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New Multifunctional Surfactants from Natural Phenolic Acids

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ABSTRACT: Several new multifunctional molecules derived from natural sources such as amino acids and hydroxycinnamic acids were synthesized. They exhibit various activities such as emulsifying, UV-protecting, and radical scavenging, thereby conforming to the latest requirements for cosmetic ingredients. The synthesis comprises only a few steps: (i) the amino acid, the acid groups of which are protected by esterification, is coupled with ferulic or caffeic acid; (ii) the *p*-hydroxyl group of the cinnamic derivative reacts with dodecyl bromide in the presence of potassium carbonate (the resulting compounds are highly lipophilic and tested as water/oil (W/O) emulsifiers); (iii) these molecules, by deprotonating the acid groups of the amino acids, with successive salification, are more hydrophilic, with stronger O/W emulsifying properties. The new multifunctional surfactants might prove useful for the treatment of multiple skin conditions, including loss of cellular antioxidants, damage from free radicals, damage from UV, and others.

KEYWORDS: *surfactants, hydroxycinnamic acids, amino acids, radical-scavenging activity, UV-filtering activity*

INTRODUCTION

In the past few years multifunctionality has attracted the interest of formulators, with the aim of obtaining products that offer a range of activities. This can be achieved by introducing two or more active ingredients, which are even more effective if they have synergism of action. Research has also pursued another strategy, based on the creation of new single molecules comprising several functions, reducing the risk of incompatibility between ingredients.

Current multifunctional ingredients and/or products including a natural extract from *Curcuma longa* (turmeric) achieve this goal, with antioxidant, skin-lightening, and UV ray protecting properties.[1] ALGUARD is a purified natural polysaccharide hydrogel extract from a red microalga (*Porphyridium* sp.) that shields the skin against irritants and oxidants and also has anti-inflammatory and immune-modulating properties.[2]

Other natural molecules for which new applications have been found include erythritol, a natural sugar alcohol used as a sweetening agent with cariostatic action.[3] New molecules with multifunctional activity have also been synthesized, such as potassium azeloyl diglycinate,[4] which has skin-lightening and sebum-normalizing properties, or Diterol AL40, a cosurfactant with deodorant, emollient, and skin-restructuring properties,[5] or perfluoropolyether phosphates (PFPE), film-forming agents with antimicrobial action that foster a good rate of skin renewal after treatment with high-acid gels and hydroalcoholic solutions.[6−8]

Phenolic compounds are widespread in the plant kingdom. These secondary plant metabolites are commonly divided into five major groups, four flavonoids, namely, the anthocyanidins, the flavonols/flavones, the flavanones, and the flavan-3-ols, and their oligomers and polymers, the proanthocyanidins. The fifth group comprises hydroxycinnamic acids, caffeic and ferulic acids.[9]

Ferulic acid is the common name for 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid, also known as 4-hydroxymethoxycinnamic acid. It is found in the seeds of various plants such as rice, wheat, and oats and in fruits and vegetables such as artichokes, pineapples, and tomatoes. Its biological properties and above all its antioxidant activity have been widely demonstrated. It is mainly used as a photoprotecting agent in sunscreens on account of its protective action against skin damage caused by UV radiation.[10,11] Ferulic acid has a wide range of therapeutic properties: it is anti-inflammatory, antiatherogenic, antidiabetic, antiaging, neuroprotective, radioprotective, and hepatoprotective. Many of these activities can be attributed to its antioxidant capacity because of its phenolic nucleus and extended side-chain conjugation. It readily forms a resonance-stabilized phenoxyl radical, which explains its potent antioxidant potential.[12]

Caffeic acid, 3,4-dihydroxycinnamic acid, and its analogues are also found widely in the plant kingdom, in coffee seeds, olives, propoli, fruits, and vegetables; it is the predominant phenolic acid in sunflower seeds. Caffeic acid and its derivatives are known for their antibacterial, antiviral, anti-inflammatory, antiatherosclerotic, antioxidant, antiproliferative, immunostimulatory, and neuroprotective actions.[13] These properties are associated with antioxidant action that displays itself through various mechanisms: free radical scavenging, chelation of metal ions, and inhibition of specific enzymes that induce free radicals and lipoperoxide formation.[13] The structural feature responsible for the antioxidant and free radical-scavenging activities is the *o*-dihydroxyl function in the catechol ring: this moiety boosts the antioxidant activity because it further stabilizes the phenolic radical. This explains why caffeic acid has greater antioxidant activity than ferulic acid.[13] Caffeic acid is also a potential protective agent against photo-oxidative skin damage.[11]

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We focused on surfactants based on natural substances, aiming to create molecules with other functions besides emulsifying and/or detergent activity. We chose surfactants from among the *N*-acyl amino acids, specifically *N*-acyl glycinates and *N*-acyl glutamates. In these molecules the hydrophilic and lipophilic moieties are respectively the amino acid and the alkyl chain. By playing on the chemical features of the alkyl chain, it is possible to influence the properties of the various molecules.

