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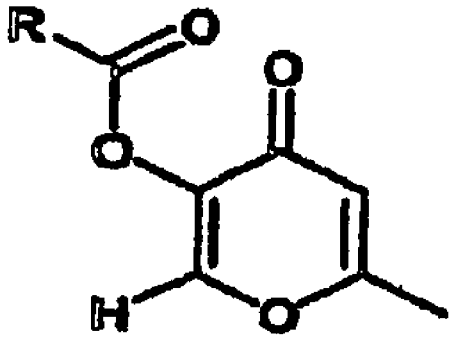
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(54) Title: 5-HYDROXY-2-METHYL-4H-PYRAN-4-ONE-ESTERS AS NOVEL TYROSINASE INHIBITORS



(I)

(57) Abstract: Skin brightening compositions based on esters of 5-hydroxy-2-methyl-4H- pyran-4-one. Also disclosed are methods of making the compositions as well as methods of using the compositions.

5-HYDROXY-2-METHYL-4H-PYRAN-4-ONE ESTERS AS NOVEL TYROSINASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to skin brightening compositions based on esters of 5-hydroxy-2-methyl-4H-pyran-4-one. Another aspect of the present invention relates to the method of making the compositions as well as methods of using the compositions.

BACKGROUND OF THE INVENTION

Skin hyperpigmentation has been directly related to the formation of melanin, a dark pigment formed via tyrosine. The initial steps in tyrosine to melanin conversion are mediated by the enzyme tyrosinase. Effective tyrosinase inhibitors may inhibit melanin formation and are used to reduce undesirable skin pigmentation (e.g. skin brightening and/or evening out skin tone and/or reducing the appearance of age spots). Currently, several tyrosinase inhibitors are used in the marketplace and include hydroquinone, kojic acid and arbutin. However, these products have various disadvantages; for example, kojic acid displays low bioavailability and thereby affords marginal efficacy.

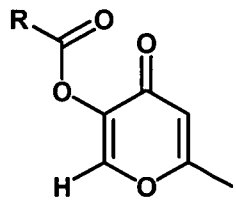
A fungal metabolic product, kojic acid has been commonly used as a skin brightening ingredient. Kojic acid has been shown to be safe and effective for topical use (see review by Burdock et al., 2001, Regulatory Toxicology and Pharmacology 33: 80-101). Kojic acid monoesters and diesters have been described (Nagai, S.; Izumi, T., US Patent 4,369,174); they appear to have excellent tyrosinase-inhibiting activity so as to inhibit skin melanin formation. This inhibition can produce excellent effects in skin brightening.

Kojic acid halogenation (i.e. chloro-kojic acid, bromo-kojic acid, etc.) and subsequent reduction to afford allomaltol (5-hydroxy-2-methyl-4H-pyran-4-one) has been previously described (for example, Liu, Z.D. et al, *Bioorg. Med. Chem.* **2001**, 9, 563-573). Furthermore, 5-hydroxy-2-methyl-4H-pyran-4-one has been described as a treatment for pigmentation disorders (Yamamoto, S. JP Patent 04036217), sunburn

prevention (Sansei Pharmaceutical Co., JP Patent 57134409), and as an antioxidant for oils and fats (Sansei Pharmaceutical Co., JP Patent 57137394). Hence, compositions based on esters of 5-hydroxy-2-methyl-4H-pyran-4-one may reduce melanin formation and enhance the potential to provide a noticeable brightening benefit with decreased skin irritation. Other likely benefits for these esters may include the potential for sunburn prevention and usage as novel antioxidants. It is the object of this invention to provide such compounds and compositions.

SUMMARY OF THE INVENTION

An embodiment of the present invention concerns an ester represented by formula 1:

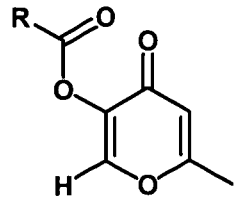


1

wherein R is C_2-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixture thereof, C_7-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio, C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$; and

R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1-C_6-alkoxy and halogen, and C_4-C_{20} hydroxyheteroaryl wherein the heteroatom is sulfur, nitrogen, oxygen or a mixture thereof.

