Design and synthesis of novel vitamin D–coumarin hybrids using microwave irradiation

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A series of novel vitamin D–coumarin hybrids were synthesised by esterification of the corresponding coumarin-3-carboxylic acids and vitamin D or vitamin D CD-ring alcohol in CH_2Cl_2 under microwave irradiation. They were obtained in higher yields (from 64–81% up to 79–87%) and shorter reaction time (from 3 h down to 15 min), compared with earlier conventional methodologies. The structures of all the target compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. This provides an attractive and alternative method for the preparation of high-value vitamin D–coumarin hybrids.

Keywords: vitamin D, coumarin, hybrids, microwave irradiation

Vitamin D is a sterol that not only plays a classical role in calcium homeostasis and bone mineralisation,[1,2] but also regulates the proliferation and differentiation of various types of cancer cells.[3–5] However, inspired by the multiple bioactivity of vitamin D, several vitamin D hybrids have been reported by different groups. For example, the hybridisation of a calcemia-inactivating A ring with a differentiation-activating CD-ring side chain developed by Posner yielded a hybrid analogue with combined powerful biological activities.[6] Steinmeyer et al. reported that the combination of phosphonate and bisphosphonate substructures with the vitamin D skeleton can produce biological activities.[7] In recent years, several esters linked to aromatic A-ring and CD-ring derivatives have been identified as improved and selective hedgehog inhibitors by Hadden and co-workers.[8,9]

Coumarins are an important class of naturally occurring compounds that have attracted much attention in recent years due to a diverse range of biological and pharmacological properties.[10–12] Many novel hybrids with coumarins have been designed and synthesised. For example, tacrine–coumarin hybrids have been designed as multifunctional cholinesterase inhibitors against Alzheimer's disease.[13,14] Coumarin–pyridine hybrids have been synthesised with promising anti-osteoporotic activities.[15] Coumarin–benzimidazole hybrids have been evaluated as potent antibacterial and anticancer agents.[16]

New hybrids may have improved activity and new biological properties compared with their individual components. Moreover, our group has discovered novel vitamin D analogues that have interesting biological profiles.[17,18] In this study, we hybridised vitamin D_2 and coumarin using microwave irradiation with the aim of developing new lead compounds with efficient and selective pharmacological activities.

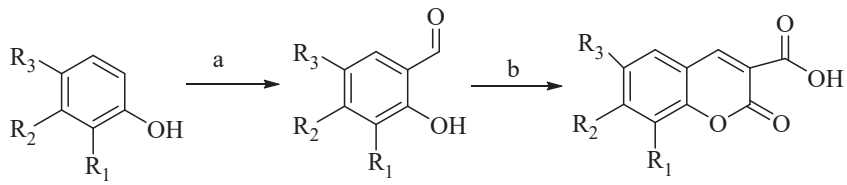
Results and discussion

Synthesis of coumarin-3-carboxylic acids

The synthetic strategy[19–21] to obtain the coumarin-3-carboxylic acids is outlined in Scheme 1. Salicylaldehyde derivatives were synthesised *via* Reimer–Thieman formylation of the corresponding substituted phenols **1b**–**h** with $CHCl_3$ and NaOH, except for **2a**, which is commercially available. At the beginning of our study, no catalyst was used, but the reaction was incomplete and the yield was low. When tributylamine was used as the catalyst, the reaction was complete with an improved yield. The resultant compounds **2a**–**h** were subsequently cyclised with diethylmalonate in the presence of piperidine in ethanol solution. On reaction completion, the mixture was hydrolysed with NaOH and acidified with HCl at room temperature to give the corresponding coumarin-3-carboxylic acids **3a**–**h**.

Synthesis of vitamin D_2–coumarin hybrids

The synthetic route for the vitamin D–coumarin hybrids is depicted in Scheme 2. In a typical procedure, in the presence



1b-h **2a-h** **3a-h**

	a	b	c	d	e	f	g	h
R_1	H	H	H	H	Cl	H	H	H
R_2	H	H	H	CH_3	H	OCH_3	H	H
R_3	H	Br	Cl	H	Cl	H	NO_2	OCH_3

(a) $CHCl_3$, NaOH, $(n\text{-}C_4H_9)_3N$, EtOH, H_2O; (b) piperidine, NaOH, HCl

Scheme 1 Synthesis of hybrids of coumarin-3-carboxylic acids.