The *N*-acyl amino acids and their salts have been widely studied and boast a variety of useful properties that make them key surfactants in numerous applications. Raw materials for synthesis are easily accessible, and synthesis gives high yields. Substantivity toward keratin, foam properties at neutral pH combined with biological compatibility, and degradability open up a broad field of applications. Acid derivatives can be used as water/oil (W/O) emulsifiers, wetting agents, and additives in hydrophobic systems, and the salts are effective detergents and solubilizers in aqueous systems.[14] The hydrophobic chain of these surfactants often comprises fatty acids such as lauric, myristic, palmitic, stearic, and oleic. We "functionalized" our molecules by introducing caffeic or ferulic acid between the amino acid and the alkyl chain moieties.

Several amides synthesized by coupling hydroxycinnamic acids with amino acids have been described, such as *N*-feruloyl-glycine,[15−22] *N*-caffeoyl-glycine,[19,23,24] and *N*-feruloyl-glutamate,[22] but none shows surfactant activity. The aim of the present study was to synthesize new multifunctional molecules of natural origin to be used in cosmetics. These were obtained by combining substances from natural sources, such as amino acids, and phenolic derivatives such as ferulic and caffeic acids. The choice of amino acids for obtaining surfactants was based on the many examples found in the literature and on a patent by Ajinomoto,[25] which reports the synthesis of glycine and alanine derivatives with long alkyl chains. Thus, we have synthesized several surfactants with W/O and O/W emulsifying properties as well as UV-filtering and antioxidant/radical-scavenging activity.

MATERIALS AND METHODS

Chemicals. Ferulic acid was purchased from Tsuno Rice Fine Chemicals Co. Caffeic acid, glycine ethyl ester hydrochloride, glutamic acid methyl ester hydrochloride, and all other solvents and reagents were purchased from Sigma-Aldrich. Compounds synthesized were analyzed and purified with TLC ALUGRAMSIL G/UV_{254} 40 × 80 mm, thickness = 0.25 mm, silica gel layer with fluorescent indicator (Macherey-Nagel GmbH, KG), preparative TLC DC-Fertigplatten Durasil-25 UV_{254} 20 × 20 cm, thickness = 2 mm, silica gel layer with fluorescent indicator (Macherey-Nagel), silica gel 60 0.063 × 0.2 mm/70−230 mesh ASTM for column chromatography (Macherey-Nagel).

To prepare emulsions we used Lanette O (cetearyl alcohol) (Henkel); Dragoxat EH (ethylhexyl ethylhexanoate) (Dragoco Gerberding GmbH); Syntesqual (polyisoprene) (Vevy Europe Spa Industria Chimica); sweet almond oil (*Prunus amygdalus* var. *dulcis* oil) [B&T]; DC 200 fluid (dimethicone) (Dow Corning); water (aqua); disodium EDTA (BASF); Kathon CG (methylchloroisothiazolinone, methylisothiazolinone) (Rohm&Haas); glycerin (Carlo Erba); Cutina GMS (glyceryl stearate) (Cognis); Cutina CP (cetyl palmitate) (Henkel); stearin (stearic acid) (Farmasystem); triethanolamine (BASF); cera bellina (polyglyceryl-3 beeswax) (Jan Dekker International); soft paraffin (petrolatum) (Galeno); mineral oil (paraffinum liquidum) (Farmasystem); and magnesium sulfate (Sigma-Aldrich). 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and ethyl alcohol were purchased from Sigma-Aldrich to test radical-scavenging activity.

Apparatus. UV−vis spectra were recorded on a Varian Cary 1E ver. 3.03 spectrophotometer, connected to a PC with Varian Cary 13 software, version 3.03. ^{1}H NMR data were acquired at room temperature on a Bruker AC-200 and a Bruker Avance operating at 200 and 400 MHz, respectively; chemical shifts (δ) are expressed in parts per million with reference to tetramethylsilane (TMS) used as internal standard. A Silverson SL mixer, a Kirk 510 stirring paddle, a Brookfield DV-II rotational viscometer, and an Orma pH-meter were used.

Synthesis. *General Procedure for the Synthesis of Compounds **3**−**5**.* The acid (10 g) and the amino acid in a 1:1 molar ratio were suspended in 250 mL of dimethylformamide (DMF) in a 500 mL round flask; triethylamine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) were added to this solution in a 1:4 molar ratio in relation to previous reagents, with a catalytic amount of dimethylaminopyridine (DMAP). The mixture was magnetically stirred under reflux for 4 h. The solvent was evaporated and the reaction product dissolved in the smallest volume of dichloromethane and then sequentially washed with 1 M HCl (100 mL), distilled water (100 mL), a saturated solution of Na_2CO_3 (100 mL), and a saturated solution of NaCl (100 mL). The organic extracts were dried on Na_2SO_4 and evaporated under vacuum. The raw products were purified by gradient column chromatography, starting with petroleum ether and gradually increasing the polarity with ethyl acetate (from 10 to 100%).

