

XANTHENEDIONE DERIVATIVES FOR THE TREATMENT OF PIGMENTATION AND SKIN AGEING DISORDERS

The present invention relates to xanthenedione derivatives and pharmaceutical or
5 cosmetic compositions that contain them, their method of preparation and their uses
particularly as medicine or as cosmetic active ingredient.

The novel compounds according to the present invention come in the form of
xanthenedione precursors. The use of these precursors enables a slow release of the
xanthenedione functions in the cutaneous medium.

10 They may be on the one hand glycosides, which stem from the condensation of
glucose and xanthenedione functions.

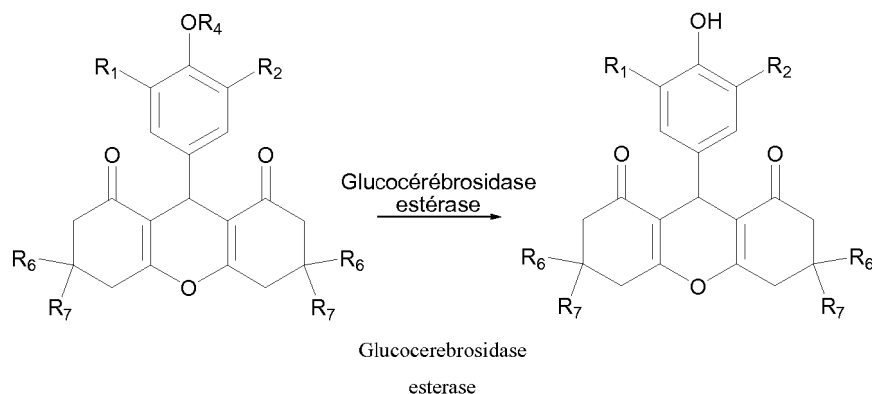
In this case, the principle of the invention is linked to the use of glucocerebrosidase,
which is a lysosomal enzyme present in all cells and thus naturally present in the skin
(Yutaka Takagi, Ernst Kriehuber, Genji Imokawa, Peter M. Elias, and Walter M.
15 Holleran, β -Glucocerebrosidase activity in mammalian stratum corneum, *The Journal of
Lipid Research*, Vol. 40, 861-869, (1999). Glucocerebrosidase hydrolyses the active
precursor, thereby releasing the biologically active substance (see diagram 1), namely
the xanthenedione function.

The enzymatic hydrolysis by glucocerebrosidase slowly releases the xanthenedione
20 function. This slow release makes it possible to avoid the over concentration of the
active ingredient. Thus, the slow release of the active ingredient ensures a better
bioavailability thereof in the cutaneous medium and thus more efficient protection.

They may be on the other hand alkyl or alkenyl ester of xanthenediones. The
esters are also easily cleavable by the esterases present in the skin (Redoules, D.,
25 Tarroux, R., Assalit, M.F. and Perié, J.J. Characterization and assay of five enzymatic
activities in the stratum corneum using tape-stripping, *Skin Pharmacol. Appl. Skin
Physiol.*, 12, 182-192 (1999)). The cleavage of the esters by the esterases present in the
skin then enables a slow diffusion of the active ingredients (see diagram 1), which
corresponds to the concept of "drug delivery".

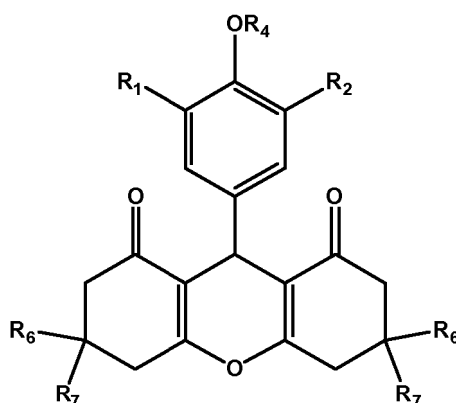
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Diagram 1: Cleavage of compounds of generic formula (I) by the esterases or
glucocerebrosidase of the skin.



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Thus, the object of the present invention is a compound of the following generic formula (I):



10 In which:

- R_1 and R_2 represent simultaneously or independently: OH, an atom of hydrogen, a C_1 - C_6 alkyl radical, a C_1 - C_6 alkoxy radical, a halogen, or $OCOR_3$;
- R_3 represents: a C_1 - C_{24} alkyl radical, a C_{12} - C_{24} alkenyl radical comprising at least one unsaturation, advantageously from 1 to 6 and preferably from 1 to 4;
- R_4 represents: COR_5 , a glucide radical substituted or not by one or more acetyl radical(s),
- R_5 represents: a C_{10} - C_{24} alkyl radical, or a C_{12} - C_{24} alkenyl radical comprising at least one unsaturation, advantageously from 1 to 6 and preferably from 1 to 4;
- 20 • R_6 and R_7 represent:
 - simultaneously a hydrogen atom or a methyl radical,

or

- when R_6 represents a hydrogen atom, R_7 represents a C_1 - C_6 alkyl radical or a phenyl substituted or not by one or more C_1 - C_3 alkoxy radical(s) or one or more halogen(s),

or

- 5 - R_6 and R_7 are bonded to each other and form a C_3 - C_6 cycloalkyl, and cosmetically and pharmaceutically acceptable salts.

Definitions:

“Alkyl radical” is taken to mean, according to the present invention, a saturated linear or branched aliphatic hydrocarbon chain and comprising the specified number of
10 carbon atoms. Methyl, ethyl and propyl may for example be cited. The alkyl radical may in particular represent the hydrocarbon chain of a C_1 - C_{24} and in particular a C_{10} - C_{24} saturated fatty acid.

The saturated fatty acids may be capric acid (10 :0), undecylic acid (11 :0), lauric acid (12 :0), tridecylic acid (13 :0), myristic acid (14 :0), pentadecylic acid
15 (15 :0), palmitic acid (16 :0), margaric acid (17 :0), stearic acid (18 :0), nonadecylic acid (19 :0), arachidic acid (20 :0), heneicosanoic acid (21 :0), behenic acid (22 :0), tricosanoic acid (23 :0), lignoceric acid (24 :0). In particular, the saturated fatty acids may be palmitic acid and stearic acid.

“Alkoxy radical” is taken to mean, according to the present invention, a linear or
20 branched hydrocarbon chain comprising the number of carbon atoms indicated and an oxygen atom for example a methoxy radical, an ethoxy radical, a propoxy radical or a butoxy radical.

“Alkenyl radical” is taken to mean, according to the present invention, a linear or branched hydrocarbon chain comprising the number of carbon atoms indicated and
25 comprising at least one unsaturation advantageously 1 to 6 and preferably 1 to 4. “Unsaturation” is taken to mean, according to the present invention, a $C=C$ double bond.

The alkenyl radical may in particular represent a hydrocarbon chain stemming from a C_{12} - C_{24} unsaturated fatty acid comprising at least one unsaturation,
30 advantageously 1 to 6 and preferably 1 to 4.

The unsaturated fatty acids may be lauroleic acid ($C_{12}:1$), myristoleic acid ($C_{14}:1$), palmitoleic acid ($C_{16}:1$), oleic acid ($C_{18}:1$), ricinoleic acid ($C_{18}:1$),

gadoleic acid (C20 :1), erucic acid (C22 :1), α -linolenic acid (C18 :3), stearidonic acid (C18 :4), eicosatrienoic acid (C20 :3), eicosatetraenoic acid (C20 :4), eicosapentaenoic acid (C20 :5), docosapentaenoic acid (C22 :5), docosaheptaenoic acid (C22 :6), tetracosapentaenoic acid (C24 :5), tetracosahexaenoic acid (C24 :6), linoleic acid (C18 :2), gamma-linolenic acid (C18 :3), eicosadienoic acid (C20 :2), dihomogamma-linolenic acid (C20 :3), arachidonic acid (C20 :4), docosatetraenoic acid (C22 :2), docosapentaenoic acid (C22 :5), adrenic acid (C22 :4) and calendic acid (C18 :3). In particular, the unsaturated fatty acids may be: α -linolenic acid (C18 :3), oleic acid (C18 :1), linoleic acid (C18 :2), gamma-linolenic acid (C18 :3) and dihomogamma-linolenic acid (C20 :3).

“Acetyl” is taken to mean a salt or an ester of acetic acid.

Halogen is taken to mean an atom of chlorine, an atom of fluorine, an atom of bromine and an atom of iodine.

“Glucide” is taken to mean, according to the present invention, a class of organic molecules containing a carbonyl group (aldehyde or ketone) and several hydroxyl (-OH) groups.

The terms glucides, monosaccharides, saccharides, carbohydrates, sugars are equivalent in the present invention.

Advantageously, the glucide of the generic formula (I) is chosen from the monosaccharides.

More advantageously, the glucide of generic formula (I) is chosen from monosaccharides of the series D.

Even more advantageously, the glucide of generic formula (I) is chosen from the C3-C6 monosaccharides of series D, such as glyceraldehyde, erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, gulose, idose, talose, glucose, galactose, mannose, fructose and derivatives thereof such as their cyclic forms when they exist, of pyranose or furanose type for example. The preferred monosaccharide in the present invention is D-glucopyranose. The glucide may be bonded to the xanthenedione derivative by an α or β osidic type bond if the bond is on the anomeric carbon of the glucide. The glucide may also be bonded to the xanthenedione derivative by a simple ether bond if the bond is formed on the oxygen of a non-anomeric carbon of the glucide.

According to an embodiment of the invention, the compounds of generic formula (I) are those for which R₁ and R₂ represent simultaneously or independently a hydrogen atom or a C₁-C₆ alkoxy radical.

According to the invention, the compounds of generic formula (I) are those for which R₄ represents COR₅.

The invention also relates to compounds of generic formula (I) for which R₅ represents a C₁₄-C₁₈ alkyl radical or a C₁₄-C₁₈ alkenyl radical comprising from 1 to 3 unsaturations.

According to an embodiment of the invention, the compounds of generic formula (I) are those for which R₄ represents a glucide substituted or not by one or more acetyl radical(s), in particular a pyranose radical, if appropriate partially or totally acetylated.

According to the invention, the compounds of generic formula (I) are those for which R₆ and R₇ represent simultaneously a methyl radical.

The compounds of generic formula (I) may be chosen from the following list of compounds:

-2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl palmitate

-(9Z,12Z)-2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl octadeca-9,12-dienoate

-(3R,4S,5S)-2-(acetoxymethyl)-6-(2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate

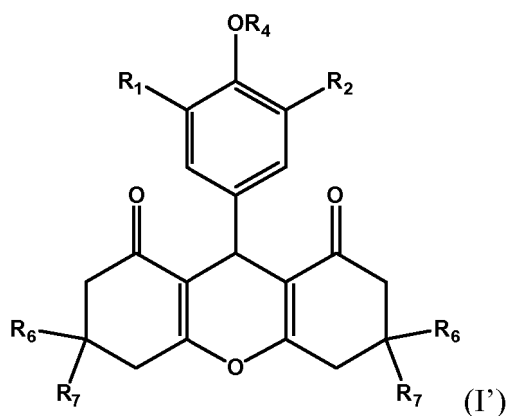
-9-(3-methoxy-4-((3S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

-(3S,4S,5S,6S)-2-(acetoxymethyl)-6-(2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate

-9-(3-methoxy-4-((2S,3S,4S,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

-(3R,4S,5S,6S)-2-(acetoxymethyl)-6-(4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate
 -3,3,6,6-tetramethyl-9-(4-((2S,3S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione.