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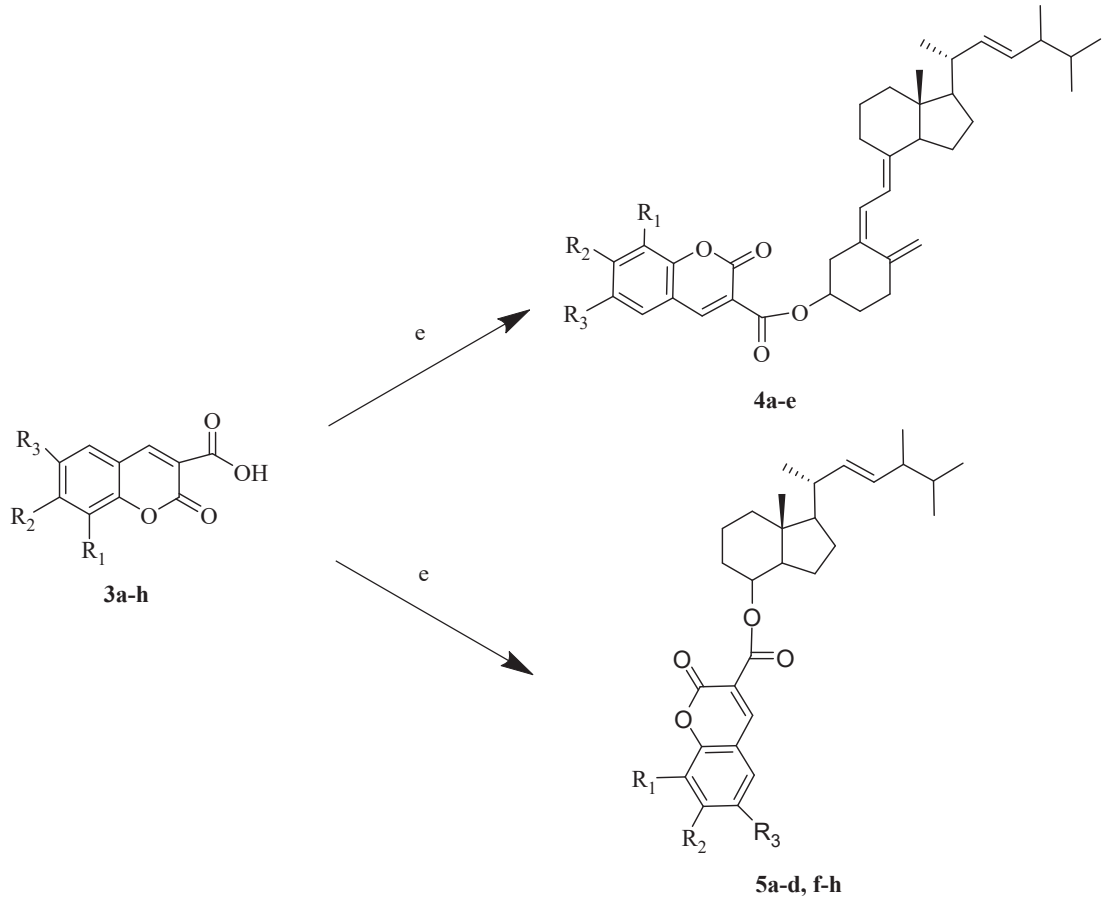

(e) DCC, DMAP, CH_2Cl_2, 400 W microwave irradiation
Scheme 2 Synthesis of vitamin D–coumarin hybrids.

Table 1 Comparison between microwave-assisted and classical reactions in the synthesis of hybrids

Entry	Hybrid	Yield (%)	
		Microwave	Classical
1	**4a**	85	71
2	**4b**	84	73
3	**4c**	81	71
4	**4d**	83	64
5	**4e**	80	68
6	**5a**	87	80
7	**5b**	86	78
8	**5c**	86	81
9	**5d**	83	71
10	**5f**	85	72
11	**5g**	80	69
12	**5h**	79	69

of *N,N′*-dicyclohexylcarbodiimide (DCC) as dehydrating agent and 4-dimethylaminopyridine (DMAP) as catalyst, coumarin-3-carboxylic acid **3h** and vitamin D or vitamin D CD-ring alcohol (which was derived from commercially available vitamin D_2 using the procedures reported by our group)[22] were dissolved in CH_2Cl_2 and refluxed to give **4a** in a yield of 71%. Extending the reaction time did not improve the yield as was the case with the other reactions. Recently, we have demonstrated the application of microwave irradiation in the synthesis of aryl ketone β-C-glycosides and novel oxime analogues of vitamin D_2. This gave high yields in very fast and clean reactions.[22] Thus, when a mixture of vitamin D, coumarin-3-carboxylic acid **3a**, DCC and DMAP in CH_2Cl_2 was irradiated in a microwave reactor at 400 W for 15 min, the reaction proceeded rapidly to give the target compound with a yield of 85%. Consequently, the other reactions were also investigated with microwave irradiation, as shown in Table 1.

