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Synthesis and antioxidant activity of long chain alkyl hydroxycinnamates

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ABSTRACT

Long chain alkyl hydroxycinnamates (**8**–**21**) were synthesized from the corresponding half esters of malonic acid (**5**–**7**) and benzaldehyde derivatives by Knoevenagel condensation. The total antioxidant capacity of these hydroxycinnamyl esters was evaluated using DPPH and ABTS assays. The observed antioxidant activity was highest for esters of caffeic acid followed by sinapic esters and ferulic esters. The parameters for drug-likeness of these hydroxycinnamyl esters were also evaluated according to the Lipinski's 'rule-of-five'. All the ester derivatives were found to violate one of the Lipinski's parameters (cLogP >5), even though they have been found to be soluble in protic solvents. The predictive topological polar surface area (TPSA) data allow concluding that they could have a good capacity for penetrating cell membranes. Therefore, one can propose these novel lipophilic compounds as potential antioxidants for tackling oxidative processes.

1. Introduction

Phenolic acids, especially hydroxycinnamic acids, such as *p*-coumaric, ferulic, caffeic and sinapic acids, are natural hydrophilic antioxidants which occur in fruits, vegetables, spices and herbs. Hydroxyl groups present on cinnamic acids are often associated with their antioxidant activity. [1]. Hydroxycinnamic acids are of particular interest because of their potential biological outline displaying antioxidant, chelating, free radical scavenging, antiallergic, anti-inflammatory, antimicrobial, antiviral, anticarcinogenic and UV filter properties [1]. However these types of phenolic acids have relatively low solubility in aprotic media. The hydrophilic character of these antioxidants reduces their effectiveness in stabilizing lipophilic systems, such as fats and oils and has been reported as a serious disadvantage if an aqueous phase is also present. The hydrophobicity of phenolic acids can be enhanced by chemical esterification of the carboxyl group of the phenolic acid with a fatty alcohol to obtain an amphiphilic molecule, which should keep its original functional properties and therefore, extend the putative applications of these natural antioxidants in oil based food processing and cosmetics. [1]. Long chain alkyl cinnamates isolated from *Sophora flavescens* have been shown to be free radical scavengers [2]. The antioxidant activity of radish sprout (*Raphanus sativus* L) has been attributed to be related mainly with the presence of sinapic acid esters [3]. Similarly, esters of long chain alcohols with caffeic acid, isolated from *Hypericum laricifolium* have been shown to inhibit COX-1 enzymes [4]. Esters of sinapic and ferulic acids with alkanols have been also used in commercial applications as sunscreens [5,6]. Recently, the occurrence of a relationship between the redox potentials and the antioxidant activity of hydroxycinnamic acids and derivatives has been demonstrated [7].

In this context, this work reports the design and synthesis of a new set of synthetic long chain alkyl cinnamyl esters using natural cinnamic acids as templates. In addition, the antioxidant activity of the hydroxylated long chain alkyl cinnamates and their precursors was studied along with the evaluation of their drug-likeness profile.

2. Results and discussions

2.1. Chemistry

Long chain alkyl cinnamates have been previously prepared by using the appropriate cinnamic acid [8,9] or acid chloride [10] and the suitable long chain alkanol. This type of study was only

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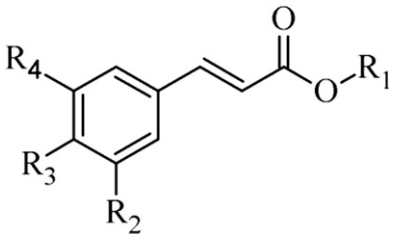
conducted for identification purposes of the corresponding natural cinnamyl esters. However the synthetic procedures reported so far involve protection and deprotection steps, operations that conduct in general to low to moderate yields [8,9]. So, herein a novel synthetic strategy is presented in which the synthesis of long chain alkyl cinnamates **8**–**21** was performed by using monomalonates **5**–**7** and substituted benzaldehyde derivatives as starting material and applying the Verley-Doebner modification of Knoevenagel condensation reaction [11,12] (Scheme 1).

Monomalonates were obtained in high yields by simply heating Meldrum's acid (2, 2-dimethyl-1, 3-dioxane-4, 6-dione) **4** with alcohols in toluene [11,13]. The half esters of malonic acid **5**–**7** were obtained by refluxing tetradecanol (**1**), hexadecanol (**2**) and octadecanol (**3**) with Meldrum's acid **4**. Half esters of malonic acid **5**, **6** and **7** are new compounds and were fully characterized on the basis of their spectral data (FT-IR, ^{1}H & ^{13}C NMR and HRESIMS).