The present invention also extends to the compound of generic formula (I'):



in which the radicals R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 have significations identical to those given previously, but in which R_4 may in addition represent a hydrogen atom or an acetyl radical, and pharmaceutically or cosmetically acceptable salts, for its use as medicine or as cosmetic active ingredient.

The invention also relates to the compounds of generic formula (I') defined above for their use in the depigmentation of the skin and/or head hair and/or body hair, in the treatment and/or in the prevention of the ageing of the skin or in the treatment and/or the prevention of the inflammation of the skin.

The invention also relates to the compounds of generic formula (I') defined above in which R_4 represents a hydrogen atom in the depigmentation of the skin and/or head hair and/or body hair, in the treatment and/or in the prevention of the ageing of the skin or in the treatment and/or the prevention of the inflammation of the skin.

The present invention relates to compounds of generic formula (I') for their use as active depigmenting ingredient, active anti-oxidant ingredient or active anti-inflammatory ingredient.

The depigmenting activity, which consists in a general manner in reducing and/or inhibiting the production of melanins responsible for pigmentation, or in

reducing the transport of melanins in dendrites, may manifest itself through different types of actions according to the present invention:

- reducing and/or eliminating pigment spots such as hyperpigmentation spots due to pro-inflammatory stress (brownish UV induced pigment spots, for example) and chloasmas, or instead;
- bleaching and/or lightening the skin and/or body hair and/or head hair, preferentially in order to:
 - ◇ unify the complexion; which is characterised by obtaining a uniform, lighter, more transparent, more radiant skin complexion. The lustre of the complexion is thus improved. The advantages obtained are particularly interesting for sensitive skins whatever their nature (dry, normal, greasy) and more particularly dull and lustreless sensitive skins, and/or;
 - ◇ treat certain unsightly pigment spots due to an epidermal hyperpigmentation, especially such as ageing spots of the skin. The depigmenting activity according to the present invention then entails the visible reduction of the intensity and the size of the pigment spots and/or preventing the appearance of additional spots.

The present invention relates to compounds of generic formula (I') in which R₄ represents a hydrogen atom for their use as depigmenting active ingredient, antioxidant active ingredient or anti-inflammatory active ingredient.

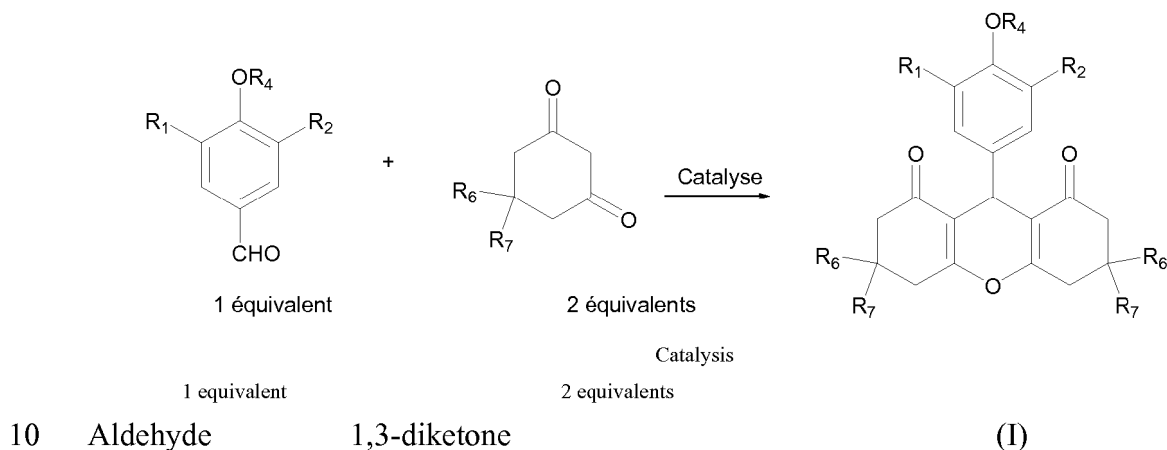
The present invention also relates to the use of cosmetic compositions comprising a compound of generic formula (I') for depigmentation of the skin and/or head hair and/or body hair, the treatment and/or the prevention of the ageing of the skin or the treatment and/or the prevention of the inflammation of the skin.

The present invention relates to a method of bleaching and/or lightening of human skin and/or body hair and/or head hair comprising the application on the skin and/or body hair and/or head hair of a cosmetic composition containing at least one compound of generic formula (I') .

The present invention relates to a cosmetic method of treatment and/or prevention of the ageing of the skin comprising the application on the skin of a cosmetic composition containing at least one compound of generic formula (I').

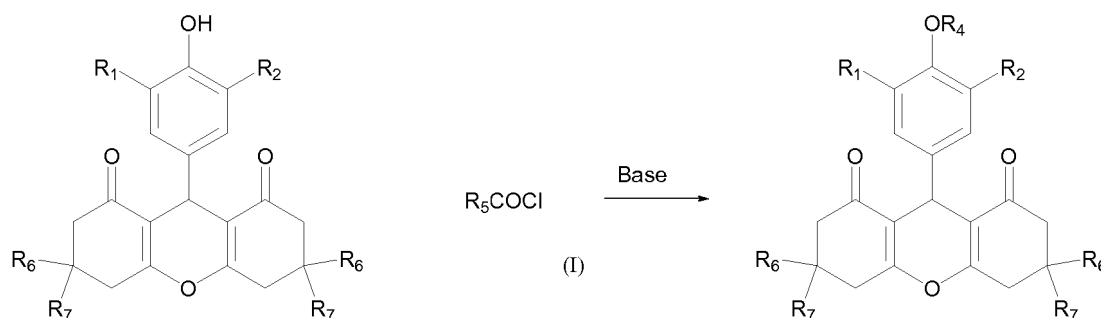
The present invention relates to a cosmetic method of treatment and/or prevention of inflammatory reactions of the skin comprising the application on the skin of a cosmetic composition containing at least one compound of generic formula (I').

The invention also extends to the method of synthesising compounds of generic formula (I), characterised in that two molecules of 1,3-diketone are made to react with an aldehyde in the presence of an acid or basic catalysis:



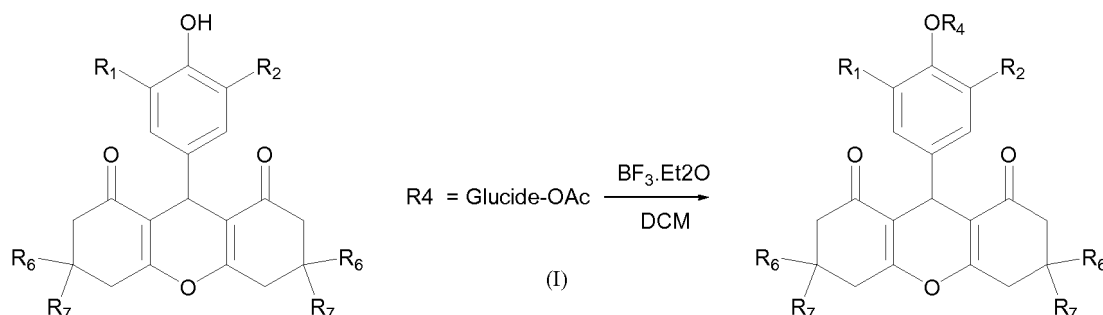
with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 having the same significations as those given in the generic formula (I).

For the synthesis of products of generic formula (I) with $R_4 = \text{COR}_5$, a phenol is made to react with a $R_5\text{COCl}$ activated carboxylic acid



with R_1 , R_2 , R_3 , R_5 , R_6 and R_7 having the same significations as those given in the generic formula (I).

For the synthesis of products of generic formula (I) with $R_4 =$ a glucide substituted by one or more acetyl radical(s), a phenol is made to react with a glucide radical substituted by one or more acetyl radical(s).

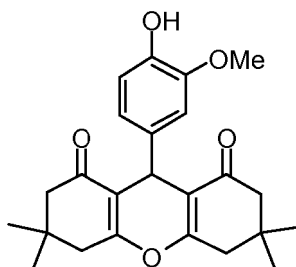


with R_1 , R_2 , R_3 , R_5 , R_6 and R_7 having the same significations as those given in the generic formula (I), which may be followed if appropriate by a saponification step.

5 1) General protocol for synthesising compounds according to the invention

Example 1:

-9-(4-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



10 General procedure A

The synthesis of the xanthenedione function is described in the literature in one or two steps from 1,3-diketone and an aldehyde in the presence of an acid or base catalysis (S. Kantevari et al., *Arkivoc* 2006, 136-148) (B. Das et al., *Catalysis Communications* 8 (2007) 535-538).

15 To a suspension of 1.40g of 5,5-dimethyl-1,3-cyclohexanedione (dimedone, 10 mmol) and 0.76g of vanillin (5 mmol) in 10mL of acetonitrile, 0.63mL of trimethylsilane chloride (5 mmol) are added. The mixture is taken to reflux to a temperature of 110°C and the solubilisation of the particles in suspension into a clear, yellow solution is observed. After 6h of reaction, the solution is cooled to ambient
20 temperature for 10 minutes then is placed for 10 minutes in an ice bath. Water is then added in order to precipitate the xanthenedione obtained. The mixture is then filtered on a sinter with distilled water, then with n-pentane. The solid is dried in the vacuum oven

for at least one night under 50mbar and at 40°C in order to obtain a white solid with a yield of 79%.

¹H NMR (400 MHz, CDCl₃) : δ : 1.00 (s, 6H) ; 1.10 (s, 6H) ; 2.20 (dd, 4H) ; 2.45 (s, 4H) ; 3.87 (s, 3H) ; 4.66 (s, 1H) ; 5.60 (s, 1H) ; 6.58 (dd, 1H) ; 6.72 (d, 1H) ; 6.99 (d, 1H).

¹³C NMR 100 MHz, CDCl₃) : δ : 27.2 ; 29.2 ; 31.2 ; 32.1 ; 40.8 ; 50.7 ; 55.8 ; 112.2 ; 113.9 ; 115.7 ; 145.8 ; 162.0 ; 196.5.

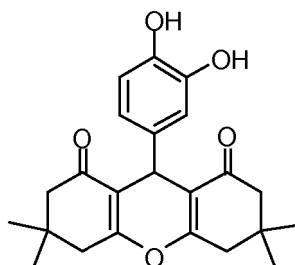
MS (ESI+): 397.1 [M+H]⁺

R_f (heptane/EtOAc ; 1/1) : 0.57

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Example 2:

-9-(3,4-dihydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



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¹H NMR (400 MHz, DMSO d₆) : δ : 0.91 (s, 6H) ; 1.02 (s, 6H) ; 2.07 (d, syst.AB, 2H) ; 2.23 (d, syst.AB, 2H) ; 2.52 (m, 4H) ; 4.37 (s, 1H) ; 6.36 (d, 1H) ; 6.53 (d, 1H) ; 6.60 (s, 1H) ; 8.58 (s, OH, 1H) ; 8.7 (s, OH, 1H).

