Synthesis and characterisation of coumarins from H-cardanol

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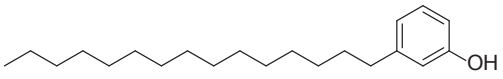
A facile conversion of H-cardanol (side-chain hydrogenated cardanol, 3-pentadecylphenol; renewable fine chemical from the cashew industry) into value added 3-acylcoumarins, including those incorporating (+) menthol or cholesterol, has been achieved. The H-cardanol coumarin hybrid compounds were low melting, lipophilic and soluble in hydrocarbon solvents. They exhibit UV characteristics typical of 7-alkyl-3-acylcoumarins.

Keywords: H-cardanol, 3-acylcoumarin, Knoevenagel condensation, menthol, cholesterol, 3-pentadecylphenol

Side-chain hydrogenated cardanol (H-cardanol, 3-pentadecylphenol) **1** is a renewable fine chemical derived from cashew nut shell liquid (CNSL), which in turn is a byproduct of the cashew industry.[1,2] Although H-cardanol has found several technological applications through exploitation of its phenolic characteristics,[3–6] there are only a few reports on its use in the synthesis of medicinally relevant heterocyclic molecules.[7–9] We have recently reported the facile synthesis and structural characterisation of H-cardanol embedded 4*H*-chromenes by a high yielding two-step protocol from readily available H-cardanol, 2-hydroxybenzaldehydes (salicylaldehydes) and *N*-alkyl/aryl-*N*-[(*E*)-1-(methylsulfanyl)-2-nitro-1-ethenyl] amines (NMSM derivatives).[10] The 2-hydroxybenzaldehyde **2** that is derived from H-cardanol[11] can be elaborated into coumarins of the type **4** by Knoevenagel condensation [12] with β-keto esters **3** (Scheme 1). Coumarins (2*H*-chromen-2-ones, 2*H*-1-benzopyran-2-ones), in general, are extremely important naturally occurring heterocyclic compounds with wide range of applications in the medicinal and technological fields.[13–17] 3-Acylcoumarins, target molecules of the present study, are known for their photosensitisation[18] and Michael acceptor [19] characteristics. With the 15C chain, coumarins of type **4** are expected to be lipophylic and soluble in hydrocarbon solvents like hexane and toluene. Previously, Tocco *et al.*[20] reported synthesis and mushroom tyrosinase enzyme inhibitory activity of a few polyethylene glycol (PEG) bound 4-alkylcoumarins from cardol, an analogue of H-cardanol.[20] Here, we report the facile and convenient synthesis and characterisation of H-cardanol embedded 3-acylcoumarins. Furthermore, we report an application of the study to the synthesis and characterisation of menthol–coumarin and cholesterol–coumarin conjugates.



1 (H-Cardanol, 3-*n*-pentadecylphenol)

Results and discussion

In an initial run, **2**, the 2-hydroxybenzaldehyde derived from H-cardanol,[5] was subjected to Knoevenagel condensation with ethyl acetoacetate **3a** to optimise the reaction conditions for the generation of coumarin **4a** (Scheme 1, Table 1). Among the basic catalysts employed at 10 mol% such as pyridine, pyrrolidine, triethylamine, piperidinium acetate and piperidine under THF reflux, the conversion worked best with piperidine (10 mol%), 1 equiv. of piperidine did not work as well (Table 1, entries 1–5). The yield increased and the reaction time decreased when the reaction was conducted with piperidine (10 mol%) in PEG-200 under microwave (MW) irradiation (Table 1, entry 7). Although reaction took place under microwave irradiation without any solvent the yield was lower (65%) and the product was not clean (entry 8). Prolonged exposure to microwave irradiation (20 min) resulted in charring (entry 9). The condensation did not take place in the absence of catalyst (entries 6 and 10). Overall, the conditions as given in entry 7 of Table 1 were taken as the best for use with other substrates. Formation of coumarin **4a** was ensured from ^{1}H and ^{13}C NMR spectroscopic data. Characteristic singlets located at δ 8.48 assignable to C4H and δ 2.71 assignable to the acetyl methyl group in its ^{1}H NMR spectrum along with the signal for the carbonyl carbon at δ 195.5 ppm in its ^{13}C NMR spectrum confirmed the assigned structure. The coumarin **4a** was readily soluble in hexane and toluene. Notwithstanding its 15C chain, **4a** was lower melting (108 °C) than its parent, 3-acetylcoumarin (119–124 °C).[21]

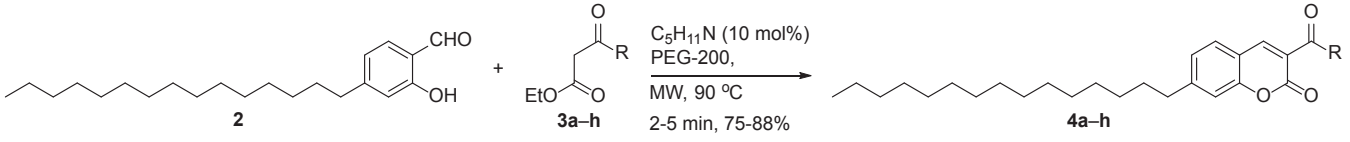
Next, we demonstrated the synthesis of H-cardanol based coumarins by reacting **2** with two more acetoacetic esters,

