 In various embodiments, the cosmetic or personal care composition for use in regulating skin quality comprises complementary combinations of two or more compounds of the present invention, in which the physicochemical characteristics include, but are not limited to, solubilities and logP values; the multiple different steps of melanogenesis including, but are not limited to, the inhibition of the melanogenesis metabolic pathway, inhibition of
25 the compounds that initiate melanogenesis, inhibition of the various stages in the melanogenesis signalling pathways such as the formation of cytokines, antagonism of different steps in the melanogenesis signalling pathway, modification of the activity of transcription factors, and down-regulation of the formation of proteins or enzymes that participate in the melanogenesis metabolic or signalling pathways including shared
30 mechanisms of action such as via the transcription factor MITF. The physicochemical characteristics further include not requiring any additional ingredients such as epidermal penetration enhancer compounds, materials and preservative chemicals to be added. This eliminates the undesirable effects which the additional ingredients may cause to the skin, including skin irritancy and sensitisation. Example 15 below illustrates these effects.

35

In some embodiments, the cosmetic or personal care composition of the present invention comprises two or more compounds selected from one of the combinations of

the compounds consisting of maltol and/or dehydroacetic acid with saccharin, sodium saccharin, zinc saccharides or copper saccharides and/or potassium acesulphame and/or theobromine. In one embodiment, the composition comprises a combination of maltol and sodium saccharin. In this embodiment, the skin lightening, skin tone and quality improving, aroma, and shelf-life extending activities are enhanced by their different but complementary individual activities in formulations. For instance, saccharin is used in combination with maltol because both possess different but complementary inhibition of melanogenesis, skin tone and quality improving properties, and different formulatory characteristics such as the different antimicrobial activities and different solubility properties of maltol and sodium saccharin which give a more effective effect (see the Examples below).

In some embodiments, the cosmetic or personal care composition comprises a combination of zinc and copper salts of the compounds as described hereinabove. The salts include homo-dimeric and hetero-dimeric zinc salts of the compounds of the present invention including salts of maltol, dehydroacetic acid, saccharin, theobromine and acesulphame. Examples of such salts include, but are not limited to, the homodimers $Zn(saccharin)_2$, $Zn(maltol)_2$, $Zn(theobromine)_2$, $Zn(dehydroacetic\ acid)_2$, $Zn(acesulphame)_2$; and the heterodimers saccharin-Zn-maltol, saccharin-Zn-acesulphame, saccharin-Zn-dehydroacetic acid, saccharin-Zn-theobromine; maltol-Zn-dehydroacetic acid, maltol-Zn-theobromine, maltol-Zn-acesulphame; dehydroacetic acid-Zn-theobromine, dehydroacetic acid-Zn-acesulphame and theobromine-Zn-acesulphame, and combinations of the corresponding copper salts of the compounds of the present invention.

In some embodiments, the cosmetic or personal care composition comprises two or more compounds which are specifically combined for particular requirements of customers with different skin types, of different ages or ethnicities, or with other individual or group topical requirements. This is done by selecting combinations of compounds that act only, or predominantly, on just those enzymes, proteins, transcription factors, etc. whose activities need to be modified to meet the specific requirements of particular groups of people or individuals (see Example 5). Exemplary embodiments of variations of formulations are shown in Examples 14 and 15.

(E) Uses

In one embodiment, the present invention relates to the use of the two or more compounds of the present invention to formulate a cosmetic or personal care composition for regulating skin quality. The regulating of skin quality includes reducing endogenous and/or UV-induced melanogenesis; reducing activities of melanogenesis metabolic pathway and/or one or more of the signalling pathways that control the activity of the melanogenesis metabolic pathway; reducing the melanin content of the skin of a subject; lightening of the skin, pigmented spots, freckles, blemishes and dark circles around the eyes of the subject. The use further comprises enhancing skin quality activities including improving the tone and smoothness of lightened skin of the subject by increasing a* (rosy-red tone) and/or reducing b* (yellow skin tone) components, reducing fine lines and wrinkles of the subject by improving skin radiance, anti-irritant properties, softness, smoothness, elasticity, and evenness of appearance of the skin.

In another embodiment, the present invention relates to the use of a cosmetic or personal care composition as described hereinabove as a skin lightening agent.

In one embodiment, the use of the compounds as described hereinabove and the combinations thereof includes combinations of homo-dimeric and hetero-dimeric zinc salts of the compounds, in particular, maltol, dehydroacetic acid, saccharin, theobromine and acesulphame. Examples of such salts include, but are not limited to, homo-dimers $Zn(saccharin)_2$, $Zn(maltol)_2$, $Zn(theobromine)_2$, $Zn(dehydroacetic\ acid)_2$, $Zn(acesulphame)_2$; and the hetero-dimers saccharin-Zn-maltol, saccharin-Zn-acesulphame, saccharin-Zn-dehydroacetic acid, saccharin-Zn-theobromine; maltol-Zn-dehydroacetic acid, maltol-Zn-theobromine, maltol-Zn-acesulphame; dehydroacetic acid-Zn-theobromine, dehydroacetic acid-Zn-acesulphame and theobromine-Zn-acesulphame. The use also includes the use of the corresponding copper salts of the compounds as described hereinabove and combinations of the zinc and copper salts of the said compounds. Homo-dimeric and hetero-dimeric zinc/copper salts lighten and improve the tone and quality of skin, including possible effects against blemishes, such as reducing acne, and to achieve formulatory advantages such as shelf-life extension of products. These effects are illustrated in (Example 11, Example 16).

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with other compounds and materials that enhance the activity of the said two or more compounds, such as with other compounds and

materials that prevent UV light from stimulating melanogenesis, for use in regulating skin quality or skin lightening. In some embodiments, the combination of the two or more compounds is selected from the group consisting of maltol and saccharin; maltol and sodium saccharin; maltol and zinc saccharide; and maltol and copper saccharide.

5

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with other compounds, plant extract and materials
10 that also have melanogenesis inhibiting activities for use in regulating skin quality or skin lightening. In some embodiments, the combination of the two or more compounds is selected from the group consisting of maltol and saccharin; maltol and sodium saccharin; maltol and zinc saccharide; and maltol and copper saccharide. Examples of the plant extract and materials include, but are not limited to, niacinamide, licorice root extract,
15 bearberry extract, alpha- and beta-arbutins, and ascorbic acid and its derivatives such as ascorbyl-2 glucoside and magnesium ascorbyl phosphate (see Example 1, Example 7, Example 12).

In further embodiments, the present invention relates to a cosmetic or personal care
20 composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with other compounds and materials that prevent UV light from stimulating melanogenesis (Example 12), for use in regulating skin quality or skin lightening. Such other compounds and materials include ultraviolet B absorbers
25 (such as octyl methoxycinnamate) and/or ultraviolet A absorbers (such as butyl methoxy dibenzoylmethane) and/or UV blocking materials such as titanium dioxide and zinc oxide, antioxidants such as tocopherol, tocopherol acetate, ascorbic acid or ascorbyl palmitate, and ascorbic acid and its derivatives. In some embodiments, the combination of the two or more compounds is selected from the group consisting of maltol and saccharin; maltol
30 and sodium saccharin; maltol and zinc saccharide; and maltol and copper saccharide.

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as
35 described hereinabove, in combination with other compounds with skin rejuvenating and anti-ageing activities (Examples 11 and 13), for use in regulating skin quality or skin lightening. Such other compounds include, but are not limited to, UV absorbing and

blocking compounds and materials; antioxidants; inhibitors of collagenase and elastase; moisturisers such as glycerol, hyaluronic acid and its salts; phytosphingosine and ceramides; niacinamide that has anti-acne and ceramide stimulating activities; alpha-hydroxy acids such as lactic, citric and glycolic acids that have desquamation activity; 5 anti-glycation agents such as garcinol, arginine and pyrrolidone carboxylic acid; anti-wrinkling active ingredients such as retinol and retinyl palmitate; and the UV absorbers and blockers; and antioxidants as described above. The composition comprising said compounds gives lightened skin younger, less aged characteristics such a smoother, softer feel and glowing appearance (Example 14).

10

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with other compounds and/or materials with 15 formulatory characteristics complementary to their use, such as with shelf-life extending properties (Example 8).

20

In other embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with other compounds for use in producing melanins of different tones and thus producing desirable skin tones in the lightened skin or maintaining the tone of lightened skin. Example of such compounds includes, but not limited to, self-tanning agents such as dihydroxyacetone.

25

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with another compound or compounds that are 30 metabolised by the melanogenesis metabolic pathway to produce melanins of different tones and thus produce desirable skin tones in the lightened skin or maintain the tone of lightened skin.

35

In some embodiments, the present invention relates to the use of the compounds and combinations of the compounds of the present invention as described hereinabove, in cosmetic and personal care product formulations, such as skin lightener creams, lotions, moisturisers, facial mists, body sprays, sunscreen products, spot and blemish creams,

eye creams, emulsions, serums, pressed serums, pastes, applicator sticks, essences, ointments, aerosols, sprays, mists, roll-ons, balms, gels, face masks, facial foams, toners, concentrates, ampoules, capsules, cosmetic waters, cosmetic compacts and foundations, soaps and body washes or in products with rejuvenating, anti-ageing or skin quality
5 improving properties (for instance, see Examples 11, 12, 13 and 14), in particular, at concentrations of up to 10%, to provide a range of benefits, and using combinations of the compounds in different absolute and relative concentrations, in particular to provide a range of products with different activities to meet the specific requirements of different groups and individuals.

10

In one embodiment, the present invention relates to the use of compounds and combinations of compounds of the present invention as described hereinabove, in edible forms, for cosmetic and personal care purposes, such as, edible supplements, edible food and beverages, edible cosmeceuticals, nutraceuticals, edible tablets and edible
15 vitamins.

20

In some embodiments, the present invention relates to a range of cosmetic formulations with complementary skin lightening, skin tone and quality improving effects and formulatory advantages, and with each formulation containing different combinations and absolute and relative concentrations of the compounds of the present invention as described hereinabove, such that each cosmetic formulations in the range provides a different combination of skin lightening, skin tone and skin quality activities and benefits.

25

In some embodiments, the present invention relates to the use of a range of different cosmetic formulations of the compounds of the present invention as described hereinabove, including their salts especially their zinc and/or copper salts to achieve and then maintain desired improvements in skin fairness, tone and quality required by users, depending on their different skin types, ages, ethnicities and life-styles such as extent of exposure to sunlight, and also on factors such as the season, time of year and fashion
30 trends, the degree of skin lightening and skin quality enhancement desired, the speed and immediacy with which those improvements are required, and also on the extent to which the enhancements needs to be maintained once the desired skin fairness and quality has been achieved. This will be achieved by using a range of different cosmetic formulations containing different combinations of the different compounds of the present
35 invention, and with the particular formulation used by any group or individual being selected based on the mechanisms of action of those ingredients best matching the changes in skin quality required by that group or individual. In addition, each formulation

will be available in at least two forms that differ in activity, to be used depending on the extent to which the quality of the skin is required to be modified and the stage in the modification process so that for instance at the end of the process a low activity formulation can be continued to be used so as to just maintain the desired skin quality
5 achieved.

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising the homo and hetero-dimeric zinc/copper salts as described hereinabove for use in lightening and improving the tone and quality of skin, treating
10 conditions such as acne, providing the skin health, wound-healing and anti-fungal benefits of zinc, and in achieving formulatory advantages such as shelf-life extension.

In some embodiments, the present invention relates to new cosmetic products containing the homo and hetero-dimeric zinc/copper salts as described hereinabove by the addition
15 of the required individual homo or hetero-dimeric salts to the products; or with the new cosmetic products prepared following the formulation of creams containing one or more of maltol, saccharin/sodium saccharin, dehydroacetic acid, acesulphame and theobromine by the addition of a cosmetically acceptable soluble or insoluble source of zinc such as zinc hydroxide or sulphate, or zinc oxide respectively (Example 16).

20 In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with one or more plant extracts. The plant extract
25 includes, but not limited to, malt, ginseng, soybean, pine tree, coffee extracts containing maltol and cocoa extracts containing theobromine.

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the
30 compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with one or more plant extracts taken from Ayurveda, Jamu, Traditional Chinese Medicine or other Traditional Oriental Medicines.

In one embodiment, the present invention relates to the use of a range of cosmetic
35 formulations of the compounds as described herein in single or multi-use forms such as capsules or in jar or tube containers and with different efficacies for use during the skin quality improving regime (Example 14).

In one embodiment, the present invention relates to the use of the compounds and combinations of the compounds in products as described herein, in products intended to lighten and/or improve the quality of skin including the lightening of pigmented spots.

5

In some embodiments, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, for use in cosmetic or personal care products to enhance the fragrance of the cosmetic or personal care products. In one embodiment, the compounds include sodium saccharin, maltol and a 50:50 w/w blend of sodium saccharin and maltol that have aroma thresholds of 0.16%, 0.09% and 0.11% respectively in an oil-in-water cream. In another embodiment, aroma-less products can be formulated using the compounds and combinations of compounds as described herein at concentrations below their aroma thresholds, or by modifying the character of the fragrance of products containing the compounds and combinations of compounds as described herein by the addition of other extracts, fragrances or compounds including the addition of l-menthol, or aroma chemicals or aroma materials such as limonene, geraniol or rose oil essence.

10

15

20

25

In one embodiment, the present invention relates to the use of compounds and combinations of compounds as described herein to make products that have both skin lightening and other skin quality benefits including the lightening of pigmented spots, blemishes and areas such as age spots (*senile lentigo*) and/or to improve the skin tone by increasing a* and/or reducing b* rosy and yellow skin tone components, and/or by reducing fine lines and wrinkles, the intensity of pigmented spots, and/or improving skin radiance, softness, smoothness and elasticity (Examples 5, 6 and 7).

30

In one embodiment, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in combination with deodorants and/or antiperspirants for use in reducing microbial activity on the skin.

35

In one embodiment, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as

described hereinabove for use in extending the shelf-lives of the cosmetic or personal care product (Example 8).

5 In one embodiment, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, for use in reducing the viscosity of the cosmetic or personal care product. This is so as to be able to include high concentrations of active ingredients, such as the formulation of high concentrations of the skin lightener compounds as described
10 herein so as to be active against pigmented spots that contain high concentrations of melanin (Example 10).

In one embodiment, the present invention relates to a cosmetic or personal care composition comprising a combination of two or more compounds, each of the
15 compounds containing the allylic or partially allylic carbonyl substructure of structure I as described hereinabove, in particular, as their zinc salts as described herein for use in reducing colour formation in cosmetic or personal care products (Example 16).

In some embodiments, the present invention relates to compositions for preserving
20 cosmetic, personal care, food, beverage and other products comprising compounds of the present invention, in particular, combinations of two or more compounds, each compound containing the allylic or partially allylic carbonyl substructure of structure I. In particular, the composition comprises maltol, dehydroacetic acid, canthaxanthin, saccharin, acesulphame, humulone, cohumulone, adhumulone, isohumulone, humulinic
25 acid, lupulone, colupulone and adlupulone and their salts and combinations thereof. The invention further includes using the composition at concentrations in the products to be preserved, in particular, but not necessarily below the taste and aroma thresholds to prevent microbial growth and/or oxidation and the consequential spoilage of those products such as by microbial contamination and/or rancidification so as to lengthen their
30 stability as safe products and thus their shelf-lives, and to replace the use of synthetic chemical preservatives such as parabens used in cosmetic and personal care products, and benzoic acid in food and beverage products (Example 8).

In accordance with an aspect of the invention, a method of regulating skin quality of a
35 subject is provided. The method comprises the step of topically applying an effective amount of the cosmetic or personal care composition of the present invention on the skin of a subject.

In accordance with another aspect of the invention, a method of skin lightening is provided. The method comprises the step of topically applying an effective amount of the cosmetic or personal care composition of the present invention on the skin of a subject,
5 for lightening of skin.

In various embodiments, the method comprises applying to the skin a cosmetic composition comprising two or more compounds including saccharin derivative and/or other compounds, each compound containing an allylic or partially allylic carbonyl
10 substructure of structure I, in an amount of active per cm^2 of skin applied per application ranging from 0.001 mg/cm^2 to 0.38 mg/cm^2 . In various embodiments, the amount of active per cm^2 of skin applied ranges from 0.001 mg/cm^2 to 0.30 mg/cm^2 per application. In various embodiments, the amount of active per cm^2 of skin applied ranges from 0.001 mg/cm^2 to 0.20 mg/cm^2 per application. In various embodiments, the amount of active per
15 cm^2 of skin applied ranges from 0.001 mg/cm^2 to 0.10 mg/cm^2 per application. In various embodiments, the amount of active per cm^2 of skin applied ranges from 0.001 mg/cm^2 to 0.05 mg/cm^2 per application. In various embodiments, the amount of active per cm^2 of skin applied ranges from 0.001 mg/cm^2 to 0.01 mg/cm^2 per application.

20 In various embodiments, the method comprises applying a cosmetic or personal care composition of the present invention on the skin of a subject once a day, twice a day, thrice a day or once every two days.

In one embodiment, the regulating of the skin quality includes reducing endogenous
25 and/or UV-induced melanogenesis, reducing activities of melanogenesis metabolic pathway and/or one or more of the signalling pathways that control the activity of the melanogenesis metabolic pathway, reducing the melanin content of the skin of the subject, and lightening of the skin, pigmented spots, freckles, blemishes and dark circles around the eyes of the subject.

30

(F) Method

In accordance with an aspect of the invention, a method of determining a composition for use in regulating or improving skin quality of a subject is provided. The method comprises
35 measuring skin quality of a subject; identifying two or more compounds with melanogenesis inhibiting activities by selecting two or more compounds, each of the

compounds containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- (i) hydroxyl-based group including -OH or -C(=)-(OH);
- (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
- (iii) ether group, -O-;
- 10 (iv) sultam group, -N(H)-S(=O)₂-;
- (v) lactam group, -N(H)-C(=O)-;
- (vi) apolar group including cyclic structures based on menthol or carotenoids;
- (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or -N(H)-C(H)=N-;
- 15 (viii) amine group, -NH₂;
- (ix) secondary amine-based group, -N(H)-; and
- (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-; and

preparing a formulation based on the measured skin quality so as to improve the skin quality using the identified compounds.

In accordance with another aspect of the invention, a method of determining a composition for use as a skin lightening agent is provided. The method comprises the steps of determining the skin type of a subject; identifying two or more compounds with melanogenesis inhibiting activities by selecting two or more compounds, each of the compounds containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- (i) hydroxyl-based group including -OH or -C(=)-(OH);
- (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
- (iii) ether group, -O-;
- 35 (iv) sultam group, -N(H)-S(=O)₂-;

- (v) lactam group, $-N(H)-C(=O)-$;
- (vi) apolar group including cyclic structures based on menthol or carotenoids;
- (vii) secondary aldimine containing group including $-N(H)-C(NH_2)=N-$ or $-N(H)-C(H)=N-$;
- 5 (viii) amine group, $-NH_2$;
- (ix) secondary amine-based group, $-N(H)-$; and
- (x) amide-based group including $-N(H)-C(=O)-$ or $-N(H)-C(=O)-N(H)-$; and

10 preparing a formulation based on the determined skin type of the subject using the identified compounds.

The combination of two or more compounds of the present invention with one or more sources of a divalent cation, in particular zinc and or copper such as one or more soluble zinc salts such as zinc sulphate, zinc chloride, zinc gluconate, zinc acetate, zinc
15 pyrrolidone carboxylate, zinc glycinate or copper gluconate; or a sparingly soluble zinc salt such as zinc oxide especially when a slow formation of the zinc salt or salts of the compound or compounds of the present invention is required and/or when the sparingly soluble zinc salt also has a cosmetic benefit itself, such as zinc oxide that in particulate
20 form has a UV protective effect or zinc ricinoleate that has deodorant properties, so that one or more homo-dimeric and/or hetero-dimeric zinc/copper salts of two or more of the compounds described herein are formed at concentrations suitable to achieve the desired effect or combination of effects as described herein.