¹³C NMR (100 MHz, DMSO d₆) : δ : 26.4 ; 28.6 ; 30.0 ; 31.7 ; 50.0 ; 114.8 ; 114.9 ; 115.8 ; 118.4 ; 135.3 ; 143.4 ; 144.4 ; 162.3 ; 195.9.

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MS (APCI) : 383.2 [M+H]⁺

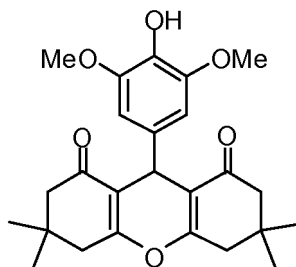
R_f (1/1; Heptane/EtOAc) : 0.75

Example 3:

9-(4-hydroxy-3,5-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

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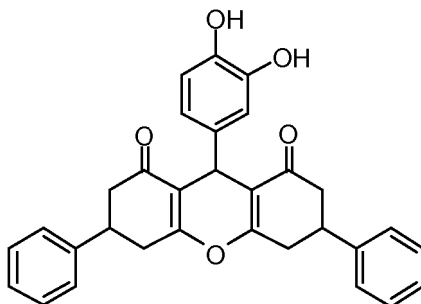
^1H NMR (400 MHz, DMSO d_6) : δ : 0.93 (s, 6H) ; 1.03 (s, 6H) ; 2.10 (d, syst.AB, 2H) ; 2.27 (d, syst.AB, 2H) ; 2.52 (m, 4H) ; 3.66 (s, 6H) ; 4.44 (s, 1H) ; 6.36 (s, 2H) ; 8.1 (s, OH, 1H).

5 ^{13}C NMR (100 MHz, DMSO d_6) : δ : 26.1 ; 28.7 ; 30.6 ; 31.7 ; 49.9 ; 55.8 ; 105.6 ; 114.4 ; 124.9 ; 134.1 ; 134.4 ; 147.4 ; 162.6 ; 196.0.

MS (ESI $^+$): 427.2 $[\text{M}+\text{H}]^+$

Example 4:

10 9-(3,4-dihydroxyphenyl)-3,6-diphenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



^1H NMR (400 MHz, CDCl_3) : δ : 2.64 (m, 4H) ; 2.83 (m, 4H) ; 3.35 (m, 1H) ; 3.46 (m, 1H) ; 4.81 (s, 1H) ; 6.38-7.04 (m, 3H) ; 7.3 (m, 10H).

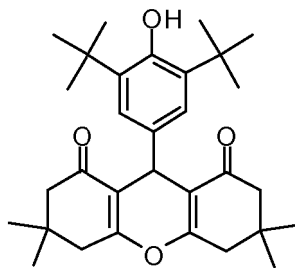
MS (APCI $^+$): 479.1 $[\text{M}+\text{H}]^+$

R_f(cyclohexane/EtOAc ; 1/1) : 0.38

Example 5:

20 9-(3,5-di-tert-butyl-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

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^1H NMR (400 MHz, CDCl_3) : δ : 0.99 (s, 6H) ; 1.10 (s, 6H) ; 1.37 (s, 18H) ; 2.20 (dd, 4H) ; 2.45 (dd, 4H) ; 4.67 (s, 1H) ; 4.98 (d, 1H) ; 7.02 (s, 2H).

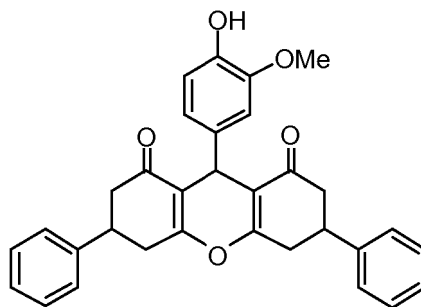
5 ^{13}C NMR (100 MHz, CDCl_3) : δ : 26.9 ; 29.4 ; 30.3 ; 31.0 ; 32.2 ; 34.1 ; 40.9 ; 50.7 ; 116.2 ; 124.8 ; 134.8 ; 134.9 ; 152.0 ; 162.0 ; 196.3.

MS (ESI+): 479.3 $[\text{M}+\text{H}]^+$

R_f (heptane/EtOAc ; 7/3) : 0.26

10 Example 6:

9-(4-hydroxy-3-methoxyphenyl)-3,6-diphenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



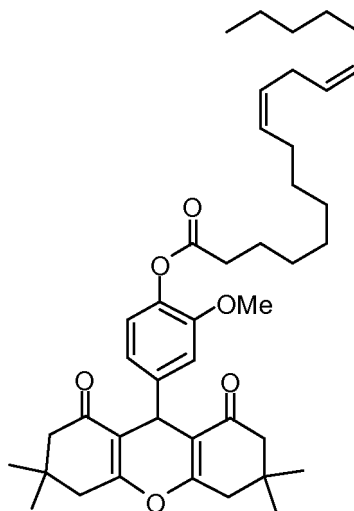
15 ^1H NMR (400 MHz, CDCl_3) : δ : 2.66 (m, 4H) ; 2.87 (m, 4H) ; 3.30 (m, 1H) ; 3.48 (m, 1H) ; 3.84 (s, 3H) ; 4.81 (s, 1H) ; 5.57 (s, 1H) ; 6.43-6.83 (m, 3H) ; 7.09-7.36 (m, 10H).

MS (ESI+): 515.0 $[\text{M}+\text{Na}]^+$

R_f (cyclohexane/EtOAc ; 1/1) : 0.51

20 Example 7:

-(9Z,12Z)-2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl octadeca-9,12-dienoate



To a solution of 0.99g of xanthenedione (example 1) (2.5mmol) in 12.5mL of anhydrous DCM under N₂ are added 417μL of triethylamine (3mmol). The mixture is cooled to 0°C by an ice bath, then 0.88mL of linoleic acid chloride are added drop by drop. After 5 minutes of stirring at 0°C, the ice bath is removed and the reaction is continued at ambient temperature overnight. The mixture is extracted with distilled water and washed with a saturated solution of NaCl before drying the organic phase with MgSO₄, which is then filtered. The solution is evaporated to dryness to obtain a yellow oil and a combiflash is carried out. A gradient of 95 : 5 to 50 : 50 in heptane/ethyl acetate is used. The pure fraction is recovered and evaporated.

The solid is dried in the oven for at least 30 minutes under 50mbar in order to obtain 1.26g of beige product with a yield of 76.5%.

¹H NMR (400 MHz, CDCl₃) : δ : 0.88 (t, 3H) ; 1.01 (s, 6H) ; 1.10 (s, 6H) ; 1.30 (m, 14H) ; 1.72 (m, 2H) ; 2.05 (m, 4H) ; 2.17 (m, 4H) ; 2.45 (s, 4H) ; 2.53 (m, 2H) ; 2.77 (t, 2H) ; 3.81 (s, 3H) ; 4.76 (s, 1H) ; 5.30 (m, 4H) ; 6.70 (dd, 1H) ; 6.74 (d, 1H) ; 7.04 (d, 1H).

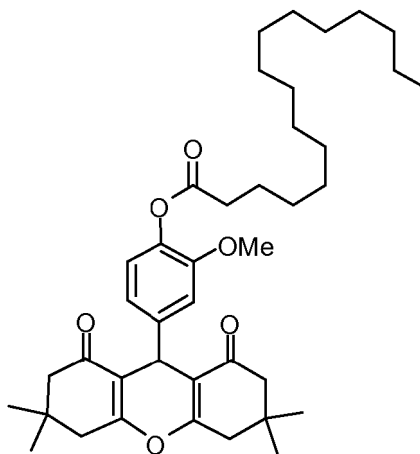
¹³C NMR (100 MHz, CDCl₃) : δ : 14.03 ; 22.51 ; 24.94 ; 25.56 ; 27.14 ; 27.35 ; 28.94 ; 29.09 ; 29.13 ; 29.17 ; 29.28 ; 29.55 ; 31.35 ; 31.45 ; 31.97 ; 32.15 ; 32.30 ; 33.96 ; 40.81 ; 50.66 ; 55.78 ; 76.68 ; 77.00 ; 77.32.

MS (ESI⁺): 659.4 [M+H]⁺

R_f (cyclohexane/EtOAc ; 2/1) : 0.52

Example 8:

2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl palmitate



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Same protocol as for example 7 from palmitoyl chloride.

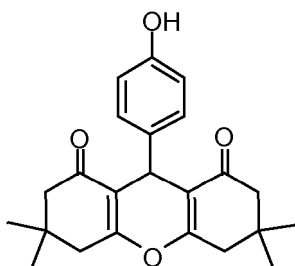
^1H NMR(400 MHz, CDCl_3) : δ : 0.89 (t, 3H) ; 1.00 (s, 6H) ; 1.10 (s, 6H) ; 1.31 (m, 22H) ; 1.39 (m, 2H) ; 1.72 (m, 4H) ; 2.22 (m, 4H) ; 2.45 (m, 4H) ; 3.81 (s, 3H) ; 4.66 (s, 1H) ; 6.69 (dd, 1H) ; 6.84 (d, 1H) ; 7.04 (d, 1H).

10 MS (ESI⁺): 652.5 $[\text{M}+\text{NH}_4]^+$
 R_f (heptane/EtOAc ; 1/1) : 0.54

15

Example 9:

9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



20

^1H NMR (400 MHz, CDCl_3) : δ : 0.99 (s, 6H) ; 1.09 (s, 6H) ; 2.20 (m, 4H) ; 2.46 (s, 4H) ; 4.66 (s, 1H) ; 5.83 (s, 1H) ; 6.54 (d, 2H) ; 7.07 (d, 2H).

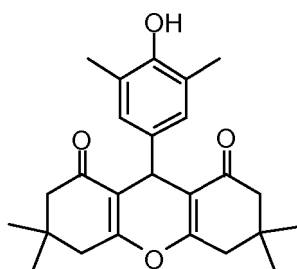
^{13}C NMR (100 MHz, CDCl_3) : δ : 27.33 ; 29.09 ; 30.89 ; 32.21 ; 40.79 ; 50.70 ; 115.22 ; 115.82 ; 129.26 ; 135.41 ; 154.74 ; 162.43 ; 197.28.

5 MS (ESI⁺): 367.2 $[\text{M}+\text{H}]^+$

R_f (cyclohexane/EtOAc ; 1/1) : 0.58

Example 10:

10 -9-(4-hydroxy-3,5-dimethylphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



^1H NMR (400 MHz, CDCl_3) : δ : 0.99 (s, 6H) ; 1.09 (s, 6H) ; 2.05 (s, 6H) ; 2.20 (s, 4H) ; 2.46 (s, 4H) ; 4.60 (s, 1H) ; 5.00 (s, 1H) ; 6.83 (s, 2H).