Another embodiment of the present invention concerns a skin brightening composition comprising and ester represented by formula 1:



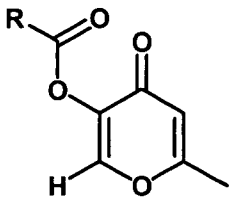
1 ; and

a dermatologically acceptable carrier,

wherein R is C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixture thereof, C_6-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio, C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$; and

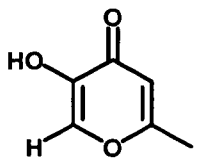
R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1-C_6-alkoxy and halogen, and C_4-C_{20} hydroxyheteroaryl wherein the heteroatom is sulfur, nitrogen, oxygen or a mixture thereof.

Yet another embodiment concerns a method for the preparation of an ester compound represented by formula **1**:



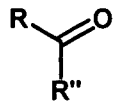
1

the method comprising reacting a compound represented by formula **2**:



2

with an acid, anhydride, or acid derivative of formula **3**:



3

to form said ester;

wherein R is C_2-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixtures thereof, C_6-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio, C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$,

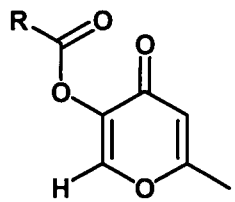
R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1-C_6-alkoxy and halogen, and C_4-C_{20} hydroxyheteroaryl wherein the heteroatoms are selected from the group consisting of sulfur, nitrogen, and oxygen;

R" is–OH, -SH, -F, -Cl, -Br, -I, or –OR'"; and

R'" is C_{1-12} *n*-alkyl, substituted C_{1-12} *n*-alkyl (e.g. $-CF_3$), C_{3-12} branched alkyl, substituted C_{3-12} branched alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl (e.g. -SO_2-R^2), aralkyl or substituted aralkyl.

DETAILED DESCRIPTION

The present invention relates to esters, skin brightening compositions which employ the esters, and methods of making and using the esters. The esters according to the present invention can be represented by the following formula 1:



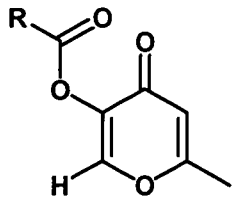
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wherein R is C_2-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixture thereof, C_7-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio,

C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$; and

R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1.C_6-alkoxy and halogen, and C_4-C_{20} hydroxyheteroaryl wherein the heteroatom is sulfur, nitrogen, oxygen or a mixture thereof.

Another embodiment concerns skin brightening compositions based on esters represented by the following formula 1:

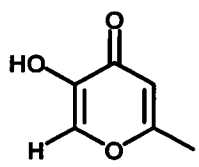


1

wherein R is C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixture thereof, C_6-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio, C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$; and

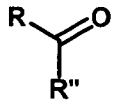
R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1.C_6-alkoxy and halogen, and C_4-C_{20} hydroxyheteroaryl wherein the heteroatom is sulfur, nitrogen, oxygen or a mixture thereof.

In an embodiment, the esters are prepared by reacting a compound represented by formula **2**:



2

with an acid, anhydride, or acid derivative of formula **3**:



3

wherein R" is–OH, -SH, -F, -Cl, -Br, -I, or –OR'''; and

R''' is C_{1-12} *n*-alkyl, substituted C_{1-12} *n*-alkyl (e.g. $-CF_3$), C_{3-12} branched alkyl, substituted C_{3-12} branched alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl (e.g. $-SO_2-R^2$), aralkyl or substituted aralkyl.

In an embodiment, the process comprises reacting a compound represented by formula **2** with an acid, anhydride, or acid derivative of formula **3** in the presence of an organic solvent (e.g. diethyl ether, tetrahydrofuran, methylene chloride, chloroform, etc.) or a mixed organic solvent. The reaction is typically allowed to run to completion, usually about 30 minutes. Shorter or longer reaction times may be required and can be determined by those of ordinary skill in the art. Upon completion of the reaction, the resulting ester can be isolated and purified by techniques known to those of ordinary skill in the art (e.g. flash chromatography, etc.).

The esters according to the present invention can be used in skin brightening compositions. Such compositions may also contain other skin brightening ingredients such as tetronic acid, tetronic acid derivatives, hydroquinone, kojic acid, 4-hydroxybenzyl alcohol, gallic acid, arbutin, α-hydroxyl acids, and fatty acid esters of ascorbic acid. Such other ingredients are known to those of skill in the art.