Or the addition of a combination of one or compounds as described herein and defined by
25 formula 1 with one or more sources of a divalent cation to a cosmetic or personal care formulation at a concentration suitable to achieve the desired effect or combination of effects as described herein.

To facilitate a better understanding of the present invention, the following examples of
30 specific embodiments are given. In no way should the following examples be read to limit or define the entire scope of the invention. One skilled in the art will recognize that the examples set out below are not an exhaustive list of the embodiments of this invention.

35 EXAMPLES

EXAMPLE 1

In-vivo skin lightening study on 28 Southeast Asian women and monitored by self-assessment, assessment by trained supervisors, and instrumentally was carried out. This double-blind CRO study proved the efficacy of maltol and sodium saccharin as skin lighteners, particularly when used as a cream containing a blend of 0.25% maltol and 5 0.25% sodium saccharin (NZW06, Tables I to III). A high quality lightened skin was produced, both as regards skin tone and other skin quality characteristics. A cream of the same composition, but containing 3.0% niacinamide (NZW01, Table II) instead of maltol and saccharin was used as a positive control.

10 The cream base used for blending the active ingredients contained the ingredients as follows: Aqua, Butyrospermum parkii, caprylic/capric triglyceride, C12-15 alkyl benzoate, cetearyl isononanoate, cyclomethicone, butylene glycol, hydroxyethyl acrylate, sodium dimethyl taurate copolymer, Aloe barbadensis leaf juice. The cream base was white in colour, with a pH range between 4.5 and 5.5.

15

The subjects were recruited and selected according to inclusion and exclusion criteria, as well as the prohibition and restriction concepts defined in the study protocol. In this study, 28 woman subjects were included by the Investigator. The age of the subjects was between 20 and 46 years old with the average age of 32.5 years.

20

The selected subjects were treated on two sides of the arms with the tested products. The tested products were identified and determined on which side of arm skin they should be applied. Subjects were briefed on how to use the tested products which they were required to use by themselves over the 28 days. The subjects were requested to avoid 25 exposure to sunlight on their arm during the study period by wearing long sleeved clothing to cover up the test site, and to do so for a seven-day period before the study began. In the seven-day period before the study began, test subjects were also told to abstain from the application of any skincare products or cosmetic products.

30 Before application of the tested product, the skin melanin index was measured at all tested sites of arm skin in each subject. The measured area was marked for the next application and the next measurement. The tested product was applied twice daily, once in the morning and once in the evening, over 28 days on each site according to the determined sites. During this period, the subjects were monitored for their usage of the 35 product every week in three ways:-

Skin melanin index was measured after 14 days of application and after 28 days of

application. Three measurements were determined at the same site using Mexameter MX 18 and the mean value was calculated. In addition, the subjects were asked to fill a questionnaire on their perceptions on day 14 and day 28. The investigators were also asked to make observations each time the subject visited the clinic (i.e. on Day 7, 14, 21 and 28). The average data from all measurements was statistically analysed using the student t test using SPSS Statistic 20 to give results in three forms:-

- a. A skin melanin index for each test site (corresponding to each test product) on D0, D14 and D28,
- b. A comparison result between the test products and the positive control, and
- c. A comparison between the test products; which were found to be statistically significant at $p < 0.001$ levels.

The main conclusions were that cream formulations containing maltol and / or sodium saccharin at an amount of 0.25% to 0.50% w/w were equally active in lightening the skins of the subjects as compared to the positive control formulation containing 3.0% w/w niacinamide. The cream containing a blend of 0.25% maltol and 0.25% saccharin (NZW 06) was preferred by the subjects, and the sample containing the 3.0% niacinamide (NZW 01) was least preferred.

Using the sample containing maltol and saccharin (NZW 06), 100% of the subjects observed and reported lightening of their skin by day 14 of the trial, with 74% noticing lightening by day 7. By comparison, only 82% of the subjects reported visible lightening by niacinamide by day 14 of the trial despite the use of a six-fold higher concentration of active ingredient. This result was confirmed when skin melanin index measurements were made using a Mexameter as the sample containing the blend of 0.25% maltol and 0.25% saccharin (NZW06) had specific activities 7.6 fold higher than the sample containing 3% niacinamide (NZW01) after use for 14 days, and 6.6 fold greater when used for 28 days (Table VI), and with these results statistically significant at $p < 0.001$ levels. However, the most active samples at 14 days, and 28 days respectively were blends of 0.25% maltol with 1.5% niacinamide (NZW04), and a blend of 0.25% sodium saccharin and 1.5% niacinamide (NZW02, Table I to III).

In addition, the preferences of the subjects were assessed. The blend of 0.25% maltol and 0.25% saccharin (NZW06) was assessed as 82% positive, 18% neutral with no negative responses, and the 3% niacinamide sample (NZW01) was assessed as 64% positive, 25% neutral and 11% negative.

Tables I to III illustrate the skin lightening effects of the various compositions by measuring the difference of skin melanin index (SMI) at day 14 and day 28. Table IV shows the method of applying the cosmetic product containing the cosmetic composition.

5 As shown in Table II, by comparing the results of NZW 01 and the other 3 combinations of products containing maltol and/or sodium saccharin, all 3 compositions yielded comparable SMI reduction to that obtained from 3% of niacinamide after 28-day applications. This statistically shows the superior specific activity of the products containing maltol and/or sodium saccharin in only an amount ranging from 0.25 wt % to

10 0.5 wt %, as compared to 3 wt % of NZW 01.

From these results, the cosmetic composition in NZW 06 was calculated to offer a 4-fold cost-in-use advantage as compared to niacinamide (see Figure 1).

15

Table I

Influence Of Products On Skin Melanin Index For Products Containing Maltol, Sodium Saccharin, Niacinamide, or Combinations of the Compounds Compared To Baseline (n = 28)

Product Code	Product	Skin Melanin Index (unit) [^]		
		Baseline	After 14 Days application	After 28 Days application
NZW 01	Cream base containing Niacinamide at 3%	280.68 ± 6.680	273.43 ± 6.369***	258.96 ± 5.920****
NZW 02	Cream base containing Sodium Saccharin at 0.25% and Niacinamide at 1.5%	293.07 ± 7.360	287.71 ± 7.433**	266.21 ± 7.352****
NZW 03	Cream base containing Maltol at 0.5%	282.96 ± 7.583	274.96 ± 7.128 **	263.00 ± 6.921 ****
NZW 04	Cream base containing Maltol at 0.25% and Niacinamide at 1.5%	269.75 ± 5.795	260.11 ± 5.735 ****	249.75 ± 5.376 ****
NZW 05	Cream base containing Sodium Saccharin at 0.5%	286.86 ± 6.714	277.64 ± 6.618 ****	260.93 ± 6.218 ****
NZW 06	Cream base containing Maltol and Sodium Saccharin at 0.25% each	287.46 ± 7.469	278.29 ± 6.932 **	263.39 ± 6.686 ****
ctrl neg	Negative control (no treatment, measured in the same subjects and the same	258.07 ± 7.294	259.89 ± 7.338	277.82 ± 8.379

condition as the subject and
condition for other tested
products)

^ mean of 3 measurements \pm SEM (Standard Error of the Mean)

* Statistically significant from baseline at $p < 0.05$

** Statistically significant from baseline at $p < 0.01$

5 *** Statistically significant from baseline at $p < 0.005$

**** Statistically significant from baseline at $p < 0.001$

Table II

**Improvement In Skin Melanin Index For Products Containing Maltol, Sodium
Saccharin, Niacinamide, or Combinations of the Compounds As Opposed To
Positive Control Containing 3% Niacinamide**

10

Product Code	Product	Skin Melanin Index (unit) ^		
		Baseline	After 14 Days application	After 28 Days application
NZW 01	Cream base containing Niacinamide at 3%	280.68 \pm 6.680	-7.250 \pm 2.625 ***	-21.714 \pm 3.473 ****
NZW 02	Cream base containing Sodium Saccharin at 0.25% and Niacinamide at 1.5%	293.07 \pm 7.360	-5.357 \pm 2.159 **	-26.857 \pm 2.379 ****
NZW 03	Cream base containing Maltol at 0.5%	282.96 \pm 7.583	-8.000 \pm 3.092 **	-19.964 \pm 2.980 ****
NZW 04	Cream base containing Maltol at 0.25% and Niacinamide at 1.5%	269.75 \pm 5.795	-9.643 \pm 2.410 ****	-20.000 \pm 2.238 ****
NZW 05	Cream base containing Sodium Saccharin at 0.5%	286.86 \pm 6.714	-9.214 \pm 2.756 ****	-25.929 \pm 3.188 ****
NZW 06	Cream base containing Maltol and Sodium Saccharin at 0.25% each	287.46 \pm 7.469	-9.179 \pm 3.500 **	-24.071 \pm 3.852 ****

- a negative sign refers to a reduction in Skin Melanin Index, i.e. indicating lightening occurring.

^ mean of 3 measurements \pm SEM (Standard Error of the Mean)

15 * "Statistically significant from baseline at $p < 0.05$

** Statistically significant from baseline at $p < 0.01$

*** Statistically significant from baseline at $p < 0.005$

**** Statistically significant from baseline at $p < 0.001$

Table III
Comparison Of The Change In Skin Melanin Index Between Products Containing Maltol, Sodium Saccharin, Niacinamide, or Combinations of the Compounds Versus Positive Control Containing 3% Niacinamide

Products to be compared			Difference in the Skin Melanin Index (unit)	
Product Code	Product	Positive Control	Product (Day 14-Day 0) - Positive Control (Day 14- Day 0)	Product (Day 28-Day 0) - Positive Control (Day 28- Day 0)
NZW 02	NZW02 - Cream base containing Sodium Saccharin at 0.25% and Niacinamide at 1.5%	Cream base containing Niacinamide at 3%	1.89 ± 2.68	-5.11 ± 3.84
NZW 03	Cream base containing Maltol at 0.5%		-0.78 ± 3.25	1.78 ± 3.46
NZW 04	Cream base containing Maltol at 0.25% and Niacinamide at 1.5%		-2.39 ± 3.12	1.75 ± 3.54
NZW 05	Cream base containing Sodium Saccharin at 0.5%		-1.96 ± 3.83	-4.18 ± 4.25
NZW 06	Cream base containing Maltol and Sodium Saccharin at 0.25% each		-1.93 ± 4.39	-2.32 ± 4.83

5 - a negative sign indicates that the product achieved a greater skin melanin index reduction as compared to the positive control

Table IV
Method of Applying the Products Containing the Cosmetic Composition

Application Area	Left and right arm skin facing medial to the body
Quantity Applied	0.16 g to 0.21 g /usage/tested area
Concentration Applied	As is (100%, without dilution)
Frequency	Twice daily, morning and evening Note: if subject showers in the morning or evening, application of test material should always be done after shower
Usage	Apply each product to each tested area which have been determined previously
Duration of Application	28 Days
Tested area	approximately 60 cm ²

10

Table V illustrates the ranking of the various compositions from best to worst based on user satisfaction measurements. The questionnaire was formulated to include the questions such as: 1) what were your first impressions after application of the various

compositions? 2) How quickly do you expect to see a lightening effect? 3) Are you satisfied with the quality of skin lightening achieved? 4) How many days after the first application of the various compositions did you observe a lightening effect? 5) are you satisfied with the quality of skin lightening achieved? 6) How many days after the first application of the test product did you observe a lightening effect?

Table V
Results of user satisfaction measurements after applying various compositions

Ranking	Number of Subject (%) Answered on various compositions					
	NZW 06 Cream base containing Maltol and Sodium Saccharin at 0.25% each	NZW 05 Cream base containing Sodium Saccharin at 0.5%	NZW 04 ream base containing Maltol at 0.25% and Niacinamide at 1.5%	NZW 03 Cream base containing Maltol at 0.5%	NZW 02 Cream base containing Sodium Saccharin at 0.25% and Niacinamide at 1.5%	NZW 01 Positive Control Cream base containing Niacinamide at 3%
1	29	14	7	11	14	25
2	7	39	18	18	14	4
3	18	7	29	14	11	21
4	21	11	14	32	14	7
5	14	21	11	4	39	11
6	11	7	21	21	7	32
Total	100	100	100	100	100	100

10

Specific activity was obtained as follows. Specific activity is the skin melanin index (SMI) reduction per gram of accumulated actives applied at a time point. It has been calculated in the following manner;

$$Specific\ activity = \frac{\Delta SMI\ T_x}{\sum Active\ Compound_{mg}T_x} .$$

15

Table VI
Comparison of Specific Activity Between Products Containing Maltol, Sodium Saccharin, Niacinamide, or Combinations of the Compounds Versus Positive Control Containing 3% Niacinamide

Product Code	Product	Skin Melanin Index (unit) [^]			
		Day 14		Day 28	
		Accumulated actives applied (g)	Specific Activity	Accumulated actives applied (g)	Specific Activity
NZW 01	Cream base containing Niacinamide at 3%	0.148	49.04 ± 17.76	0.319	68.03 ± 10.88
NZW 02	Cream base containing Sodium Saccharin at 0.25% and Niacinamide at 1.5%	0.089	59.74 ± 24.08	0.189	142.00 ± 12.58
NZW 03	Cream base containing Maltol at 0.5%	0.025	315.71 ± 122.02	0.053	371.35 ± 55.43
NZW 04	Cream base containing Maltol at 0.25% and Niacinamide at 1.5%	0.080	120.00 ± 29.99	0.171	117.29 ± 13.12
NZW 05	Cream base containing Sodium Saccharin at 0.5%	0.024	378.24 ± 113.14	0.052	503.28 ± 61.88
NZW 06	Cream base containing Maltol and Sodium Saccharin at 0.25% each	0.025	370.42 ± 141.24	0.052	464.69 ± 74.36

5

EXAMPLE 2

As part of the same study that was carried out in Example 1, data was collected and the

skin lightening effects on the 28 subjects were observed as follows.

Data were collected from the 28 subjects who were each treated with 3 test samples consisting of (i) maltol ("M"); (ii) sodium saccharin ("S"); and (iii) a combination of maltol
5 and sodium saccharin ("M+S") for 28 days. The data were collected on Day 14 and Day 28.

The 28 subjects were firstly classified into three categories: 'Got darker' [SMI>0]; 'No
10 change' [SMI=0]; 'Got lighter' [SMI<0]. The results obtained were as follows:

Table VII

Product Code	'Got darker' [SMI>0]	No change' [SMI=0]	'Got lighter' [SMI<0]
M14	7	0	21
M28	3	0	25
S14	4	2	22
S28	0	0	28
M+S14	9	1	18
M+S28	2	0	26

For those subjects whose skin got lighter, the degree of SMI reduction was also obtained,
subdivided into categories, where the values represent SMI reductions. Data presented
15 below were cumulative, i.e. as the magnitude of SMI reduction increased, the number of
subjects was a subset of those in the previous (lower SMI reduction) category. The
results obtained were shown in the Table VIII below.

Table VIII

SMI reduction	<0	<5	<10	<15	<20	<25	<30	<35	<40	<45	<50	<55
M14	21	14	11	6	5	3	3	2	2	1	0	0
M28	25	25	21	17	13	10	5	4	2	2	2	1
S14	22	16	10	8	6	4	2	2	0	0	0	0
S28	28	28	22	18	15	14	9	8	5	5	3	3
M+S14	18	14	9	9	6	6	5	3	2	2	1	0
M+S28	26	24	19	18	14	10	9	7	7	6	3	3

The above results show that for maltol (M), sodium saccharin (S) and a combination of maltol and sodium saccharin (M+S), SMI reductions were larger at the 28-day time point than at the 14-day time point. Further analysis on the 28-day time point data was then carried out. The goal of the analysis was to determine whether a combination of the two active ingredients, maltol and sodium saccharin, was more effective in reducing SMI than the individual active ingredients.

A linear regression analysis method was selected for the analysis. The R² statistic is based on the distances of individual data points from the linear regression (best fit line), and has values between 0 and 1. R² provides a measure of the proportion of the variability in the data that the factor of interest accounts for. The significance level was set at 5% (i.e. P values < 0.05 are considered to indicate a significant difference between groups).

The first comparison was made between the degree of SMI reduction with the combination of maltol and sodium saccharin and the mean SMI reduction for those treated with maltol or sodium saccharin alone. The mean values for maltol (M) or sodium saccharin (S) are:

Table IX

Mean values for Maltol (M) or Sodium Saccharin (S)		
<0: 26.5	<20: 14	<40: 3.5
<5: 26.5	<25: 12	<45: 3.5
<10: 21.5	<30: 7.0	<50: 2.5
<15: 17.5	<35: 6.0	<55: 2.0

The difference in the number of people between M+S as compared to mean(M or S) was calculated for each SMI reduction category. A linear regression of these data produced a line with positive slope, an R² value of 0.44 and a P value of 0.020 (see Figure 8). The x-intercept of the regression line was at SMI = 23.4.

Further analysis was carried out to compare the SMI reduction between M+S and M alone or S alone.

Figure 9 shows the comparison between M+S and M alone, with the difference in number of people between M+S and M alone plotted against the magnitude of SMI reduction. A linear regression of these data produced a line with positive slope, an R^2 value of 0.26 and a P value of 0.038. The x-intercept of the regression line was at SMI = 5.1.

5

Figure 10 shows the comparison between M+S and S alone. The difference in the number of people between M+S and S alone is plotted for each SMI reduction category. A linear regression of these data produced a line with positive slope, with an R^2 value of 0.44 and a P value of 0.019. The x-intercept of the regression line was at SMI = 41.8.

10

Conclusions

The P value for the linear regression analysis indicates that there is a significant difference between M+S and mean(M or S) in terms of SMI reduction. The x-intercept of the linear regression at SMI = 23.4 indicates that more people had larger SMI reductions with M+S as compared to the mean of M or S alone.

15

Breaking this down into comparison of M+S with M alone or S alone, again there was a significant difference for M+S as compared to M or S. In the comparison between M+S and M, the x-intercept of the linear regression was SMI = 5.1, indicating that more people had larger SMI reductions with M+S than with M alone. In contrast, in the comparison between M+S and S alone, the linear regression had an x-intercept of 41.8, indicating that fewer people had smaller SMI reductions with M+S than with S alone. Overall, the above analyses suggest that maltol (M) and saccharin (S) may have additive effects on SMI reduction.

20

25

EXAMPLE 3

In-vitro Melanogenesis Inhibition Evaluation

30

The melanogenesis inhibiting activity of next cohort of compounds as measured in B16 cultured melanocyte cells was evaluated, using kojic acid as a positive control, and compared to maltol and sodium saccharin whose in-vivo activities are already proven in Example 1:

35

Table X

IC50 of skin lightening actives tested in B16 cell melanogenesis inhibition assays.

IC50 (g/l)	
Acetylsalicylic Acid	0.262
Inosine Monophosphate (IMP)	0.227
Uracil	0.143
SS + Guanine	0.141
SS + Citrazinic Acid	0.137
Isatoic Anhydride	0.132
TB + ASK	0.131
SS + ASK	0.119
IMP + SS	0.117
SS + TB	0.108
M + SS + TB	0.101
Phthalimide	0.089
IMP + M	0.086
Citrazinic Acid	0.077
Erythorbic Acid	0.073
Dehydroacetic Acid (DHAA)	0.073
Hypoxanthine	0.07
Maltol (M)	0.065
Ethyl Maltol	0.059
Acesulphame K (ASK)	0.058
SS + DHAA	0.057
Guanine	0.056
Sodium Saccharin (SS)	0.055
M + SS	0.046
Theobromine (TB)	0.037
M + TB	0.037
Kojic acid (Standard)	0.051

Melanogenesis inhibiting activities were obtained as follows. B16 melanocyte cells were
 5 cultured in a T75 flask and allowed to grow to a high confluency. The appropriate
 volumes of compounds were added into the 24 well-plates. Cells were dislodged from the
 T75 flask and counted using a haemocytometer. Fresh DMEM (phenol red-free)
 containing 10% FBS was added to dilute the cells to an appropriate density, 0.025×10^6
 10 cells for a 24 well-plate. Cells were aspirated and transferred accordingly into the wells,
 each containing different compounds of varying concentrations, specifically 25 μ M, 75 μ M,
 100 μ M, 200 μ M and 300 μ M. The 24 well-plates were then incubated for 3 days. After the

treatment, the wells were washed with PBS and 1M NaOH solution was added into each well and incubated at 37°C for 2 hours, to lyse the cells to allow full release of the melanin. Optical densities (ODs) were measured at 480 nm using a BioTek Synergy HTX multi-mode reader. The results were automatically recorded in an excel spreadsheet.