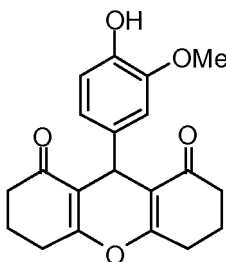
15 ^{13}C NMR (100 MHz, CDCl_3) : δ : 15.95 ; 27.31 ; 29.15 ; 30.85 ; 32.19 ; 40.82 ; 50.77 ; 115.90 ; 122.56 ; 128.43 ; 135.49 ; 150.79 ; 161.96 ; 196.72.

MS (ESI⁺): 395.2 $[\text{M}+\text{H}]^+$

R_f (cyclohexane/EtOAc ; 1/1) : 0.64

20 Example 11:

-9-(4-hydroxy-3-methoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



^1H NMR (400 MHz, CDCl_3) : δ : 2.00 (m, 4H) ; 2.33 (m, 4H) ; 2.60 (m, 4H) ; 3.87 (s, 3H) ; 4.73 (s, 1H) ; 5.49 (s, 1H) ; 6.53 (dd, 1H) ; 6.73 (d, 1H) ; 7.07 (d, 1H).

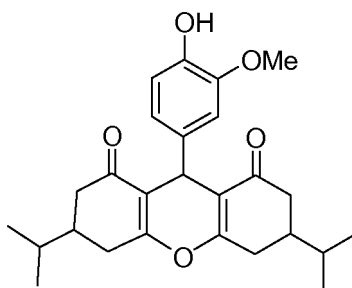
MS (ESI+): 358.2 $[\text{M}+\text{NH}_4]^+$

R_f (cyclohexane/EtOAc ; 3/7) : 0.39

5

Example 12:

-9-(4-hydroxy-3-methoxyphenyl)-3,6-diisopropyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



10

^1H NMR (400 MHz, CDCl_3) : δ : 0.92 (m, 12H) ; 1.60 (m, 2H) ; 1.70 (m, 2H) ; 2.10 (m, 2H) ; 2.30 (m, 2H) ; 2.45 (m, 2H) ; 2.65 (m, 2H) ; 3.88 (s, 3H) ; 4.70 (s, 1H) ; 5.62 (s, 1H) ; 6.51 (m, 1H) ; 6.72 (m, 1H) ; 7.07 (m, 1H).

15 MS (ESI+): 425.2 $[\text{M}+\text{H}]^+$

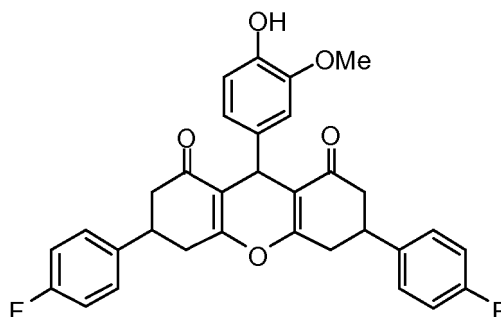
R_f (cyclohexane /EtOAc ; 1/1) : 0.65

20

Example 13:

-3,6-bis(4-fluorophenyl)-9-(4-hydroxy-3-methoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

17



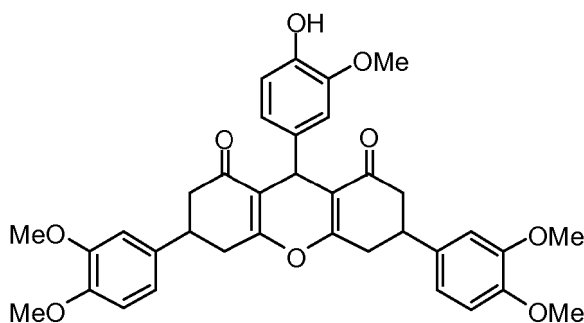
^1H NMR (400 MHz, CDCl_3) : δ : 2.30 (m, 4H) ; 2.78 (m, 4H) ; 3.00 (m, 1H) ; 3.40 (m, 1H) ; 3.54 (s, 1H) ; 3.84 (m, 3H) ; 5.50 (s, 1H) ; 6.40 (m, 1H) ; 6.68 (m, 1H) ; 6.90 (m, 1H) ; 7.08 (m, 4H) ; 7.25 (m, 4H).

MS (ESI⁺): 547.2 $[\text{M}+\text{NH}_4]^+$

R_f (cyclohexane/EtOAc ; 1/1) : 0.50

Example 14:

10 -3,6-bis(3,4-dimethoxyphenyl)-9-(4-hydroxy-3-methoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



15 ^1H NMR (400 MHz, CDCl_3) : δ : 2.65 (m, 4H) ; 2.87 (m, 4H) ; 3.31 (m, 1H) ; 3.47 (m, 1H) ; 3.85 (m, 15H) ; 4.80 (m, 1H) ; 5.53 (s, 1H) ; 6.50 (m, 1H) ; 6.70 (m, 6H) ; 7.10 (m, 1H) ; 7.30 (m, 1H).

MS (ESI⁺): 630.3 $[\text{M} + \text{NH}_4]^+$

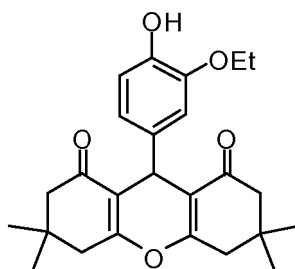
R_f (cyclohexane/EtOAc ; 3/7) : 0.42

20

Example 15:

-9-(3-ethoxy-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

18



^1H NMR (400 MHz, CDCl_3) : δ : 0.99 (s, 6H) ; 1.09 (s, 6H) ; 1.40 (t, 3H) ; 2.20 (m, 4H) ; 2.46 (s, 4H) ; 4.13 (s, 2H) ; 4.64 (s, 1H) ; 5.56 (s, 1H) ; 6.56 (dd, 1H) ; 6.73 (d, 1H) ; 6.98 (d, 1H).

^{13}C NMR (100 MHz, CDCl_3) : δ : 14.79 ; 27.21 ; 29.22 ; 31.21 ; 32.11 ; 40.76 ; 50.69 ; 64.22 ; 113.05 ; 113.78 ; 115.71 ; 119.82 ; 136.26 ; 144.02 ; 145.07 ; 162.00 ; 196.52.

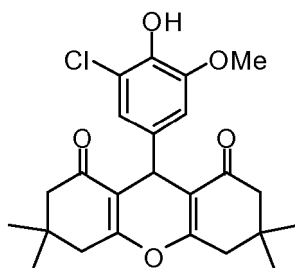
MS (ESI⁺): 411.2 $[\text{M}+\text{H}]^+$

R_f (cyclohexane/EtOAc ; 1/1) : 0.50

10

Example 16:

-9-(3-chloro-4-hydroxy-5-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



15

^1H NMR (400 MHz, CDCl_3) : δ : 1.00 (s, 6H) ; 1.10 (s, 6H) ; 2.20 (m, 4H) ; 2.47 (s, 4H) ; 3.90 (s, 3H) ; 4.64 (s, 1H) ; 5.73 (s, 1H) ; 6.61 (d, 1H) ; 6.97 (d, 1H).

^{13}C NMR (100 MHz, CDCl_3) : δ : 27.34 ; 29.18 ; 31.33 ; 32.20 ; 40.80 ; 50.71 ; 56.29 ; 111.18 ; 115.21 ; 118.82 ; 120.41 ; 136.59 ; 140.44 ; 146.72 ; 162.37 ; 196.55.

MS (ESI⁺): 431.1 $[\text{M}+\text{H}]^+$

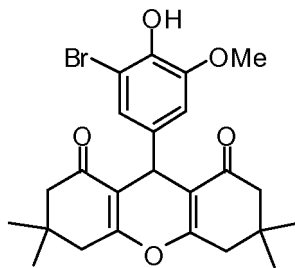
R_f (cyclohexane/EtOAc ; 1/1) : 0.48

Example 17:

-9-(3-bromo-4-hydroxy-5-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

25

19



^1H NMR (400 MHz, CDCl_3) : δ : 1.00 (s, 6H) ; 1.10 (s, 6H) ; 2.20 (m, 4H) ; 2.47 (s, 4H) ; 3.90 (s, 3H) ; 4.64 (s, 1H) ; 5.80 (s, 1H) ; 6.74 (d, 1H) ; 7.01 (d, 1H).

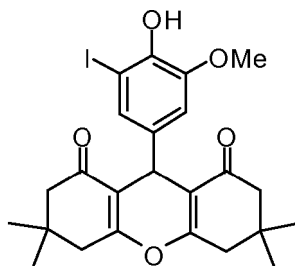
5 ^{13}C NMR (100 MHz, CDCl_3) : δ : 27.31 ; 29.17 ; 31.25 ; 32.19 ; 40.78 ; 50.69 ; 56.26 ; 107.57 ; 111.84 ; 115.19 ; 123.17 ; 137.19 ; 141.50 ; 146.50 ; 162.36 ; 196.55.

MS (ESI⁺): 475.0 $[\text{M}+\text{H}]^+$

R_f(cyclohexane/EtOAc ; 1/1) : 0.37

10 Example 18:

-9-(4-hydroxy-3-iodo-5-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



15 ^1H NMR (400 MHz, CDCl_3) : δ : 1.00 (s, 6H) ; 1.10 (s, 6H) ; 2.20 (m, 4H) ; 2.47 (s, 4H) ; 3.89 (s, 3H) ; 4.61 (s, 1H) ; 6.00 (s, 1H) ; 6.92 (d, 1H) ; 7.04 (d, 1H).

^{13}C NMR 100 MHz, CDCl_3) : δ : 27.25 ; 29.19 ; 31.03 ; 32.18 ; 40.76 ; 50.67 ; 56.15 ; 80.60 ; 112.78 ; 115.20 ; 128.93 ; 138.05 ; 144.07 ; 145.35 ; 162.30 ; 196.54.

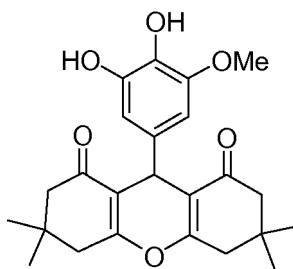
MS (ESI⁺): 523.1 $[\text{M}+\text{H}]^+$

20 R_f(cyclohexane/EtOAc ; 1/1) : 0.47

Example 19:

-9-(3,4-dihydroxy-5-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

20



^1H NMR (400 MHz, CDCl_3) : δ : 1.00 (s, 6H) ; 1.10 (s, 6H) ; 2.17 (m, 4H) ; 2.45 (s, 4H) ; 3.85 (s, 3H) ; 4.64 (s, 1H) ; 5.47 (s, 2H) ; 6.31 (d, 1H) ; 6.65 (d, 1H).