*(E)-Ethyl-2-(3-(4-hydroxy-3-methoxyphenyl)acrylamido)acetate (**3**):* yield, 54%; ^{1}H NMR, δ 1.25 (t, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.15 (d, 2H, CH_2), 4.22 (q, 2H, OCH_2), 5.80 (s, 1H, OH), 6.10 (bt, 1H, NH), 6.35 (d, 1H, =CH—C=O), 6.90 (d, 1H, CH(Ar)), 7.00 (bd, 1H, CH(Ar)), 7.08 (bd, 1H, CH(Ar)), 7.55 (d, 1H, Ar—CH=).

*(E)-Dimethyl-2-(3-(4-hydroxy-3-methoxyphenyl)acrylamido)-pentanedioate (**4**):* yield, 75%; ^{1}H NMR, δ 1.98 (m, 1H, CH—$\underline{CH_2}$−), 2.20 (m, 1H, CH—$\underline{CH_2}$−), 2.35 (m, 2H, −CH_2—CO−), 3.57 (s, 3H, $COOCH_3$), 3.67 (s, 3H, $COOCH_3$), 3.83 (s, 3H, OCH_3), 4.69 (m, 1H, −CH−), 6.05 (bp, 1H, OH), 6.20 (d, 1H, =CH—CO−), 6.38 (bd, 1H, NH), 6.8 (d, 1H, CH(Ar)), 6.9 (s, 1H, CH(Ar)), 6.95 (d, 1H, CH(Ar)), 7.45 (d, 1H, Ar—CH=).

*(E)-Ethyl-2(3-(3,4-dihydroxyphenyl)acrylamido)acetate (**5**):* yield, 32%; ^{1}H NMR, δ 1.05 (t, 3H, CH_3), 3.6 (s, 2H, CH_2—CO), 4.2 (q, 2H, O—CH_2), 6.4 (d, 1H, CH—CO), 6.85−7.10 (m, 3H, (Ar)), 7.55 (d, 1H, Ar—CH=).

*General Procedure for the Synthesis of Compounds **7**−**9**.* The amide (1 g) and the dodecyl bromide in a 1:1 molar ratio were added to a suspension of anhydrous K_2CO_3 (2:1 molar ratio with respect to the amide) in anhydrous acetone (50 mL) in a 100 mL round flask. A catalytic amount of KI was added to boost the reaction rate. The reaction mixture was magnetically stirred, under reflux, in an oil bath at 80 °C for nearly 24 h. The solution was filtered and the solvent evaporated under vacuum. The residue was mixed with distilled water (50 mL) and extracted with chloroform (3 × 50 mL). The organic solution was dried on Na_2SO_4 and the solvent eliminated by evaporation under vacuum. The raw products were purified by gradient column chromatography following the procedure previously described. The synthesis of compound **8** gave the formation of byproduct **10**.

*(E)-Ethyl-2-(3-(4-dodecyloxy-3-methoxyphenyl)acrylamido)-acetate (**7**):* yield, 53%; ^{1}H NMR, δ 0.85 (t, 6H, 2 × CH_3), 1.25 (bp, 18H, 9 × CH_2), 1.85 (m, 2H, O—CH_2—$\underline{CH_2}$), 3.80 (s, 3H, OCH_3), 4.05 (t, 2H, O—$\underline{CH_2}$—CH_2), 4.15 (d, 2H, CH_2), 4.25 (q, 2H, O—$\underline{CH_2}$—CH_3), 6.10 (bt, 1H, NH), 6.30 (d, 1H, =CH—C=O), 6.80 (d, 1H, CH(Ar)), 7.00 (d, 1H, CH(Ar)), 7,03 (bd, 1H, CH(Ar)), 7.55 (d, 1H, Ar—CH=).

*(E)-Dimethyl-2-(3-(4-dodecyloxy-3-methoxyphenyl)acrylamido)-pentanedioate (**8**):* yield, 72%; ^{1}H NMR, δ 0.81 (t, 3H, CH_3), 1.23 (bp, 16H, 8 × CH_2), 1.43 (m, 2H, O—CH_2—CH_2—$\underline{CH_2}$), 1.85 (m, 2H, O—CH_2—$\underline{CH_2}$), 2.08 (m, 1H, CH—CH_2), 2.25 (m, 1H, CH—CH_2), 2.45 (m, 2H, −CH_2—CO), 3.65 (s, 3H, $COOCH_3$), 3.75 (s, 3H, $COOCH_3$), 3.85 (s, 3H, OCH_3), 4.03 (t, 2H, OCH_2−), 4.75 (m, 1H, −CH−), 6.38 (bt, 1H, NH), 6.5 (d, 1H, =CH—C=O), 6.73 (d, 1H, CH(Ar)), 7.09 (d, 1H, CH(Ar)), 7.55 (d, 1H, CH(Ar)), 7.76 (d, 1H, Ar—CH=).