Further condensation of monomalonates **5**–**7** with protocatechualdehyde, vanillin, syringaldehyde, 4-hydroxybenzaldehyde, 4-methoxybenzaldehyde, veratraldehyde, and benzaldehyde in the presence of dry pyridine and β-alanine was performed through a Verley-Doebner modification of Knoevenagel condensation [12] giving alkyl cinnamates (**8**–**21**) (see Table 1) in good yields ranging from 85% to quantitative. The long chain alkyl cinnamates **9**, **12** and **14** are new compounds, characterized by detail spectral data (FT-IR, ^{1}H & ^{13}C NMR and HRESIMS) and reported in the experimental section whereas the known compounds (**8**, **10**, **11**, **13**, **15**–**21**) were characterized by spectral data and compared with literature reports.

Table 1
Long chain alkyl cinnamyl esters (**8**–**21**).



Cinnamates	R_1	R_2	R_3	R_4	Yield %	Reference
8	$C_{14}H_{29}$	H	OH	H	95	[9]
9	$C_{14}H_{29}$	H	OCH_3	H	95	N[#]
10	$C_{14}H_{29}$	OH	OH	H	91	[9]
11	$C_{14}H_{29}$	OCH_3	OH	H	Quant.[#]	[25]
12	$C_{14}H_{29}$	OCH_3	OH	OCH_3	85	N
13	$C_{16}H_{33}$	OH	OH	H	Quant.	[24]
14	$C_{16}H_{33}$	OCH_3	OCH_3	H	88	N
15	$C_{16}H_{33}$	OCH_3	OH	H	Quant.	[2]
16	$C_{16}H_{33}$	OCH_3	OH	OCH_3	94	[2]
17	$C_{16}H_{33}$	H	H	H	95	[27]
18	$C_{18}H_{37}$	OH	OH	H	89	[24]
19	$C_{18}H_{37}$	OCH_3	OH	H	97	[28]
20	$C_{18}H_{37}$	OCH_3	OH	OCH_3	93	[29]
21	$C_{18}H_{37}$	H	H	H	95	[29]

Quant.-Quantitative, N-New.

2.2. Evaluation of the total antioxidant capacity (TAC) of the cinnamic derivatives

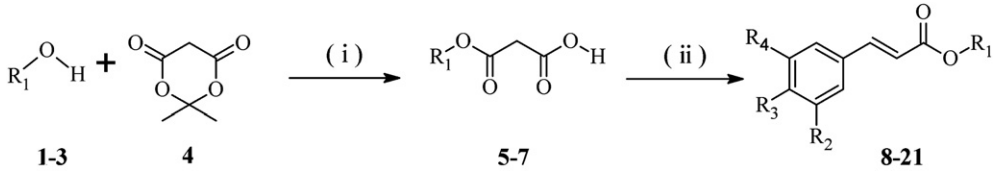
Total antioxidant capacity (TAC) assays have been often used to determine the hierarchy of radical-scavenging abilities of potential phenolic antioxidant compounds that work either through electron- or H- donating mechanisms [14,15]. Accordingly, DPPH$^{\bullet}$ (2,2′-diphenyl-1-picrylhydrazyl radical) and ABTS$^{\bullet+}$ (2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)) assays were used to assess the radical-scavenging ability of hydroxycinnamic ester derivatives (Table 2). Out of the 10 hydroxycinnamic esters only compounds **8**, **10**, **11**, **12**, **13**, **18**, **19** and **20** were evaluated for antioxidant activity since esters **15** and **16** were isolated from natural sources and have been evaluated earlier [2]. The TEAC values of the compounds under study obtained from the ABTS$^{\bullet+}$ decolourization assay are presented in Table 2. The radical-scavenging ability was only determined for the most outstanding antioxidants (based on DPPH data). Trolox, the water-soluble vitamin E analogue, was used as standard.

The radical-scavenging ability data obtained for hydroxycinnamic esters against DPPH were in good agreement with the expected activities of this type of phenolic systems: it is higher when a catechol group is present (caffeic series), and lower when the *meta*-hydroxyl function is substituted by a methoxyl group (ferulic series), having the sinapic series intermediate values (Table 2) [7,16]. In the same series the lipophilic esters exhibit approximately the same antioxidant performance.