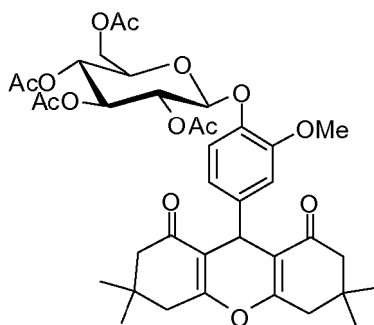
5 ^{13}C NMR (100 MHz, CDCl_3) : δ : 27.40 ; 29.06 ; 31.33 ; 32.10 ; 40.73 ; 50.66 ; 55.97 ; 104.89 ; 107.54 ; 115.55 ; 131.04 ; 135.94 ; 143.68 ; 146.35 ; 162.23 ; 196.84.

MS (ESI⁺): 413.2 $[\text{M}+\text{H}]^+$

R_f (cyclohexane/EtOAc ; 3/7) : 0.66

10 Example 20:

-(3R,4S,5S)-2-(acetoxymethyl)-6-(2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate



15 Product obtained according to the general procedure A from glucosylated vanillin, the synthesis of which is described in the literature (*Chemical and pharmaceutical bulletin*, 51(11), 1268-1272; 2003).

The product is obtained after purification on silica in the form of a white solid.

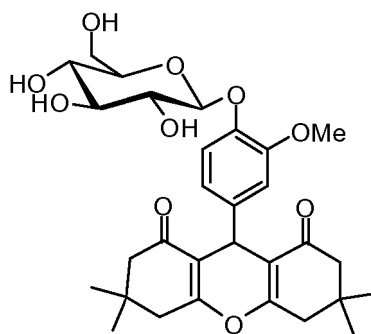
20 ^1H NMR (400 MHz, CDCl_3) : δ : 0.97 (s, 3H) ; 1.02 (s, 3H) ; 1.10 (s, 3H) ; 1.11 (s, 3H) ; 2.02 (s, 3H) ; 2.03 (s, 3H) ; 2.05 (s, 3H) ; 2.06 (s, 3H) ; 2.21 (m, 4H) ; 2.45 (m, 4H) ; 3.71 (m, 1H) ; 3.81 (s, 3H) ; 4.11 (dd, 1H) ; 4.25 (dd, 1H) ; 4.69 (s, 1H) ; 4.88 (d, 1H) ; 5.13 (dd, 1H) ; 5.24 (m, 2H) ; 6.64 (dd, 1H) ; 6.92 (d, 1H) ; 6.99 (d, 1H).

^{13}C NMR (100 MHz, CDCl_3) : δ :20.56; 20.61; 20.68; 26.85; 27.13; 27.30; 29.25; 31.47; 32.12; 32.15; 40.79; 50.67; 50.70; 55.94; 61.86; 68.40; 71.14; 71.69; 72.60; 100.69; 113.85; 115.33; 115.54; 119.74; 120.05; 140.99; 144.29; 150.09; 162.13; 162.46; 169.38; 169.39; 170.23; 170.61; 196.42; 196.64.

5 MS (APCI $^{+}$): 727.2 $[\text{M}+\text{H}]^{+}$

Example 21:

-9-(3-methoxy-4-((3S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione



10

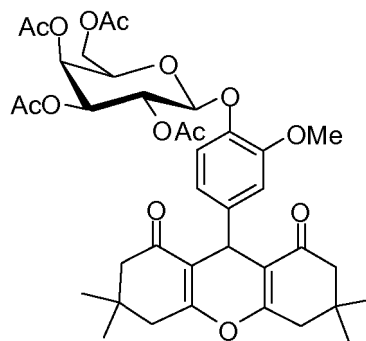
A solution of the example 20 in anhydrous methanol is treated by a solution of sodium methylate according to the procedure described in the following reference. The product is then obtained in the form of a white solid. (*European Journal of Medicinal*
 15 *Chemistry* 43 (2008) 2549-2556)

^1H NMR (300 MHz, CD_3OD) : δ : 1.00 (s, 6H) ; 1.12 (s, 6H) ; 2.17 (d, 2H) ; 2.33 (d, 2H) ; 2.58 (2d, 4H) ; 3.36 (m, 2H); 3.39 (m, 2H); 3.70 (m, 1H); 3.85 (m, 1H) ; 3.87 (s, 3H) ; 4.60 (s, 1H) ; 4.82 (d, 1H) ; 6.73 (d, 1H) ; 6.97 (s, 1H) ; 7.03 (d, 1H).

20 MS (ESI $^{+}$): 581.1 $[\text{M}+\text{Na}]^{+}$

25 Example 22:

-(3S,4S,5S,6S)-2-(acetoxymethyl)-6-(2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate



Product obtained according to the procedure described for example 20 from galactosylated vanillin, the synthesis of which is described in the literature (*European Journal of Medicinal Chemistry*, 43 (2008) 166-173)

5 The product is obtained after purification on silica in the form of a white solid.

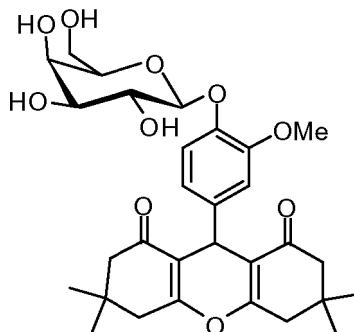
^1H NMR (400 MHz, CDCl_3) : δ : 0.97 (s, 3H) ; 1.02 (s, 3H) ; 1.10 (s, 3H) ; 1.11 (s, 3H) ; 2.00 (s, 3H) ; 2.02 (s, 3H) ; 2.07 (s, 3H) ; 2.15 (s, 3H) ; 2.21 (m, 4H) ; 2.45 (m, 4H) ; 3.81 (m, 1H) ; 3.92 (t, 1H) ; 4.12 (m, 1H) ; 4.69 (s, 1H) ; 4.83 (d, 1H) ; 5.06 (dd, 1H) ; 5.43 (m, 2H) ; 6.63 (dd, 1H) ; 6.92 (d, 1H) ; 6.99 (d, 1H)..

10 MS (APCI+): 727.4 $[\text{M}+\text{H}]^+$, 744.4 $[\text{M}+\text{NH}_4]^+$.

Example 23:

-9-(3-methoxy-4-((2S,3S,4S,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-

15 1,8(2H)-dione

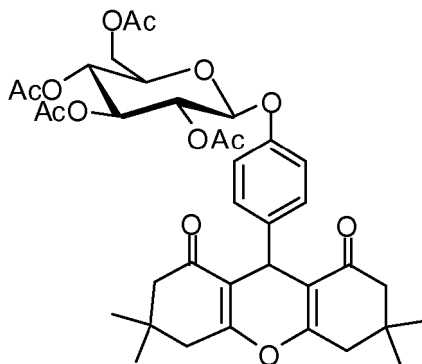


A solution of example 22 in anhydrous methanol is treated by a solution of sodium methylate according to the procedure described in the following reference. The product is then obtained in the form of a white solid. (*European Journal of Medicinal Chemistry*, 43 (2008) 2549-2556)

^1H NMR (400 MHz, CDCl_3) : δ : 0.92 (s, 6H) ; 1.15 (s, 6H) ; 2.09 (dd, 2H) ; 2.11 (dd, 2H) ; 2.54 (m, 4H) ; 3.57 (m, 3H) ; 3.68 (s, 3H) ; 4.47 (m, 2H) ; 4.62 (t, 1H) ; 4.80 (dd, 2H) ; 4.98 (d, 1H) ; 6.63 (dd, 1H) ; 6.72 (d, 1H) ; 6.91 (d, 1H).

5 Example 24:

-(3R,4S,5S,6S)-2-(acetoxymethyl)-6-(4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate



10 Product obtained according to the general procedure from glucosylated vanillin, the synthesis of which is described in the literature (*Chemical and pharmaceutical bulletin*, 51(11), 1268-1272 ; 2003).

The product is obtained after purification on silica in the form of a white solid.

15 ^1H NMR (400 MHz, CDCl_3) : δ : 0.98 (s, 6H) ; 1.10 (s, 6H) ; 2.02 (s, 3H) ; 2.03 (s, 3H) ; 2.05 (s, 3H) ; 2.06 (s, 3H) ; 2.20 (m, 4H) ; 2.45 (m, 4H) ; 3.81 (m, 1H) ; 4.13 (dd, 1H) ; 4.28 (dd, 1H) ; 4.70 (s, 1H) ; 5.01 (d, 1H) ; 5.14 (dd, 1H) ; 5.24 (m, 2H) ; 6.83 (d, 2H) ; 7.21 (d, 2H).

MS (ESI⁺): 697.3 $[\text{M}+\text{H}]^+$; 714.3 $[\text{M}+\text{NH}_4]^+$.

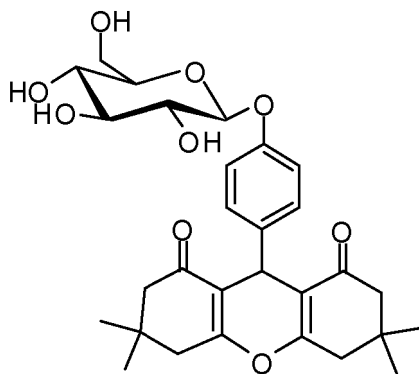
20

Example 25:

-3,3,6,6-tetramethyl-9-(4-((2S,3S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

25

24



A solution of example 24 in anhydrous methanol is treated by a solution of sodium methylate according to the procedure described in the following reference. The product is then obtained in the form of a white solid. (*European Journal of Medicinal*

5 *Chemistry*, 43 (2008) 2549-2556)

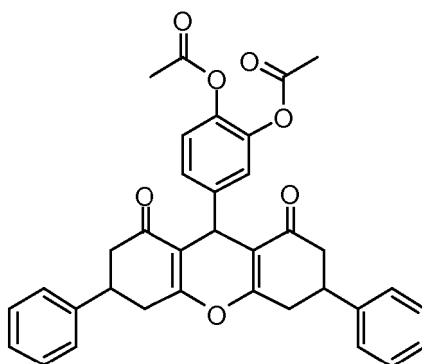
^1H NMR (300 MHz, CD_3OD): δ : 0.88 (s, 6H); 1.0 (s, 6H); 2.20 (d, 2H); 2.42 (d, 2H); 2.52 (2d, 4H); 3.20 (m, 2H); 3.28 (m, 4H); 3.57 (dd, 1H); 3.76 (d, 1H); 4.49 (s, 1H); 4.73 (d, 1H); 6.84 (d, 2H); 7.06 (d, 1H).

10 ^{13}C NMR (75 MHz, CD_3OD): δ : 27.7; 27.8; 29.8; 29.9; 32.7; 33.6; 41.8; 51.9; 62.9; 71.7; 75.3; 78.3; 78.4; 102.7; 117.0; 117.6; 130.9; 140.0; 158.0; 165.4; 199.7.

MS (ESI⁺): 529.3 $[\text{M}+\text{H}]^+$; 546.3 $[\text{M}+\text{NH}_4]^+$; 551.2 $[\text{M}+\text{Na}]^+$.

Example 26:

15 4-(1,8-dioxo-3,6-diphenyl-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)-1,2-phenylene diacetate



prepared from 3,4-diacetoxybenzaldehyde.