Table 1 Optimisation of reaction conditions for the synthesis of **4a**[a]

Entry	Base (10 mol%)	Solvent	Time	Yield/%
1	Pyridine	THF	8 h	80
2	Pyrrolidine	THF	10 h	77
3	Et_3N	THF	20 h	75
4	Piperidinium acetate	THF	15 h	80
5	Piperidine	THF	10 h	84
6	No catalyst	THF	24 h	No reaction
7	Piperidine	PEG-200/MW[b]	2 min	88
8	Piperidine	No solvent	5 min	65
9	Piperidine	PEG-200/MW[b]	20 min	Charring
10	No catalyst	PEG-200/MW[b]	5 min	No reaction

[a]Stoichiometry:**2**, 3.0 mmol (0.1 g); **3a**, 3.3 mmol (0.043 g); THF (3 mL when present).

[b]Microwave irradiation of 2.45 GHz, 90 °C in a monomode microwave oven; PEG-200, 0.4 g.



Scheme 1 Synthesis of H-cardanol embedded 3-acylcoumarins.

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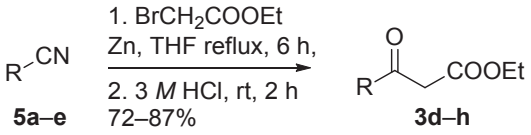
namely ethyl 3-oxopentanoate **3b** and ethyl 4-methyl-3-oxopentanoate **3c** under the optimised conditions to realise coumarins **4b**–**c** respectively in good yield (Scheme 1, Table 2). **2** was then reacted with β-keto esters **3d**–**g** which incorporated heteroatoms like oxygen and sulfur in the acetyl side-chain, with an intention to generate coumarins **4d**–**g** (Table 2). Oxygen atoms in the side chain are likely to impart hydrophilic characteristics to the coumarins (*e.g.* **4d**–**f**). On the other hand, a sulfur atom in the side chain (*e.g.* **4g**) could impart binding characteristics for some transition metal ions and is also open for further oxidation. Required β-keto esters **3d**–**g** were prepared from corresponding nitriles **5a**–**d** and ethyl bromoacetate by applying the Blaise reaction (Scheme 2, Table 3).[23–27] Knoevenagel condensation of **2** with **3d**–**g** provided 3-acylcoumarins **4d**–**g** without any difficulty (Scheme 1 and Table 2). Similarly the reaction of **2** with the β-keto ester **3h** (prepared by the Blaise reaction from **5e**) provided the coumarin **4h** as a waxy solid. The coumarin **4h** can be viewed as a molecule with two long hydrocarbon chains of 15 and 18 carbon atoms present on either side of the central polar coumarin ring. The coumarin **4h** melted at 72–74 °C, which is much lower than its parent 3-acetylcoumarin (119–124 °C) and it is highly soluble in hydrocarbon solvents like *n*-hexane and toluene. The UV absorption spectrum of **4h** (λ_{max} = 344 nm, log ε = 4.13) resembled the UV absorption spectrum of 7-methyl-3-acetylcoumarin[28] (λ_{max} = 345 nm, log ε = 4.46), which indicates that the chromophore remained unaltered by introduction of long hydrocarbon chain.



Scheme 2 The Blaise route to β-keto esters **3d**–**h**.

Table 2 3-Acylcoumarins by Knoevenagel condensation of H-cardanol with various β-keto esters

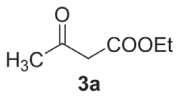
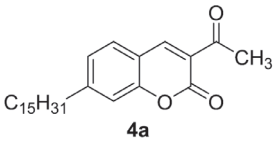
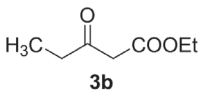
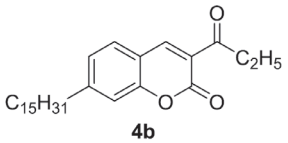
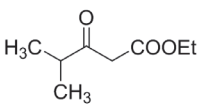
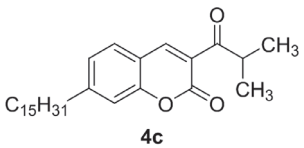
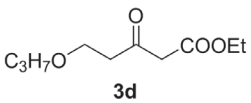
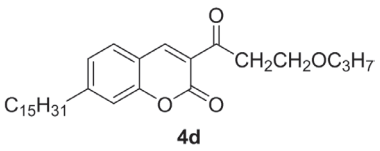
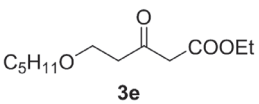
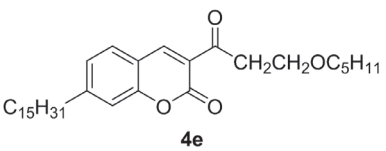
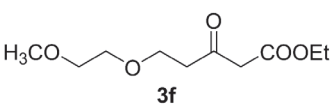
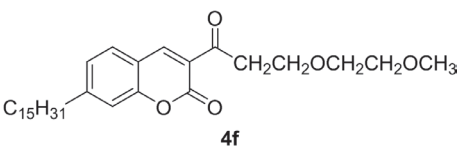
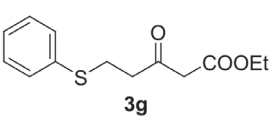
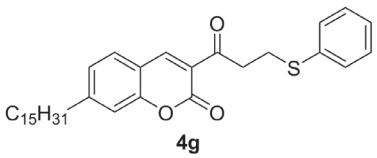
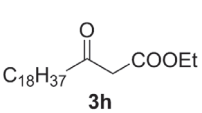
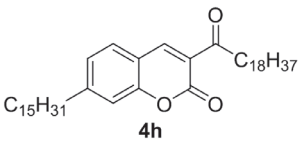
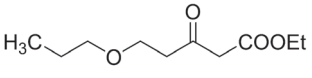
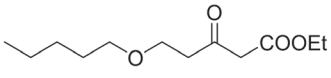
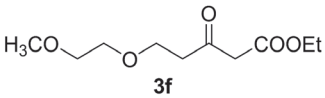
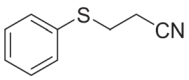
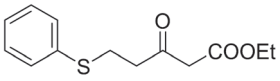
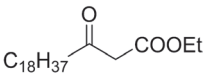
No.	Substrate (**3a**–**h**)	Product (**4a**–**h**)	Yield/%
1	 **3a**	 **4a**	88
2	 **3b**	 **4b**	84
3	 **3c**	 **4c**	80
4	 **3d**	 **4d**	82
5	 **3e**	 **4e**	83
6	 **3f**	 **4f**	75
7	 **3g**	 **4g**	83
8	 **3h**	 **4h**	84