According to the data obtained in the ABTS assay, only caffeic acid and its esters disclose an antioxidant activity similar to that presented by Trolox. The results obtained are in good agreement with the expected activities of this type of phenolic systems since it was described that the ability of an antioxidant to scavenge the artificial long-lived radical monocation ABTS$^{\bullet+}$ depend on the resonance stabilization energy of the phenoxyl radical species [16]. The antiradical properties obtained for the known hydroxycinnamic derivatives (**8**, **10**) compare well with published values [9,16–19]. Moreover, the ABTS results follow the same tendency, although not as noticeable, verified from the results obtained with the DPPH method.

2.3. Calculation of drug-likeness properties

Drug-likeness can be deduced as a delicate balance among the molecular properties of a compound that directly influence its pharmacodynamics and pharmacokinetics and ultimately affect their absorption, distribution, metabolism, and excretion in human body like a drug [20]. In general, these parameters allow to ascertain a poor oral absorption, or membrane permeability, that occurs when the evaluated molecules present values higher than five H-bond donors (HBD), 10 H-bond acceptors (HBA), molecular weight (MW) > 500 Da and LogP (cLogP) > 5 (Lipinski's 'rule-of-five') [21].



(i) Toluene, reflux, 4 hr (ii) benzaldehyde derivatives, pyridine, β-alanine

Scheme 1. Synthesis of long chain alkyl cinnamates **8**–**21** from monomalonates **5**–**7**.

Table 2
Structural properties of the phenolic acids and derivatives under study.[a]

TPSA	DPPH IC_{50} (μm)	$ABTS^{\bullet+}$[b]	Molecular weight	miLog*P*[a]	n-ROTB	*n*-ON acceptors	*n*-ONNH donors	Volume	TPSA
p-coumaric acid	>100	–[c]	164.16	1.43	2	3	2	146.48	57.53
8	>100	–[c]	360.54	8.43	16	3	1	382.43	46.53
Caffeic acid	**34.1**	**0.95**	180.16	0.94	2	4	3	154.50	77.76
10	31.9	0.98	376.54	8.05	16	4	2	390.45	66.76
13	33.0	0.96	404.59	8.72	18	4	2	424.05	66.76
18	38.0	1.02	432.64	9.12	20	4	2	457.66	66.76
Ferulic acid	**111.6**	**1.76**	194.19	1.25	3	4	2	172.02	66.76
11	110.2	1.66	390.56	8.30	17	4	1	407.97	55.77
19	117.0	1.80	446.67	9.22	21	4	1	475.18	55.77
Sinapic acid	**66.0**	**1.14**	224.21	1.26	4	5	2	197.57	75.99
12	77.2	1.18	420.59	8.32	18	5	1	433.52	65.00
20	77.1	1.16	476.70	9.22	22	5	1	500.73	65.00

[a] n-ROTB, number of rotatable bonds; n-OHNH, number of hydrogen bond donors; n-ON, number of hydrogen acceptors; TPSA, topological polar surface area.
[b] mmol AH equivalent to 1 mmol Trolox.
[c] not determined.

However, it is important to note that there are many violations of this rule among existing drugs and *vice versa*, and therefore, qualifying the "rule of five" does not guarantee that a molecule is "drug-like" [20]. Topological polar surface area (TPSA) is now been recognized as a good indicator of drug absorbance in the intestines, Caco-2 monolayers penetration, and blood–brain barrier crossing [22].

The mentioned parameters were calculated for the hydroxycinnamic esters in analysis and the results are depicted in Table 2. From the data obtained, one can notice that the phenolic acids are not able to cross membranes effectively, once they have a log$D \leq 1$. The alkyl cinnamic esters possess an adequate number of proton acceptor and proton donor groups to ensure efficient interaction with the hydrogen-bonding groups of the receptors. Hydrogen-bonding capacity has been also identified as an important parameter for describing drug permeability [20,21]. All the ester derivatives were found to violate one of the Lipinski's parameters (logP (cLogP) > 5), although they have been found to have solubility in protic solvents. Accordingly to their predictive TPSA data it seems that this type of cinnamic esters could have a good capacity for penetrating cell membranes.