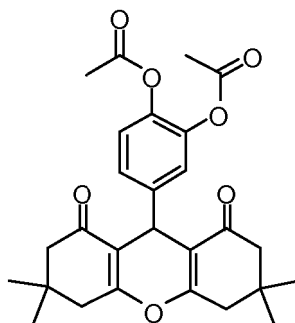
20 ^1H NMR (400 MHz, CDCl_3): δ : 2.27 (s, 6H); 2.30 (m, 4H); 2.83 (m, 4H); 3.4 (m, 1H); 3.5 (m, 1H); 4.93 (s, 1H); 7.04 (m, 3H); 7.3 (m, 10H).

MS (ESI⁺): 563.2 [M+H]⁺

R_f (cyclohexane/EtOAc ; 1/1) : 0.40

Example 27:

- 5 -4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)-1,2-phenylene diacetate



prepared from 3,4-diacetoxybenzaldehyde.

- ¹H NMR (400 MHz, CDCl₃) : δ : 0.99 (s, 6H) ; 1.09 (s, 6H) ; 1.88 (s, 3H) ; 2.22 (m, 4H)
10 ; 2.46 (s, 4H) ; 4.77 (s, 1H) ; 7.04 (dd, 1H) ; 7.20 (d, 1H) ; 7.22 (d, 1H).

¹³C NMR (100 MHz, CDCl₃) : δ : 20.62 ; 27.46 ; 29.04 ; 31.08 ; 32.17 ; 40.77 ; 50.59 ;
115.03 ; 122.62 ; 122.88 ; 126.55 ; 140.34 ; 141.61 ; 142.58 ; 162.50 ; 167.91 ; 168.16 ;
196.50.

MS (ESI⁺): 467.1 [M+H]⁺

- 15 R_f (cyclohexane/EtOAc ; 3/7) : 0.38

2) Experimental test protocol.

A) Melanin assay test in B16-F10 cells:

- 20 Principle:

This involves a test of measuring the synthesis of melanin by colorimetric assay on a murine melanoma cell line: the B16-F10 line. This test enables the depigmenting power of active ingredients to be evaluated.

- The B16-F10 cells are cultured in 96-well plates in DMEM medium,
25 supplemented with FCS (foetal calf serum), and incubated 24 hours at 37°C, 5% CO₂.
The cells are then stimulated with 0.1 μM α-MSH (to stimulate the synthesis of melanin, the stimulation observed is around 150%) and treated 72 hours with the active

ingredients to be tested. Each concentration of active ingredient is tested at least in triplicate. The total melanin followed by the intracellular melanin dissolved in the lysis buffer are then assayed by absorbance reading at 405 nm. The total proteins are assayed in the lysate and the results are expressed in mg melanin / mg proteins. The percentage of activity is calculated as follows:

$$\% \text{ activity} = \frac{\text{Normalised average of control} - \text{Normalised average of treated}}{\text{Normalised average of control}} \times 100$$

A negative value indicates an inhibition, whereas a positive value indicates an induction of the synthesis of melanin.

- General experimental conditions:

- Equipment:

- CO₂ cell incubator (Heraeus), Oven, Centrifuge (Heraeus), Laminar air flow fume hood, 96-well clear bottomed plates – Falcon, sterile cones - Treff Lab, Polylabo, Mithras LB940 (Berthold Technologies)- 154/MIPA/003

- Biological equipment:

- B16-F10 cell line between P10 and P20 (murine melanocytes) (ATCC, CRL-6475)

- Reagents

- DMEM without phenol red (GIBCOBRL, 31053-028), 200 mM Glutamax-I Supplement (GIBCOBRL, 35050-038), D-PBS (GIBCOBRL, 14190-094), Foetal calf serum (Invitrogen, 10270-098), Trypsine-EDTA (GIBCOBRL, 25300-054), NaOH (Sigma, S8045-500G), DMSO (Sigma, 471267-1L), Nle, Phe – Melanocyte Stimulating Hormone (Sigma, M-8764), Melanin (Sigma, M-0418), BCA-COPPER (SIGMA, B9643 AND C2284), BSA (SIGMA, P0914)

B) Test for the study of the antioxidant capacity by chemiluminescence (Photochem Analytik Jena)

- Principle:

This test is used to determine the antioxidant capacity of molecules. It is a method that generates free radicals by a photochemical signal. The intensity of the oxidation is 1000 times greater than those obtained under normal conditions.

The detection is performed by chemiluminescence. It enables the evaluation of
5 hydrosoluble and liposoluble antioxidant molecules or extracts.

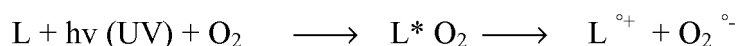
The results are expressed respectively in equivalent quantity of vitamin C or Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid). The sensitivity is of the order of the nanomole.

The antioxidant activity studied in this test represents the capacity to specifically
10 trap the superoxide anions by chemiluminescence.

The quantified results are expressed in equivalent Trolox (standard), i.e. in “μg of product for 1μg of Trolox”. This signifies that a quantity x of sample is required to obtain an activity equivalent to the activity detected for 1μg of standard. It is an antioxidant power relative to a reference, which can be determined independently of the
15 tested concentration.

- Generation of oxygenated free radicals:

The superoxide radical: $O_2^{\circ-}$ is generated by a photochemical reaction:



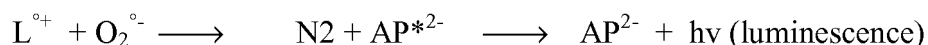
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L^* : luminol in the excited state

$L^{\circ+}$: luminol radical

- Detection of the signal:

Part of the superoxide anions is quenched by anti-oxidants. The remaining free
25 radicals are quantified by chemiluminescence.



AP^{*2-} : aminophthalate in the excited state

Name	Conditions	Photosensitising	Antioxidant
Blank	100% $O_2^{\circ-}$ generated	+	-

Standards	Standard range: From 1 to 3 nmol	+	Vitamin C or Trolox
Test	+/- $O_2^{\bullet-}$ generated	+	Molecule x to be tested

3) Experimental test results.

A) Melanin assay test in B16-F10 cells:

The results are shown in summary Table 1 below.

- Interpretation of results:

- 5 IC50 represents the concentration for which 50% melanin synthesis inhibition is observed.

It may be observed that the majority of compounds tested have good melanin synthesis inhibition capacity. The compounds according to the invention have good depigmenting activity.

- 10 B) Test for the study of the antioxidant capacity by chemiluminiscence (Photochem Analytik Jena)

The results are also given in summary Table 1 below.

The majority of the compounds have good antioxidant activity. The scale for interpreting the results is the following:

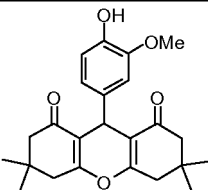
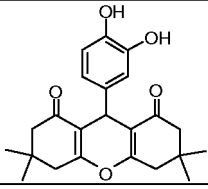
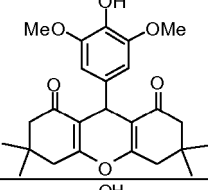
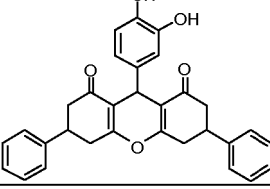
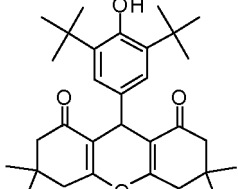
Products	μg sample for 1 μg of Trolox	Activity
Vitamin C	0.1 to 3.0	Very good
BHT	3.01 to 50	Good
Cysteine	50.1 to 1000	Medium
Albumin	> 1000	Low
Lipoic acid	Negative	Nil

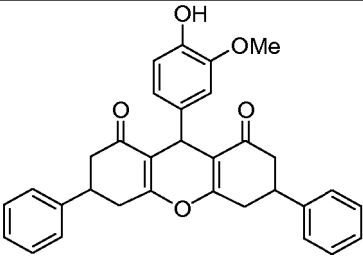
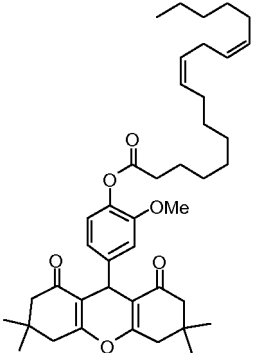
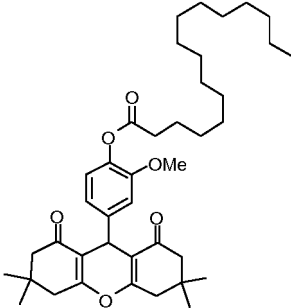
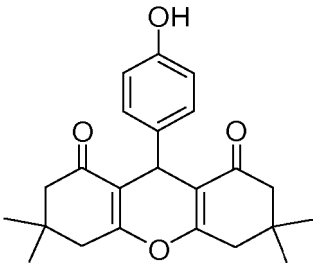
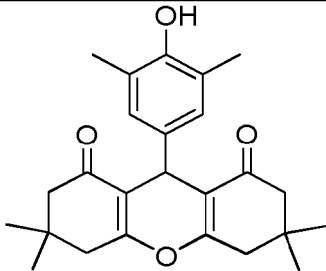
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Most of the compounds have results comparable to vitamin C. All of the compounds show results below 1000 μg of Trolox (74 μg being the lowest result obtained with example 30); thus, they all have worthwhile anti-oxidant activity.

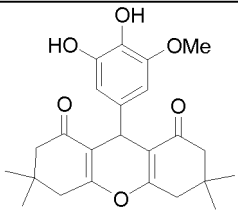
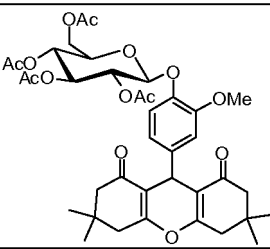
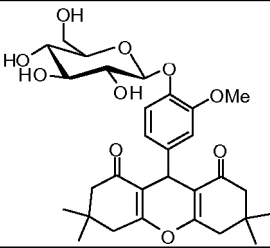
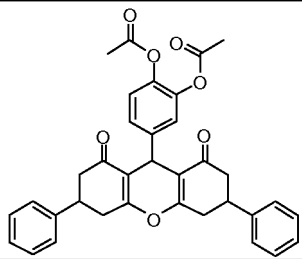
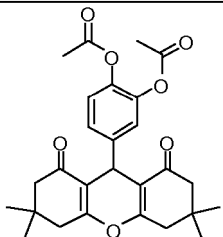
This antioxidant activity of the compounds that are the object of the present invention, objectified by the trapping of free radicals, has also made it possible to propose their use in the treatment and/or the prevention of inflammations of the skin (“Free radicals in inflammation: second messengers and mediators of tissue destruction”, V. R. Winrow et al. <http://bmb.oxfordjournals.org/cgi/content/abstract/49/3/506>).