Table 3 Synthesis of β-keto esters

No.	Substrate (**5a–e**)	Product (**3a–h**)	Yield/%
1	*n*-$C_3H_7OCH_2CH_2CN$ **5a**	 **3d**	72
2	*n*-$C_5H_{11}OCH_2CH_2CN$ **5b**	 **3e**	79
3	$CH_3OCH_2CH_2OCH_2CH_2CN$ **5c**	 **3f**	84
4	 **5d**	 **3g**	87
5	*n*-$C_{18}H_{37}$ CN **5e**	 **3h**	85

Sources: **3d–e**: ref. 24; **3f**: ref. 27; **3g**: ref 23; **3h**: ref 25.

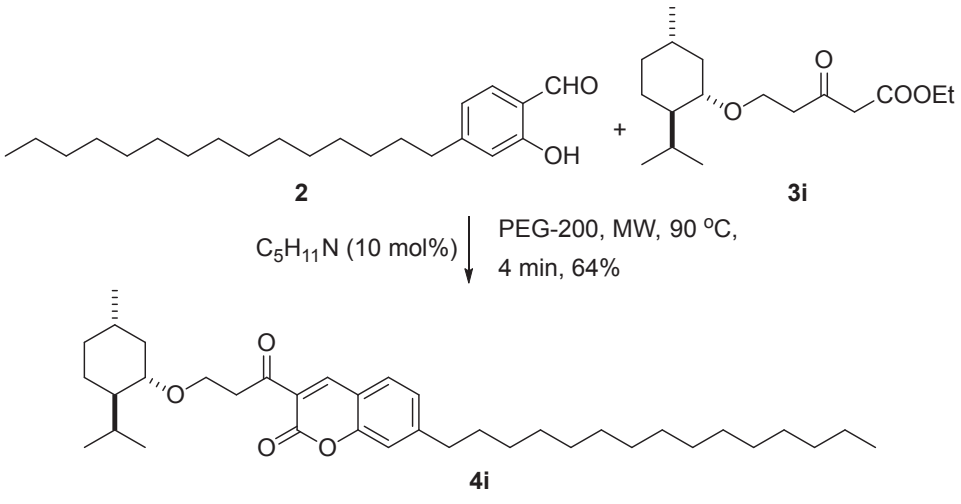
Subsequent to the above study, we reacted **2** with two β-keto esters **3i** and **3j** derived from naturally occurring secondary alcohols, namely (+) menthol and cholesterol respectively. The reaction of **2** with the β-keto ester from (+) menthol **3i** provided the menthol-coumarin conjugate **4i** in good yield (Scheme 3). Similarly, the reaction of the β-keto ester **3j** derived from cholesterol reacted with **2** to furnish the cholesterol-coumarin conjugate **4j** (Scheme 4). The UV and the ^{1}H and ^{13}C NMR spectra of coumarin-menthol conjugate **4i** and coumarin-cholesterol conjugate **4j** were as expected from a combination of the spectra of the parent coumarin **4a** and the natural product concerned. The cholesterol-coumarin conjugate **4j** has the potential to exhibit cholesteric liquid crystalline properties. Regrettably, however, the conjugate **4j** exhibited a low melting range (88–92 °C), which indicates that the molecule is not useful for exploitation as a liquid crystalline material.