3. Experimental section

3.1. General

Meldrum's acid was prepared according to literature procedure [23]. Melting points were recorded using Thiele tube and are uncorrected. UV spectra were recorded on a Shimadzu UV-2450 UV–Visible spectrophotometer. IR spectra were recorded as KBr diluted pellets on a Shimadzu (IR Prestige-21) FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively on a Bruker WT 300 FT-NMR instrument with TMS as internal standard. Chemical shifts are recorded in δ values and coupling constant (*J*) are given in Hz. The multiplicities of carbon signals were obtained from distortionless enhancement by polarization transfer (DEPT). High resolution mass spectra (HRMS-ESI+) were performed on a microTOF (focus) mass spectrometer. Ions were generated using an ApolloII (ESI) source. Ionization was achieved by electrospray, using a voltage of 4500 V applied to the needle, and a counter voltage between 100 and 150 V applied to the capillary. All yields refer to isolated products unless stated otherwise.

3.2. Synthesis of half esters of malonic acid (**5**–**7**)

Equimolar quantities (10 mmol) of appropriate alcohols **1**–**3** and Meldrum's acid **4** were refluxed in toluene (5 mL) for 4 h. The reaction was cooled to room temperature and then extracted with saturated $NaHCO_3$ solution. The bicarbonate layer was neutralized with conc. HCl to release the half esters of malonic acid, which were extracted with diethyl ether, washed with water, dried over anhydrous Na_2SO_4 and evaporated to yield pure half esters of malonic acid **5**–**7**.

3.2.1. Monotetradecyl malonate (**5**)

Colorless solid; yield 95%; m.p. 45 °C (Petroleum ether); IR (KBr, cm^{-1}): 3225–3500, 2918, 1744 (ester CO), 1692 (acid CO), 1284, 1166, 825; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, $J = 6.6$ Hz, 3H, H-14′), 1.26 (bs, 22H, H-3′-13′), 1.65 (m, 2H, H-2′), 3.43 (s, 2H, H-2), 4.17 (t, $J = 6.6$ Hz, 2H, H-1′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (C-14′), 22.7 (C-13′), 25.8 (C-3′), 28.4(C-2′), 29.3 (C-4′, 11′), 29.6 (C-5′-10′), 31.9 (C-12′), 40.5 (C-2), 65.7 (C-1′), 167.3 (C-3), 170.6 (C-1); HRESIMS: *m/z* 323.2195 $(M + Na)^+$; Calcd for $C_{17}H_{32}O_4Na^+$: 323.2198.

3.2.2. Monohexadecyl malonate (**6**)

Colorless solid; yield 90%; m.p. 59 °C (Petroleum ether); IR (KBr, cm^{-1}): 2400–3600, 1744 (ester CO), 1695 (acid CO), 1283, 1166, 750; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, $J = 6.6$ Hz, 3H, H-16′), 1.26 (bs, 26H, H-3′-15′), 1.67 (m, 2H, H-2′), 3.45 (s, 2H, H-2), 4.20 (t, $J = 6.6$ Hz, 2H, H-1′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (C-16′), 22.7 (C-15′), 25.7 (C-3′), 28.4 (C-2′), 29.3 (C-4′, 13′), 29.7 (C-5′-12′), 31.9 (C-14′), 40.6 (C-2), 65.7 (C-1′), 167.2 (C-3), 170.9 (C-1); HRESIMS: *m/z* 351.2516 $(M + Na)^+$; Calcd for $C_{19}H_{36}O_4Na^+$: 351.2511.

3.2.3. Monooctadecyl malonate (**7**)

Colorless solid; yield 96%; m.p. 65 °C (Petroleum ether); IR (KBr, cm^{-1}): 2400–3600, 1745 (ester CO), 1693(acid CO), 1284, 1166, 750; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, $J = 6.6$ Hz, 3H, H-18′), 1.26 (bs, 30H, H-3′-17′), 1.69 (m, 2H, H-2′), 3.44 (s, 2H, H-2), 4.19 (t, $J = 6.6$ Hz, 2H, H-1′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (C-18′), 22.7 (C-17′), 25.7 (C-3′), 28.4 (C-2′), 29.3 (C-4′, 15′), 29.7 (C-5′-14′), 31.9 (C-16′), 40.5 (C-2), 65.7 (C-1′), 167.3 (C-3), 170.3 (C-1); HRESIMS: *m/z* 379.2827 $(M + Na)^+$; Calcd for $C_{21}H_{40}O_4Na^+$: 379.2824.