5 EXAMPLE 4

Cytotoxicity activities to determine cell viability were obtained as follows. B16 melanocyte cells were plated in a 24 well-plate one day before the actual assay. Fresh DMEM (with phenol red) containing 10% FBS was added to dilute the cells to an appropriate density,
10 0.025 × 10⁶ cells for a 24 well-plate. 1ml of the DMEM with 10% FBS was added to each well. The cells in each well were treated with appropriate concentration of compounds (i.e. 75µM, 100µM and 300µM). The well-plate with treated cells were then left in the incubator at 37°C, 5% CO₂ for approximately 16 hours overnight. The media was removed and 1ml of PBS solution was added into each well to wash and remove the
15 colour of the phenol red in the DMEM. Then, 1ml of fresh PBS was added into each individual well. 15µl of the prepared Resazurin stock solution was added (8µg/ml) into each well containing the compounds. The Resazurin stock solution was prepared by adding 800µg of Resazurin sodium salt in 10ml of PBS (pH 7.4) to make a concentration of 80µg/ml, which was further diluted by adding 0.1ml of the 80µg/ml solution to 0.9ml of
20 PBS to make 8µg/ml of stock solution. The well-plates were incubated at 37°C for 2 hours. The plate was immediately read, after 2 hours, using a BioTek Synergy HTX multi-mode reader at an emission and excitation wavelength of 600nm and 528nm respectively, with a gain of 35. The results were automatically recorded in an excel spreadsheet.

25 Figure 11 shows the result of the cytotoxicity tests of the compounds on the B16 melanocytes. To assess the sufficient cell viability of the B16 cells upon reaction with the compounds at various concentrations, a fluorescence value greater than 50 is required. From the results obtained, most of the compounds had a fluorescence value of 50 and above except for ethyl maltol which resulted in cell toxicity at concentrations greater than
30 100µM. This suggests that the compounds do not cause a great loss in cell viability and that the reduction in melanin is not due to loss in cell viability but due to melanogenesis inhibition.

EXAMPLE 5

35

Skin Tone Measurements

Figure 2 shows the improvement on skin tone after applying the cream containing 0.25% maltol and 0.25% saccharin twice daily for 28 days. The a* (rosy-red tone) and b* (yellow tone) components of the skin tone were monitored.

The cream base used for blending the active ingredients contained the ingredients as follows: Aqua, Butyrospermum parkii, caprylic/capric triglyceride, C12-15 alkyl benzoate, cetearyl isononanoate, cyclomethicone, butylene glycol, hydroxyethyl acrylate, sodium dimethyl taurate copolymer, Aloe barbadensis leaf juice. The cream base was white in colour, with a pH range between 4.5 and 5.5.

Over the 28-day period, the a* (rosy-red tone) component of Indian skin increased, and the b* (yellow tone) component of Indian and Chinese skins decreased. For comparison, the widely used skin lightener niacinamide had diametrically opposite effects on Chinese skin and especially on Indian skin. Before starting the study, all subjects' melanin index, L*a*b* and ITA value were measured at the tested site using Mexameter MX18 and Courage+Khazaka (CK) Colorimeter CL 400. Photos and instrument measurements were taken at the start of the testing (Day 0), during the testing (D2, D5, D7, D9, D12) and after the testing (D14, D21 and D28). The materials were applied twice daily, once in the morning and once in the evening (if the subject was to shower in the morning or the evening, the test material was applied after the shower) to intact skin of the arm for 14 days. Each subject applied 5 products on the left arm. Subjects wore an arm sleeve over part of the right arm for the occluded site, so as to provide 2 negative controls, one occluded from light and UV-radiation (right arm) and one covered under fabric (left arm) so as to understand the effect of melanogenesis even when no light is passing through. The tested areas were evaluated on their skin melanin index, L*a*b* and ITA after D2, D5, D7, D9, D12, D14, D21 and D28 of application using Mexameter MX 18 and CK Colorimeter CL400.

EXAMPLE 6

Skin Quality Analysis

As part of the same experiment above, general skin quality effects were also observed. Over the 28 days, the skins of the Indian and Chinese subjects became brighter, smoother and more youthful looking.

EXAMPLE 7Further Skin Quality Analysis Study

5

This analysis was carried out using the IOMA™ Micro Electro Mechanical Systems (MEMS) technology to photographically analyse the condition of the skin. It provides details of 12 different attributes, hydration, desquamation, fine lines, wrinkles, sagging, redness, UV damage, bacterial activity, clogged pores, bags and eyelids, and dark circles and line lines around eyes. Each of the conditions was measured on a scale of 1-15, with 1 being the ideal. The rationale of this further analysis was to gain independently assessed data for the efficacy of a cream containing 1.5% maltol and 1.5% sodium saccharin applied to the face. This was done using a subject who had been using a high quality commercial cosmetic product on a daily basis for several years previously, and who continued to use this product as well as the cream containing 1.5% maltol and 1.5% saccharin during the trial. The commercial product (SK-II™ Facial Wash) contained water, glycerin, Galactomyces ferment filtrate, niacinamide, butylene glycol, sucrose polycottonseedate, isopropyl isostearate, isohexadecane, dimethicone, cetyl alcohol, polyacrylamide, panthenol, polymethylsilsesquioxane, tocopheryl acetate, stearyl alcohol, C13-14 isoparaffin, benzyl alcohol, methylparaben, dimethiconol, PEG-100 stearate, stearic acid, disodium EDTA, laureth-7, propylparaben, cetearyl alcohol, cetearyl glucoside, ethylparaben, fragrance, sodium hydroxide, Saccharomyces cerevisiae extract, palmitoyl dipeptide-7 and hexapeptide-3.

25 During the trial, the cream containing 1.5% maltol and 1.5% saccharin was applied to the face, particularly to the skin underneath the eyes, every morning. 0.5g of the cream was applied on the left side of the face and 0.4g was applied on the right side of the face. The subject first patted the cream on the sides of the face, followed by massaging the cream into the sides of the face, on the cheeks, but particularly on the upper cheekbone and under the eye area, with the remainder of the cream being applied onto the forehead but not on the nose. The cream base used for blending the active ingredients contained the following ingredients: Aqua, disodium EDTA, Ultrez-20, glycerine, methyl gluceth-20, PEG-20 methyl glucose sesquistearate, isopropyl isostearate/isopropyl myristate, Tween 20, and NaOH. The cream base was white in colour, with a pH ranges between 6 and 7.

35 IOMA instrumental assessments were made on Day 0, Day 14, Day 28 and Day 135, and the imaging was carried out in the late afternoon. After 28 days, a 60% reduction in dark circles around the eyes, and a 54% reduction in fine lines around the eyes were

observed. After 4.5 months of using the cream, a re-examination showed that improvements to the reduction of dark circles and fine lines around the eyes had continued. The reduction in fine lines was also apparent elsewhere on the skin. Cell regeneration on the face was enhanced and UV damage was reduced.

5

Figure 3 shows the effect of the cream containing 1.5% maltol and 1.5% sodium saccharin on dark circles and fine lines around eyes after 28 days of application. The experimental results show that there was a 60% improvement in decreasing dark circles around the eyes and 54% improvement in decreasing fine lines around the eyes. This is despite the subject being a regular long-term user of the SK-II facial wash. The significant improvements observed were in addition to those which had already been achieved.

10

Table XI

100 = Ideal	Day 0	Day 14	Day 28		Overall Improvement by:
Dark circles	27 / 100	73 / 100 ↑	87 / 100 ↑	→	↑ 60%
Eye fine lines	13 / 100	67 / 100 ↑	67 / 100 ↔	→	↑ 54%

Data collected using a commercial unit; 100 being the ideal skin condition

15

EXAMPLE 8**Antimicrobial Activity**

20 Figure 4 shows the result of antimicrobial activity in the samples.

To assess resistance to microbial contamination, a cream containing 0.25% maltol and 0.25% sodium saccharin (NZW 06) was inoculated with 10^5 - 10^6 CFU/ml *Pseudomonas aeruginosa* and incubated at 37°C for 28 days (with reference to ISO 11903 method). The cream base used for blending the active ingredients contained the ingredients as follows: Aqua, disodium EDTA, Ultrez-20, glycerine, methyl gluceth-20, PEG-20 methyl glucose sesquistearate, isopropyl isostearate/isopropyl myristate, Tween 20, and NaOH. The cream base was white in colour, with a pH range between 6 and 7. Market sample (Nivea) containing chemical preservatives was chosen as the control.

25
30

At the end of this period, it was observed that the control sample contained 3.9×10^5 CFU/ml, but both the cream containing maltol and sodium saccharin (NZW 06), and the

market sample containing chemical preservatives were entirely free of microbial colonies. This suggests that the product containing NZW 06 does not require additional chemical preservatives. This therefore saves on formulation costs, and allows for preservative-free consumer claims to be made.

5

Both sodium saccharin and maltol, when tested individually at 0.05 % completely inhibited the growth of *P. aeruginosa*.

EXAMPLE 9

10

Colour and Stability Test

The appearance such as the colour of the product containing 1 wt% maltol and 1 wt% sodium saccharin was evaluated (Figure 5) via a colour and physical stability trial. A blended composition (2 wt% BC containing 1wt% maltol and 1 wt% sodium saccharin) was stored in the oven at 45°C for 30 days, together with a control containing 2 wt% of kojic acid (KA). The accelerated colour generation was monitored via image taking as well as RGB (Red, Green, Blue) analysis, where a pure white colour represents (255,255,255).

20

The cream base used for blending the active ingredients contained the ingredients as follows: Aqua, Butyrospermum parkii, caprylic/capric triglyceride, C12-15 alkyl benzoate, cetearyl isononanoate, cyclomethicone, butylene glycol, hydroxyethyl acrylate, sodium dimethyl taurate copolymer, Aloe barbadensis leaf juice. The cream base was white in colour, with a pH ranges between 4.5 and 5.5. At the start of the trial, the test creams had RGB values of (188, 187, 167).

25

It was observed at the end of the trial that the cream containing 2 wt% KA was found to darken from white colour to dark yellow and finally to dark brown with a RGB value of (87,40,27). It also turned watery upon prolonged storage at 45°C. On the contrary, the appearance and texture of the cream containing 2 wt% BC was well maintained with only very slight discoloration, with RGB readings of (167,160,142). This provides advantages of sales and storage of the creams in tropical climates or in the summer where there exists a high demand for skin lightening and skin quality products.

35

EXAMPLE 10

Rheological properties of the creams with different cosmetic compositions were evaluated based on viscosity measurements. The individually tested samples were dissolved in a base cream (control) with a viscosity of 25,000 mPa·s. The cream base used for blending the active ingredients contained the ingredients as follows: Aqua, Butyrospermum parkii, caprylic/capric triglyceride, C12-15 alkyl benzoate, cetearyl isononanoate, cyclomethicone, butylene glycol, hydroxyethyl acrylate, sodium dimethyl taurate copolymer, Aloe barbadensis leaf juice. The cream base was white in colour, with a pH ranges between 4.5 and 5.5.

When maltol and sodium saccharin were added in an equal ratio to give a 0.5 wt% solution, the viscosity of the cream was reduced to 22,000 mPa·s. When maltol and sodium saccharin were dissolved in an equal ratio at 2 wt%, the viscosity of the cream was reduced to 11,000mPa·s. By comparison, when ascorbic acid-2-glucoside (AA2G) was added to make a 0.5 wt% cream, the viscosity of the resulting cream increased to 26,000 mPa·s. These results are as shown in Figure 6.

This test showed that the addition of maltol and sodium saccharin from 0.5 wt% onward reduced the viscosity of the cream as opposed to an addition with 2% AA2G. A significant drop in viscosity was observed upon increasing the amount of maltol and sodium saccharin up to 2 wt%. A reduced viscosity (creamy in texture) provides an advantage to ensure proper dispersal, and easy application and absorption of the cream on skin. Further, it also provides flexible formulatory advantage since a reduced viscosity allows for the possibility of the addition of more active compounds or functional ingredients (e.g. emulsifiers, emollients, etc.)

25

EXAMPLE 11

A blend containing 0.25% maltol and 0.25% sodium saccharin(NZW 06) was successfully incorporated into the following commercial skin lightening cum anti-ageing formulation, containing water, cyclopentasiloxane, ethylhexyl methoxycinnamate, 4-methylbenzylidene camphor, cetareth-12, glycerin, cetyl alcohol, polymethyl metacrylate, diisopropyl sebacate, isodecyl neopentanoate, lauryl lactate, glyceryl stearate, PEG-100 Stearate, Vitis vinifera (Grape) seed oil, carbomer, phenoxyethanol, butyl methoxydibenzoylmethane, tocopheryl acetate, triethanolamine, parfum (fragrance), chlorphenesin, hydrolysed wheat protein, tetrasodium EDTA, magnesium aspartate, zinc gluconate, BHT, Faex extract (Yeast extract), benzyl salicylate, hydroxyisohexyl 3-

cyclohexene carboxaldehyde, copper gluconate, hexyl cinnamal, methylisothiazolinone, sodium hyaluronate, ethylhexylglycerin, linalool, alpha-isomethyl ionone, sodium chloride, geraniol, limonene, butylphenyl methylpropional, with no change to the colour, consistency, or physical appearance to the formulation.

5

EXAMPLE 12

A blend containing 0.25% maltol and 0.25% sodium saccharin (NZW 06) was successfully incorporated into the following two commercial skin lightening formulations with no change to the colour, consistency, or physical appearance to the formulation:

10

(i) Commercial skin lightening formulation containing water, palmitic acid & stearic acid, niacinamide, glycerin, cetearyl ethylhexanoate and isopropyl myristate, ethylhexyl methoxycinnamate, butylmethoxydibenzoylmethane, hydroxystearic acid, sodium ascorbyl phosphate, tocopheryl acetate, allantoin, pyridoxine hydrochloride, cetyl alcohol, dimethicone, titanium dioxide and aluminium hydroxide and stearic acid, phenoxyethanol, methylparaben, propylparaben, potassium hydroxide, titanium dioxide and dimethicone, disodium EDTA, CI77491, isopropyl titanium triisostearate, triethoxysilylethyl polydimethylsiloxylethyl dimethicone, CI 15510, CI 17200, and Perfume;

15
20

(ii) Commercial skin lightening formulation containing water, stearic acid, ethylhexyl methoxycinnamate, glycerine, isopropyl myristate, niacinamide, fragrance, potassium hydroxide, phenoxyethanol, methylisothiazolinone, cetyl alcohol, coco caprylate/caprinate, butyl methoxydibenzoylmethane, Crocus sativus flower extract, titanium dioxide (and) caprylic/capric triglyceride (and) polyhydroxystearic acid (and) alumina, acrylates/C10-30 alkyl acrylate crosspolymer, disodium EDTA, tocopheryl acetate, Medicago sativa extract, and CI 15985.

25

EXAMPLE 13

30

A blend containing 0.25% maltol and 0.25% sodium saccharin (NZW 06) was successfully incorporated into the following commercial anti-ageing formulation comprising octinoxate 7.5%, oxybenzone 5.0%, octisalate 5.0%, octocrylene 2.2%, avobenzone 2.0%; Inactive Ingredients: water, dimethicone, C12-15 alkyl benzoate, butylene glycol, cyclopentasiloxane, isostearyl neopentanoate, Theobroma cacao (Cocoa) seed butter, dimethicone/vinyl dimethicone crosspolymer, Butyrospermum parkii (Shea butter) extract, Ppg-2 Isoceteth-20 Acetate, glycerol, caprylic/capric triglyceride,

35

ceramide 1, ceramide 3, ceramide 6, Alpinia speciosa leaf extract, Hibiscus abelmoschuss seed extract, Trifolium pratense (clover) flower extract, sodium hyaluronate, ascorbyl palmitate, retinyl linoleate, retinyl palmitate, tocopherol, tocopheryl acetate, cetearyl dimethicone crosspolymer, isohexadecane, acetyl octapeptide-3, 5 propylene glycol, sodium PCA, trehalose, urea, hydrogenated lecithin, lecithin, phospholipids, phytosphingosine, polyphosphorylcholine glycol acrylate, sucrose, cetearyl alcohol, cholesterol, sodium lauroyl lactylate, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, polysorbate 80, trideceth-6, acrylamide/sodium acrylate copolymer, polyquaternium-51, PEG-8, acrylates/C10-30 alkyl acrylate 10 crosspolymer, carbomer, xanthan gum, sodium hydroxide, BHT, mineral oil/paraffinum liquidum/huile minérale, dimethiconol, phenyl trimethicone, parfum/fragrance, alpha-isomethyl ionone, benzyl benzoate, butylphenyl methylpropional, citral, citronellol, eugenol, geraniol, hexyl cinnamal, hydroxyisohexyl 3-cyclohexene carboxaldehyde, limonene, linalool, benzoic acid, butylparaben, ethylparaben, isobutylparaben, 15 methylparaben, phenoxyethanol, potassium sorbate, propylparaben, chlorphenesin, Red 4 (Ci 14700) and Yellow 6 (Ci 15985).

EXAMPLE 14

20 Multiple serum formulations which may be used in single or multi-use cosmetic forms such as capsules or in jar or in tube containers were prepared as follows:

- a) Water 96.3%, 3% of a blended powder (containing 10% Maltol and 90% Sodium Saccharin), 0.6% xanthan gum, 0.1% DS-Hydroceramide 50.
- 25 b) Water 96.3%, 3% of a blended powder (containing 9.9% Maltol, 89.5% Sodium Saccharin, 0.6% Menthol), 0.6% xanthan gum, 0.1% DS-Hydroceramide 50.
- c) Water 96.3%, 1.5% of a blended powder (containing 9.9% Maltol, 89.5% Sodium Saccharin, 0.6% Menthol), 0.6% xanthan gum, 0.1% DS-Hydroceramide 50.
- 30 d) Water 96.3%, 6% of a blended powder (containing 9.9% Maltol, 89.5% Sodium Saccharin, 0.6% Menthol), 0.6% xanthan gum, 0.1% DS-Hydroceramide 50.

EXAMPLE 15

A cream containing multiple active ingredients was prepared as follows:

35

Acesulphame K, sodium saccharin, maltol, dehydroacetic acid and theobromine each at a concentration of 0.25% were blended together into a base cream. The cream base used

for blending the active ingredients contained the ingredients as follows: Aqua, disodium EDTA, Ultrez-20, glycerin, methyl gluceth-20, PEG-20 methyl glucose sesquistearate, isopropyl isostearate/isopropyl myristate, Tween 20, and NaOH. The cream base was white in colour, with a pH ranges between 6 and 7. The resultant blended cream was even, smooth and had superior skin feel as compared to the original unblended cream base.