Conclusion

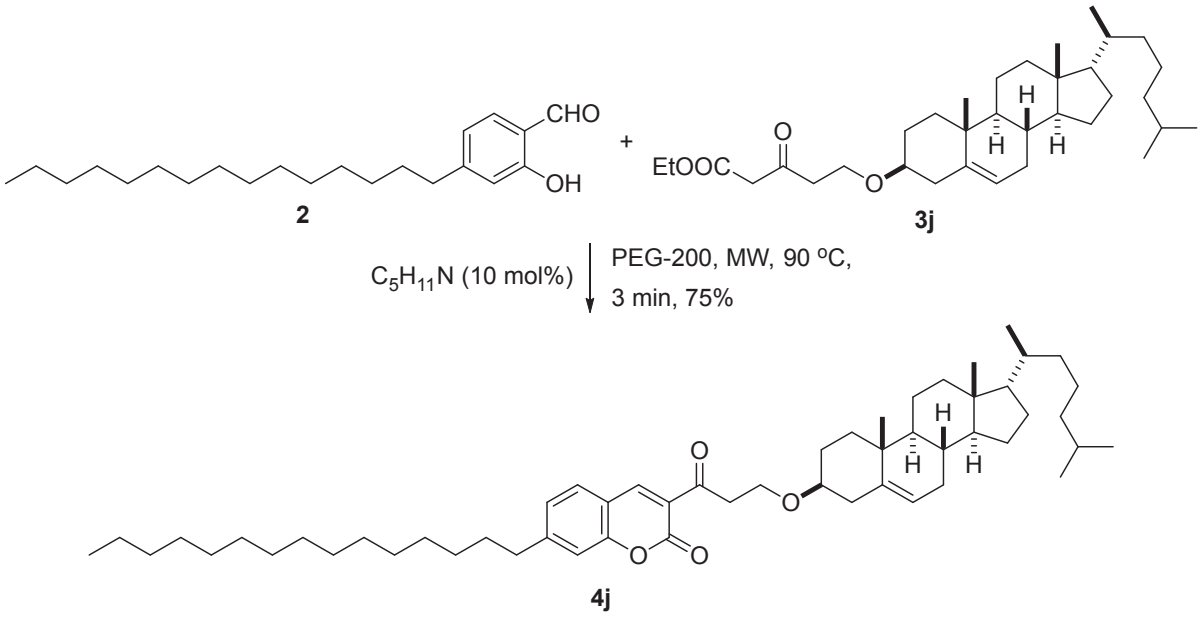
We have described the facile synthesis of H-cardanol embedded 3-acylcoumarins with variable C3-side-chains, including some with heteroatoms. The study has been extended to the synthesis of a 3-acylcoumarin with a 15C chain on the coumarin aromatic ring and an 18C chain on the C3 acyl group. Furthermore, we have described the synthesis and characterisation of coumarin-menthol and coumarin-cholesterol conjugates with 15C side chains. We anticipate that the lipophilic characteristics of the H-cardanol embedded coumarins will make them lead molecules for further developments towards the applications in the medicinal and technological fields.

Experimental

All reagents and solvents were purchased from Sigma-Aldrich, E-Merck or SRL, India. Melting points were uncorrected and were determined using open-ended capillary tubes on a VEEGO VMP-DS instrument. TLC was performed with silica gel-G (SRL, India) or silica gel GF-254 (E-Merck) using hexanes/ethyl acetate as eluent and the spots were visualised by short exposure to iodine vapour or UV light. Column chromatography was carried on silica gel (100–200 mesh, SRL Chemicals, India) using an increasing percentage of ethyl acetate in hexanes. UV spectra were recorded from dilute solutions in $CHCl_3$ on a Shimadju UV-2450 double beam spectrometer. IR spectra were recorded from KBr pellets on a Bomem



Scheme 3 Synthesis of menthol-coumarin conjugate **4i**.



Scheme 4 Synthesis of cholesterol-coumarin conjugate **4j**.

MB104 spectrometer and a Nicolet-6700 spectrometer. The ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and DEPT spectra were recorded in $CDCl_3$, CCl_4:$CDCl_3$ (1 : 1) with a Bruker 400 MHz instrument and TMS (0 ppm) as internal standard; *J* values are in Hz. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constant, integration. High resolution mass spectra were recorded on a Waters Q-TOF micro mass spectrometer using electron spray ionisation mode. Cardanol was purchased from Sabari Industries Sedurapet, Pondicherry. Cardanol was hydrogenated using a Parr hydrogenation apparatus in IIT Madras, Chennai to obtain H-Cardanol.[29,30] The β-keto esters **3b–j** are known compounds and were prepared according to literature procedures.[23–27] Microwave experiments were conducted on Anton Paar GmbH Monowave 300 single-mode microwave reactor.

*Synthesis of 3-acetyl-7-pentadecyl-2*H*-chromen-2-one* **4a***; general procedure*