Typically, topical application to skin sites is accomplished in association with a carrier, and particularly one in which the active ingredient is soluble per se or is effectively solubilized (e.g., as an emulsion or microemulsion). Where employed, the carrier is inert in the sense of not bringing about a deactivation or oxidation of active or adjunct ingredient(s), and in the sense of not bringing about any adverse effect on the skin areas to which it is applied. For example, the compounds according to the present invention are applied in admixture with a dermatologically acceptable carrier or vehicle (e.g., as a lotion, cream, ointment, soap, stick, or the like) so as to facilitate topical application and, in some cases, provide additional beneficial effects as might be brought about, e.g., by moisturizing of the affected skin areas. While the carrier for dermatological compositions can consist of a relatively simple solvent or dispersant

such as water, it is generally preferred that the carrier comprise a composition more conducive to topical application. In particular, a dermatological composition which will form a film or layer on the skin to which it is applied so as to localize the application and provide some resistance to washing off by immersion in water or by perspiration and/or aid in the percutaneous delivery of the active agent. Many preparations are known in the art, and include lotions containing oils and/or alcohols and emollients such as olive oil, hydrocarbon oils and waxes, silicone oils, other vegetable, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters or alcohols or alcohol ethers, lecithin, lanolin and derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids and the like, and generally also emulsifiers (nonionic, cationic, or anionic), although some of the emollients inherently possess emulsifying properties. These same general ingredients can be formulated into a cream rather than a lotion, or into gels, or into solid sticks by utilization of different proportions of the ingredients and/or by inclusion of thickening agents such as gums or other forms of hydrophilic colloids. Such compositions are referred to herein as dermally, dermatologically; or pharmaceutically acceptable carriers.

Suitable carriers include water, alcohols, oils and the like, chosen for their ability to dissolve or disperse ingredients used in the treatment. In some embodiments, active and/or adjunct ingredients are added to a sunscreen or sunblock formulations so that topical application has the further advantage of preventing repigmentation during and/or after treatment. Preferred formulae of this type are SPF 15 or higher. Many of these preferred embodiments contain titanium dioxide or zinc oxide which additionally soothe and lubricate the skin and help minimize side effects in sensitive skin and with formulations containing high concentrations of bleaching ingredients.

Generally in the practice of methods of the invention, the composition is topically applied to darker skin areas on a subject in a predetermined or as-needed regimen either at intervals by application of a lotion or the like, it generally being the case that gradual brightening is noted with each successive application. Insofar as has been determined based upon *in vitro* studies, no adverse side effects are encountered.

"Therapeutically effective amount" or "effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The "therapeutically effective amount" can vary depending on the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be readily apparent to those skilled in the art or capable of determination by routine experimentation.

"Treating" or "treatment" of any disease or disorder refers to arresting or ameliorating a disease, disorder, or at least one of the clinical symptoms of a disease or disorder, reducing the risk of acquiring a disease, disorder, or at least one of the clinical symptoms of a disease or disorder, reducing the development of a disease, disorder or at least one of the clinical symptoms of the disease or disorder, or reducing the risk of developing a disease or disorder or at least one of the clinical symptoms of a disease or disorder. "Treating" or "treatment" also refers to inhibiting the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both, or inhibiting at least one physical parameter which may not be discernible to the subject. Further, "treating" or "treatment" refers to delaying or preventing the onset or reoccurrence of the disease or disorder or at least symptoms thereof in a subject which may be exposed to or predisposed to or may have previously suffered from a disease or disorder even though that subject does not yet experience or display symptoms of the disease or disorder.

Typical compositions of the invention contain from about 6.00% to about 0.01% by weight, from about 4.00% to about 0.25% by weight, from about 2.00% to about 0.50% by weight, or from about 1.50% to about 1.00% by weight of the esters according to formula 1 described above. Lower concentrations may be employed for less pronounced conditions (e.g. hyperpigmentation and in sunscreens and sunblocks

used after skin brightening treatment) and higher concentrations may be employed with more acute conditions.

It should be understood that the ingredients particularly mentioned above are merely examples and that some embodiments of formulations comprising the compositions of the present invention include other suitable components and agents. The compositions of the invention may be used for, among other things, pharmaceutical and cosmetic purposes and may be formulated with different ingredients according to the desired use.