EXAMPLE 16

10 A cream containing 0.5% sodium saccharin, 0.5% maltol and 2% zinc oxide was prepared as follows:

0.05% of Disodium EDTA was added to 78.55% water and stirred until fully dissolved. 0.5% of Ultrez 20 was added to the mixture while the mixture was continuously stirred. 2% glycerin, 1% methyl gluceth-20, 0.75% PEG-20 methyl glucose sesquistearate, 0.5% maltol, 0.5% sodium saccharin were then added, while the mixture was heated to 70-80°C with constant stirring. An oil phase was prepared by blending 10g of petrolatum/beeswax/petroleum jelly blend containing 2% zinc oxide, 0.5% methyl glucose sesquisterate, 4% isopropyl myristate and 1.65% Tween 20 together while the blend was heated to a temperature of 70-80°C. Once the temperatures of the two phases were equal, the two phases were combined and stirred until the temperature of the mixture dropped to 60°C. pH of the mixture was then adjusted to between pH 6 and 7 with sodium hydroxide.

25 EXAMPLE 17

In-vivo skin lightening study on 83 Indian female subjects (who were divided into four groups) and monitored by self-assessment, assessment by dermatologists, and instrumentally was carried out. This double-blind Clinical Research Organisation (CRO) study proved the efficacy of skin lightening and skin quality among four test products. Group A subjects tested a commercially available market sample in cream base (TP3M). Group B subjects tested a pink water gel moisturiser chassis with 0.5% Maltol and 0.5% Sodium Saccharin post-added into the gel (TP21). Group C subjects tested the pink water gel moisturiser chassis of the same composition as in Group B as a placebo, with no other actives post-added. (TP4P). Group D subjects tested the pink water gel moisturiser chassis of the same composition as in Group C with 3% Niacinamide post-added into the

gel (TP13). A cream of the same composition, but containing 3.0% niacinamide (TP13, Table VIII) instead of maltol and saccharin was used as a positive control.

5 The Pink Water Gel Moisturiser Chassis as used in TP21, TP4P and TP13 is defined as containing the following ingredients (as per their US INCI Name): Dimethicone, Hydrogenated Polydecene, Pentaerythrityl tetraisostearate, DC 1403 (Dimethicone; Dimethiconol), Tocopheryl Acetate, Water, Disodium EDTA, Glycerin, Butylene Glycol, Pentylene Glycol, Sodium Hyaluronate, Xanthan gum, Carbomer, Methylparaben, Sodium hydroxide, Rose Damascena Organic Distillate 1:20 SB 721033 (Rosa
10 Damascena Flower Water; Citric Acid, Water, Sodium Benzoate; Potassium Sorbate), Honey, Phenoxyethanol, Fragrance, Colorant. Niacinamide and the 1% Maltol and Sodium Saccharin mixture was respectively post-added into the pink water gel moisturiser chassis.

15 The commercially available market sample in cream base labelled TP3M is defined as containing the following active ingredients: Water, stearic acid, niacinamide, glycerin, cetearyl ethylhexanoate, ethylhexyl methoxycinnamate, titanium dioxide, cetyl alcohol, dimethicone, potassium hydroxide, butylmethoxydibenzoylmethane, perfume, tocopheryl acetate, sodium ascorbyl phosphate, phenoxyethanol, methylparaben, allantoin,
20 propylparaben, hydroxystearic acid, isopropyl myristate, disodium EDTA, aluminium hydroxide, triethoxysilylethylpolydimethylsiloxyethyl dimethicone, dimethicone, isopropyl titanium triisostearate, pyridoxine hydrochloride, BHT, CI 77491, CI 17200, CI 15510.

The subjects were recruited and selected according to inclusion and exclusion criteria, as
25 well as the prohibition and restriction concepts defined in the study protocol. In this study, 83 female subjects were included by the Investigator. The age of the subjects was between 18-25 years old with the average age of each of the four groups being 21.3, 21.41, 20.83, and 21.35 years respectively.

30 The selected subjects were treated on the entire face with the tested products. Subjects were briefed on how to use the tested products which they were required to use by themselves over the 56 days. The subjects were instructed to avoid direct facial sun exposure throughout the course of the study. Test subjects were also told to abstain from using new skincare products or cosmetic products, or change their existing brands,
35 before and during the course of the clinical study.

Before application of the tested product, the skin melanin index was measured at all tested sites of the cheeks in each subject. The tested product was applied twice daily, once in the morning and once in the evening, over 56 days on the entire face. During this period, the subjects were monitored for their usage of the product every week in three
5 ways:-

Skin melanin index was measured after 7, 14, 28 and 56 days of application. Three measurements were determined at the same site using Mexameter MX 18 and Chromameter, and the mean value was calculated. In addition, the subjects were asked
10 to assess their skin and score the skin attributes as per self-assessment questionnaire on Day 0, Day 7, Day 14, Day 28 and Day 56. The investigators were also asked to make observations each time the subject visited the clinic (i.e. on Day 7, 14, 21, 28, and 56). The average data from all measurements was statistically analysed using the paired t test using R software to give results in three forms:-

15

- a. A skin melanin index for each test site (corresponding to each test product) on D0, D7, D14, D28, and D56
- b. A comparison result between the test products and the positive control, and
- c. A comparison between the test products; which were found to be statistically
20 significant at $p < 0.05$ levels.

The main conclusions were that cream formulations containing maltol and sodium saccharin at an amount of 1% w/w were equally active in lightening the skin of the subjects as compared to the positive control formulation containing 3.0% w/w
25 niacinamide. The cream containing a blend of 0.5% maltol and 0.5% saccharin (TP21) was preferred by the subjects, and the sample containing the 3.0% niacinamide (TP13) was least preferred (See Table XVI).

Using the sample containing maltol and saccharin (TP21), 95% of the subjects observed
30 and reported lightening of their skin by day 7 of the trial. This result was confirmed when skin melanin index measurements were made using a Mexameter as the sample containing the blend of 0.5% maltol and 0.5% saccharin (TP21) had specific activities 8.4 fold higher than the sample containing 3% niacinamide (TP13) after use for 7 days, and 4.6 fold greater when used for 14 and 28 days, and with these results statistically
35 significant at $p < 0.05$ levels (See Table XIV).

Tables XII to XIII illustrate the skin lightening effects of the various compositions by

- measuring the difference of skin melanin index (SMI) at day 14 and day 56. Table XIV shows the specific activities obtained for TP21 and TP13 and how they compare against each other. Table XV shows the method of applying the cosmetic product containing the cosmetic composition. As shown in Table XIII, the results of TP21 consistently yielded
- 5 comparable or better SMI reduction as compared to the 3 other compositions (TP3M, TP4P, TP13) after 56-day applications. This statistically shows the superior specific activity of the products containing maltol and sodium saccharin in only an amount of 1% Maltol and Sodium Saccharin, as compared to 3 wt% Niacinamide in TP13.
- 10 From these results, the cosmetic composition in TP21 was calculated to offer a 2-fold cost-in-use advantage as compared to niacinamide.

Table XII
Skin Melanin Index for Products Compared To Baseline

Group	Product Code	Product	Skin Melanin Index (unit) ^				
			Baseline	After 7 Days application	After 14 Days application	After 28 Days application	After 56 Days application
A (N=20)	TP3M	Cream base containing Niacinamide at 1.21% (amongst other actives as measured externally via HPLC)	443.12 ± 127.83	434.1 ± 133.19	433.18 ± 136.08	431.40 ± 132.43	426.11 ± 143.61
B (N=20)	TP21	Cream base containing Sodium Saccharin at 0.5% and Maltol at 0.5%	492.90 ± 104.81	482 ± 104.03	483.88 ± 106.70	480.04 ± 100.74	470.47 ± 96.14
C (N=22)	TP4P	Gel Chassis (control)	443.39 ± 97.86	437.67 ± 95.95	439.23 ± 95.03	436.14 ± 95.47	430.40 ± 92.22
D (N=21)	TP13	Cream base containing Niacinamide at 3%	450.10 ± 116.15	446.26 ± 117.84	440.41 ± 118.43	441.85 ± 117.45	440.13 ± 117.11

Table XIII
Improvement In Skin Melanin Index For TP21 Containing 0.5% Maltol & 0.5%
Sodium Saccharin compared against TP3M, TP4P and TP13

Product Code	Product	Skin Melanin Index (unit) ^A				
		Baseline	After 7 Days application	After 14 Days application	After 28 Days application	After 56 Days application
A (N=20)	TP3M Cream base containing Niacinamide at 1.21% (amongst other actives as measured externally via HPLC)	443.12 ± 127.83	-9.02 ± 15.79	-9.93 ± 18.42	-11.72 ± 20.26	-17.01 ± 15.78
B (N=20)	TP21 Cream base containing Sodium Saccharin at 0.5% and Maltol at 0.5%	492.90 ± 104.81	-10.73 ± 9.57	-9.02 ± 14.46	-12.86 ± 13.81	-22.43 ± 8.67
C (N=22)	TP4P Gel Chassis (control)	443.39 ± 97.86	-5.71 ± 12.77	-4.16 ± 21.16	-7.24 ± 22.31	-12.99 ± 5.64
D (N=21)	TP13 Cream base containing Niacinamide at 3%	450.10 ± 116.15	-3.83 ± 9.58	-5.85 ± 11.04	-8.25 ± 15.19	-9.97 ± 0.96

- 5 Specific activity has been obtained as follows. Specific activity is the skin melanin index (SMI) reduction per gram of accumulated actives applied at a time point. It has been calculated in the following manner;

$$\text{Specific activity} = \frac{\Delta SMI T_x}{\sum \text{Active Compound}_{mgT_x}} .$$

10

15

Table XIV
Specific Activity For TP21 as compared against TP13 at Day 7, 14 and 28

Group	Product Code	Product	Skin Melanin Index (unit) ^					
			Day 7		Day 14		Day 28	
			Accumulated actives applied (g)	Specific Activity	Accumulated actives applied (g)	Specific Activity	Accumulated actives applied (g)	Specific Activity
B (N=20)	TP21	Cream base containing Sodium Saccharin at 0.5% and Maltol at 0.5%	0.084	127.74 ± 113.93	0.168	53.68 ± 86.06	0.336	38.27 ± 41.10
D (N=21)	TP13	Cream base containing Niacinamide at 3%	0.252	15.21 ± 38.03	0.504	11.61 ± 21.9	1.01	8.16 ± 15.04

5

Table XV
Method of Applying the Products Containing the Cosmetic Composition

Application Area	Whole face
Quantity Applied	A quantity equivalent to 1 mg/cm ² of sample to be applied onto whole face at each application. (i.e. 2mg/cm ² daily). As such, a quantity ranging between 0.5g to 0.6g should be applied on the face at each application, with a range of 1 to 1.2g per day.
Concentration Applied	As per the product issued to the subject
Frequency	Twice daily, morning and evening Note: if subject showers in the morning or evening, application of test material should always be done after shower
Usage	Apply each product on entire face

Duration of Application	56 Days
-------------------------	---------

Table XI illustrates the percentage of subjects who were satisfied with the products from Day 7 to Day 28.

5

Table XVI

Results of user satisfaction measurements after applying various products

Q: Are you satisfied with the quality of skin lightening achieved?			
A: Choose 1: Very Satisfied, Satisfied, Average, Not Satisfied			
Product	Day 7	Day 14	Day 28
TP3M	85	75	80
TP21	76	90	85
TP4P	68	77	82
TP13	62	57	80
Q: If this product would be available on the market, would you use it?			
A: Yes/No			
Product	%Yes	%No	
TP3M	95	5	
TP21	100	0	
TP4P	91	9	
TP13	90	10	

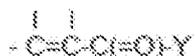
10 Although the foregoing invention has been described in some detail by way of illustration and example, and with regard to one or more embodiments, for the purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes, variations and modifications may be made thereto without departing from the scope of the invention.

15 It should be appreciated by the person skilled in the art that variations and combinations of features described above, not being alternative or substitutes, may be combined to form yet further embodiments falling within the intended scope of the invention.

Claims:

1. A cosmetic or personal care composition for regulating skin quality, the composition comprising:

5 two or more compounds, each compound containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein

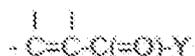
10 Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- (i) hydroxyl-based group including -OH or -C(=)-(OH);
- (ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
- 15 (iii) ether group, -O-;
- (iv) sultam group, -N(H)-S(=O)₂-;
- (v) lactam group, -N(H)-C(=O)-;
- (vi) apolar group including cyclic structures based on menthol or carotenoids;
- (vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or
- 20 -N(H)-C(H)=N-;
- (viii) amine group, -NH₂;
- (ix) secondary amine-based group, -N(H)-; and
- (x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-;

25 their derivatives, isomers, salts and/or combination thereof; and a cosmetically acceptable vehicle.

2. A cosmetic or personal care composition for skin lightening, the composition comprising:

30 two or more compounds, each compound containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein

Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

5

(i) hydroxyl-based group including -OH or -C(=)-(OH);

(ii) carbonyl-based group including -C(=)-C(=O)-CH₃;

(iii) ether group, -O-;

(iv) sultam group, -N(H)-S(=O)₂-;

10

(v) lactam group, -N(H)-C(=O)-;

(vi) apolar group including cyclic structures based on menthol or carotenoids;

(vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or -N(H)-C(H)=N-;

(viii) amine group, -NH₂;

15

(ix) secondary amine group, -N(H)-; and

(x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-;

their derivatives, isomers, salts and/or combination thereof; and
a cosmetically acceptable vehicle.

20

3. The cosmetic or personal care composition according to claim 1 or 2, wherein the two or more compounds are selected from one or more of the following groups:

25

(a) gamma-pyrone compound and their salts thereof having the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the hydroxyl group;

30

(b) gamma-pyrone compound and their salts thereof having the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the carbonyl group;

35

(c) sultam compound and their salts thereof containing the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of the sulphonamide group forming a sultam ring structure;

(d) indole-like compound and their salts thereof composed of bicyclic aromatic and heterocyclic five membered rings containing the allylic carbonyl substructure

immediately adjacent to the second substructure Y consisting of an amide group and forming a lactam structure;

5 (e) cyclohex-2-enone-like compound and their salts thereof having the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y that contains a second unsaturated bond making the compound diallylic or partially diallylic;

10 (f) adenine-like compound and their salts thereof with five and six-membered heterobicyclic structures containing the allylic or partially allylic carbonyl substructure adjacent to the second substructure Y consisting of one or more secondary aldimine groups and one or more secondary amine groups; and

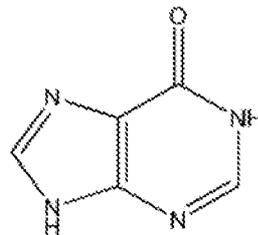
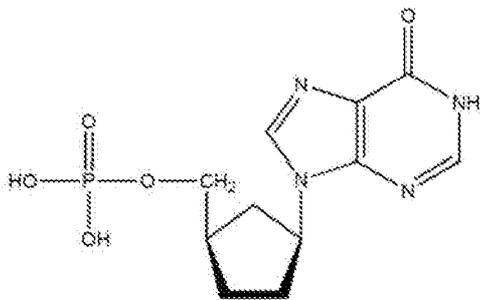
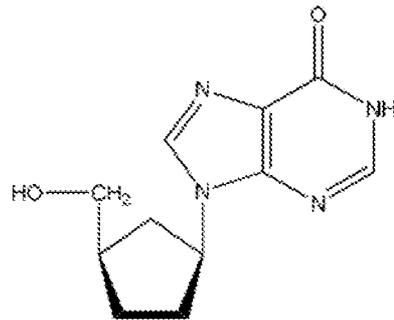
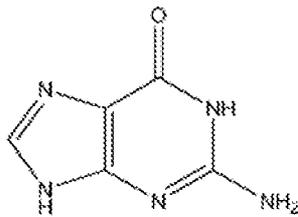
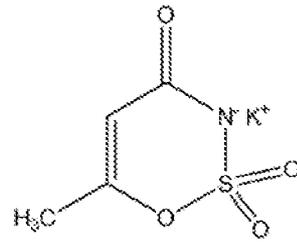
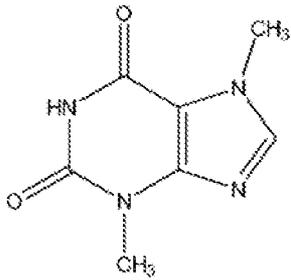
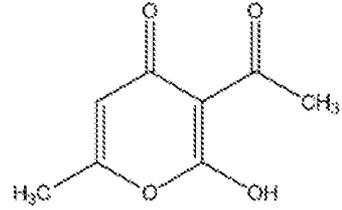
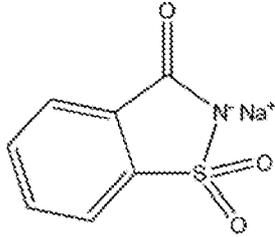
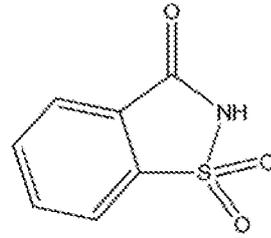
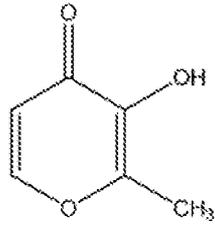
15 (g) purine-like or xanthine-like compound and their salts thereof containing the allylic or partially allylic carbonyl substructure immediately adjacent to the second substructure Y consisting of a secondary amine group or the N(H)-C(=O)-N(H)-group.

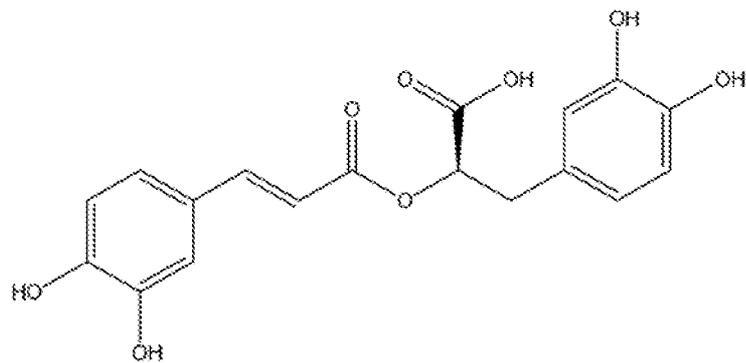
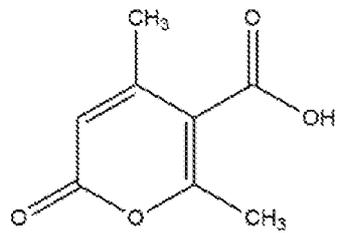
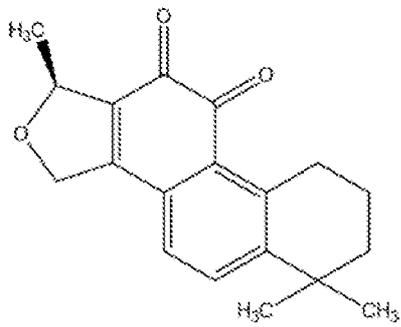
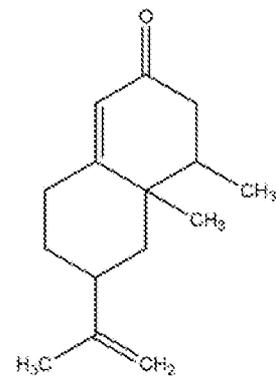
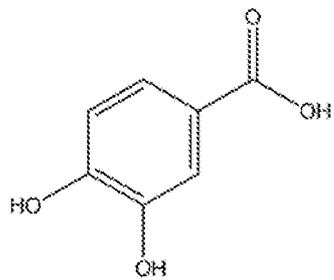
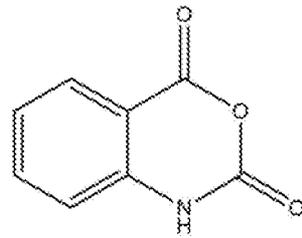
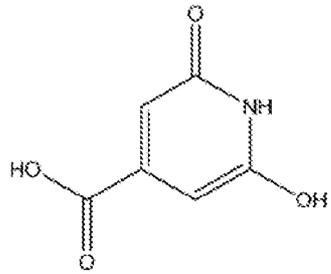
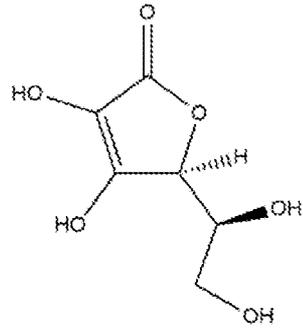
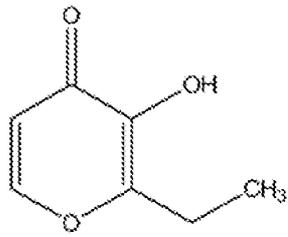
20 4. The cosmetic or personal care composition according to claim 1 or 2, wherein the two or more compounds each contain different Y substructure.