Conclusion

In summary, a group of vitamin D–coumarin hybrids were successfully synthesised by microwave irradiation, following our laboratory precedents and the principle of molecular hybridisation. Compared with conventional methodologies, this methodology offers attractive features, including higher yields and shorter reaction time. We consider that the successful synthesis of the target compound could provide an experimental foundation for synthesising vitamin D hybrids to develop bioactive molecules that could be used as new medicines.

Experimental

All operations were carried out under an atmosphere of ultrahigh-purity argon in oven-dried glass. Most of the organic compounds utilised in this study were commercial products of the highest purity. The reactions were monitored by thin-layer chromatography (TLC). Microwave irradiation was performed in a MAS-1 microwave reactor apparatus (Shanghai Sineo Microwave Chemistry Technology Co., Ltd). HRMS spectra were obtained on a Bruker Apex II by means of the ESI technique. ^{1}H NMR spectra were recorded at 500 MHz with a Bruker Avance III 500 NMR spectrometer in $CDCl_3$. ^{13}C NMR were recorded at 125 MHz with a Bruker Avance III 500 NMR spectrometer in $CDCl_3$.

Synthesis of compounds **2b**–**h**; *general procedure*

$CHCl_3$ (0.5 mL) was added dropwise to a stirred mixture of the corresponding phenol (4 mmol), tributylamine (0.08 mmol), and

NaOH (14.4 mmol) in ethanol and water at 60 °C. After completion of the addition, the reaction mixture was stirred for 40 min at 60 °C, then cooled, and acidified to pH 2 with HCl (2 N). The organic layer was collected and the aqueous layer was extracted with chloroform. The combined organic solution was evaporated under reduced pressure and purified by chromatography to give the target compounds **2b**–**h**.

Synthesis of compounds **3a**–**h**; *general procedure*

A stirred solution of intermediate **2** (10 mmol) in EtOH was treated with methylmalonate (11 mmol), piperidine (50 μL) and glacial acetic acid. The mixture was heated under reflux for 6 h. This mixture was treated slowly with a 0.5% NaOH aqueous solution and stirred for 0.5 h at this temperature. The mixture was then poured into cool water, acidified to pH 2 with HCl (2 N), filtered and washed with alcohol to give the compounds **3a**–**h**. The melting points of compounds **3a**–**h** are given in the ESI.

Synthesis of compounds **4a**–**e**, **5a**–**d**,**f**–**h** *by classical route; general procedure*

DCC (5 mmol) and DMAP (0.5 mmol) were added to a solution of the coumarin-3-carboxylic acids (6 mmol) and vitamin D_2 or vitamin D_2 CD-ring alcohol (5 mmol). The resulting mixture was refluxed for 2 h to form the corresponding hybrids. On reaction completion, they were extracted with ethyl acetate (2 × 50 mL), washed with water (2 × 60 mL) and brine (2 × 60 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by silica gel column chromatography to yield the target compounds.

Synthesis of compounds **4a**–**e**, **5a**–**d**,**f**–**h** *under microwave irradiation; general procedure*

A mixture of coumarin-3-carboxylic acid (6 mmol), vitamin D_2 or vitamin D_2 CD-ring alcohol (5 mmol), DCC (5 mmol) and DMAP (0.5 mmol) was irradiated in a MAS-1 microwave reactor apparatus at 400 W for 15 min. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (2 × 50 mL), washed with water (2 × 60 mL) and brine (2 × 60 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by silica gel column chromatography to give compounds **4a**–**e**, **5a**–**d**,**f**–**h**.

Compound **4a**: White solid; yield 85%; m.p. 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (1H, s), 7.67 (1H, m), 7.60 (1H, m), 7.33 (2H, d, *J* = 8.0 Hz), 6.25 (1H, d, *J* = 11.2 Hz), 6.06 (1H, d, *J* = 11.2 Hz), 5.28 (3H, m), 5.09 (1H, s), 4.87 (1H, d, *J* = 1.7 Hz), 2.85 (1H, m), 2.70 (1H, d, *J* = 13.4 Hz), 2.60 (2H, m), 2.35 (1H, m), 2.13 (6H, m), 1.90 (1H, m), 1.74 (3H, m), 1.56 (3H, m), 1.39 (3H, m), 1.01 (3H, d, *J* = 6.6 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 0.83 (6H, t, *J* = 7.2 Hz), 0.56 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.34, 156.79, 155.29, 148.27, 144.60, 142.73, 135.77, 134.41, 134.27, 132.13, 129.65, 124.95, 122.92, 118.79, 118.05, 117.64, 116.94, 113.10, 77.27, 77.01, 73.60, 56.65, 46.03, 42.99, 42.17, 40.57, 33.27, 32.31, 32.02, 29.24, 27.98, 23.74, 22.41, 21.30, 20.14, 19.83, 17.77, 12.44. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{48}O_4$ [M + Na]$^+$: 591.3445; found: 591.3459.