The invention further includes packages, vessels, or any other type of container that contain a 5-hydroxy-2-methyl-4H-pyran-4-one ester, blends thereof, or any composition comprising a 5-hydroxy-2-methyl-4H-pyran-4-one ester formulation of the present invention.

EXAMPLES

The processes provided by the present invention are further illustrated by the following examples.

***In vitro* assay**: Tyrosinase catalyzes the first two biosynthetic steps in the tyrosine to melanin pathway. Tyrosinase hydroxylates tyrosine to dihydroxyphenylalanine (L-DOPA) and subsequently oxidizes L-DOPA to dopaquinone. One method to determine compound tyrosinase inhibition activity utilizes dopaquinone formation; L-DOPA oxidation forms dopaquinone and monitored at 475 nm. The enzyme assay was largely based on the method described in Zhang, JP., Chen, QX., Song, KK., & Xie, JJ. *Food Chemistry* **2006**, *95*, 579-584.

First, compound solubility gets evaluated in an aqueous environment and appropriate dilutions are prepared in either water or dimethyl sulfoxide. Dilutions are prepared from stock solutions, typically to measure final inhibitor concentrations ranging from 10nM to 10mM.

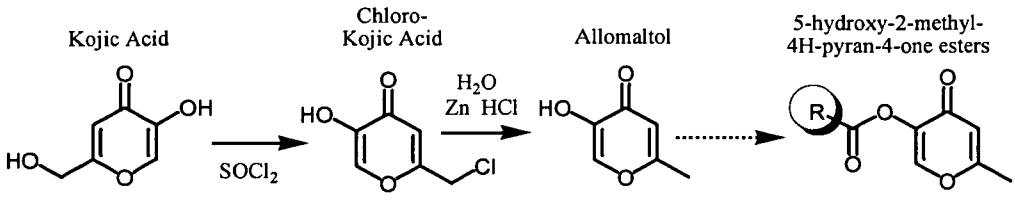
The assay mixture is composed of 50 mM Na_2HPO_4/NaH_2PO_4 pH 7.0 and 0.5 mM L-DOPA. The enzymatic reaction is commenced by addition of 18 Units of mushroom tyrosinase (Sigma T3824). A baseline initial rate of tyrosinase activity is measured at 475nm using a Beckman Coulter DU 800 UV/Vis Spectrophotometer in 1.0 ml reaction format at 30 °C, then a 25ul aliquot of the inhibitor solution is added/mixed and the change in rate is noted. The change in rate relates to the percent inhibition of tyrosinase due to the presence of the inhibitor. Inhibitory effects of any DMSO present are minimized by limiting the final concentration to 2.5% and accounting for any background inhibition with DMSO blanks for each assay.

The degree of tyrosinase inhibition was measured in terms of the concentration of inhibitor necessary to inhibit tyrosinase by 50%, the EC_{50} value. This was determined by sigmoidal dose-response curves generated in Graphpad Prizm® Version 4 by plotting the log of inhibitor concentration against the rate response (% inhibition).

It should be understood that the assay method mentioned above merely describes general procedures and that other suitable components, reagent concentrations, and/or agents and/or analytical equipment may be used.

Chemical Synthesis: The general methods to prepare 5-hydroxy-2-methyl-4H-pyran-4-one esters are illustrated below.

Synthesis of 5-hydroxy-2-methyl-4H-pyran-4-one esters



Preparation of 2-(chloromethyl)-5-hydroxy-4H-pyran-4-one (chloro-kojic acid): Kojic Acid (50.0 g; 352 mmol) – an inhibitor of tyrosinase with an EC_{50} of 17.0 μM – was carefully added in portions over 30 min to a stirring solution of thionyl chloride (150 mL) containing hexanes (100 mL). After an additional 3.5 hours of stirring, the product was collected by Büchner filtration and washed with hexanes (2 x 50 mL). The light yellow solid was dried over night under vacuum to afford chloro-kojic acid (50.9 g; 90% yield). Chloro-kojic acid was found to be a more potent inhibitor of tyrosinase than kojic acid with an EC_{50} of 6.8 μM. ^{1}H NMR (DMSO-d_6) δ 9.30 (br s, 1H; 5-OH); 8.12 (s, 1H; 6-H); 6.56 (s, 1H; 3-H); 4.66 (s, 2H; 2-CH_2Cl).