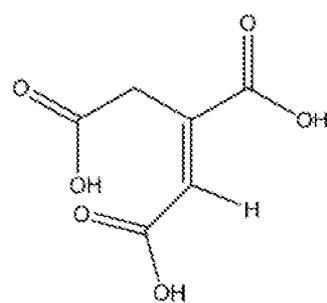
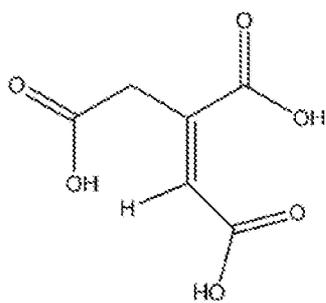
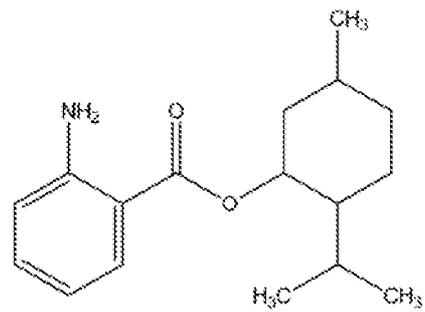
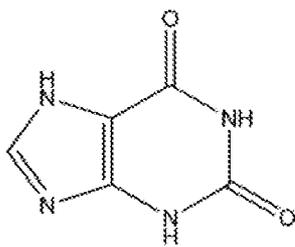
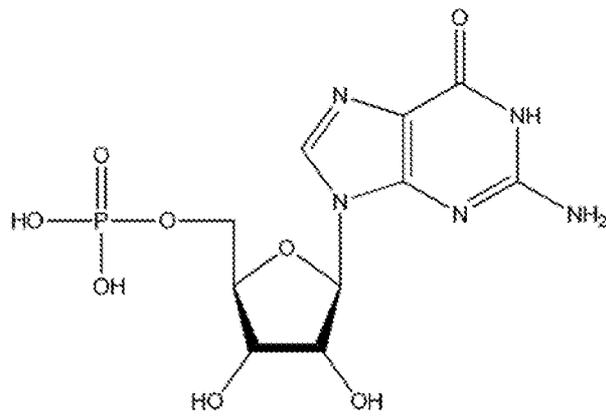
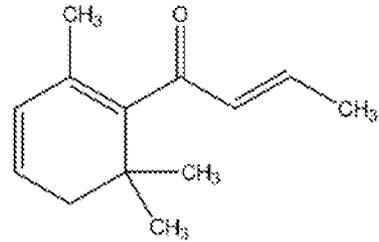
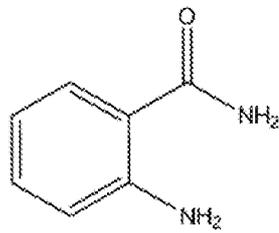
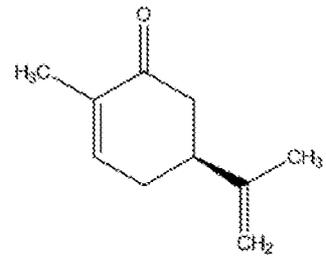
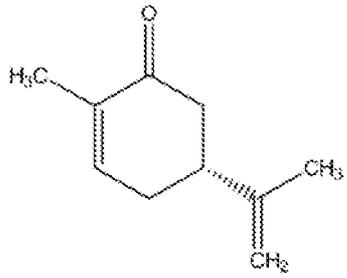
25 5. The cosmetic or personal care composition according to claim 1 or 2, wherein the two or more compounds each contain different Y substructure, with each of the Y substructures selected from the different groups (i)-(x).

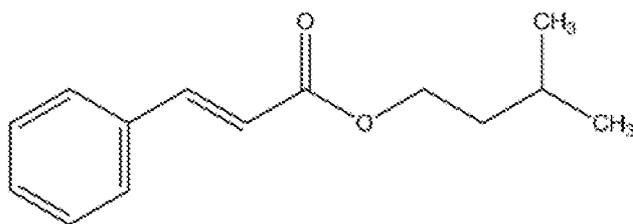
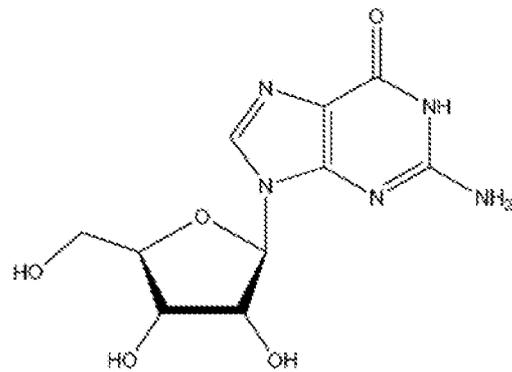
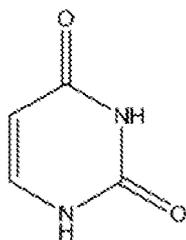
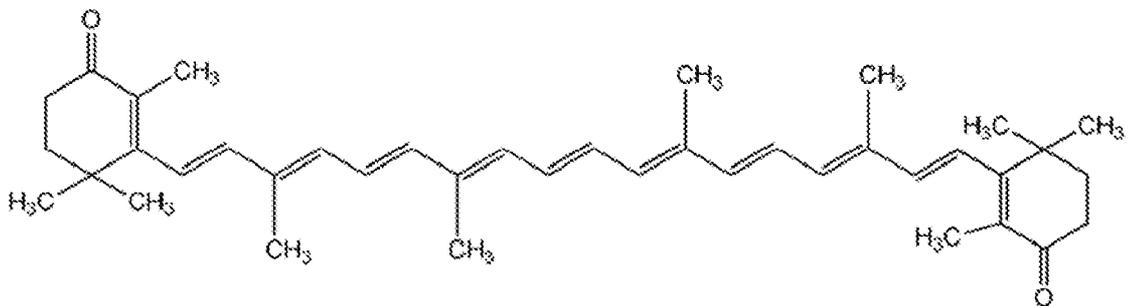
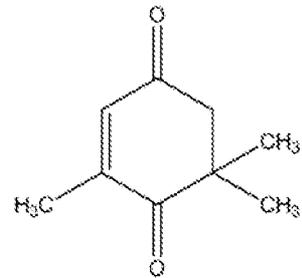
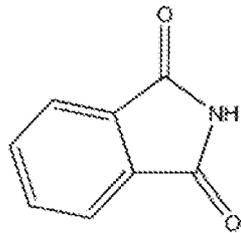
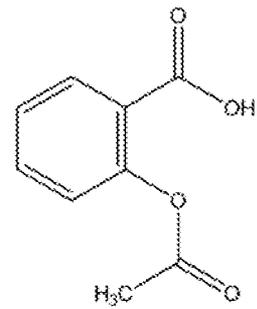
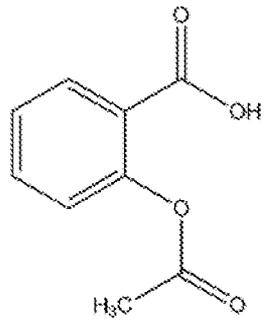
6. The cosmetic or personal care composition according to claim 1 or 2, wherein the composition comprises two or more compounds containing the same or different Y substructure selected from the same or different groups (i)-(x), and one or more other skin lightening agents.

30 7. The cosmetic or personal care composition according to claim 3, wherein the two or more compounds are selected from the group consisting of:









and their derivatives, isomers, salts and/or combination thereof.

8. The cosmetic or personal care composition according to claim 7, wherein the two or more compounds are selected from the group consisting of saccharin, maltol and theobromine.

5 9. The cosmetic or personal care composition according to claim 8, wherein the composition comprises saccharin and maltol.

10. The cosmetic or personal care composition according to claim 8, wherein the composition comprises maltol and theobromine.

10

11. The cosmetic or personal care composition according to claim 8, wherein the composition comprises saccharin, maltol and theobromine.

12. The cosmetic or personal care composition according to claim 3, wherein the
15 composition comprises saccharin, maltol, theobromine, acesulphame-K and dehydroacetic acid.

13. The cosmetic or personal care composition according to claim 3, wherein the
20 composition comprises maltol in an amount of 0.01 to 10 wt% based on the total weight of the composition.

14. The cosmetic or personal care composition according to claim 3, wherein the composition comprises saccharin in an amount of 0.01 to 70 wt% based on the total weight of the composition.

25

15. The cosmetic or personal care composition according to claim 3, wherein each of the two or more compounds is provided in the form of an extract derived from a plant material or yeast.

30 16. The cosmetic or personal care composition according to claim 8, wherein the maltol and/or theobromine is provided in the form of an extract derived from a plant material or yeast.

35 17. The cosmetic or personal care composition according to claim 3, wherein the composition further comprises zinc or copper cation forming homo-dimer or/or hetero-dimer of the two or more compounds.

18. The cosmetic or personal care composition according to claim 1, wherein the regulating of skin quality includes reducing endogenous and/or UV-induced melanogenesis; reducing activities of melanogenesis metabolic pathway and/or one or more of the signalling pathways that control the activity of the melanogenesis metabolic pathway; reducing the melanin content of the skin of a subject; lightening of the skin, pigmented spots, freckles, blemishes and dark circles around the eyes of the subject.

19. The cosmetic or personal care composition according to claim 18, wherein the regulating of skin quality further includes enhancing skin quality activities including improving the tone and smoothness of lightened skin of the subject by increasing a* (rosy-red tone) and/or reducing b* (yellow skin tone) components, reducing fine lines and wrinkles of the subject by improving skin radiance, anti-irritant properties, softness, smoothness, elasticity, and evenness of appearance of the skin.

20. The cosmetic or personal care composition according to claim 1 or 2, wherein the two or more compounds having antibacterial properties and viscosity reducing properties when formulated into the composition.

21. Use of a cosmetic or personal care composition as claimed in claim 1 for regulating skin quality, wherein the regulating of skin quality includes reducing endogenous and/or UV-induced melanogenesis; reducing activities of melanogenesis metabolic pathway and/or one or more of the signalling pathways that control the activity of the melanogenesis metabolic pathway; reducing the melanin content of the skin of a subject; lightening of the skin, pigmented spots, freckles, blemishes and dark circles around the eyes of the subject.

22. The use according to claim 21, further comprising enhancing skin quality activities including improving the tone and smoothness of lightened skin of the subject by increasing a* (rosy-red tone) and/or reducing b* (yellow skin tone) components, reducing fine lines and wrinkles of the subject by improving skin radiance, anti-irritant properties, softness, smoothness, elasticity, and evenness of appearance of the skin.

23. Use of a cosmetic or personal care composition as claimed in claim 2 as a skin lightening agent.

24. A method of regulating skin quality of a subject comprising the step of topically applying an effective amount of the cosmetic or personal care composition as claimed in claim 3 on the skin of a subject.

5 25. The method according to claim 24, wherein the regulating of the skin quality includes reducing endogenous and/or UV-induced melanogenesis, reducing activities of melanogenesis metabolic pathway and/or one or more of the signalling pathways that control the activity of the melanogenesis metabolic pathway, reducing the melanin content of the skin of the subject, and lightening of the skin, pigmented spots, freckles, 10 blemishes and dark circles around the eyes of the subject.

26. A method of skin lightening comprising the step of topically applying an effective amount of the cosmetic or personal care composition as claimed in claim 3 or 8 on the skin of a subject, for lightening of skin.

15

27. A method of determining a composition for use in regulating or improving skin quality of a subject, the method comprising:

measuring skin quality of a subject;

identifying two or more compounds with melanogenesis inhibiting activities by

20 selecting two or more compounds, each of the compounds containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein

25 Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

i) hydroxyl-based group including -OH or -C(=)-(OH);

ii) carbonyl-based group including -C(=)-C(=O)-CH₃;

30 iii) ether group, -O-;

iv) sultam group, -N(H)-S(=O)₂-;

v) lactam group, -N(H)-C(=O)-;

vi) apolar group including cyclic structures based on menthol or carotenoids;

vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or

35 -N(H)-C(H)=N-;

viii) amine group, -NH₂;

- ix) secondary amine-based group, -N(H)-; and
- x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-; and

5 preparing a formulation based on the measured skin quality so as to improve the skin quality using the identified compounds.

28. A method of determining a composition for use as a skin lightening agent, the method comprising:

determining the skin type of a subject;

10 identifying two or more compounds with melanogenesis inhibiting activities by selecting two or more compounds, each of the compounds containing an allylic or partially allylic carbonyl substructure having the following structure I:



wherein

15

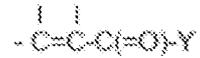
Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- i) hydroxyl-based group including -OH or -C(=)-(OH);
- 20 ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
- iii) ether group, -O-;
- iv) sultam group, -N(H)-S(=O)₂-;
- v) lactam group, -N(H)-C(=O)-;
- vi) apolar group including cyclic structures based on menthol or carotenoids;
- 25 vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or -N(H)-C(H)=N-;
- viii) amine group, -NH₂;
- ix) secondary amine-based group, -N(H)-; and
- x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-; and

30

preparing a formulation based on the determined skin type of the subject using the identified compounds.

29. A method of identifying a compound with melanogenesis inhibiting activities by selecting a compound containing an allylic or partially allylic carbonyl substructure having the following structure I:



5 wherein

Y is a second substructure immediately adjacent to the allylic or partially allylic carbonyl substructure and is selected from one of the following groups consisting of:

- 10 i) hydroxyl-based group including -OH or -C(=)-OH);
 ii) carbonyl-based group including -C(=)-C(=O)-CH₃;
 iii) ether group, -O-;
 iv) sultam group, -N(H)-S(=O)₂-;
 v) lactam group, -N(H)-C(=O)-;
 15 vi) apolar group including cyclic structures based on menthol or carotenoids;
 vii) secondary aldimine containing group including -N(H)-C(NH₂)=N- or
 -N(H)-C(H)=N-;
 viii) amine group, -NH₂;
 ix) secondary amine-based group, -N(H)-; and
 20 x) amide-based group including -N(H)-C(=O)- or -N(H)-C(=O)-N(H)-.