Compound **4b**: White solid; yield 84%; m.p. 145–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (1H, s), 7.72 (2H, m), 7.23 (1H, d, *J* = 8.7 Hz), 6.23 (1H, d, *J* = 11.2 Hz), 6.06 (1H, d, *J* = 11.2 Hz), 5.28 (3H, m), 5.09 (1H, s), 4.87 (1H, d, *J* = 2.0 Hz), 2.78 (1H, d, *J* = 13.8 Hz), 2.67 (1H, d, *J* = 13.5 Hz,), 2.60 (2H, m,), 2.34 (1H, m), 2.12 (5H, m), 1.85 (1H, d, *J* = 12.9 Hz), 1.78 (4H, m), 1.57 (3H, m), 1.36 (3H, m), 1.01 (3H, d, *J* = 6.6 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 0.86 (6H, m), 0.56 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.72, 154.90, 152.91, 145.63, 143.36, 141.74, 135.81, 134.60, 133.12, 130.99, 130.53, 121.84, 118.80, 118.37, 117.51, 116.44, 116.27, 111.97, 76.29, 75.78, 72.59, 55.48, 44.89, 41.82, 40.93, 39.39, 32.11, 30.98, 30.68, 28.09, 26.78, 22.58, 21.27, 20.12, 18.96, 18.65, 16.60, 11.27. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{47}BrO_4$ [M + Na]$^+$: 669.2550; found: 669.2551.

Compound **4c**: White solid; yield 81%; m.p. 150–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (1H, s), 7.58 (2H, m), 7.30 (1H, d, *J* = 8.8 Hz), 6.24 (1H, d, *J* = 11.2 Hz), 6.06 (1H, d, *J* = 11.3 Hz), 5.29 (3H, m), 5.10 (1H, s), 4.88 (1H, d, *J* = 2.1 Hz), 2.83 (1H, m), 2.68 (1H, d, *J* = 13.5), 2.60 (2H, m), 2.34 (1H, m), 2.09 (6H, m), 1.85 (2H, d, *J* = 12.9), 1.68 (4H, m), 1.47 (3H, d, *J* = 12.9), 1.34 (3H, m), 1.02 (3H, d, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 0.87 (6H, m), 0.56 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.60, 156.04, 153.24, 146.11, 144.34, 142.80, 135.44, 133.89, 131.33, 128.98, 127.15, 123.22, 118.75, 117.86, 117.27, 116.44, 111.85, 73.79, 55.22, 45.41, 41.83, 40.94, 39.40, 32.50, 30.86, 28.87, 26.49, 22.58, 21.26, 20.12, 18.80, 16.60, 12.42. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{47}ClO_4$ [M + Na]$^+$: 625.3055; found: 625.3059.

Compound **4d**: White solid; yield 83%; m.p. 131–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (1H, s), 7.43 (1H, d, *J* = 8.3 Hz), 7.11 (2H, d, *J* = 5.2 Hz), 6.23 (1H, d, *J* = 11.2 Hz), 6.05 (1H, d, *J* = 11.2 Hz), 5.19 (3H, d, *J* = 9.0 Hz), 5.07 (1H, s), 4.85 (1H, d, *J* = 2.0 Hz), 2.84 (1H, m), 2.68 (1H, d, *J* = 13.4 Hz), 2.58 (m, 5H), 2.26 (1H, s), 2.11 (6H, m), 1.84 (1H, d, *J* = 6.6 Hz), 1.73 (3H, m), 1.57 (3H, m), 1.36 (6H, m), 1.00 (3H, d, *J* = 6.6 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 0.81 (6H, t, *J* = 7.2 Hz), 0.55 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.31, 155.91, 154.31, 147.22, 145.21, 143.47, 141.50, 134.60, 133.16, 130.95, 128.19, 125.10, 121.71, 116.48, 115.87, 114.54, 111.88, 76.10, 75.84, 72.24, 55.47, 44.85, 41.81, 41.02, 39.40, 32.10, 31.16, 30.86, 28.70, 28.06, 26.80, 22.56, 21.23, 21.12, 20.12, 18.97, 18.65, 16.60, 11.26. HRMS (ESI) *m*/*z* calcd for $C_{39}H_{50}O_4$ [M + Na]$^+$: 605.3601; found: 605.3604.