Table 1: Results of the experimental tests

Example	Structure	Results activity B _{16-F10} IC ₅₀	µg of sample for 1 µg of Trolox
Example 1		50 µM	2.1
Example 2		20 µM	0.03
Example 3		45 µM	0.72
Example 4		7 µM	0.001
Example 5		2 µM	50
Example 6		6 µM	2.46

			
Example 7		-	19.7
Example 8		-	-
Example 9		37 μ M	7.39
Example 10		-	4.10

Example 11		-	1.07
Example 12		16 μ M	1.64
Example 13		-	2.52
Example 14		-	2.27
Example 15		19 μ M	1.79
Example 16		-31% to 20 μ M	5.20
Example 17		-	5.18
Example 18		-	4.66

Example 19		-22% to 10 μ M	0.02
Example 20		-	-
Example 21		69 μ M	-
Example 26		-28% to 20 μ M	-
Example 27		-	0.096

C) Test of reconstructed epidermises for the study of depigmenting activity

- 5 The compounds of examples 8 and 21 were formulated at the concentration of 0.5% in a Simplex formula according to the example of composition A. Melanoderm-B (Black) or Melanoderm A (Asian) (MatTek, USA) reconstructed epidermis models were used. The reference compound chosen is kojic acid titrated to 2% in aqueous solution. The culture medium is changed every day. The products are applied by topical mode on
- 10 the epidermis every two days. For the application, the epidermises are rinsed with PBS and the product to be tested is then applied.

A preliminary toxicity study made it possible to determine that the dose to apply for each treatment is 25 μ L.

The morphology and the quantity of melanocytes in the tissue are not modified by the application of the products.

- 5 The tissues were observed on D3, D7, D10, D14 (Melanoderm B) or D6, D10, D14 and D21 (Melanoderm A) by 3 independent experts.

Simplex Composition A formula:

Code	Nom commercial	Quantité g / 100 g
1	Eau purifiée	65,55
2	Finsolv TN	10
3	Myritol 318	10
4	Paraffine liquide 352	5
5	Arlacel 165	5
6	Propylène glycol	3
7	Sépiplus 400	1,25
8	Actif	0
9	EDTA 2 Na	0,2

10

Code	Trade name	Quantity g/100 g
1	Purified water	65.55
2	Finsolv TN	10
3	Myritol 318	10
4	Liquid paraffin 352	5
5	Arlacel 165	5
6	Propylene glycol	3
7	Sepiplus 400	1.25
8	Active ingredient	0
9	2 Na EDTA	0.2

15

- 20 The results observed on the Melanoderm B model are given in Table 2 below:

25

Table 2: Epidermis rating (3 independent observers) vs. negative control (water)

	Formula	Observations
--	---------	--------------

		D3	D7	D10	D14
Negative control (water)					
2% kojic acid	2% aqueous sol.	C (2/3)	C (3/3)	C (2/3)	C (2/3)
Simplex control formula		C (1/3)	C (2/3)	F (1/3)	F (1/3)
Example 8	0.5% Simplex	C (3/3)	C (3/3)	C (3/3)	C (3/3)
Example 21	0.5% Simplex	C (2/3)	C (3/3)	C (3/3)	C (2/3)

Dx: day of dosage or observation

C: epidermis colour lighter (depigmented) vs. absolute control

F: epidermis colour darker (propigmented) vs. absolute control

I: epidermis colour identical vs. absolute control

5 (X/X): number of observations for the effect observed

The coloration of the epidermis is compared to that of the negative control (water). The Simplex control formula does not show any macroscopic depigmenting effect (except on D7): this formula thus does not have any specific effect with respect to the negative control. On the other hand, the formulas containing the compounds according to example 8 or example 21 show a macroscopic depigmenting effect on D3, D7, D10 and D14 on the Melanoderm B (Black) epidermis model. These results indeed show a specific depigmenting effect for formulated examples 8 and 21.

The results observed on the Melanoderm A model are recorded in table 3 below:

15 Table 3: Epidermis rating (3 independent observers) vs. Simplex control formula

	Formula/Vehicle	Observations			
		D6	D10	D14	D21
Example 8	0.5% Simplex	C (3/3)	C (3/3)	C (2/3)	C(3/3)
Kojic acid	2% aqueous sol.	C (3/3)	C (3/3)	C (3/3)	C(3/3)

Dx: day of the dosage or the observation

C: epidermis colour lighter (depigmented) vs. corresponding control

F: epidermis colour darker (propigmented) vs. corresponding control

I: epidermis colour identical vs. corresponding control

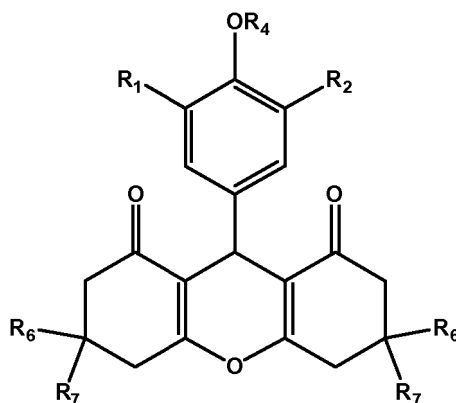
20 (X/X): number of observations for the effect observed

The formula containing example 8 was also tested in a Melanoderm-A (Asian) model. The coloration of the epidermis is compared to that of the simplex control

formula. The formula containing example 8 shows a macroscopic depigmenting effect on D6, D10, D14, D21. The melanin assay carried out according to the technique described by S. Bessous-Touya (J. Invest. Dermatol. 111: 1103-1109 (1998)), shows a reduction of 4.1 μg of melanin with respect to the epidermises treated by the Simplex control formula.

4) Compositions

The present invention also relates to a pharmaceutical or cosmetic composition, characterised in that it comprises as active ingredient at least one compound of generic formula (I'):



in which the radicals R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 have identical significations to those given previously, but in which R_4 may represent in addition a hydrogen atom or an acetyl radical in association with a pharmaceutically or cosmetically acceptable excipient.

The pharmaceutical or cosmetic composition according to the invention is characterised in that the quantity of compound of generic formula (I') varies between 0.01% and 10% by weight and preferably from 0.1% to 5% by weight with respect to the total weight of the composition.

The pharmaceutical or cosmetic composition comprising a compound of generic formula (I') according to the invention is characterised in that it is intended for the depigmentation of the skin and/or head hair and/or body hair, the treatment and/or the prevention of ageing of the skin or the treatment and/or the prevention of the inflammation of the skin.

The composition according to the invention may moreover comprise conventional cosmetic adjuvants especially chosen from fatty phases, organic solvents,

thickeners, softeners, opacifiers, stabilisers, emollients, anti-foaming agents, hydrating agents, fragrances, humectants, gelling agents, preservatives such as parabenes, polymers, fillers, sequestering agents, bactericides, odour absorbents, alkalising or acidifying agents, surfactants, pH adjusters, anti-free radicals, antioxidants, vitamins E and C, α -hydroxyacids, or thermal water such as Avène thermal water or any other ingredient normally used in cosmetics, in particular for the production of compositions of this type.

The composition according to the invention may moreover comprise a fatty phase. The fatty phase may be constituted of an oil or a wax or mixtures thereof, and also comprise fatty acids, fatty alcohols, and fatty acid esters. The oils may be chosen from animal, plant, mineral or synthetic oils and especially among vaseline oil, paraffin oil, silicone oils, volatile or not such as dimethicone; isoparaffins, polyolefins, fluorinated and perfluorinated oils. Similarly, the waxes may be chosen from animal, fossil, plant or synthetic waxes such as bee waxes, candelilla waxes, canauba waxes, karite butter, petroleum wax (or microcrystalline wax), paraffin, and mixtures thereof.

The composition according to the invention may moreover comprise a polyol miscible in water at ambient temperature (around 25°C), especially chosen from polyols having particularly from 2 to 20 carbon atoms, preferably having from 2 to 10 carbon atoms, and preferentially having from 2 to 6 carbon atoms, such as glycerine; derivatives of glycol such as propylene glycol, butylene glycol, pentylene glycol, hexylene glycol, dipropylene glycol, diethylene glycol; glycol ethers such as C₁-C₄ alkyl ethers of mono-, di- or tri-propylene glycol, C₁-C₄ alkyl ethers of mono-, di- or tri-ethylene glycol; and mixtures thereof.

The composition according to the invention may also comprise thickening agents or rheology modification agents, such as for example non ionic ethoxylated hydrophobically modified urethanes, polycarboxylic acid thickeners such as copolymers of acrylates/steareth-20 methacrylate, carbomers, acrylate copolymers and mixtures thereof.

The composition according to the invention may also comprise acids and bases making it possible to adjust the pH range of said composition. The bases may be inorganic (sodium hydroxide, potassium hydroxide, aqueous ammonia, etc.) or organic

such as mono-, di- or tri-ethanolamine, aminomethylpropanediol, N-methyl-glucamine, basic amino acids such as arginine and lysine, and mixtures thereof.

The composition according to the invention may also comprise skin conditioning agents. Examples of skin conditioning agents include, but are not limited to, emulsifying agents, anionic, cationic and non ionic emulsifiers such as sodium lauryl sulphate, sodium dioctyl sulphosuccinate, sodium stearate, sorbitan ester; ethoxylated fatty acids; ethoxylated fatty alcohols such as trideceth-9 and PEG-5 ethylhexanoate; stearic acid; any other emulsifier and conditioning agent known to those skilled in the art; and mixtures thereof.

The composition according to the invention may moreover contain other active ingredients leading to a complementary effect.

The composition according to the invention may be in any form appropriate for a topical application, particularly on the skin and/ or the head hair. In particular, they can be in the form of emulsions obtained by the dispersion of an oily phase in an aqueous phase, for example an oil-in-water or water-in-oil or multiple emulsion, or in the form of a gel, or in the form of an injectable filler, or a liquid, paste or solid anhydrous product, or in the form of a dispersion in the presence of spherules. The composition according to the invention may also be less fluid and be in the form of a white or coloured cream, an ointment, a milk, a lotion, a serum, a paste, a mask, a powder, a solid stick, or, if appropriate, an aerosol, a foam or a spray.

Example of composition:

Ingredients (trade names)	INCI designation	Percentage by weight	Function
I. Purified water	Water	QS 100%	
Hydrolite 5	Pentylene Glycol	3	Humectant, Preservative
EDTA, 2Na	Disodium EDTA	0.1	Complexing agent
Microcare PM4	Phenoxyethanol-Parabene	0.8	Preservatives

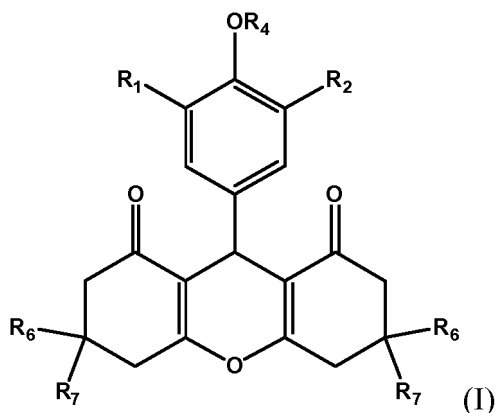
PCL Hydrosoluble	Trideceth-9 & PEG-5 Ethylhexanoate	1.5	Aqueous emollient
II. Pemulen TR-1	Acrylates/C10-30 Alkyl Crosspolymer	0.5	Gelling agent, stabilising agent
III. Stearine TP	Stearic acid	2	Emulsifier, consistency factor
Liquid PCL	Cetearylethylhexanoate & Isopropylmyristate	3	Emollient
DC200	Dimethicone	0.3	Emollient
Myritol 318	Capric or caprylic triglycerides	3	Emollient
Primol 352	Liquid paraffin	2	Emollient
IV. Depigmenting active ingredient: Compound of generic formula (I')			Active ingredient
V. Sodium hydroxide	NaOH	0.08	pH adjuster

In such a composition, the percentage of active ingredient can vary between 0.01% and 10% by weight and preferably from 0.1% to 5% by weight with respect to the total weight of the composition.