To a solution of 2-hydroxy-4-pentadecyl-benzaldehyde (formylated cardanol) **2** (0.1 g, 3.0 mmol) and ethyl acetoacetate **3a** (0.043 g, 3.3 mmol) in PEG-200 (0.3 g, 5 equiv) taken in a 10 mL thick walled glass tube fitted with a rubber septum, piperidine (2.5 mg, 10 mol%) was added as a solution in PEG-200 (0.1 mL) and then irradiated with microwaves at 90 °C in a mono-mode microwave oven. The reaction was monitored by TLC at 5 min intervals for completion (2 min). Subsequently, to the cooled reaction mixture dichloromethane (DCM; 15 mL) and water (7 mL) were added. The aqueous phase was extracted with 10 mL of DCM twice. The combined DCM solutions were washed with water (2 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure resulted in the crude product, which was subjected to column chromatography on silica gel by eluting with increasing amount of ethyl acetate in hexanes (0% to 20%) to yield **4a** (0.105 g, 88%) as a white powder; m.p. 108–110 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 342 nm (log ε = 4.09), 302 nm (log ε = 4.21), 241 nm (log ε = 4.31); IR (KBr) ν_{max} 2921, 2848, 1741, 1612, 1417, 1209, 979 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.16–7.14 (m, 2H), 2.73–2.69 (m, 5H), 1.16–1.68 (m, 2H), 1.34–1.24 (m, 24H), 0.88–0.84 (br t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 159.5, 155.6, 151.4, 147.5, 129.9, 125.6, 123.2, 116.13, 116.11, 36.3, 31.9, 30.8, 30.5, 29.66 (3 × CH_2), 29.63 (2 × CH_2), 29.59, 29.50, 29.38, 29.33, 29.1, 22.6, 14.0 ppm; calcd for $C_{26}H_{39}O_3$ $(M+H)^+$ 399.2899; found 399.2900.

*7-Pentadecyl-3-propionyl-2*H*-chromen-2-one* (**4b**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 3-oxo-pentanoic acid ethyl ester **3b** (0.047 g, 3.3 mmol) according to the general procedure provided **4b** in 84% yield (0.110 g) as a white powder; m.p. 105–106 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 343 nm (log ε = 4.11), 308 nm (log ε = 4.31), 243 nm (log ε = 4.01); IR (KBr) ν_{max} 2921, 2849, 1732, 1678, 1613, 1545, 1190, 1041, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) δ 8.47 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.15–7.12 (m, 2H), 3.14 (q, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.66–1.60 (m, 2H), 1.30–1.29 (m, 24H), 1.17 (t. *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4) δ 198.4, 159.2, 155.5, 151.1, 147.3, 129.8, 125.5, 123.3, 116.2, 116.0, 36.3, 35.9, 31.9, 30.8, 29.67 (3 × CH_2), 29.63 (2 × CH_2), 29.60, 29.5, 29.40, 29.34, 29.1, 22.6, 14.1, 7.9 ppm; HRMS (ESI$^+$); calcd for $C_{27}H_{40}O_3$ $(M+Na)^+$ 435.2875; found 435.2880.

*3-Isobutyryl-7-pentadecyl-2*H*-chromen-2-one* (**4c**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 4-methyl-3-oxo-pentanoic acid ethyl ester **3c** (0.052 g, 3.3 mmol) according to the general procedure provided **4c** in 80% yield (0.102 g) as a white powder; m.p. 111–113 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 342 nm (log ε = 4.18), 297 nm (log ε = 4.32), 241 nm (log ε = 4.12); IR (KBr) ν_{max} 2920, 2852, 1724, 1613, 1548, 1464, 1196, 784 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.16–7.13 (m, 2H), 3.86 (sep, *J* = 6.8 Hz, 1H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.65–1.61 (m, 2H), 1.24 (br s, 24H), 1.17 (d, *J* = 6.8 Hz, 6H), 0.88–0.85 (br t, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 159.3, 155.5, 151.2, 147.9, 129.8, 125.7, 123.5, 116.4, 116.2, 38.6, 36.4, 32.0, 31.0, 29.8 (3 × CH_2), 29.79 (2 × CH_2), 29.76, 29.6, 29.5, 29.4, 29.3, 22.8, 18.4, 14.2 ppm; calcd for $C_{28}H_{43}O_3$ $(M+H)^+$ 427.3212; found 427.3216.

*7-Pentadecyl-3-(3-propoxypropanoyl)-2*H*-chromen-2-one* (**4d**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 3-oxo-5-propoxy-pentanoic acid ethyl ester **3d** (0.07 g, 3.3 mmol) according to the general procedure provided **4d** in 82% yield (0.115 g) as a white powder; m.p. 85–87 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 344 nm (log ε = 4.15), 307 nm (log ε = 4.41), 242 nm (log ε = 4.01); IR (KBr) ν_{max} 2922, 2851, 1735, 1615, 1544, 1187, 1119, 890, 769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) δ 8.45 (s, 1H), 7.53 (d, *J* = 6.2 Hz, 1H), 7.16–7.12 (m, 2H), 3.80 (t, *J* = 6.2 Hz, 2H), 3.41–3.36 (m, 4H), 2.71 (t, *J* = 8.0 Hz, 2H), 1.65 (t, *J* = 8.0 Hz, 2H), 1.59–1.53 (m, 2H), 1.31–1.25 (m, 24H), 0.90–0.87 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4) δ 195.9, 159.1, 155.5, 151.1, 147.3, 129.8, 125.5, 123.5, 116.19, 116.13, 72.7, 65.4, 42.7, 36.3, 31.9, 30.8, 29.68 (3 × CH_2), 29.64

(2×CH_2), 29.61, 29.5, 29.4, 29.3, 29.1, 22.8, 22.6, 14.1, 10.5 ppm; calcd for $C_{30}H_{47}O_4$ $(M+H)^+$ 471.3474; found 471.3464.