3.3. Synthesis of long chain alkyl cinnamates (**8**–**21**)

Equimolar quantities (2 mmol) of the appropriate half ester of malonic acid and the appropriate benzaldehyde derivative along with dry pyridine (1.0 mL) and β-alanine (12–15 mg) were refluxed for 90–110 min. For hydroxybenzaldehydes the reaction mixtures were kept at room temperature in Erlenmeyer flasks with loosely fitted bar corks for 2 weeks. Reaction mixture was cooled in an ice

bath and conc. HCl (1.0 mL) was added. Extraction with diethyl ether or filtration on a Buchner funnel afforded the crude cinnamates, **8**–**21** which were further purified by recrystallization.

*3.3.1. Trans-tetradecyl-3-(4-hydroxyphenyl) propenoate (**8**)*

Colorless solid; m.p. 89 °C (methanol) (lit. [9] 88–90 °C); HRESIMS: *m/z* 383.2554 $(M + Na)^+$; Calcd for $C_{23}H_{36}O_3Na^+$: 383.2557. Identical with ref [9].

*3.3.2. Trans-tetradecyl-3-(4-methoxyphenyl) propenoate (**9**)*

Colorless solid; m.p. 51 °C (methanol); UV (MeOH): 309, 226 nm; IR (KBr, cm^{-1}): 2916, 1707 (CO), 1606, 1517, 1182, 825; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 6.6 Hz, 3H, H-14′), 1.26 (bs, 22H, H-3′-13′), 1.69 (m, 2H, H-2′), 3.84 (s, 3H, OCH_3), 4.18 (t, *J* = 6.6 Hz, 2H, H-1′), 6.31 (d, *J* = 15.9 Hz, 1H, H-2), 6.90 (d, *J* = 8.8 Hz, 2H, H-6, 8), 7.48 (d, *J* = 8.8 Hz, 2H, H-5, 9), 7.64 (d, *J* = 15.9 Hz, 1H, H-3); HRESIMS: *m/z* 397.2704 $(M + Na)^+$; Calcd for $C_{24}H_{38}O_3Na^+$: 397.2713.

*3.3.3. Trans-tetradecyl-3-(3,4-dihydroxyphenyl)propenoate (**10**)*

Colorless solid; m.p. 106 °C (methanol) (lit [9,24]. 108–109 °C); HRESIMS: *m/z* 399.2508 $(M + Na)^+$; Calcd for $C_{23}H_{36}O_4Na^+$: 399.2506. Identical with ref [9] and [24].

*3.3.4. Trans-tetradecyl-3-(4-hydroxy-3-methoxyphenyl) propenoate (**11**)*

Colorless solid; m.p. 70 °C (methanol) (lit [25]. 76 °C); identical with ref [25].

*3.3.5. Trans-tetradecyl-3-(3,5-dimethoxy-4-hydroxyphenyl) propenoate (**12**)*

Colorless solid; m.p. 62 °C (methanol); UV (MeOH): 327, 240 nm; IR (KBr, cm^{-1}): 3554 (OH), 2917, 1709 (CO), 1639, 1516, 1181, 843; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.6 Hz, 3H, H-14′), 1.25 (bs, 22H, H-3′-13′), 1.69 (m, 2H, H-2′), 3.91 (s, 6H, 2 × OCH_3), 4.18 (t, *J* = 6.6 Hz, 2H, H-1′), 5.81 (s, 1H, OH), 6.30 (d, *J* = 15.9 Hz, 1H, H-2), 6.77 (s, 2H, H-5, 9), 7.58 (d, *J* = 15.9 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (C-14′), 22.7 (C-13′), 25.9 (C-3′), 28.8 (C-2′), 29.2 (C-4′), 29.3 (C-11′), 29.6 (C-5′-10′), 31.9 (C-12′), 56.3 (2 × OCH_3), 64.6 (C-1′), 105.1 (C-5, 9), 116.1 (C-2), 126.0 (C-4), 137.1 (C-7), 144.8 (C-3), 147.2 (C-6, 8), 167.2 (C-1); HRESIMS: *m/z* 443.2762 $(M + Na)^+$; Calcd for $C_{25}H_{40}O_5Na^+$: 443.2768.