Claims

1. Compound of generic formula (I):

5



in which:

10 R_1 and R_2 represent simultaneously or independently: OH, a hydrogen atom, a C_1 - C_6 alkyl radical, a C_1 - C_6 alkoxy radical, a halogen, or $OCOR_3$;

R_3 represents: a C_1 - C_{24} alkyl radical, a C_{12} - C_{24} alkenyl radical comprising at least one unsaturation, advantageously from 1 to 6 and preferably from 1 to 4;

R_4 represents: COR_5 , a glucide substituted or not by one or more acetyl radical(s);

15 R_5 represents: a C_{10} - C_{24} alkyl radical, or a C_{12} - C_{24} alkenyl radical comprising at least one unsaturation, advantageously from 1 to 6 and preferably from 1 to 4;

R_6 and R_7 represent:

- simultaneously a hydrogen atom or a methyl radical,

or

20 - when R_6 represents a hydrogen atom, R_7 represents a C_1 - C_6 alkyl radical or a phenyl substituted or not by one or more C_1 - C_3 alkoxy radical(s) or one or more halogen(s)

or

- R_6 and R_7 are bonded to each other and form a C_3 - C_6 cycloalkyl,

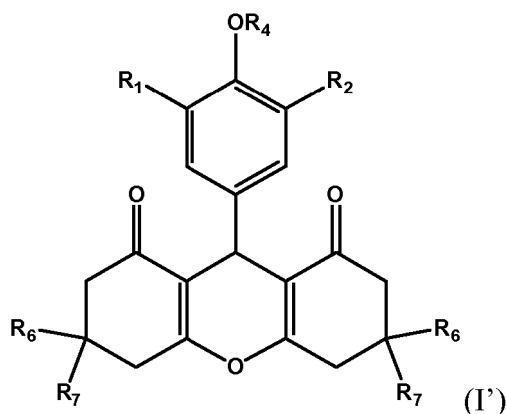
and pharmaceutically or cosmetically acceptable salts.

25 2. Compound of generic formula (I) according to claim 1, characterised in that R_1 and R_2 represent simultaneously or independently a hydrogen atom or a C_1 - C_6 alkoxy radical.

3. Compound of generic formula (I) according to one of claims 1 to 2, characterised in that R₄ represents COR₅.
- 5 4. Compound of generic formula (I) according to one of claims 1 to 3, characterised in that R₅ represents a C₁₄-C₁₈ alkyl radical or a C₁₄-C₁₈ alkenyl radical comprising from 1 to 3 unsaturations.
5. Compound of generic formula (I) according to one of claims 1 to 3, characterised in
10 that R₄ represents a pyranose radical, which may be partially or totally acetylated.
6. Compound of generic formula (I) according to one of claims 1 to 5, characterised in that R₆ and R₇ represent simultaneously a methyl radical.
- 15 7. Compound of generic formula (I) according to one of claims 1 to 6, characterised in that it is chosen from one of the following compounds:
 - 2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl palmitate
 - (9Z,12Z)-2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenyl octadeca-9,12-dienoate
 - 20 -(3R,4S,5S)-2-(acetoxymethyl)-6-(2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate
 - 9-(3-methoxy-4-((3S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione
 - 25 -(3S,4S,5S,6S)-2-(acetoxymethyl)-6-(2-methoxy-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate
 - 9-(3-methoxy-4-((2S,3S,4S,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione
 - 30

5 -(3R,4S,5S,6S)-2-(acetoxymethyl)-6-(4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate
 -3,3,6,6-tetramethyl-9-(4-((2S,3S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione.

8. Compound of generic formula (I'):



10

in which the radicals R₁, R₂, R₃, R₄, R₅, R₆ and R₇ have identical significations to those given in claims 1 to 6, but in which R₄ may in addition represent a hydrogen atom or an acetylated radical, and cosmetically or pharmaceutically acceptable salts, for its use as medicine or as cosmetic active ingredient.

15

9. Compound of generic formula (I') according to claim 8, characterised in that R₄ represents a hydrogen atom for its use as medicine or as cosmetic active ingredient.

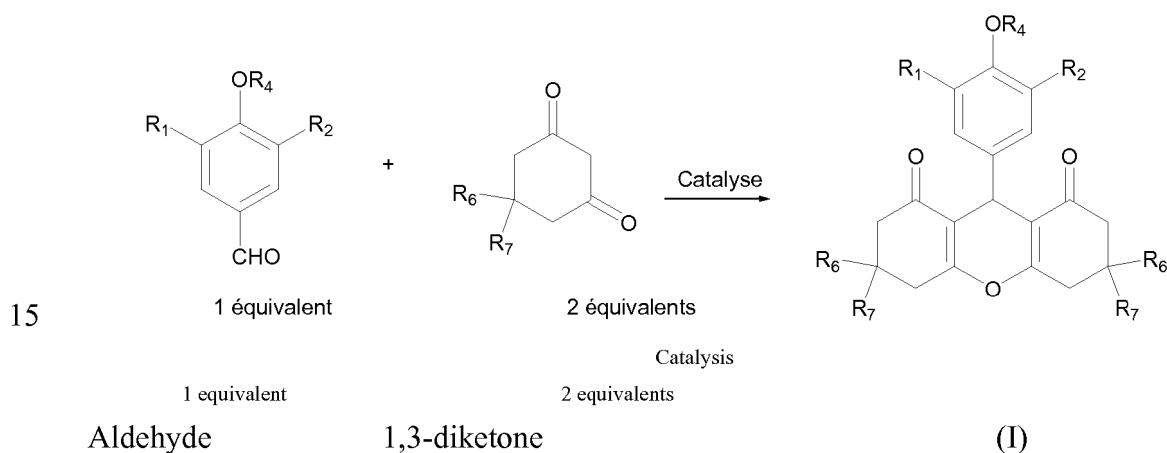
20 10. Compound of generic formula (I') according to one of claims 8 or 9 for its use in the depigmentation of the skin and/or head hair and/or body hair, in the treatment and/or the prevention of the ageing of the skin or in the treatment and/or the prevention of the inflammation of the skin.

25 11. Pharmaceutical or cosmetic composition, characterised in that it comprises as active ingredient at least one compound of generic formula (I') as defined according to claims 8 to 9 in association with a pharmaceutically or cosmetically acceptable excipient.

12. Pharmaceutical or cosmetic composition according to claim 11, characterised in that the quantity of compound of formula (I') varies between 0.01% and 10% by weight and preferably from 0.1% to 5% by weight with respect to the total weight of the composition.

13. Pharmaceutical or cosmetic composition according to one of claims 11 or 12, for its use in the depigmentation of the skin and/or head hair and/or body hair, in the treatment and/or in the prevention of the ageing of the skin or in the treatment and/or in the prevention of the inflammation of the skin.

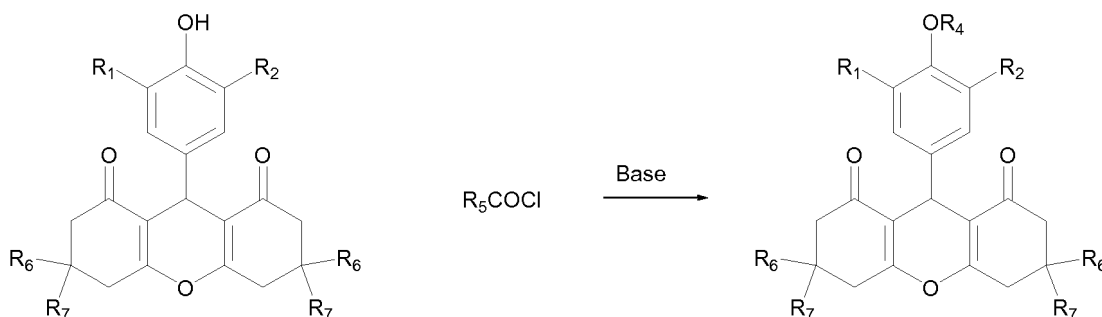
14. Method for synthesising compounds of generic formula (I) according to one of claims 1 to 7, characterised in that two molecules of 1,3-diketone are made to react with an aldehyde in the presence of an acid or basic catalysis:



20 with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 having the same significations as in claims 1 to 6.

15. Method for synthesising compounds of generic formula (I) according to one of claims 1 to 4 and 6, characterised in that a phenol is made to react with a $R_5\text{COCl}$ activated carboxylic acid in the presence of a base:

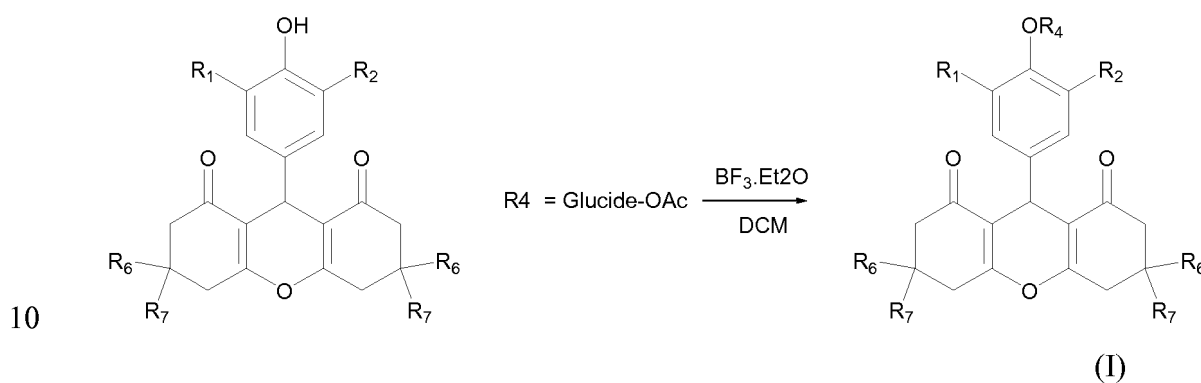
25



with R_1 , R_2 , R_3 , R_5 , R_6 and R_7 having the same significations as in claims 1 to 6 and R_4 represents COR_5 .

5

16. Method for synthesising compounds of generic formula (I) according to one of claims 1 to 2 and 5 to 6, characterised in that a phenol is made to react with a glucide radical substituted by one or more acetyl radical(s) in the presence of a Lewis acid (BF_3 , Et_2O):



10

with R_1 , R_2 , R_3 , R_5 , R_6 and R_7 having the same significations as in claims 1 to 6, and R_4 represents a glucide radical substituted by one or more acetyl radical(s), which may if appropriate be followed by a saponification step.