*7-Pentadecyl-3-(3-(pentyloxy)propanoyl)-2*H*-chromen-2-one* (**4e**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 3-oxo-5-pentyloxy-pentanoic acid ethyl ester **3e** (0.076 g, 3.3 mmol) according to the general procedure provided **4e** in 83% yield (0.125 g) as a white powder; m.p. 80–82 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 343 nm (log ε=4.12), 307 nm (log ε=4.38), 241 nm (log ε=4.12); IR (KBr) ν_{max} 2924, 2851, 1736, 1612, 1547, 1187, 888, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3+CCl_4$) δ 8.45 (s, 1H), 7.52 (d, *J*=8.0 Hz, 1H), 7.16–7.12 (m, 2H), 3.79 (t, *J*=8.0 Hz, 2H), 3.44–3.36 (m, 4H),2.71 (t, *J*=8.0 Hz, 2H), 1.65–1.55 (m, 2H), 1.54–1.49 (m, 2H), 1.31–1.25 (m, 28H), 0.89–0.84 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3+CCl_4$) δ 196.1, 159.2, 155.5, 151.2, 147.4, 129.8, 125.5, 123.5, 116.17, 116.12, 71.1, 65.5, 42.7, 36.3, 31.9, 30.8, 29.67 (3×CH_2), 29.64 (2×CH_2), 29.61, 29.5, 29.4, 29.34, 29.31, 29.1, 28.3, 22.6, 22.4, 14.1, 14.0 ppm; calcd for $C_{32}H_{51}O_4$ $(M+H)^+$ 499.3787; found 499.3789.

*3-(3-(2-Methoxyethoxy)propanoyl)-7-pentadecyl-2*H*-chromen-2-one* (**4f**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 5-(2-methoxy-ethoxy)-3-oxo-pentanoic acid ethyl ester **3f** (0.072 g, 3.3 mmol) according to the general procedure provided **4f** in 75% yield (0.110 g) as a white powder; m.p. 120–122 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 341 nm (log ε=4.16), 310 nm (log ε=4.34), 241 nm (log ε=4.14); IR (KBr) ν_{max} 2919, 2850, 1732, 1678, 1614, 1545, 1185, 1124, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.52 (d, *J*=8.3 Hz, 1H), 7.15–7.13 (m, 2H), 3.87 (t, *J*=6.2 Hz, 2H), 3.63–3.61 (m, 2H), 3.52–3.50 (m, 2H), 3.42 (t, *J*=6.1 Hz, 2H), 3.34 (s, 3H), 2.70 (t, *J*=7.5 Hz, 2H), 1.67–1.65 (m, 2H), 1.30–1.24 (m, 24H), 0.86 (t *J*=6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 159.3, 155.5, 151.4, 147.6, 129.9, 125.6, 123.2, 116.1 (2×CH_2), 71.8, 70.2, 66.0, 58.9, 42.6, 36.3, 31.9, 30.8, 29.66 (3×CH_2), 29.63 (2×CH_2), 29.60, 29.5, 29.38, 29.33, 29.1, 22.6, 14.0 ppm; calcd for $C_{30}H_{47}O_5$ $(M+H)^+$ 487.3424; found 487.3419.

*7-Pentadecyl-3-(3-(phenylthio)propanoyl)-2*H*-chromen-2-one* (**4g**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 3-oxo-5-phenylsulfanyl-pentanoic acid ethyl ester **3g** (0.083 g, 3.3 mmol) according to the general procedure provided **4g** in 83% yield (0.130 g) as a white powder; m.p. 132–134 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 349 nm (log ε=4.15), 308 nm (log ε=4.21), 242 nm (log ε=4.08); IR (KBr) ν_{max} 2918, 2850, 1738, 1677, 1614, 1430, 1183, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.53 (d, *J*=9.2 Hz, 1H), 7.37–7.35 (m, 2H), 7.28–7.25 (m, 2H), 7.18–7.14 (m, 3H), 3.48 (t, *J*=6.8 Hz, 2H), 3.28 (t, *J*=7.2 Hz, 2H), 2.71 (t, *J*=7.2 Hz, 2H), 1.64 (t, *J*=7.2 Hz, 2H), 1.30–1.24 (m, 24H), 0.87 (t, *J*=6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 159.4, 155.6, 151.8, 148.1, 136.1, 130.1, 129.6 (2×CH_2), 129.0 (2×CH_2), 126.3, 125.8, 122.8, 116.27, 116.21, 42.5, 36.4, 32.0, 30.9, 29.8 (3×CH_2), 29.79, 29.77, 29.74, 29.6, 29.5, 29.4, 29.3, 28.1, 22.8, 14.2 ppm; calcd for $C_{33}H_{45}O_3S$ $(M+H)^+$ 521.3089; found 521.3069.