*(E)-Ethyl-2-(3-(4-dodecyloxy-3-hydroxyphenyl)acrylamido)-acetate (**9**):* yield, 92%; ^{1}H NMR, δ 0.85 (t, 6H, 2 × CH_3), 1.25 (bp, 2H, O—CH_2—$\underline{CH_2}$), 4.05 (t, 2H, O—$\underline{CH_2}$—CH_2), 4.25 (q, 2H, O—$\underline{CH_2}$—CH_3), 6.10 (bt, 1H, NH), 6.30 (d, 1H, CH—C=O), 6.80

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(d, 1H, CH(Ar)), 7.00 (d, 1H, CH(Ar)), 7.03 (bd, 1H, CH(Ar)), 7.55 (d, 1H, Ar—CH═).

*(E)-Dimethyl-2-(3-(4-((E)-3-(4-(dodecyloxy)-3-methylphenyl)-acryloyloxy)methoxyphenyl)acrylamido)pentanedioate (**10**):* ^{1}H NMR, δ 0.85 (t, 3H, CH_3—CH_2), 1.2−1.4 (bp, 16H, −$(CH_2)_8$−), 1.45 (bp, 2H, −O—CH_2—CH_2—$\underline{CH_2}$−), 1.83 (bp, 2H, −O—CH_2—$\underline{CH_2}$−), 2.08 (m, 1H, CH—$\underline{CH_2}$−), 2.3 (m, 1H, −CH—CH_2), 2.45 (m, 2H, −CH_2—CO−), 3.65 (s, 3H, −$COOCH_3$), 3.75 (s, 3H, −$COOCH_3$), 3.84 (s, 3H, −OCH_3), 3.89 (s, 3H, −OCH_3), 4.03 (t, 2H, −OCH_2), 4.75 (m, 1H, −NH—CH−), 6.35 (d, 1H, −NH—CH−), 6.4 (bp, 1H, NH), 6.50 (d, 1H, −CH(Ar)), 6.85 (d, 1H, (Ar)), 7.04−7.15 (m, 5H, (Ar)), 7.55 (d, 1H, −CH—CO), 7.8 (d, 1H, −CH—CO−).

*General Procedure for the Synthesis of Compounds **11**−**13**.* The compound (1.4 g) was dissolved in the minimum volume of methanol and mixed with an aqueous solution of LiOH (1:1.4 molar ratio). The total volume was brought to 50 mL by adding distilled water. The reaction mixture was magnetically stirred under reflux in an oil bath at 100 °C for 6 h. The raw product was extracted with ethyl ether (2 × 50 mL), and then the aqueous solution was acidified with concentrated HCl and extracted with ethyl ether (3 × 50 mL) and chloroform (2 × 50 mL). The organic extracts were dried on Na_2SO_4 and evaporated under low pressure. The product was purified by column chromatography.

*(E)-2-(3-(4-Dodecyloxy-3-methoxyphenyl)acrylamido)acetic acid (**11**):* yield, 92%; ^{1}H NMR, δ 0.85 (t, 3H, CH_3), 1.25 (bp, 16H, 8 × CH_2), 1.40 (m, 2H, O—CH_2—CH_2—$\underline{CH_2}$), 1.70 (m, 2H, O—CH_2—$\underline{CH_2}$—CH_2), 3.80 (s, 3H, OCH_3), 3.83 (d, 2H, CH_2), 3.97 (t, 2H, OCH_2), 6.60 (d, 1H, CH—C═O), 6.97 (d, 1H, CH(Ar)), 7.10 (dd, 1H, CH(Ar)), 7,18 (d, 1H, CH(Ar)), 7.37 (d, 1H, Ar—CH═), 8.18 (bt, 1H, NH).

*(E)-Ethyl-2-(3-(4-dodecyloxy-3-methoxyphenyl)acrylamido)-5-methoxy-5-oxopentanoic acid (**12**):* yield, 39%; ^{1}H NMR, δ 0.86 (t, 3H, CH_3), 1.34 (m, 18H, 9 × CH_2), 1.77 (m, 2H, OCH_2—$\underline{CH_2}$), 2.00 (m, 1H, CH—$\underline{CH_2}$), 2.20 (m, 1H, CH—$\underline{CH_2}$), 2.42 (m, 2H, −CH_2—CO), 3.22 (s, 3H, OCH_3), 3.84 (bt, 2H, OCH_2), 4.00 (m, 1H, −CH−), 6.52 (d, 1H, ═CH—C═O), 6.94 (m, 1H, CH(Ar)), 7.10 (bd, 1H, CH(Ar)), 7.16 (bd, 1H, CH(Ar)), 7.47 (d, 1H, Ar—CH═).