*3.3.6. 3.3Trans-hexadecyl-3-(3,4-dihydroxyphenyl)propenoate (**13**)*

Colorless solid; m.p. 102 °C (methanol) (lit [24]. 110–111 °C); UV (MeOH): 329, 219 nm; IR (KBr, cm^{-1}): 3481 (OH), 3312 (OH), 2918, 1684 (CO), 1606, 1286, 1180, 974, 815; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.6 Hz, 3H, H-16′), 1.25 (bs, 26H, H-3′-15′), 1.67 (m, 2H, H-2′), 4.18 (t, *J* = 6.75 Hz, 2H, H-1′), 5.69 (bs, 2H, 2 × OH), 6.27 (d, *J* = 15.9 Hz, 1H, H-2), 6.87 (d, *J* = 8.1 Hz, 1H, H-8), 7.02 (dd, *J* = 8.1, 1.8 Hz, 1H, H-9), 7.09 (d, *J* = 1.8 Hz, 1H, H-5), 7.57 (d, *J* = 15.9 Hz, 1H, H-3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.4 (C-16′), 21.6 (C-15′), 24.9 (C-3′), 27.7 (C-2′), 28.1 (C-4′, 13′), 28.5 (C-5′-12′), 30.8 (C-14′), 63.2 (C-1′), 113.5 (C-2), 114.3 (C-8), 115.2 (C-5), 120.8 (C-9), 125.0 (C-4), 144.5 (C-6), 145.1 (C-3), 147.9 (C-7), 166.1 (C-1); HRESIMS: *m/z* 427.2815 $(M + Na)^+$; Calcd for $C_{25}H_{40}O_4Na^+$: 427.2819.

*3.3.7. Trans-hexadecyl-3-(3,4-dimethoxyphenyl) propenoate (**14**)*

Colorless solid; m.p. 67 °C (methanol); UV (MeOH): 322, 295, 235, 218 nm; IR (KBr, cm^{-1}): 2916, 1720 (CO), 1514, 1271, 976, 843; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.6 Hz, 3H, H-16′), 1.25 (bs, 26H, H-3′-15′), 1.69 (m, 2H, H-2′), 3.91 (s, 6H, 2 × OCH_3), 4.18 (t, *J* = 6.6 Hz, 2H, H-1′), 6.31 (d, *J* = 15.9 Hz, 1H, H-2), 6.86 (d, *J* = 8.4 Hz, 1H, H-8), 7.05 (d, *J* = 1.8 Hz, 1H, H-5), 7.10 (dd, *J* = 8.1, 1.8 Hz, 1H, H-9), 7.62 (d, *J* = 15.9 Hz, 1H, H-3); HRESIMS: *m/z* 455.3149 $(M + Na)^+$; Calcd for $C_{27}H_{44}O_4Na^+$: 455.3132.

*3.3.8. Trans-hexadecyl-3-(4-hydroxy-3-methoxyphenyl) propenoate (**15**)*

Colorless solid; m.p. 69 °C (methanol) (lit [26,2]. 61–63 °C); identical with ref [26] and [2].

*3.3.9. Trans-hexadecyl-3-(3,5-dimethoxy-4-hydroxyphenyl) propenoate (**16**)*

Colorless solid; m.p. 60 °C (methanol); HRESIMS: *m/z* 471.3078 $(M + Na)^+$; Calcd for $C_{27}H_{44}O_5Na^+$: 471.3081. Identical with ref [2].

*3.3.10. Trans-hexadecyl-3-phenylpropenoate (**17**)*

Colorless solid; m.p. 38 °C (Petroleum ether) (lit [27]. 39.6–40.6 °C); UV (MeOH): 276, 217 nm; IR (KBr, cm^{-1}): 2924, 1717 (CO), 1638, 1310, 1167, 766; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 6.6 Hz, 3H, H-16′), 1.25 (bs, 26H, H-3′-15′), 1.69 (m, 2H, H-2′), 4.20 (t, *J* = 6.6 Hz, 2H, H-1′), 6.44 (d, *J* = 15.9 Hz, 1H, H-2), 7.37–7.53 (m, 5H, Ar-H), 7.68 (d, *J* = 15.9 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (C-16′), 22.7 (C-15′), 25.9 (C-3′), 28.7 (C-2′), 29.2 (C-4′), 29.3 (C-13′), 29.7 (C-5′-12′), 31.9 (C-14′), 64.7 (C-1′), 118.3 (C-2), 128.0 (C-5, 9), 128.8 (C-6, 8), 130.2 (C-4), 134.5 (C-7), 144.5 (C-3), 167.1 (C-1); HRESIMS: *m/z* 395.2924 $(M + Na)^+$; Calcd for $C_{25}H_{40}O_2Na^+$: 395.2921.