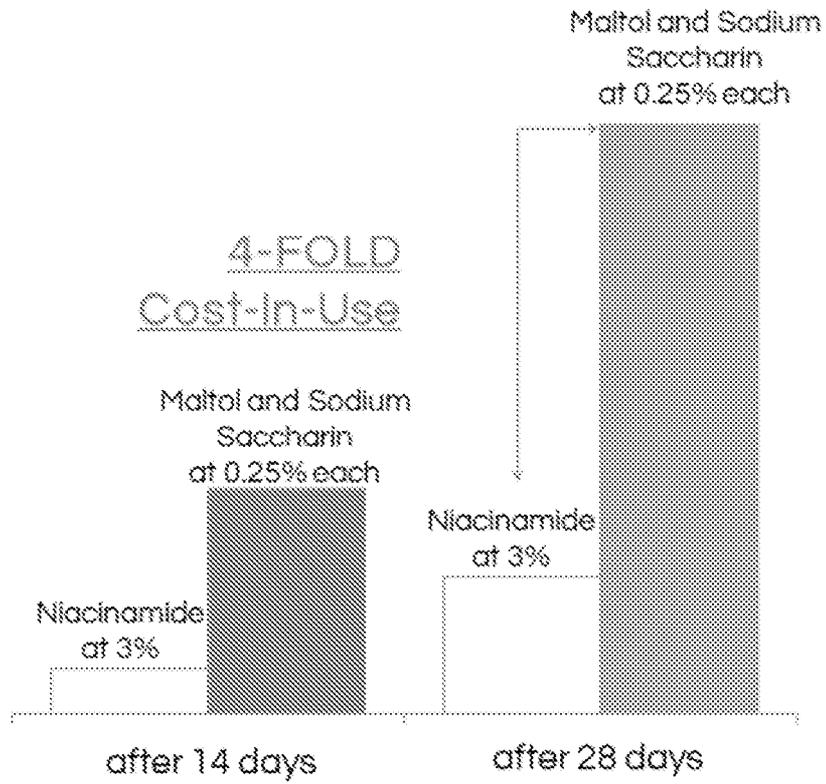


Figure 1

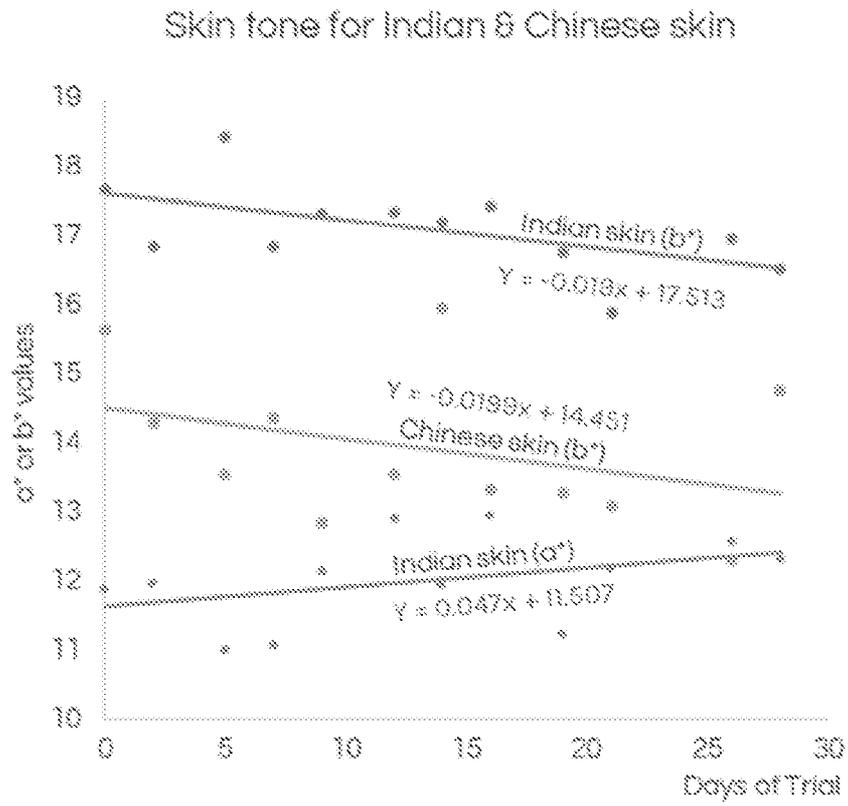


Figure 2

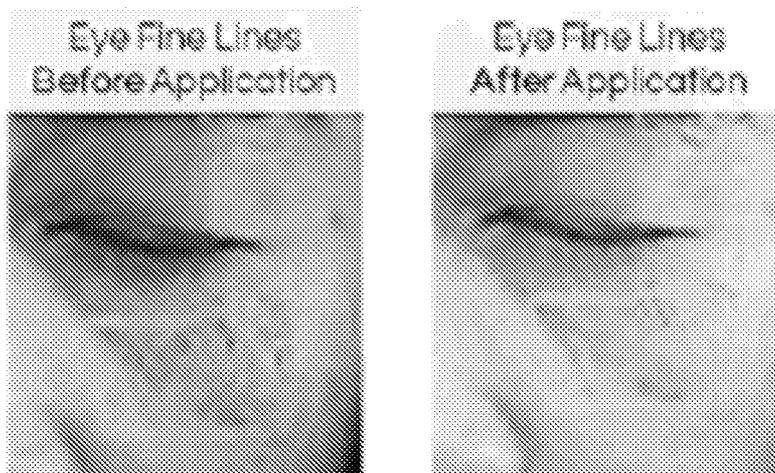


Figure 3

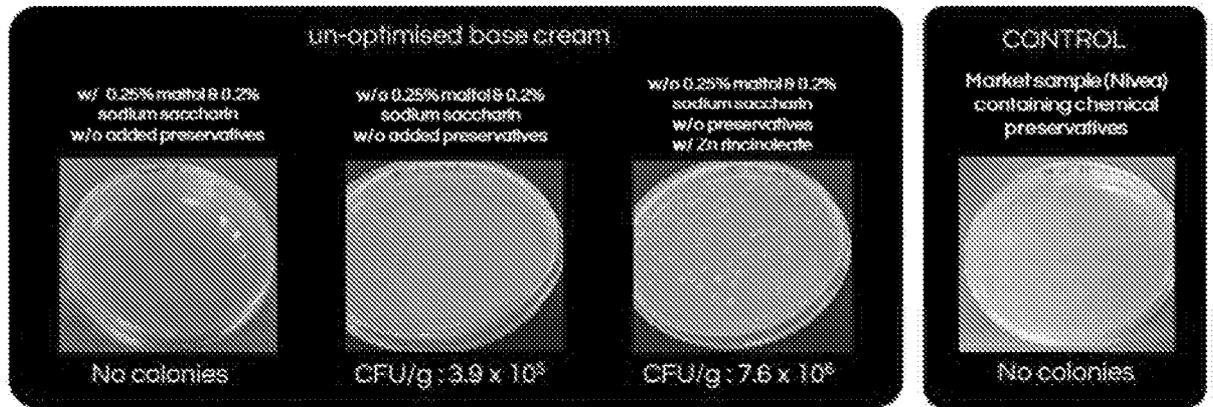
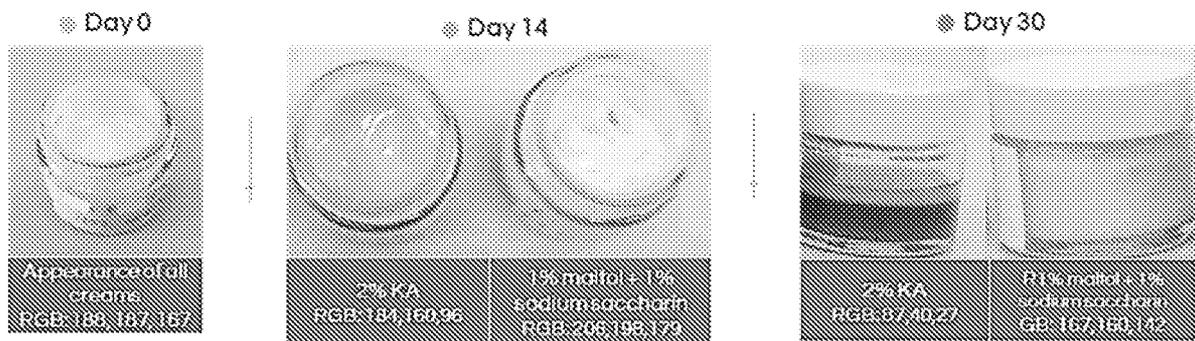


Figure 4



*RGB of pure white colour: 255, 255, 255

Figure 5

Cream Viscosities

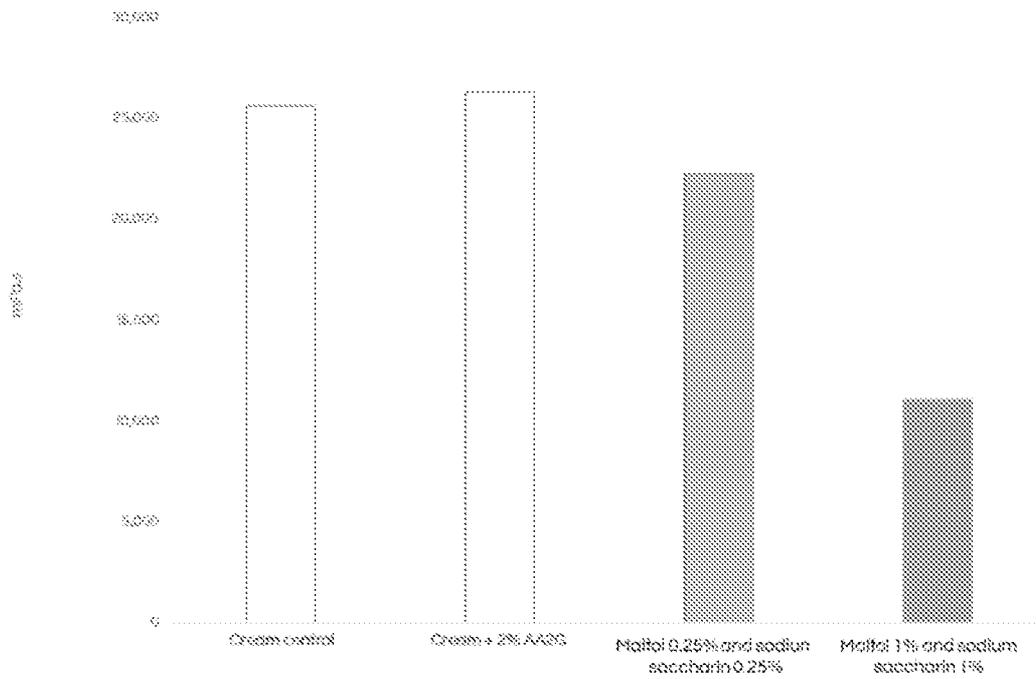


Figure 6

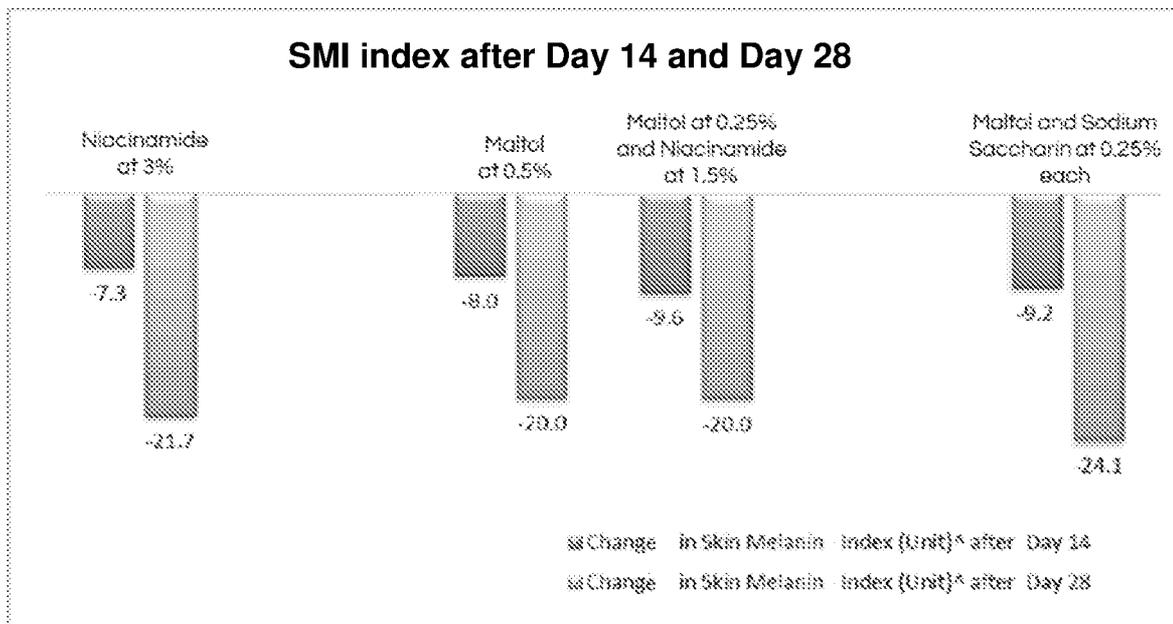


Figure 7

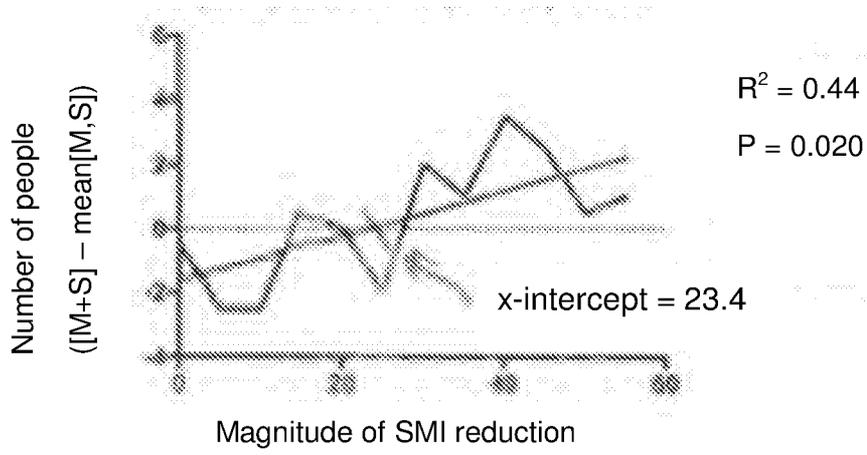


Figure 8

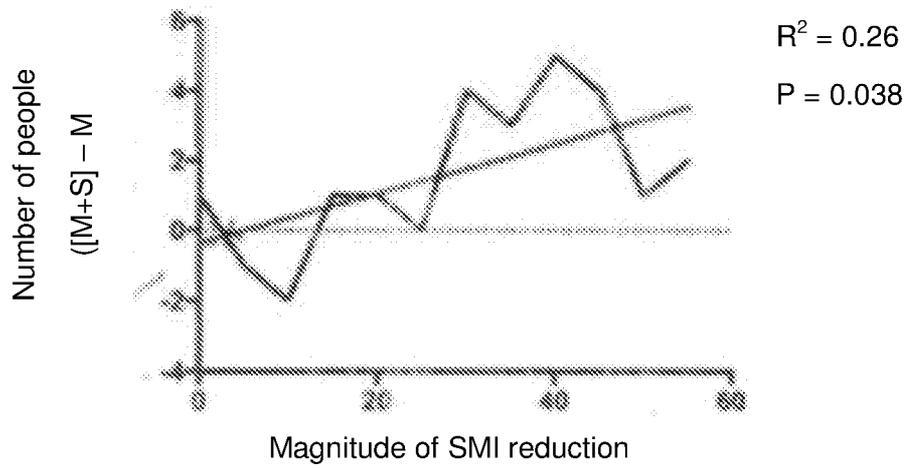


Figure 9

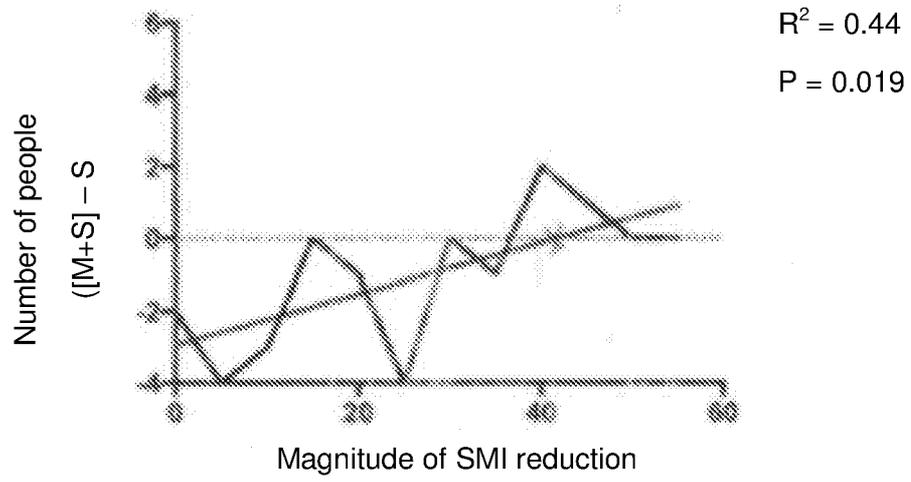


Figure 10

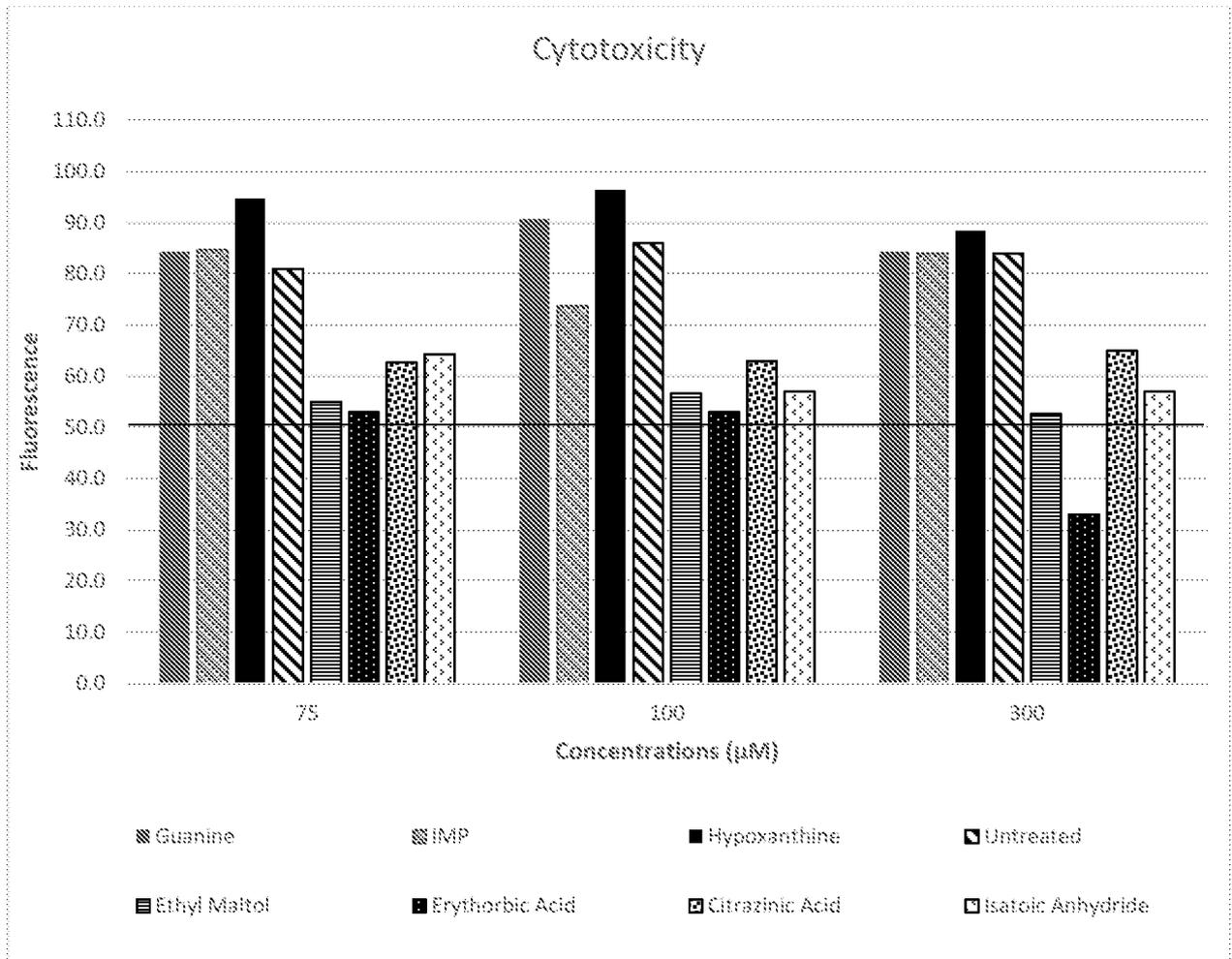


Figure 11

A. CLASSIFICATION OF SUBJECT MATTER

[See Supplemental Sheet]

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)

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)

Epoque (Epodoc, WPIAP) keywords: saccharin, maltol, theobromine, acesulfame K, dehydroacetic acid, skin, melanogenesis, skin lighten, skin whiten, skin tone, skin colour, complexion & like terms/synonyms in various combinations; **STN (Medline, Embase, Biosis) keywords:** saccharin, maltol, theobromine, acesulfame K, dehydroacetic acid, skin, white, pigment, melanogenesis, melanin, light, freckle, blemish, skin tone, skin colour, complexion, viscosity, antibacterial & like terms/synonyms in various combinations; **STN (registry, CAPlus/HCAPlus) registry numbers of the compounds of claim 7 and keywords:** melanogenesis, skin, cutaneous, skin tone, skin colour, complexion, whiten, lighten, freckle, blemish, viscosity reduction, antibacterial & like terms/synonyms in various combinations; **Patentscope/AusPat/Intess/PAMS Nose/Espacenet/Google Patents:** Applicant & Inventor search; **Google/Google Patents/Google Scholar/EspaceNet keywords:** Aspirin, skin lightening, combination, saccharin, theobromine, maltol, dehydroacetic acid, acesulfame K, hypoxanthine, ascorbic acid, vitamin C, protocatechuic acid, rosmarinic acid, carvone, xanthine, acetylsalicylic acid, isoamyl cinnamate, skin, niacinamide, depigment, hyperpigment, skin lightener, skin whitener, combination, plant extract, melanogenesis inhibition, ginseng, theobroma, *Curcuma zedoaria*, *Aloe vera*, metal, copper, zinc, complex, Zn(maltol)₂, A61Q19/02, viscosity, antibacterial & like/related terms/synonyms/plurals in various combinations

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Documents are listed in the continuation of Box C		

 Further documents are listed in the continuation of Box C 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	"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	
"E" earlier application or patent but published on or after the international filing date	"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	
"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)	"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	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
6 April 2017Date of mailing of the international search report
06 April 2017

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
Email address: pct@ipaaustralia.gov.au

Authorised officer

Corrina Parker
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No. 0262223661

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/SG2017/050030
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2000/047045 A1 (ZYLEPSIS LIMITED) 17 August 2000 abstract; page 8, lines 20-21; tables 14, 16; claims 1, 6	1-5,18,19,21-29
X	WO 2000/047179 A1 (ZYLEPSIS LIMITED) 17 August 2000 abstract; table 6; examples 13, 14; claims 1, 3, 6-9, 13	1-7,18,19,21-29
X	WO 2003/051325 A1 (ZYLEPSIS LIMITED) 26 June 2003 abstract; page 12, lines 5-23; table 6; examples 5, 6; claim 4	1-7,18,19,21-29
X	US 5164185 A (CHARPIN, I., et al) 17 November 1992 abstract; examples 1, 2, 5, 6; claims 1, 6, 7, 15, 18, 19	1-6,18,19,21-29
X	US 2010/0204204 A1 (ZAWOROTKO, M., et al) 12 August 2010 abstract; paragraphs [0108], [0128], [0130]; examples 1-4, 6, 8-15, 18; claims 2, 6, 7, 18	1-5,7,18,19
X	WO 2014/160690 A1 (CELGENE CORPORATION) 02 October 2014 abstract; paragraphs [0015], [0064], [00191]; sections 5.2.1, 5.2.2, 5.2.5, 5.2.6, 5.2.10; claims 1, 2, 3, 7, 19, 23, 39	1-5,7,14,18,19
X	US 2004/0081672 A1 (GUPTA, S.K.) 29 April 2004 paragraph [0001]; examples 3, 10, 11, 12, 14	1-6,18,19,21-26
X	US 2006/0216254 A1 (MAJMUDAR, G. AND ZHAO, W.) 28 September 2006 abstract; paragraphs [0017], [0091]; tables 1, 2, 5	1-6,18,19,21-29
X	US 2007/0166251 A1 (DAYAN, N. AND RIEMER, J.A.) 19 July 2007 abstract; claims 1-6, 14, 16	1-7,18,19,21-29
X	US 2012/0177586 A1 (MEHTA, R.C., et al) 12 July 2012 abstract; page 41; example 15; claims 1-3, 5, 9, 17, 18, 20-22, 26, 27, 29	1-6,18,19,21-29
X	WO 2014/170239 A1 (SYMRISE AG) 23 October 2014 claims 1-6; table 5; examples 6-8	1-6,18,19,21-29
X	US 6365137 B1 (AUST, D.T. AND WILMOTT, J.M.) 02 April 2002 claims 1, 2, 10-13, 20	1-7,18,19,21-26
X	US 2004/0166069 A1 (GUPTA, S.K.) 26 August 2004 paragraph [0042]; Examples 10 and 11 ; claim 1	1-6,18,19, 21-29
X	US 2008/0181920 A1 (BUERGER, A., et al) 31 July 2008 examples 1, 2, 5, 6, 10, 11; claims 22, 27-29	1-6,18,19,21-29
X	JP 2002193737 A (KATAKURA CHIKKARIN CO LTD, KOSE CORP) 10 July 2002, Google Patents translation used for examination purposes abstract; paragraphs [0007], [0015], [0017], [0018], [0063]; claims 3, 4, 6, 7	1-6,18,19,21-29
X	US 2004/0161435 A1 (GUPTA, S.K.) 19 August 2004 examples 6, 11, 15, 16; claims 1, 2	1-7,18,19, 21-29
X	US 2007/0009474 A1 (XIE, S., et al) 11 January 2007 paragraphs [0017]-[0018], [0074], [0075]; examples 1, 2, 6-8, 10 ; claims 1, 7, 11	1-6,18,19,21-26