Preparation of 5-hydroxy-2-methyl-4H-pyran-4-one (allomaltol): Chloro-kojic Acid (20.0 g; 125 mmol) – an inhibitor of tyrosinase with an EC_{50} of 6.8 μM – was added in portions to HPLC grade water (60 mL) and heated with an oil bath to ~50 °C. Zinc dust (16.2 grams) was carefully added in portions (5 min). An addition funnel was then attached. The reaction temperature was then increased to ~70 °C and concentrated HCl (37 mL) was added drop-wise over 60 min; the reaction was vigorously stirred for an additional 3 hours. Next, excess zinc was removed via hot Büchner filtration. Standard extraction and purification methods afforded allomaltol (10.3 g; 81.7 mmol; 65% yiled); see Liu, Z.D. et al, *Bioorg. Med. Chem.* **2001**, 9, 563-573. Allomaltol was found to be a more potent inhibitor of tyrosinase than kojic acid

with an EC_{50} of 3.4 μM. ^1H NMR (DMSO-d_6) δ 9.3-8.3 (br s, 1H; 5-OH); 7.97 (s, 1H; 6-H); 6.23 (s, 1H; 3-H); 2.24 (s, 3H; 2-CH_3).

Preparation of 6-methyl-4-oxo-4H-pyran-3-yl acetate: Allomaltol (600 mg; 4.76 mmol) was weighed out into a round bottom flask (100 ml) containing a stir-bar. The contents were diluted with anhydrous THF (~20 ml) and stirred (~5 min) to afford a solution. Next, trimethyl amine (833 μl; 6.33 mmol; 1.33 equiv.) was added drop-wise and the contents stirred (~5 min). Acetic anhydride (641 μl; 5.00 mmol) was then added drop-wise, capped and stirred at room temperature. The reaction was monitored via silica gel TLC. Once complete, the reaction mixture was concentrated under reduced pressure and the contents purified by silica gel chromatography to afford 650 mg product (3.87 mmol; 81% yield). This compound was found to have an EC_{50} of 106 μM. ^1H NMR (DMSO-d_6) δ 8.39 (s, 1H; 2-H); 6.36 (s, 1H; 5-H); 2.30 (s, 3H); 2.24 (s, 3H).

Preparation of 6-methyl-4-oxo-4H-pyran-3-yl propanoate: Allomaltol (600 mg; 4.76 mmol) was weighed out into a round bottom flask (100 ml) containing a stir-bar. The contents were diluted with anhydrous THF (~20 ml) and stirred (~5 min) to afford a solution. Next, trimethyl amine (833 μl; 6.33 mmol; 1.33 equiv.) was added drop-wise and the contents stirred (~5 min). Propionic anhydride (473 μl; 5.00 mmol) was then added drop-wise, capped and stirred at room temperature. The reaction was monitored via silica gel TLC. Once complete, the reaction mixture was concentrated under reduced pressure and the contents purified by silica gel chromatography to afford (680 mg product; 3.73 mmol; 78% yield). This compound was found to have an EC_{50} of 620 μM. ^1H NMR (DMSO-d_6) δ 8.39 (s, 1H; 2-H); 6.36 (s, 1H; 5-H); 2.59-2.55 (q, 2H; -CH_2-); 2.29 (s, 3H; 6-CH_3); 1.13-1.08 (t, 3H; -CH_3).

Preparation of 6-methyl-4-oxo-4H-pyran-3-yl hexanoate: Allomaltol (600 mg; 4.76 mmol) was weighed out into a round bottom flask (100 ml) containing a stir-bar. The contents were diluted with anhydrous THF (~20 ml) and stirred (~5 min) to afford a solution. Next, trimethyl amine (833 μl; 6.33 mmol; 1.33 equiv.) was added

drop-wise and the contents stirred (~5 min). Hexanoic anhydride (1030 µl; 954 mg; 4.45 mmol) was then added drop-wise, capped and stirred at room temperature. The reaction was monitored via silica gel TLC. Once complete, the reaction mixture was concentrated under reduced pressure and the contents purified by silica gel chromatography to afford 760 mg of light yellow crystalline product (3.39 mmol; 76% yield). This compound was found to have an EC_{50} of 354 µM. ^1H NMR (DMSO-d_6) δ 8.39 (s, 1H; 2-H); 6.35 (s, 1H; 5-H); 2.54-2.52 (t, 2H); 2.29 (s, 3H; 6-CH_3); 1.62-1.58 (p, 2H); 1.35-1.24 (m, 4H); 0.89-0.86 (t, 3H; -CH_3).