*3.3.11. 3.3.Trans-octadecyl-3-(3,4-dihydroxyphenyl) propenoate (**18**)*

Colorless solid; m.p. 108 °C (methanol) (lit [24]. 110–112 °C); UV (MeOH): 328, 219 nm; IR (KBr, cm^{-1}): 3481 (OH), 3311 (OH), 2918, 1684 (CO), 1606, 1284, 1180, 974, 815; ^1H NMR (300 MHz, DMSO-d_6) δ: 0.84 (t, *J* = 6.6 Hz, 3H, H-18′), 1.22 (bs, 30H, H-3′-17′), 1.61 (m, 2H, H-2′), 4.09 (t, *J* = 6.45 Hz, 2H, H-1′), 6.25 (d, *J* = 15.9 Hz, 1H, H-2), 6.75 (d, *J* = 8.1 Hz, 1H, H-8), 7.0 (dd, *J* = 8.1, 1.8 Hz, 1H, H-9), 7.04 (d, *J* = 1.8 Hz, 1H, H-5), 7.45 (d, *J* = 15.9 Hz, 1H, H-3), 9.17 (s, 1H, OH), 9.61 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.4 (C-18′), 21.6 (C-17′), 24.9 (C-3′), 27.8 (C-2′), 28.2 (C-4′, 15′), 28.5 (C-5′-14′), 30.8 (C-16′), 63.2 (C-1′), 113.5 (C-2), 114.2 (C-8), 115.2 (C-5), 120.8 (C-9), 125.0 (C-4), 144.5 (C-3), 145.1 (C-6), 147.9 (C-7), 166.1 (C-1); HRESIMS: *m/z* 455.3135 $(M + Na)^+$; Calcd for $C_{27}H_{44}O_4Na^+$: 455.3132.

*3.3.12. Trans-octadecyl-3-(4-hydroxy-3-methoxyphenyl) propenoate (**19**)*

Colorless solid; m.p. 104 °C (methanol) (lit [28]. 110 °C); identical with ref [28].

*3.3.13. Trans-octadecyl-3-(3,5-dimethoxy-4-hydroxyphenyl) propenoate (**20**)*

Colorless solid; m.p. 72 °C (methanol) (lit [29]. 72–73 °C); UV (MeOH): 327, 236 nm; IR (KBr, cm^{-1}): 3533 (OH), 2917, 1708 (CO), 1638, 1516, 1181, 836; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.6 Hz, 3H, H-18′), 1.25 (bs, 30H, H-3′-17′), 1.70 (m, 2H, H-2′), 3.92 (s, 6H, 2 × OCH_3), 4.19 (t, *J* = 6.6 Hz, 2H, H-1′), 5.78 (s, 1H, OH), 6.30 (d, *J* = 15.9 Hz, 1H, H-2), 6.77 (s, 2H, H-5, 9), 7.59 (d, *J* = 15.9 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (C-18′), 22.7 (C-17′), 25.9 (C-3′), 28.8 (C-2′), 29.2 (C-4′), 29.3 (C-15′), 29.7 (C-5′-14′), 31.9 (C-16′), 56.3 (2 × OCH_3), 64.6 (C-1′), 105.1 (C-5, 9), 116.1 (C-2), 126.0 (C-4), 137.1 (C-7), 144.8 (C-3), 147.2 (C-6, 8), 167.2 (C-1); HRESIMS: *m/z* 499.3398 $(M + Na)^+$; Calcd for $C_{29}H_{48}O_5Na^+$: 499.3394.

*3.3.14. Trans-octadecyl-3-phenylpropenoate (**21**)*

Colorless solid; m.p. 45 °C (petroleum ether) (lit [29]. 45–46 °C); UV (MeOH): 276, 218 nm; IR (KBr, cm^{-1}): 2920, 1713 (CO), 1639, 1311, 1175, 766; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 6.6 Hz, 3H, H-18′), 1.26 (bs, 30H, H-3′-17′), 1.69 (m, 2H, H-2′), 4.20 (t, *J* = 6.6 Hz, 2H, H-1′), 6.44 (d, *J* = 15.9 Hz, 1H, H-2), 7.37–7.55 (m, 5H, Ar-H), 7.68 (d, *J* = 15.9 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (C-18′), 22.7 (C-17′), 25.9 (C-3′), 28.7 (C-2′), 29.3 (C-4′), 29.6 (C-15′), 29.7 (C-5′-14′), 31.9 (C-16′), 64.7 (C-1′), 118.3 (C-2), 128.0 (C-5, 9), 128.8 (C-6, 8),

130.2 (C-4), 134.5 (C-7), 144.5 (C-3), 167.1 (C-1); HRESIMS: *m/z* 423.3235 $(M + Na)^+$; Calcd for $C_{27}H_{44}O_2Na^+$: 423.3233.