*3-Nonadecanoyl-7-pentadecyl-2*H*-chromen-2-one* (**4h**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 3-oxo-henicosanoic acid ethyl ester **3h** (0.12 g, 3.3 mmol) according to the general procedure provided **4h** in 84% yield (0.160 g) as a white waxy solid; m.p. 72–74 °C; R_f (80% hexanes/EtOAc) 0.6; UV ($CHCl_3$), 344 nm (log ε=4.13), 308 nm (log ε=4.34), 243 nm (log ε=4.11); IR (KBr) ν_{max} 2922, 2851, 1730, 1618, 1550, 1467, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.53 (d, *J*=7.6 Hz, 1H), 7.16–7.13 (m, 2H), 3.11 (t, *J*=7.6 Hz, 2H), 2.71 (t, *J*=7.6 Hz, 2H), 1.69–1.62 (m, 4H), 1.58 (s, 4H),1.30–1.25 (m, 50H), 0.87 (t, *J*=6.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 159.4, 155.4, 151.2, 147.3, 129.8, 125.5, 123.5, 116.1, 116.0, 42.5 (2×CH_2), 36.3 (2×CH_2), 31.9 (3×CH_2), 30.8 (2×CH_2), 29.6 (5×CH_2), 29.5 (4×CH_2), 29.39 (2×CH_2), 29.34 (2×CH_2), 29.2 (2×CH_2), 29.1 (2×CH_2), 23.9 (2×CH_2), 22.6 (3×CH_2), 14.1 (2×CH_2) ppm; calcd for $C_{43}H_{73}O_3$ $(M+H)^+$ 637.5559; found 637.5535.

*3-(3-(Menthyloxypropanoyl)-7-pentadecyl-2*H*-chromen-2-one* (**4i**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 5-(2-isopropyl-5-methyl-cyclohexyloxy)-3-oxo-pentanoic acid ethyl ester **3h** (0.098 g, 3.3 mmol) according to the general procedure provided **4h** in 64% yield (0.110 g) as a white powder; m.p. 118–120 °C; R_f (80% hexanes/EtOAc) 0.6; $[\alpha]_D$ =–28.21° (c=1, $CHCl_3$); UV ($CHCl_3$), 345 nm (log ε=4.12), 306 nm (log ε=4.36), 241 nm (log ε=4.09); IR (KBr) ν_{max} 2925, 2858, 1735, 1691, 1612, 1460, 1179, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3+CCl_4$) δ 8.42 (s, 1H), 7.52 (d, *J*=8.0 Hz, 1H), 7.16–7.13 (m, 2H), 3.98–3.95 (m, 1H), 3.70–3.65 (m, 1H), 3.37–3.33 (m, 2H), 3.03 (t, *J*=4.0 Hz, 1H), 2.71 (t. *J*=7.6 Hz, 2H), 2.12–2.08 (m, 2H),1.64–1.55 (m, 6H), 1.25 (br, 27H), 0.88 (t, *J*=6.4 Hz, 6H), 0.81 (d, *J*=7.2 Hz, 3H), 0.70 (d, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3+CCl_4$) δ 196.6, 159.4, 155.7, 151.3, 147.4, 129.9, 125.7, 123.8, 116.38, 116.33, 79.5, 63.5, 48.3, 43.3, 40.4, 36.6, 34.7, 31.7, 31.0, 29.87 (3 CH_2), 28.83 (3×CH_2), 29.80, 29.7, 29.59, 29.54, 29.3, 25.6, 23.5, 22.8, 22.5, 21.1, 16.4, 14.3 ppm; calcd for $C_{37}H_{59}O_4$ $(M+H)^+$ 567.4413; found 567.4392.

*3-(3-(Cholesteryloxy)propanoyl)-7-pentadecyl-2*H*-chromen-2-one* (**4j**): The reaction of 2-hydroxy-4-pentadecyl-benzaldehyde **2** (0.1 g, 3.0 mmol) and 5-cholesteryl-3-oxo-pentanoic acid ethyl ester **3j** (0.17 g, 3.3 mmol) according to the general procedure provided **4j** in 75% yield (0.180 g) as a white powder; m.p. 88–92 °C; R_f (90% hexanes/EtOAc) 0.6; $[\alpha]_D$ =–32.2° (c=1, $CHCl_3$); UV ($CHCl_3$), 345 nm (log ε=4.14), 293 nm (log ε=4.24), 243 nm (log ε=4.12); IR (KBr) ν_{max} 2925, 2856, 1731, 1676, 1607, 1462, 1183, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.53 (d, *J*=7.8 Hz, 1H), 7.16–7.13 (m, 2H), 5.32 (m, 1H), 3.86 (t, *J*=6.3 Hz, 2H), 3.38 (t, *J*=6.1 Hz, 2H), 3.22–3.14 (m, 1H), 2.71 (t, *J*=7.5 Hz, 2H), 2.59–2.53 (m, 1H), 2.37–2.32 (m, 1H), 2.19–2.12 (m, 1H), 2.01–1.93 (m, 3H), 1.90–1.79 (m, 4H), 1.64–0.66 (m, 62H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 159.5, 155.6, 151.5, 147.6, 141.1, 130.0, 125.8, 123.6, 121.6, 116.3 (2×CH_2), 79.4, 62.9, 56.9, 56.3, 53.5, 50.3, 43.3, 42.4, 39.9, 39.6, 39.1, 37.3, 37.0, 36.4, 36.3, 35.9 (2×CH_2), 32.0, 31.0, 29.85 (2×CH_2), 29.80 (2×CH_2), 29.7, 29.6, 29.56, 29.51, 29.3, 28.5, 28.3, 28.1, 24.4, 23.9, 22.9, 22.8, 22.7, 21.2, 19.5, 18.8, 14.2 (2×CH_2), 12.0 ppm; calcd for $C_{54}H_{85}O_4$ $(M+H)^+$ 797.6448; found 797.6410.