Preparation of 6-methyl-4-oxo-4H-pyran-3-yl octanoate: Allomaltol (600 mg; 4.76 mmol) was weighed out into a round bottom flask (100 ml) containing a stir-bar. The contents were diluted with anhydrous THF (~20 ml) and stirred (~5 min) to afford a solution. Next, trimethyl amine (833 µl; 6.33 mmol; 1.33 equiv.) was added drop-wise and the contents stirred (~5 min). Octanoyl chloride (770 µl; 724 mg; 4.45 mmol) was then added drop-wise, capped and stirred at room temperature. The reaction was monitored via silica gel TLC. Once complete, the reaction mixture was concentrated under reduced pressure and the contents purified by silica gel chromatography to afford 1.01 g of light yellow crystalline product (4.00 mmol; 90% yield). This compound was found to have an EC_{50} of 532 µM. ^1H NMR (DMSO-d_6) δ 8.39 (s, 1H; 2-H); 6.35 (s, 1H; 5-H); 2.54-2.52 (t, 2H); 2.29 (s, 3H; 6-CH_3); 1.60-1.58 (p, 2H); 1.34-1.31 (m, 2H), 1.31-1.24 (m, 6H); 0.87-0.85 (t, 3H; -CH_3).

Preparation of 6-methyl-4-oxo-4H-pyran-3-yl benzoate: Allomaltol (600 mg; 4.76 mmol) was weighed out into a round bottom flask (100 ml) containing a stir-bar. The contents were diluted with anhydrous THF (~20 ml) and stirred (~5 min) to afford a solution. Next, trimethyl amine (833 µl; 6.33 mmol; 1.33 equiv.) was added drop-wise and the contents stirred (~5 min). Benzoyl chloride (517 µl; 627 mg; 4.46 mmol) was then added drop-wise, capped and stirred at room temperature. The reaction was monitored via silica gel TLC. Once complete, the reaction mixture was concentrated under reduced pressure and the contents purified by silica gel chromatography to afford 930 mg of light yellow crystalline product (4.04 mmol;

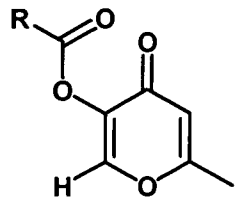
91% yield). This compound was found to have an EC_{50} of > 1 mM. ^1H NMR (DMSO-d_6) δ 8.58 (s, 1H; 2-H); 8.09-8.07 (dd, 2H); 7.78-7.76 (t, 1H); 7.63-7.59 (t, 2H); 6.43 (s, 1H; 5-H); 2.34 (s, -3H; 6-CH_3).

Preparation of 6-methyl-4-oxo-4H-pyran-3-yl 4-fluorobenzoate: Allomaltol (600 mg; 4.76 mmol) was weighed out into a round bottom flask (100 ml) containing a stir-bar. The contents were diluted with anhydrous THF (~20 ml) and stirred (~5 min) to afford a solution. Next, trimethyl amine (840 µl) was added drop-wise and the contents stirred (~5 min). 4-Fluorobenzoyl chloride (600 µl) was then added drop-wise, capped and stirred at room temperature. The reaction was monitored via silica gel TLC. Once complete, the reaction mixture was concentrated under reduced pressure and the contents purified by silica gel chromatography to afford 1.04 g crystalline product (4.19 mmol; 88% yield). This compound was found to have an EC_{50} of > 1 mM. ^1H NMR (DMSO-d_6) δ 8.59 (s, 1H; 2-H); 8.18-8.13 (dd, 2H); 7.47-7.41 (t, 2H); 6.44 (s, 1H; 5-H); 2.34 (s, -3H; 6-CH_3).