*(E)-Ethyl-2-(3-(4-dodecyloxy-3-hydroxyphenyl)acrylamido)acetic acid (**13**):* yield, 71%; ^{1}H NMR, δ 0.86 (t, 3H, CH_3), 1.23 (bp, 16H, 8 × CH_2), 1.42 (m, 2H, $OCH_2CH_2\underline{CH_2}$), 1.81 (m, 2H, $OCH_2\underline{CH_2}$), 4.02 (t, 2H, OCH_2), 4.15 (d, 2H, CH_2COOH), 6.07 (bt, 1H, NH), 6.31 (d, 1H, ═CH—C═O), 6.49 (bp, 1H, OH), 6.83 (d, 1H, CH(Ar)), 7.02 (d, 1H, CH(Ar)), 7.05 (dd, 1H, CH(Ar)), 7.57 (d, 1H, Ar—CH═).

UV Analysis. For UV analysis the products were dissolved in a mixture of tetrahydrofuran (THF) and distilled water (9:1). Quartz cells with 1 cm path length were used, and the concentrations of the samples were around 0.08 mg/mL.

Emulsifying Activity. Each lipophilic product (**7**−**9**) was tested in W/O emulsions for which compositions are given in Table 1.

Table 1. Composition of the W/O Basic Emulsion

		ingredient	INCI name	% w/w
A	1	surfactant		5.0
	2	cera bellina	polyglyceryl-3 beeswax	5.0
	3	soft paraffin	petrolatum	5.0
	4	mineral oil	paraffinum liquidum	25.0
B	5	water	aqua	q.s. 100
	6	glycerin	glycerin	4.5
	7	magnesium sulfate	magnesium sulfate	0.5

Procedure: heat 1, 2, 3, and 4 to 60−65 °C (A phase); disperse 7 in 5 and heat to 70 °C, then add 6 (B phase). Add B slowly to A while stirring and homogenize.

Each hydrophilic product (**11**−**13**) was tested in two O/W basic emulsions, lotion (fluid emulsion) and cream (consistent emulsion), for which compositions are given in Table 2. *Procedure*: mix 1, 2, 3, 4, 5, 6, and 7 and heat to 70 °C (phase A); heat 8 to 75 °C and then add 9 and 10 (phase B). Add B to A while stirring and homogenize. Let the emulsion cool under stirring, then at 40 °C add 11 and 12 dispersed in water (10 mL) (phase C).

Table 2. Composition of O/W Emulsions

		ingredient	INCI name	fluid emulsion % w/w	consistent emulsion % w/w
A	1	Lanette O	cetetaryl alcohol	2.00	2.00
	2	sweet almond oil	*Prunus amygdalus dulcis* oil	2.00	7.00
	3	Cutina GMS	glyceryl stearate		1.00
	4	Cutina CP	cetyl palmitate		2.00
	5	stearin	stearic acid		7.00
	6	DC 200 fluid	dimethicone	1.00	1.00
	7	surfactant		0.50	1.00
B	8	water	aqua	q.s. 100	q.s. 100
	9	glycerin	glycerin	4.50	4.50
	10	triethanolamine	triethanolamine	q.s.	q.s
C	11	disodium EDTA	disodium EDTA	0.15	0.15
	12	Kathon CG	methylchloroisothiazolinone, methylisothiazolinone	0.05	0.05

Emulsion stability was evaluated using the following accelerated aging processes at some time during 3 months: (a) storage at 5, 25, and 40 °C; (b) storage at hot/cold cycle (5−40 °C, two cycles per 24 h); (c) centrifugation at 3000 rpm at room temperature.

Radical-Scavenging Activity. Radical-scavenging activity of some compounds was measured by the DPPH method. In this test DPPH radical scavenging is followed by recording the decrease in the absorbance at 517 nm, which is due to antioxidants or radical species.[26] We followed the method described by Blois:[27] 3 mM solutions of the compounds in ethanol were prepared, and 100 μL of each was added to 5 mL of DPPH (160 mM in ethanol). The samples were diluted 1:3 in ethanol, and the loss of absorbance at 517 nm was read after 30 min of incubation at room temperature in the dark. DPPH solution in ethanol served as the control. Analyses were run in triplicate. Radical-scavenging activity was expressed as a percentage of the inhibition of DPPH absorbance and calculated as $100 - (A_s/A_c \times 100)$, where A_s and A_c are the absorbances of the samples with and without the inhibitors, respectively.

RESULTS

Synthesis. These compounds were synthesized through a three-step procedure. The first step was the formation of the amides **3**, **4**, and **5** by reacting ferulic (**1a**) and caffeic (**1b**) acids with the ethyl ester of glycine (**2a**) or the dimethyl ester of glutamic acid (**2b**) using a coupling reaction.[15,16,18,20] The reaction was accomplished in the presence of EDC, TEA, and DMAP as catalysts, according to the scheme reported in Figure 1. Yields were higher for ferulic acid derivatives **3** and **4** (54 and 75%, respectively) than for the amide of caffeic acid (32%).