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/SG2017/050030
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0027706 A1 (SHAPIRO, S.S., et al) 02 February 2012 abstract; examples 15, 18; tables J, F	1-6,18,19,21-29
X	US 4990330 A (OYAMA, Y.) 05 February 1991 abstract; table 1; table 2	1-7,18,19,21-29
X Y	US 2005/0214332 A1 (OSBORNE, R., et al) 29 September 2005 abstract; paragraphs [0007], [0020], [0021], [0038], [0045]-[0046], [0059]-[0061], [0134]-[0135]; example 8 example 8	1-7,18,19,21-29 12
X	JP 2014114291 A (SHOWA DENKO KK) 26 June 2014, Google Patents translation used for examination purposes formulation example 2; claim 62	1-7,18,19,21-29
X Y	JP 2015059119 A (SANSHO SEIYAKU CO LTD) 30 March 2015, Google Patents translation used for examination purposes Formulation Example 2 Formulation Example 2	1-6,18,19,21-29 12
X Y	WO 2000/069408 A1 (THE PROCTER & GAMBLE COMPANY) 23 November 2000 abstract; page 28, lines 8-20; claims 1-7, 9, 10 abstract; page 28, lines 8-20; claims 1-7, 9, 10	1-7,18,19,21-26 8,10,11,12,16
X	CN 105106101 A (WANG DAN) 02 December 2015, Google Patents translation used for examination purposes examples 1-3; claim 1	1-7,18,19,21-26
X Y	WO 2001/017497 A1 (GHISALBERTI, C.) 15 March 2001 page 22 - example 4; claims 1, 5, 6, 8-11, 14, 15; claim 4 last two compounds page 22 - example 4; claims 1, 5, 6, 8-11, 14, 15; claim 4 last two compounds	1-7,13,18,19,21-29 8,9,10,11,12,16
X	JP 07-157495 A (KAO CORP) 20 June 1995, Patent Abstracts of Japan used for English translation abstract; paragraphs [0004], [0007]; claims	1-7,18,19,21-29
X	KRISHNAMOORTHY, J.R., et al., "Extract combinations of <i>Curcuma zedoaria</i> and <i>Aloe vera</i> inhibit melanin synthesis and dendrite formation in murine melanoma cells". <i>Journal of Applied Cosmetology</i> , 2010, vol. 28, pages 103-108 summary; results; discussion – paragraph 1	1-6,15,18,19,21-29
X	Eve Fresh [retrieved from internet on 23 February 2017] <URL: https://www.saralhealth.com/dr-jrks-eve-fresh-cream-25-gm > published on 25 March 2015 as per Wayback Machine whole document	1-6,15,18,19,21-29
X	US 2009/0028969 A1 (SENE, G., et al) 29 January 2009 abstract; paragraph [0066]; example 5; claims 2-5, 7	1-6,15,18,19,21-29
X	US 2012/0220545 A1 (ORLOW, S.J. AND KOMATSU, L.I.) 30 August 2012 abstract; paragraphs [0028]-[0029], [0030]-[0035], [0037], [0274], [0275]; table 1; claims 1, 52, 58, 66, 76, 77, 80, 81, 83, 86	1-6,15,18,19,21-29

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/SG2017/050030
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	JP 2004284999 A (KOSE CORP) 14 October 2004, Google Patents translation used for examination purposes abstract; production examples 1-10; examples 16, 17 abstract; production examples 1-10; examples 16, 17	1-5,15,18,19,21,22,24,25 12
X	US 2014/0179747 A1 (LEWIS II, J.A. AND DINARDO, J.C.) 26 June 2014 paragraphs [0016]-[0017], [0028], [0032]-[0044], [0085]; claims 39, 41	1-6,15,18,19,21-26
X	US 2013/0129651 A1 (MIYAKE, M., et al) 23 May 2013 example 12; claims 1-4, 6, 8	1-7,18,19,21-29
X Y	WO 2003/051325 A1 (ZYLEPSIS LIMITED) 26 June 2003 page 10, line 27, page 11, line 27-page 12, line 13, pages 27-28; compounds 1-8; table 1; examples 5, 6; claims 1, 4, 6-9 page 10, line 27; table 1	1-7,14,18,19,21-29 8,9,11,12,16
X Y	US 2014/0227363 A1 (DRAPEAU, C., et al) 14 August 2014 abstract; table 3 abstract; table 3	1-7,15,18,19,21,22,24,25 8,10,11,12,16
X Y	DE 102004050563 A1 (HENKEL AG & CO) 20 April 2006, Google Patents translation used for examination purposes paragraph [0074] paragraph [0074]	1-7,15,18,19,21-26 8,10,11,12,16
A	ZHU, W. AND GAO, J. "The Use of Botanical Extracts as Topical Skin-Lightening Agents for the Improvement of Skin Pigmentation Disorders". <i>Journal of Investigative Dermatology Symposium Proceedings</i> , 2008, vol. 13, pages 20-24 page 23 - Ginseng	
A	KIM, K. "Effect of ginseng and ginsenosides on melanogenesis and their mechanism of action". <i>Journal of Ginseng Research</i> , 2015, vol. 39, pages 1-6 whole document	
A	HAMDI, O.A.A., et al, "Cytotoxic Constituents from the Rhizomes of <i>Curcuma zedoaria</i> ". <i>The Scientific World Journal</i> , 2014, Volume 2014, Article ID 321943, 11 pages whole document	
A	HAMMAN, J.H., "Composition and Applications of <i>Aloe vera</i> Leaf Gel". <i>Molecules</i> , 2008, vol. 13, pages 1599-1616 whole document - specifically table 1	
A	SATO, K., et al, "Down-Regulation of Tyrosinase Expression by Acetylsalicylic Acid in Murine B16 Melanoma". <i>Biological & Pharmaceutical Bulletin</i> , 2008, vol. 31, no. 1, pages 33-37	
A	KAHN, V. "Multiple Effects of Maltol and Kojic Acid on Enzymatic Browning". <i>ACS Symposium Series</i> , 1995, Vol. 600, Chapter 22, pages 277-294 abstract	
X	WO 2000/038648 A1 (C3D S.A.R.L.) 06 July 2000 claims 1, 3, 6, 8, 10, 11	1-7,13,18,19,21-29

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/SG2017/050030
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	claims 1, 3, 6, 8, 10, 11	8,9,10,11,12,16
X	US 2008/0287533 A1 (GUPTA, S.K.) 20 November 2008 paragraphs [0066], [0071], [0134], [0181]-[0228]; figure 4 - compounds V-VIII; claims 1, 5, 7, 8, 9, 12, 13 15-19	1-7,17-19,21-29

Supplemental Box – IPC Marks*A61K 31/425 (2006.01)**A61K 31/351 (2006.01)**A61K 31/522 (2006.01)**A61K 31/39 (2006.01)**A61K 31/375 (2006.01)**A61K 31/4412 (2006.01)**A61K 31/536 (2006.01)**A61K 31/192 (2006.01)**A61K 31/122 (2006.01)**A61K 31/343 (2006.01)**A61K 31/216 (2006.01)**A61K 31/166 (2006.01)**A61K 31/12 (2006.01)**A61K 31/245 (2006.01)**A61K 31/194 (2006.01)**A61K 31/616 (2006.01)**A61K 31/4035 (2006.01)**A61K 31/513 (2006.01)**A61K 31/216 (2006.01)**A61Q 19/02 (2006.01)**A61Q 19/08 (2006.01)*

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2000/047045 A1	17 August 2000	WO 0047045 A1	17 Aug 2000
		AU 2557500 A	29 Aug 2000
		AU 2557600 A	29 Aug 2000
		AU 2557800 A	29 Aug 2000
		EP 1150652 A1	07 Nov 2001
		EP 1151129 A2	07 Nov 2001
		JP 2002536022 A	29 Oct 2002
		JP 2002536393 A	29 Oct 2002
		US 2003072726 A1	17 Apr 2003
		WO 0047179 A1	17 Aug 2000
		WO 0047758 A2	17 Aug 2000
		WO 2000/047179 A1	17 August 2000
AU 2557500 A	29 Aug 2000		
AU 2557600 A	29 Aug 2000		
AU 2557800 A	29 Aug 2000		
EP 1150652 A1	07 Nov 2001		
EP 1151129 A2	07 Nov 2001		
JP 2002536022 A	29 Oct 2002		
JP 2002536393 A	29 Oct 2002		
US 2003072726 A1	17 Apr 2003		
WO 0047045 A1	17 Aug 2000		
WO 0047758 A2	17 Aug 2000		
WO 2003/051325 A1	26 June 2003		
		AU 2002347372 A1	30 Jun 2003
		AU 2002347379 A1	09 Jul 2003
		EP 1454123 A2	08 Sep 2004
		EP 1454123 B1	17 Mar 2010
		EP 1455747 A1	15 Sep 2004
		GB 2383127 A	18 Jun 2003
		GB 2383127 B	20 Oct 2004
		JP 2005513476 A	12 May 2005
		US 2005068536 A1	31 Mar 2005
		US 7245379 B2	17 Jul 2007
		US 2007268489 A1	22 Nov 2007
		US 7477384 B2	13 Jan 2009

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 2010079756 A1	01 Apr 2010
		US 2011216319 A1	08 Sep 2011
		US 2012307245 A1	06 Dec 2012
		US 2013271762 A1	17 Oct 2013
		US 2014146315 A1	29 May 2014
		US 2016178518 A1	23 Jun 2016
		WO 03054525 A2	03 Jul 2003

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 5164185 A	17 November 1992	US 5164185 A	17 Nov 1992
		AR 244545 A1	30 Nov 1993
		AU 6628890 A	16 May 1991
		AU 638768 B2	08 Jul 1993
		BR 9006960 A	12 Nov 1991
		CA 2044269 A1	21 Apr 1991
		EP 0450040 A1	09 Oct 1991
		EP 0450040 B1	09 May 2001
		ES 2085192 A1	16 May 1996
		ES 2085192 B1	01 Feb 1997
		FR 2653336 A1	26 Apr 1991
		FR 2653336 B1	08 Apr 1994
		GB 2244005 A	20 Nov 1991
		GB 2244005 B	13 Oct 1993
		IT 9021795 A1	21 Apr 1991
		IT 1251741 B	23 May 1995
		JP H04502476 A	07 May 1992
		JP 2659618 B2	30 Sep 1997
		MX 173203 B	08 Feb 1994
		WO 9105543 A1	02 May 1991
ZA 9008398 B	28 Aug 1991		
US 2010/0204204 A1	12 August 2010	US 2010204204 A1	12 Aug 2010
		EP 2167043 A2	31 Mar 2010
		US 2010173984 A1	08 Jul 2010
		US 8471044 B2	25 Jun 2013
		US 2015250797 A1	10 Sep 2015
		WO 2008153938 A2	18 Dec 2008
		WO 2008153945 A2	18 Dec 2008
WO 2014/160690 A1	02 October 2014	WO 2014160690 A1	02 Oct 2014
		US 2016039785 A1	11 Feb 2016
US 2004/0081672 A1	29 April 2004	US 2004081672 A1	29 Apr 2004
		AU 2012304886 A1	20 Mar 2014
		AU 2012304886 B2	29 Sep 2016
		CA 2846898 A1	14 Mar 2013

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		CN 103987391 A	13 Aug 2014
		EP 2755664 A2	23 Jul 2014
		HK 1200172 A1	31 Jul 2015
		JP 2014528008 A	23 Oct 2014
		KR 20140064920 A	28 May 2014
		US 2005048008 A1	03 Mar 2005
		US 7320797 B2	22 Jan 2008
		US 2007099886 A1	03 May 2007
		US 7427690 B2	23 Sep 2008
		US 2007092461 A1	26 Apr 2007
		US 7547454 B2	16 Jun 2009
		US 2006183708 A1	17 Aug 2006
		US 7569558 B2	04 Aug 2009
		US 2008287536 A1	20 Nov 2008
		US 7572933 B2	11 Aug 2009
		US 2007098663 A1	03 May 2007
		US 7592002 B2	22 Sep 2009
		US 2007189992 A1	16 Aug 2007
		US 7597879 B2	06 Oct 2009
		US 2009042846 A1	12 Feb 2009
		US 7615546 B2	10 Nov 2009
		US 2009074691 A1	19 Mar 2009
		US 7777073 B2	17 Aug 2010
		US 2009253668 A1	08 Oct 2009
		US 7834210 B2	16 Nov 2010
		US 2008287533 A1	20 Nov 2008
		US 7842723 B2	30 Nov 2010
		US 2009269291 A1	29 Oct 2009
		US 7993630 B2	09 Aug 2011
		US 2010331274 A1	30 Dec 2010
		US 8211873 B2	03 Jul 2012
		US 2011190202 A1	04 Aug 2011
		US 8212076 B2	03 Jul 2012
		US 2011059907 A1	10 Mar 2011
		US 8227426 B2	24 Jul 2012
		US 8258343 B1	04 Sep 2012

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 2012264696 A1	18 Oct 2012
		US 8293943 B1	23 Oct 2012
		US 2011124573 A1	26 May 2011
		US 8314070 B2	20 Nov 2012
		US 2013028854 A1	31 Jan 2013
		US 8394851 B2	12 Mar 2013
		US 2012035130 A1	09 Feb 2012
		US 8410079 B2	02 Apr 2013
		US 8569269 B1	29 Oct 2013
		US 2013072673 A1	21 Mar 2013
		US 8586730 B2	19 Nov 2013
		US 2013172291 A1	04 Jul 2013
		US 8871748 B2	28 Oct 2014
		US 2004067890 A1	08 Apr 2004
		US 2004092482 A1	13 May 2004
		US 2004105894 A1	03 Jun 2004
		US 2004185069 A1	23 Sep 2004
		US 2004208902 A1	21 Oct 2004
		US 2004228884 A1	18 Nov 2004
		US 2005058672 A1	17 Mar 2005
		US 2005271608 A1	08 Dec 2005
		US 2005276761 A1	15 Dec 2005
		US 2006045860 A1	02 Mar 2006
		US 2006110415 A1	25 May 2006
		US 2006127430 A1	15 Jun 2006
		US 2006147508 A1	06 Jul 2006
		US 2007041924 A1	22 Feb 2007
		US 2007166255 A1	19 Jul 2007
		US 2007166339 A1	19 Jul 2007
		US 2007237834 A1	11 Oct 2007
		US 2008139507 A1	12 Jun 2008
		US 2008254130 A1	16 Oct 2008
		US 2008255228 A1	16 Oct 2008
		US 2009130154 A1	21 May 2009
		US 2009209642 A1	20 Aug 2009
		US 2012189569 A1	26 Jul 2012

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 2013267483 A1	10 Oct 2013
		WO 2013036286 A2	14 Mar 2013

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2006/0216254 A1	28 September 2006	US 2006216254 A1	28 Sep 2006
		AU 2006227205 A1	28 Sep 2006
		BR PI0609575 A2	20 Apr 2010
		BR PI0609575 B1	12 Jul 2016
		CA 2601571 A1	28 Sep 2006
		CN 101166506 A	23 Apr 2008
		CN 101166506 B	25 Jan 2012
		EA 200702056 A1	28 Apr 2008
		EA 015357 B1	30 Jun 2011
		EP 1871334 A2	02 Jan 2008
		EP 1871334 B1	12 Oct 2011
		HK 1096241 A2	25 May 2007
		HK 1112182 A1	16 Dec 2011
		KR 20080025036 A	19 Mar 2008
		MX 2007011784 A	14 Mar 2008
		TW 200716197 A	01 May 2007
		WO 2006102289 A2	28 Sep 2006
US 2007/0166251 A1	19 July 2007	US 2007166251 A1	19 Jul 2007
		BR PI0519445 A2	20 Jan 2009
		CA 2594546 A1	27 Jul 2006
		CN 101141943 A	12 Mar 2008
		EP 1835884 A2	26 Sep 2007
		JP 2008526963 A	24 Jul 2008
		KR 20070097092 A	02 Oct 2007
		MX 2007008573 A	14 Jan 2008
		US 2008214669 A1	04 Sep 2008
		WO 2006078399 A2	27 Jul 2006
US 2012/0177586 A1	12 July 2012	US 2012177586 A1	12 Jul 2012
		US 8236288 B2	07 Aug 2012
		AU 2012204164 A1	25 Jul 2013
		AU 2016201597 A1	31 Mar 2016
		CA 2823647 A1	12 Jul 2012
		CA 2932130 A1	12 Jul 2012
		CN 103442702 A	11 Dec 2013
		CN 103442702 B	10 Feb 2016

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 2661264 A1	13 Nov 2013
		JP 2014505687 A	06 Mar 2014
		KR 20140071273 A	11 Jun 2014
		SG 191879 A1	30 Aug 2013
		SG 10201602752X A	30 May 2016
		US 2013177511 A1	11 Jul 2013
		US 8778315 B2	15 Jul 2014
		US 2013034510 A1	07 Feb 2013
		US 8865138 B2	21 Oct 2014
		US 2013171081 A1	04 Jul 2013
		US 9044404 B2	02 Jun 2015
		US 2015257991 A1	17 Sep 2015
		WO 2012094638 A1	12 Jul 2012

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2014/170239 A1	23 October 2014	WO 2014170239 A1	23 Oct 2014
		CN 105392531 A	09 Mar 2016
		EP 2789369 A1	15 Oct 2014
		JP 2014205667 A	30 Oct 2014
		US 2016067163 A1	10 Mar 2016
US 6365137 B1	02 April 2002	US 6365137 B1	02 Apr 2002
US 2004/0166069 A1	26 August 2004	US 2004166069 A1	26 Aug 2004
US 2008/0181920 A1	31 July 2008	US 2008181920 A1	31 Jul 2008
		DE 102007005093 A1	31 Jul 2008
JP 2002193737 A	10 July 2002	JP 2002193737 A	10 Jul 2002
		JP 4597362 B2	15 Dec 2010
US 2004/0161435 A1	19 August 2004	US 2004161435 A1	19 Aug 2004
US 2007/0009474 A1	11 January 2007	US 2007009474 A1	11 Jan 2007
		AU 2004218346 A1	16 Sep 2004
		AU 2004218346 B2	16 Nov 2006
		AU 2004260656 A1	10 Feb 2005
		AU 2004287448 A1	19 May 2005
		AU 2005221169 A1	22 Sep 2005
		BR PI0408062 A	14 Feb 2006
		BR PI0412756 A	26 Sep 2006
		BR PI0416052 A	02 Jan 2007
		CA 2516501 A1	16 Sep 2004
		CA 2529632 A1	10 Feb 2005
		CA 2542145 A1	19 May 2005
		CA 2559877 A1	22 Sep 2005
		CN 1756528 A	05 Apr 2006
		CN 1822812 A	23 Aug 2006
		CN 1822812 B	26 May 2010
		CN 1870965 A	29 Nov 2006
		CN 1870968 A	29 Nov 2006
		CN 1929759 A	14 Mar 2007
		CN 101217999 A	09 Jul 2008