The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

We claim:

1. An ester represented by formula 1:

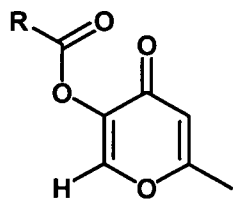


1

wherein R is C_2-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixture thereof, C_7-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio, C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$; and

R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1.C_6-alkoxy and halogen, and C_4-C_{20} hydroxyheteroaryl wherein the heteroatom is sulfur, nitrogen, oxygen or a mixture thereof.

2. A skin brightening composition comprising an ester represented by formula 1:



1 ; and

a dermatologically acceptable carrier,

wherein R is C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixture thereof, C_6-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio, C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$; and

R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1.C_6-alkoxy and halogen, and C_4-C_{20}

hydroxyheteroaryl wherein the heteroatom is sulfur, nitrogen, oxygen or a mixture thereof.

3. The composition according to claim 2, wherein said ester is present in an amount of from about 6.00% to about 0.01% by weight.

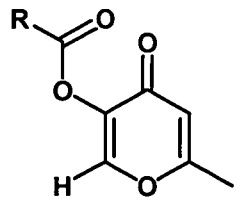
4. The composition according to claim 3, wherein said ester is present in an amount of from about 4.0% to about 0.10% by weight.

5. The composition according to claim 4, wherein said ester is present in an amount of from about 2.0% to about 0.50% by weight.

6. A method of brightening skin, comprising applying the composition according to claim 2 to skin.

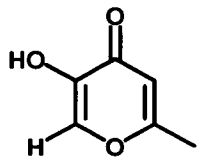
7. The method according to claim 6, wherein said composition is applied to skin in a predetermined regimen or in an as-needed regimen until a desired level of skin brightening is achieve.

8. A method for the preparation of an ester compound represented by formula **1**:



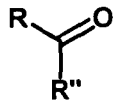
1

the method comprising reacting a compound represented by formula **2**:



2

with an acid, anhydride, or acid derivative of formula **3**:



3

to form said ester;

wherein wherein R is C_2-C_{24} alkyl, C_2-C_{24} alkenyl, C_4-C_{24} dienyl, C_6-C_{24} trienyl, C_8-C_{24} tetraenyl, or a mixtures thereof, C_6-C_{14} aryl, substituted C_6-C_{14} aryl, C_1-C_{14}-alkoxy, halogen, carboxy, cyano, C_1-C_{14}-alkanoyloxy, C_1-C_{14}-alkylthio, C_1-C_{14}-alkylsulfonyl, trifluoromethyl, hydroxy, C_2-C_{14}-alkoxycarbonyl, C_2-C_{14}-alkanoylamino, -O-R^2, S-R^2, -SO_2-R^2, -$NHSO_2R^2$ or -$NHCO_2R^2$,

R^2 is phenyl, naphthyl, or phenyl or naphthly substituted with one to three groups selected from C_1-C_6-alkyl, C_6-C_{10} aryl, C_1-C_6-alkoxy and halogen, and C_4-C_{20} hydroxyheteroaryl wherein the heteroatoms are selected from the group consisting of sulfur, nitrogen, and oxygen;

R" is–OH, -SH, -F, -Cl, -Br, -I, or –OR'"; and

R'" is C_{1-12} *n*-alkyl, substituted C_{1-12} *n*-alkyl , C_{3-12} branched alkyl, substituted C_{3-12} branched alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl , aralkyl or substituted aralkyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/000823

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D309/38 A61K31/351 A61P17/00 A61Q17/00

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)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BEELIK, ANDREW ET AL: "Some new reactions and derivatives of kojic acid" CANADIAN JOURNAL OF CHEMISTRY , 33, 1361-74 CODEN: CJCHAG; ISSN: 0008-4042, 1955, XP002525435 page 1365	1,2,8
X	ICHIMOTO, ITSUO ET AL: "Studies on kojic acid and its related .gamma.-pyrone compounds. VI. Catalytic hydrogenation of kojic acid" AGRICULTURAL AND BIOLOGICAL CHEMISTRY , 28(10), 723-7 CODEN: ABCHA6; ISSN: 0002-1369, 1964, XP002525436 page 726	1,2,8

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2009	29/05/2009

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/000823

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 4 369 174 A (NAGAI SUMIYOSHI [JP] ET AL) 18 January 1983 (1983-01-18) cited in the application column 2, line 12 - line 21	1-8

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Information on patent family members

International application No
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