The second step was to introduce the alkyl chain by etherification to increase the lipophilic behavior of the molecule and balance the hydrophilic moiety. Thus, the emulsifying capacity is oriented toward W/O emulsions. The amides **3**−**5** were alkylated by introducing a 12-carbon alkyl chain on the phenolic hydroxyl group. We selected a chain that, as we have previously demonstrated in several UV filters, adopts a particular folded main conformation.[28−30] The reaction was accomplished by treating the amides with dodecyl bromide (**6**) and potassium carbonate in anhydrous acetone, according to the scheme shown in Figure 2.

The C_{12} ethers **7** and **8** were obtained in 53 and 71% yields, respectively, and **9** gave a very high yield (92%). The synthesis

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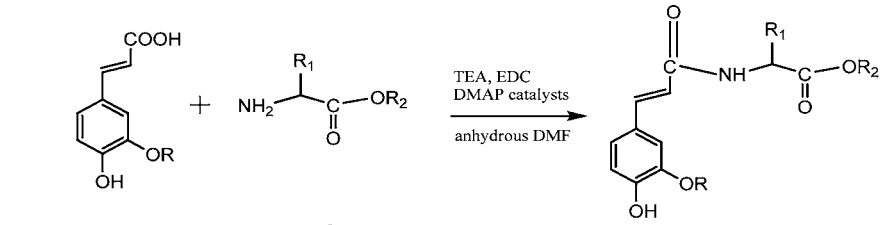


1

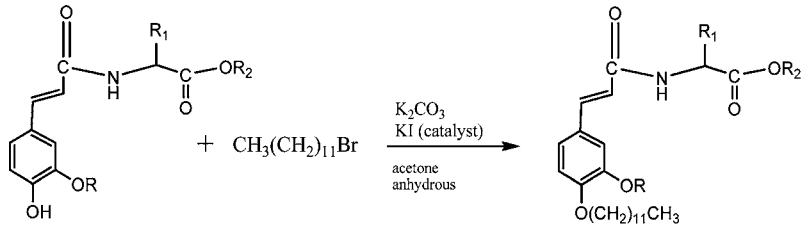
2

1a: Ferulic acid: R = CH_3
1b: Caffeic acid: R = H

2a: Glycine ethyl ester: R_1=H; R_2=CH_2CH_3
2b: Glutamic acid dimethyl ester: R_1 = $CH_2CH_2COOCH_3$; R_2 = CH_3

3: R = CH_3 ; R_1 = H ; R_2 = CH_2CH_3
4: R = CH_3 ; R_1 = $CH_2CH_2COOCH_3$; R_2 = CH_3
5: R = H ; R_1 = H ; R_2 = CH_2CH_3

Figure 1. Synthesis pathway of amide derivatives of ferulic (**3** and **4**) and caffeic (**5**) acids with glycine and glutamic acid by coupling reaction.



3,4,5 **6**

7: R = CH_3 ; R_1 = H ; R_2 = CH_2CH_3
8: R = CH_3 ; R_1 = $CH_2CH_2COOCH_3$; R_2 = CH_3
9: R = H ; R_1 = H ; R_2 = CH_2CH_3

Figure 2. Synthesis of C_{12} ether derivatives **7**, **8**, and **9** by introducing a 12-carbon alkyl chain on the phenolic hydroxyl group.

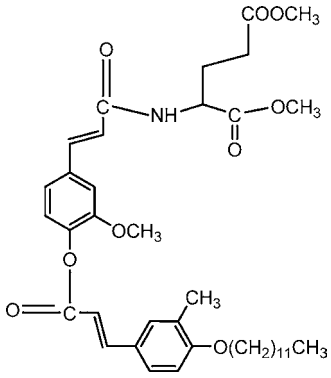
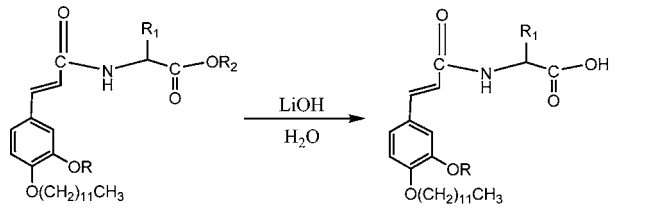


Figure 3. Chemical structure of byproduct **10**.



7,8,9

11: R = CH_3 ; R_1 = H
12: R = CH_3 ; R_1 = $CH_2CH_2COOCH_3$
13: R = H ; R_1 = H

Figure 4. Scheme of hydrolysis of the ethero-esters **7**, **8**, and **9** to obtain compounds **11**, **12**, and **13** with the free carboxylic group.

of compound **8** gave two products. After chromatographic separation and NMR analysis, these molecules were identified as compound **8** and a byproduct **10** containing two ferulic acid moieties. In this last compound the phenolic hydroxyl group was esterified with a second molecule of ferulic acid (Figure 3).