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 1603529 A2	14 Dec 2005
		EP 1603529 B1	27 Apr 2016
		EP 1651178 A2	03 May 2006
		EP 1677747 A1	12 Jul 2006
		EP 1694289 A1	30 Aug 2006
		EP 1722656 A1	22 Nov 2006
		EP 1901817 A2	26 Mar 2008
		EP 2997960 A1	23 Mar 2016
		JP 2006515329 A	25 May 2006
		JP 4234137 B2	04 Mar 2009
		JP 2006528935 A	28 Dec 2006
		JP 2009500394 A	08 Jan 2009
		KR 20070056170 A	31 May 2007
		KR 100786045 B1	17 Dec 2007
		KR 20050107479 A	11 Nov 2005
		KR 100825695 B1	29 Apr 2008
		KR 20060037341 A	03 May 2006
		KR 100833831 B1	02 Jun 2008
		KR 20060073971 A	29 Jun 2006
		MX PA05009392 A	04 Nov 2005
		MX PA06000930 A	30 Mar 2006
		MX PA06004826 A	03 Jul 2006
		MX PA06004827 A	03 Jul 2006
		US 2004175347 A1	09 Sep 2004
		US 2004176273 A1	09 Sep 2004
		US 2005019356 A1	27 Jan 2005
		US 2005112160 A1	26 May 2005
		US 2005214332 A1	29 Sep 2005
		US 2005220828 A1	06 Oct 2005
		US 2006074097 A1	06 Apr 2006
		US 2008076720 A1	27 Mar 2008
		US 2010278765 A1	04 Nov 2010
		WO 2004078158 A2	16 Sep 2004
		WO 2005011627 A2	10 Feb 2005
		WO 2005044218 A1	19 May 2005
		WO 2005044219 A1	19 May 2005

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		WO 2005087043 A1	22 Sep 2005
		WO 2007007255 A2	18 Jan 2007

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2012/0027706 A1	02 February 2012	US 2012027706 A1	02 Feb 2012
		AR 016780 A1	01 Aug 2001
		AU 4881900 A	15 Feb 2001
		AU 779448 B2	27 Jan 2005
		AU 1443301 A	06 Jun 2001
		AU 8756698 A	16 Feb 1999
		AU 2004208740 A1	24 Mar 2005
		AU 2005203301 A1	16 Feb 2006
		AU 2010246469 A1	16 Dec 2010
		AU 2010246469 B2	22 Dec 2011
		BR 0003184 A	18 Dec 2001
		BR 0007404 A	09 Apr 2002
		BR 0300830 A	17 Aug 2004
		BR 9806118 A	31 Aug 1999
		BR 9816322 B1	15 Jul 2014
		BR PI0405445 A	08 Nov 2005
		BR PI0503227 A	16 May 2006
		CA 2267077 A1	04 Feb 1999
		CA 2314569 A1	27 Jan 2001
		CA 2358958 A1	17 May 2001
		CA 2423524 A1	27 Sep 2003
		CA 2480925 A1	10 Mar 2005
		CA 2513936 A1	30 Jan 2006
		CN 1283507 A	14 Feb 2001
		CN 1234735 A	10 Nov 1999
		CN 1234735 B	16 Sep 2015
		CN 1342064 A	27 Mar 2002
		CN 1795926 A	05 Jul 2006
		CN 1795926 B	26 May 2010
		EP 0948308 A1	13 Oct 1999
		EP 0948308 B1	25 Feb 2004
		EP 1077063 A2	21 Feb 2001
		EP 1077063 B1	29 Aug 2007
		EP 1139974 A1	10 Oct 2001
		EP 1139974 B1	19 Oct 2011

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 1348441 A1	01 Oct 2003
		EP 1348441 B1	05 Jul 2006
		EP 1514536 A1	16 Mar 2005
		EP 1514536 B1	08 Apr 2009
		HK 1032543 A1	04 Jul 2008
		HU 0000216 A2	28 Jun 2000
		ID 22061 A	26 Aug 1999
		JP 2001502360 A	20 Feb 2001
		JP 4401441 B2	20 Jan 2010
		JP 2001081011 A	27 Mar 2001
		JP 4808304 B2	02 Nov 2011
		JP 2003513895 A	15 Apr 2003
		JP 2005082600 A	31 Mar 2005
		JP 2006045229 A	16 Feb 2006
		JP 2009114187 A	28 May 2009
		KR 20000068645 A	25 Nov 2000
		KR 100691395 B1	09 Mar 2007
		KR 20010049880 A	15 Jun 2001
		KR 100778086 B1	26 Nov 2007
		KR 100928211 B1	25 Nov 2009
		KR 20050026889 A	16 Mar 2005
		KR 101151317 B1	08 Jun 2012
		KR 20120042806 A	03 May 2012
		KR 101364470 B1	19 Feb 2014
		KR 20060048931 A	18 May 2006
		MX PA00007388 A	09 Mar 2004
		MX PA01006891 A	24 Apr 2002
		MX PA05008219 A	01 Feb 2006
		PL 333284 A1	22 Nov 1999
		TW 557216 B	11 Oct 2003
		TW I292715 B	21 Jan 2008
		TW I315989 B	21 Oct 2009
		TW 200526259 A	16 Aug 2005
		US 6323219 B1	27 Nov 2001
		US 2002065300 A1	30 May 2002
		US 6750229 B2	15 Jun 2004

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 2003064049 A1	03 Apr 2003
		US 7309688 B2	18 Dec 2007
		US 2004247713 A1	09 Dec 2004
		US 7879823 B2	01 Feb 2011
		US 8039026 B1	18 Oct 2011
		US 2004131710 A1	08 Jul 2004
		US 8093293 B2	10 Jan 2012
		US 2005036963 A1	17 Feb 2005
		US 8106094 B2	31 Jan 2012
		US 2004062731 A1	01 Apr 2004
		US 8431550 B2	30 Apr 2013
		US 2005244523 A1	03 Nov 2005
		US 2008249029 A1	09 Oct 2008
		WO 0134099 A1	17 May 2001
		WO 9904752 A2	04 Feb 1999
		ZA 9806679 B	27 Jan 2000

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 4990330 A	05 February 1991	US 4990330 A	05 Feb 1991
		AU 2152088 A	06 Apr 1989
		AU 614299 B2	29 Aug 1991
		DE 3832219 A1	13 Apr 1989
		EP 0308919 A1	29 Mar 1989
		JP S6483011 A	28 Mar 1989
		JP 2565513 B2	18 Dec 1996
		KR 940000671 B1	27 Jan 1994
US 2005/0214332 A1	29 September 2005	US 2005214332 A1	29 Sep 2005
		AU 2004218346 A1	16 Sep 2004
		AU 2004218346 B2	16 Nov 2006
		AU 2004260656 A1	10 Feb 2005
		AU 2004287448 A1	19 May 2005
		AU 2005221169 A1	22 Sep 2005
		BR PI0408062 A	14 Feb 2006
		BR PI0412756 A	26 Sep 2006
		BR PI0416052 A	02 Jan 2007
		CA 2516501 A1	16 Sep 2004
		CA 2529632 A1	10 Feb 2005
		CA 2542145 A1	19 May 2005
		CA 2559877 A1	22 Sep 2005
		CN 1756528 A	05 Apr 2006
		CN 1822812 A	23 Aug 2006
		CN 1822812 B	26 May 2010
		CN 1870965 A	29 Nov 2006
		CN 1870968 A	29 Nov 2006
		CN 1929759 A	14 Mar 2007
		CN 101217999 A	09 Jul 2008
		EP 1603529 A2	14 Dec 2005
		EP 1603529 B1	27 Apr 2016
		EP 1651178 A2	03 May 2006
		EP 1677747 A1	12 Jul 2006
EP 1694289 A1	30 Aug 2006		
EP 1722656 A1	22 Nov 2006		
EP 1901817 A2	26 Mar 2008		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 2997960 A1	23 Mar 2016
		JP 2006515329 A	25 May 2006
		JP 4234137 B2	04 Mar 2009
		JP 2006528935 A	28 Dec 2006
		JP 2009500394 A	08 Jan 2009
		KR 20070056170 A	31 May 2007
		KR 100786045 B1	17 Dec 2007
		KR 20050107479 A	11 Nov 2005
		KR 100825695 B1	29 Apr 2008
		KR 20060037341 A	03 May 2006
		KR 100833831 B1	02 Jun 2008
		KR 20060073971 A	29 Jun 2006
		MX PA05009392 A	04 Nov 2005
		MX PA06000930 A	30 Mar 2006
		MX PA06004826 A	03 Jul 2006
		MX PA06004827 A	03 Jul 2006
		US 2004175347 A1	09 Sep 2004
		US 2004176273 A1	09 Sep 2004
		US 2005019356 A1	27 Jan 2005
		US 2005112160 A1	26 May 2005
		US 2005220828 A1	06 Oct 2005
		US 2006074097 A1	06 Apr 2006
		US 2007009474 A1	11 Jan 2007
		US 2008076720 A1	27 Mar 2008
		US 2010278765 A1	04 Nov 2010
		WO 2004078158 A2	16 Sep 2004
		WO 2005011627 A2	10 Feb 2005
		WO 2005044218 A1	19 May 2005
		WO 2005044219 A1	19 May 2005
		WO 2005087043 A1	22 Sep 2005
		WO 2007007255 A2	18 Jan 2007

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
JP 2014114291 A	26 June 2014	JP 2014114291 A	26 Jun 2014
JP 2015059119 A	30 March 2015	JP 2015059119 A	30 Mar 2015
WO 2000/069408 A1	23 November 2000	WO 0069408 A1	23 Nov 2000
		AU 5026800 A	05 Dec 2000
		BR 0010551 A	13 Feb 2002
		CA 2373194 A1	23 Nov 2000
		CN 1355689 A	26 Jun 2002
		EP 1178776 A1	13 Feb 2002
		JP 2002544218 A	24 Dec 2002
		MX PA01011866 A	06 May 2002
CN 105106101 A	02 December 2015	CN 105106101 A	02 Dec 2015
WO 2001/017497 A1	15 March 2001	WO 0117497 A1	15 Mar 2001
		AU 6720100 A	10 Apr 2001
		IT MI991895 A1	09 Mar 2001
		IT 1316059 B1	28 Mar 2003
JP 07-157495 A	20 June 1995	None	
US 2009/0028969 A1	29 January 2009	US 2009028969 A1	29 Jan 2009
		AR 059545 A1	09 Apr 2008
		CA 2644045 A1	07 Sep 2007
		CN 101394900 A	25 Mar 2009
		EP 1996295 A1	03 Dec 2008
		JP 2009529499 A	20 Aug 2009
		KR 20080097487 A	05 Nov 2008
		PE 01352008 A1	06 Apr 2008
		RU 2008138390 A	10 Apr 2010
		TW 200808368 A	16 Feb 2008
		UY 30173 A1	28 Sep 2007
		WO 2007098873 A1	07 Sep 2007

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s			
Publication Number	Publication Date	Publication Number	Publication Date		
US 2012/0220545 A1	30 August 2012	US 2012220545 A1	30 Aug 2012		
		US 8772252 B2	08 Jul 2014		
		WO 2012103487 A1	02 Aug 2012		
JP 2004284999 A	14 October 2004	JP 2004284999 A	14 Oct 2004		
		JP 4109564 B2	02 Jul 2008		
US 2014/0179747 A1	26 June 2014	US 2014179747 A1	26 Jun 2014		
		US 9326932 B2	03 May 2016		
		AU 2012287067 A1	20 Feb 2014		
		AU 2012287067 A2	20 Feb 2014		
		AU 2012287067 B2	08 Dec 2016		
		CA 2842946 A1	31 Jan 2013		
		EP 2736484 A1	04 Jun 2014		
		US 2016206536 A1	21 Jul 2016		
		US 9585822 B2	07 Mar 2017		
		US 2016206549 A1	21 Jul 2016		
		WO 2013016257 A1	31 Jan 2013		
		US 2013/0129651 A1	23 May 2013	US 2013129651 A1	23 May 2013
				EP 2601930 A1	12 Jun 2013
JP 5837497 B2	24 Dec 2015				
TW 201219060 A	16 May 2012				
TW I513472 B	21 Dec 2015				
US 2014205553 A1	24 Jul 2014				
WO 2012017911 A1	09 Feb 2012				
WO 2003/051325 A1	26 June 2003	WO 03051325 A1	26 Jun 2003		
		AU 2002347372 A1	30 Jun 2003		
		AU 2002347379 A1	09 Jul 2003		
		EP 1454123 A2	08 Sep 2004		
		EP 1454123 B1	17 Mar 2010		
		EP 1455747 A1	15 Sep 2004		
		GB 2383127 A	18 Jun 2003		
		GB 2383127 B	20 Oct 2004		
		JP 2005513476 A	12 May 2005		
		US 2005068536 A1	31 Mar 2005		
		US 7245379 B2	17 Jul 2007		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 2007268489 A1	22 Nov 2007
		US 7477384 B2	13 Jan 2009
		US 2010079756 A1	01 Apr 2010
		US 2011216319 A1	08 Sep 2011
		US 2012307245 A1	06 Dec 2012
		US 2013271762 A1	17 Oct 2013
		US 2014146315 A1	29 May 2014
		US 2016178518 A1	23 Jun 2016
		WO 03054525 A2	03 Jul 2003

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2014/0227363 A1	14 August 2014	US 2014227363 A1	14 Aug 2014
		US 9289375 B2	22 Mar 2016
		CA 2841133 A1	14 Feb 2013
		EC SP14013202 A	31 May 2014
		EP 2739155 A1	11 Jun 2014
		HK 1198320 A1	02 Apr 2015
		JP 2014521698 A	28 Aug 2014
		KR 20140048258 A	23 Apr 2014
		MX 2014001318 A	21 Mar 2014
		RU 2014108308 A	10 Sep 2015
		WO 2013022788 A1	14 Feb 2013
DE 102004050563 A1	20 April 2006	DE 102004050563 A1	20 Apr 2006
		DE 102004039550 A1	23 Feb 2006
		DE 102004046686 A1	06 Apr 2006
		DE 102004055541 A1	18 May 2006
		DE 102004057858 A1	29 Jun 2006
		DE 102005000868 A1	20 Apr 2006
		DE 102005022626 A1	16 Nov 2006
		DE 102005026357 A1	28 Dec 2006
		EP 1640041 A2	29 Mar 2006
		EP 1776084 A1	25 Apr 2007
		EP 1776087 A1	25 Apr 2007
		EP 1776087 B1	25 Jun 2014
		EP 1791515 A1	06 Jun 2007
		EP 1799311 A2	27 Jun 2007
		EP 1800119 A2	27 Jun 2007
		EP 1812121 A1	01 Aug 2007
		EP 2275078 A2	19 Jan 2011
		EP 2275078 B1	07 Dec 2016
		RU 2007122285 A	27 Dec 2008
		WO 2006018149 A1	23 Feb 2006
		WO 2006018198 A1	23 Feb 2006
WO 2006034750 A1	06 Apr 2006		
WO 2006042625 A2	27 Apr 2006		
WO 2006042627 A2	27 Apr 2006		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date

WO 2006053688 A1

26 May 2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2000/038648 A1	06 July 2000	WO 0038648 A1	06 Jul 2000
		FR 2787711 A1	30 Jun 2000
		FR 2787711 B1	06 Dec 2002
US 2008/0287533 A1	20 November 2008	US 2008287533 A1	20 Nov 2008
		US 7842723 B2	30 Nov 2010
		AU 2012304886 A1	20 Mar 2014
		AU 2012304886 B2	29 Sep 2016
		CA 2846898 A1	14 Mar 2013
		CN 103987391 A	13 Aug 2014
		EP 2755664 A2	23 Jul 2014
		HK 1200172 A1	31 Jul 2015
		JP 2014528008 A	23 Oct 2014
		KR 20140064920 A	28 May 2014
		US 2005048008 A1	03 Mar 2005
		US 7320797 B2	22 Jan 2008
		US 2007099886 A1	03 May 2007
		US 7427690 B2	23 Sep 2008
		US 2007092461 A1	26 Apr 2007
		US 7547454 B2	16 Jun 2009
		US 2006183708 A1	17 Aug 2006
US 7569558 B2	04 Aug 2009		
US 2008287536 A1	20 Nov 2008		
US 7572933 B2	11 Aug 2009		
US 2007098663 A1	03 May 2007		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 7592002 B2	22 Sep 2009
		US 2007189992 A1	16 Aug 2007
		US 7597879 B2	06 Oct 2009
		US 2009042846 A1	12 Feb 2009
		US 7615546 B2	10 Nov 2009
		US 2009074691 A1	19 Mar 2009
		US 7777073 B2	17 Aug 2010
		US 2009253668 A1	08 Oct 2009
		US 7834210 B2	16 Nov 2010
		US 2009269291 A1	29 Oct 2009
		US 7993630 B2	09 Aug 2011
		US 2010331274 A1	30 Dec 2010
		US 8211873 B2	03 Jul 2012
		US 2011190202 A1	04 Aug 2011
		US 8212076 B2	03 Jul 2012
		US 2011059907 A1	10 Mar 2011
		US 8227426 B2	24 Jul 2012
		US 8258343 B1	04 Sep 2012
		US 2012264696 A1	18 Oct 2012
		US 8293943 B1	23 Oct 2012
		US 2011124573 A1	26 May 2011
		US 8314070 B2	20 Nov 2012
		US 2013028854 A1	31 Jan 2013
		US 8394851 B2	12 Mar 2013
		US 2012035130 A1	09 Feb 2012
		US 8410079 B2	02 Apr 2013
		US 8569269 B1	29 Oct 2013
		US 2013072673 A1	21 Mar 2013
		US 8586730 B2	19 Nov 2013
		US 2013172291 A1	04 Jul 2013
		US 8871748 B2	28 Oct 2014
		US 2004067890 A1	08 Apr 2004
		US 2004081672 A1	29 Apr 2004
		US 2004092482 A1	13 May 2004
		US 2004105894 A1	03 Jun 2004
		US 2004185069 A1	23 Sep 2004

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050030

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 2004208902 A1	21 Oct 2004
		US 2004228884 A1	18 Nov 2004
		US 2005058672 A1	17 Mar 2005
		US 2005271608 A1	08 Dec 2005
		US 2005276761 A1	15 Dec 2005
		US 2006045860 A1	02 Mar 2006
		US 2006110415 A1	25 May 2006
		US 2006127430 A1	15 Jun 2006
		US 2006147508 A1	06 Jul 2006
		US 2007041924 A1	22 Feb 2007
		US 2007166255 A1	19 Jul 2007
		US 2007166339 A1	19 Jul 2007
		US 2007237834 A1	11 Oct 2007
		US 2008139507 A1	12 Jun 2008
		US 2008254130 A1	16 Oct 2008
		US 2008255228 A1	16 Oct 2008
		US 2009130154 A1	21 May 2009
		US 2009209642 A1	20 Aug 2009
		US 2012189569 A1	26 Jul 2012
		US 2013267483 A1	10 Oct 2013
		WO 2013036286 A2	14 Mar 2013

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)