3.4. Determination of antioxidant activity

(i) The DPPH$^\bullet$ assay. Total antioxidant capacity assay was performed using DPPH as radical source. Radical-scavenging activity was spectrophotometrically evaluated in a Powerwave XS Microplate Reader (Bio-Tek Instruments, Inc) by monitoring the disappearance of 1,1-diphenyl-2-picrylhydrazyl (DPPH) at 515 nm, as previously reported [14]. Increasing concentrations of the different hydroxy cinnamates, were prepared in duplicate, in ethanol. Each solution (20 μL) was added to 180 μL of DPPH radical solution (0.1 mM) in a 96-well microplate and absorbances were recorded every minute for a 45 min period. The absorbance of a blank control (20 μL ethanol plus 180 μL of radical) was set as 100% of radical (0% bleaching).

Radical-scavenging activity, expressed as the percentage of inhibition, was calculated according to the formula: % Inhibition = [(Acontrol − Asample)/Acontrol] × 100, where Acontrol is the absorbance of the DPPH solution without the sample (blank control) and *A*sample is the absorbance of the tested hydroxycinnamate. IC50 values were calculated as the minimum concentration of each sample required to inhibit 50% of the DPPH radical.

(ii) The ABTS$^{\bullet+}$ assay. The radical-scavenging activity of tested compounds was measured by the Trolox equivalent antioxidant capacity (TEAC) assay, as previously described [15,16]. This method is based on the ability of hydrogen-donating antioxidants to decolorize the preformed radical monocation of 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS$^{\bullet+}$), generated by oxidation of ABTS with potassium persulfate. The ABTS$^{\bullet+}$ solution was prepared by reaction of 10 mL of a 7 mM aqueous ABTS solution and 163 μL of a 150 mM (2.45 mM final concentration) potassium persulfate solution. After storage in the dark for 16 h, the radical cation solution was diluted in ethanol until the initial absorbance value of 0.7 ± 0.04 at 734 nm was reached. Solutions of 0.5, 1.0 and 1.5 mM for each cinnamic acid or ester were prepared (to achieve a 20–80% decrease in the initial absorbance of the reaction solution). An aliquot of the compound solution (20 μL) was added to 180 μL of the radical solution in a 96-well microplate. The decrease in absorbance was recorded at 0 and after 6 min. Antioxidant concentration vs. % absorbance reduction data were graphically plotted. The concentration of antioxidant giving the same percentage reduction of absorbance at 734 nm as the 1 mM Trolox solution was calculated from the three-point graphs.

3.4.1. Data analysis

Each experiment was performed in triplicate. Statistical comparisons of both assays were done by one-way ANOVA followed by the multiple Duncan test ($P < 0.05$).

3.5. Calculation of drug-likeness properties

The parameters for drug-likeness were evaluated according to the Lipinski's 'rule-of-five', using the Molinspiration WebME Editor 1.16. [http://www.molinspiration.com].

4. Conclusion

Long chain alkyl hydroxy cinnamates (**8**–**21**) were synthesized from the corresponding half esters of malonic acid (**5**–**7**) and benzaldehyde derivatives by Knoevenagel condensation in good yields (85% to quantitative). The antioxidant activity of eight hydroxycinnamyl esters was studied using DPPH and ABTS assays. The radical-scavenging ability data obtained for hydroxycinnamic esters against DPPH and ABTS radicals were in good agreement with the expected activities of this type of phenolic systems as it has been demonstrated earlier [7]: it is higher when a catechol group is present (caffeic series), and lower when the *meta*-hydroxyl function is substituted by a methoxyl group (ferulic series), having the sinapic series with intermediate values. The esterification does not significantly modify the antioxidant activity of precursors, a fact that is in accordance with the main objective of the work. These novel agents have the advantage of being synthesized from natural products, while providing a value-added use for oil systems. Accordingly, they could be formulated into standard UV-absorbing daily-wear cosmetic, hair and skin care and sunscreen formulations. Due to its antioxidant properties, lipophilicity and capacity of absorbing UVB radiation the dihydroxycinnamic derivatives could also be applied for topical formulations to treat erythema and/or other skin diseases.

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