The last step was hydrolysis of the ester to obtain the free carboxylic group, which can then be deprotonated to give anionic O/W emulsifiers. The esters were hydrolyzed by reacting products **7**, **8**, and **9** with an aqueous solution of LiOH to obtain the corresponding acids **11**, **12**, and **13** (Figure 4). Yields were good or very good for compounds **11** (92%) and **13** (71%) but lower for **12** (39%).

UV Analysis. Spectrophotometric analysis was done on compounds **7**–**9** and **11**–**13** and the intermediates **3**–**5**. Table 3 shows the wavelengths corresponding to absorption maxima (λ_{max}) and the logarithms of molar extinction coefficients (log ε). Ferulic (**1a**) and caffeic (**1b**) acids gave λ_{max} at 322 and 323 nm, respectively, in THF/H_2O (9:1) because of their aromatic moieties conjugated with the double bond of the side chain. All of the derivatives had an ipsochromic effect relation to the acids **1a** and **1b**, which was more evident in the free acids **11**–**13**.

Caffeic acid derivatives (**5**, **9**, and **13**) gave lower log ε values than the parent compound **1b**. Ferulic acid derivatives **3** and **4** had nearly the same log ε values as the parent compound **1a** but lower for the other derivatives, especially compounds containing the glutamic acid moiety. However, compounds **7** and **11** containing the glycine moiety had good UV-filtering properties (log $\varepsilon \geq 4$).

Emulsifying Activity. All synthesized molecules had emulsifying properties. The structures of compounds **7**–**9** had lipophilic characteristics, so their use will be restricted to W/O formulations. The synthetic molecules were examined by mixing them (5% concentration) in a standard cream for which the composition is given in Table 1.

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Table 3. UV Data (in THF/H_2O 9:1) of Compounds Synthesized in Comparison with Ferulic (1a) and Caffeic (1b) Acids

compd	λ_{max} (nm)	log ε
1a	322	4.33
1b	323	4.35
3	318	4.34
4	320	4.29
5	322	3.71
7	318	4.02
8	319	3.86
9	320	3.82
11	317	4.14
12	317	3.57
13	316	3.34

Table 4. Emulsifying Activity Results of Compounds 7−9 and 11−13

surfactant	W/O basic emulsion	O/W fluid emulsion	O/W consistent emulsion
7	stable emulsion 1		
8	stable emulsion 2		
9	stable emulsion 3		
11		stable emulsion 4	stable emulsion 5
12		stable emulsion 6	stable emulsion 7
13		stable emulsion 8	stable emulsion 9

The emulsifying power of products **11−13** can be tested in O/W emulsions because the free salifiable carboxylic function increases their hydrophilic properties. The emulsifying power of these compounds, after salification with triethanolamine, was determined in fluid and consistent emulsions. The compounds were then mixed (0.5 and 1.0%) in two standard formulations for which compositions are given in Table 2. Table 4 shows the emulsifying activity.

The preparations were characterized by measuring the pH (only in O/W emulsion) at 25 °C (10% in water) and the viscosity at 0.5 and 1 rpm at 25 °C and by evaluating their organoleptic properties and stability by accelerated aging tests (centrifugation and different storage conditions, 5, 25, 40 °C, and cycle 5/40 °C). Table 5 sets out the results. All formulations remained stable with time (3 months) without showing signs of separation. The viscosity diagrams, when determinable, indicated a typical pseudoplastic behavior. The internal phase droplet size, analyzed by optical microscope, was 5−10 μm.

Radical-Scavenging Activity. As preliminary screening for the scavenging activity of ferulic and caffeic acids and some of their derivatives and intermediates (Figure 5) we tested their quenching activity against DPPH in homogeneous phase. DPPH is a stable free radical used to assess the antioxidant activity of different compounds that act by electron or hydrogen transfer. Of the compounds containing the caffeic acid moiety, we tested surfactant **9** and intermediate **5** (with two free hydroxyl groups). Surfactant **12** and intermediates **4** (one free hydroxyl group) and **3** (glycine ester) were tested among the compounds with the ferulic acid moiety. The radical-scavenging activities are reported in Table 6.

Free caffeic acid was more active than free ferulic acid, in agreement with other results.[11,31,32] Caffeic acid derivatives had lower activity than the free acid, and compound **9** (with only one free hydroxyl group) was the least active. However, intermediate **5** showed greater activity than free caffeic acid.

The ferulic acid derivatives had lower activity than the free acid. However, we noted a certain influence of the amino acid moiety: derivative **3** (glycine ester) had far greater activity than the corresponding compound **4** (glutamic acid ester). This can be attributed to the substantial steric hindrance of glutamic acid that reduces the availability of the aromatic hydroxyl group. Derivative **12** also gave an interesting result: the aromatic hydroxyl group was blocked but still showed some activity, probably due to the amino acid itself.