Electronic Supplementary Information

The UV, IR, ^1H, ^{13}C and DEPT-135 NMR spectra of **4a**–**j**, and the UV spectrum of 3-acetyl-7-methyl-2*H*-chromen-2-one have been deposited in the ESI available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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References

1 J.H.P. Tyman, *Synthetic and natural phenols*. Elsevier, Amsterdam, 1996.
2 J.H.P. Tyman, *Chem. Soc. Rev.*, 1979, **8**, 499–537.
3 C. Voirin, S. Caillol, N.V. Sadavarte, B.V. Tawade, B. Boutevinab and P.P. Wadgaonkar, *Polym. Chem*., 2014, **5**, 3142–3162.
4 R.L. Quirino, T.F. Garrison and M.R. Kessler, *Green Chem*., 2014, **16**, 1700–1715.
5 V.S. Balachandran, S.R. Jadhav, P.K. Vemula and G. John, *Chem. Soc. Rev*., 2013, **42**, 427–438.
6 M.C. Lubi and E.T. Thachil, *Des Monomers Polym*., 2000, **3**, 123–153.
7 A. Minigher, E. Benedetti, O.D. Giacomo, P. Campaner and V. Aroulmoji, *Nat. Prod. Commun*., 2009, **4**, 521–528.
8 O.A. Attanasi, R. Del Sole, P. Filipponea, S.E. Mazzettoc, G. Mele and G. Vasapollo, *J. Porphyrins Phthalocyanines*, 2004, **8**, 1276–1284.
9 G. Mele, R. Del Sole, G. Vasapollo, E. Garcia-Lopez, L. Palmisano, S.E. Mazzetto, O.A. Attanasi and P. Filippone, *Green Chem*., 2004, **6**, 604–608.
10 H.S.P. Rao and M. Kamalraj, *Nat. Prod. Commun*., 2014, **9**, 1333–1340.
11 P. Payne, J.H.P. Tyman, S.K. Mehet and A. Ninagawa, *J. Chem. Res*., 2006, 402–405.

12 E.C. Horning, M.G. Horning and D.A. Dimmig, *Org. Synth., Coll.* Vol. III, 1955, 165–167.
13 R.D.H. Murray, J. Mendez and S.A. Brown, *The natural coumarins: occurrence, chemistry and biochemistry*. John Wiley and Sons, New York, 1982.
14 R. O'Kennedy and R.D. Thornes, eds. *Coumarins: biology, applications and mode of action*. Wiley, Chichester, 1997.
15 J.D. Hepworth, *Comprehensive heterocyclic chemistry*, A.R. Katritzky and C.W. Rees, eds. Pergamon, New York, 1984, Vol. 3, pp. 799–810.
16 J.D. Hepworth, C.D. Gabbutt and B.M. Heron, in *Comprehensive heterocyclic chemistry-II*, A.R. Katritzky, C.W. Rees and E.F.V. Scriven, eds. Pergamon, New York, 1996, Vol. 5, pp. 417–434.
17 M.A. Brimble, J.S. Gibson and J. Sperry, *Comprehensive heterocyclic chemistry-III*; A.R. Katritzky, C.W. Rees and E.F.V. Scriven, eds. Pergamon, New York, 2008, Vol. 7.08, pp. 425–697.
18 D.P. Specht, P.A. Martic and S. Farid, *Tetrahedron,* 1982, **38**, 1203–1211.
19 V.D.N. Sastry and T.R. Seshadri, *Proc. Ind. Acad. Sci*., 1942, **16A**, 29–35; *Chem. Abstr*., 1943, **37**, 880.
20 G. Tocco, A. Fais, G. Meli, M. Begala, G. Podda, M.B. Fadda, M. Corda, O.A. Attanasi, P. Filippone and S. Berretta, *Bioorg. Med. Chem. Lett*., 2009, **19**, 36–39.
21 3-Acetylcoumarin, CAS 3949-36-8; ChemSpider ID: 69959 (http://www.chemspider.com/Chemical-Structure.69959.html).
22 H.S.P. Rao, S. Rafi and K. Padmavathy, *Tetrahedron*, 2008, **64**, 8037–8043.
23 H.S.P. Rao, S. Rafi and K. Padmavathy, *Lett. Org. Chem*., 2008, **64**, 527–529.
24 H.S.P. Rao and A. Desai, *Ind. J. Chem. B*, 2014, 000.
25 H.S.P. Rao, K. Padmavathy, K. Vasantham and S. Rafi, *Synth. Commun*., 2009, **39**, 1825–1834.
26 H.S.P. Rao, A. Desai, I. Sarkar, M. Mohapatra and A.K. Mishra, *Phys. Chem. Chem. Phys*., 2014, **16**, 1247–1256.
27 H.S.P. Rao, M. Babu and A. Desai, *RSC Adv*., 2014, **4**, 11064–11072.
28 F.M. Dean, A. Robertson and W.B. Whalley, *J. Chem. Soc*., 1950, 895–902.
29 R. Paramshivappa, P.P. Kumar, P.J. Vithayathil and A.S. Rao, *J. Agric. Food Chem*., 2001, **49**, 2548–2551.
30 P.P. Kumar, R. Paramshivappa and P.J. Vithayathil, *J. Agric. Food Chem*., 2002, **50**, 4705–4708.