DISCUSSION

We obtained several surfactants that combine an emulsifying property with UV-protecting and radical-scavenging activities. These molecules can be classified as "natural surfactants" because their polar head is a natural amino acid: glycine or glutamic acid. The lipophilic features come from the alkyl chain, and the UV-protecting and radical-scavenging activities come from natural molecules with such properties, such as ferulic and caffeic acids.

We synthesized the molecules through a short three-step procedure. Compounds **7−9**, with their strong lipophilic behavior, present W/O emulsifying properties, producing stable emulsions with both polar and medium-polar lipids (data not shown). Compounds **11−13**, which have a free carboxylic function, are more hydrophilic, so they are O/W emulsifiers. Thus, we obtained fluid, consistent, and stable emulsions with pseudoplastic rheological behavior. The introduction of a molecule with UV-filtering properties transferred this capacity to these compounds, although it was slightly weaker than that of the parent compound.

Table 5. Organoleptic and Physicochemical Characteristics of Emulsions

			viscosity (cps)			
surfactant	emulsion	pH	0.5 rpm	1 rpm	color	appearance
7	basic W/O 1	not determined	too viscous		yellow	homogeneous
8	basic W/O 2	not determined	too viscous		white	homogeneous
9	basic W/O 3	not determined	too viscous		pale yellow	homogeneous
11	fluid O/W 4	7.50	8900	5300	yellow	homogeneous
11	cream O/W 5	7.02	too viscous		yellow	homogeneous
12	fluid O/W 6	6.69	1800	1050	white	homogeneous
12	cream O/W 7	5.65	6300	4200	white	homogeneous
13	fluid O/W 8	7.65	7400	5550	pale yellow	homogeneous
13	cream O/W 9	6.27	too viscous		pale yellow	homogeneous

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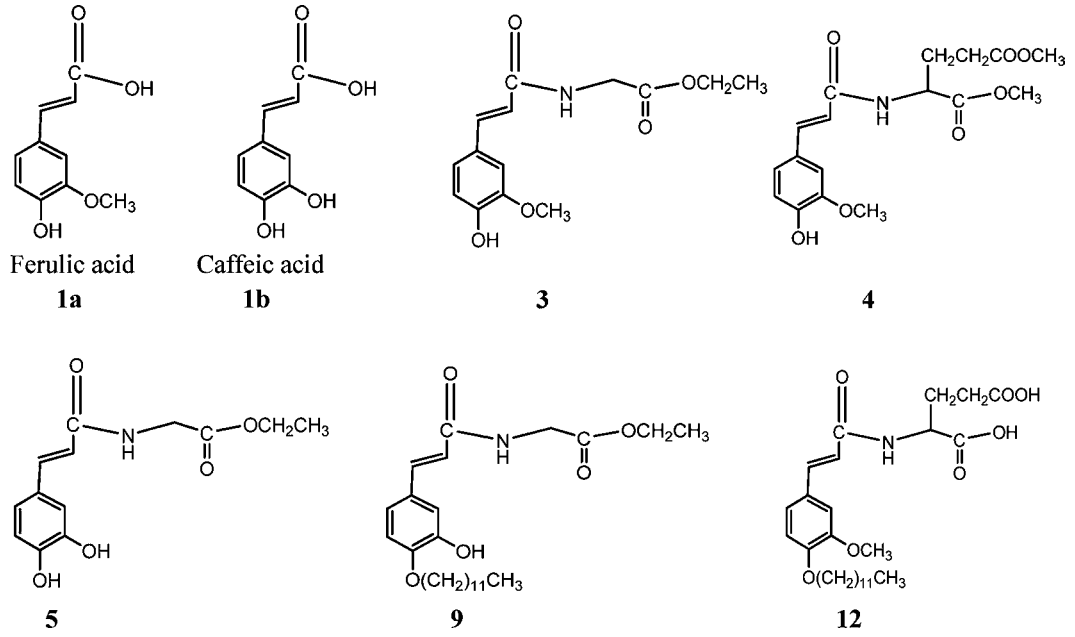

Figure 5. Structures of ferulic (**1a**) and caffeic (**1b**) acids and some of their derivatives tested for scavenging activity against the DPPH radical.

Table 6. DPPH Radical Scavenging Activity

sample	inhibition of DPPH ± SD (%)	sample	inhibition of DPPH ± SD (%)
1a (ferulic acid)	19.52 ± 0.15	**5**	27.33 ± 0.26
1b (caffeic acid)	51.09 ± 0.18	**9**	7.79 ± 0.22
3	16.30 ± 0.42	**12**	5.10 ± 0.15
4	3.14 ± 1.40		

The radical-scavenging activity of these molecules also seems interesting. These experimental data are still only preliminary, obtained by applying a model in homogeneous solution.

These new cosmetic ingredients hold promise in view of their potential application because they conform to the requirements of the cosmetic field, such as natural derivatization and multiple activity. They might prove useful in antiaging creams and UV sunscreens.

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