Compound **4e**: Yellow solid; yield 80%; m.p. 147–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (1H, s), 7.70 (1H, d, *J* = 2.3 Hz), 7.48 (1H, d, *J* = 2.3 Hz), 6.26 (1H, d, *J* = 11.2 Hz), 6.09 (1H, d, *J* = 11.3 Hz), 5.30 (3H, m), 5.13 (1H, s), 4.91 (1H, d, *J* = 2.1 Hz), 2.82 (1H, d, *J* = 13.9 Hz), 2.71 (1H, d, *J* = 3.3 Hz), 2.63 (2H, m), 2.32 (1H, s), 2.16 (5H, m), 1.88 (1H, d, *J* = 6.6 Hz), 1.80 (3H, m), 1.62 (1H, d, *J* = 7.6 Hz), 1.53 (3H, d, *J* =14.4 Hz), 1.32 (3H, d, *J* = 12.9 Hz), 1.05 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.91 (6H, m), 0.59 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.39, 153.77, 148.44, 145.27, 143.34, 141.80, 134.63, 132.95, 131.04, 128.89, 126.01, 121.90, 119.69, 118.67, 116.47, 112.06, 72.91, 55.53, 44.93, 41.86, 40.92, 39.44, 32.14, 30.97, 30.71, 28.14, 26.80, 22.61, 21.29, 20.15, 18.98, 18.68, 16.62, 11.29. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{46}Cl_2O_4$ [M + Na]$^+$: 659.2665; found: 659.2668.

Compound **5a**: White solid; yield 87%; m.p. 142–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (1H, s), 7.69 (2H, m), 7.38 (2H, m), 5.40 (1H, d, *J* = 1.9 Hz), 5.17 (2H, d, *J* = 7.5 Hz), 2.01 (3H, d, *J* = 9.4 Hz), 1.87 (2H, m), 1.73 (1H, m), 1.50 (6H, d, *J* = 4.9 Hz), 1.25 (6H, d, *J* = 15.2 Hz), 1.17 (1H, m), 1.00 (6H, d, *J* = 6.8 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.81 (6H, t, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.92, 155.54, 154.12, 146.81, 134.47, 133.13, 131.02, 128.46, 123.73, 118.04, 116.95, 115.75, 72.54, 55.36, 50.58, 41.81, 40.82, 38.88, 32.08, 29.55, 28.70, 26.52, 21.71, 19.81, 18.96, 18.65, 17.02, 16.63, 12.47. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{38}O_4$ [M + Na]$^+$: 473.2662; found: 473.2666.

Compound **5b**: White solid; yield 86%; m.p. 168–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (1H, s), 7.80 (2H, m), 7.22 (1H, d, *J* = 8.8 Hz), 5.39 (1H, d, *J* = 2.1 Hz), 5.16 (2H, d, *J* = 7.7 Hz), 2.09 (3H, m), 1.87 (2H, m), 1.75 (1H, d, *J* = 7.8 Hz), 1.73 (1H, m), 1.59 (6H, m), 1.30 (4H, m), 1.12 (1H, t, *J* = 8.3 Hz), 0.98 (6H, q, *J* = 7.0 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.83 (6H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.49, 154.80, 152.90, 145.32, 135.73, 134.42, 131.05, 130.50, 119.14, 118.42, 117.50, 116.23, 72.89, 55.33, 50.53, 41.80, 40.80, 38.85, 32.08, 29.50, 28.69, 26.50, 21.70, 19.81, 18.97, 18.65, 16.99, 16.63, 12.49. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{37}BrO_4$ [M + Na]$^+$: 551.1767; found: 551.1769.

Compound **5c**: White solid; yield 86%; m.p. 165–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (1H, s), 7.57 (2H, d, *J* = 7.0 Hz), 7.30 (1H, d, *J* = 8.5 Hz), 5.41 (1H, d, *J* = 2.1 Hz), 5.25 (2H, m), 2.01 (3H, m, *J* = 15.5 Hz), 1.90 (2H, m), 1.75 (1H, m), 1.63 (6H, m), 1.50 (3H, m), 1.33 (3H, m), 1.14 (1H, t, *J* = 9.6 Hz), 1.00 (6H, d, *J* = 5.9 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 0.82 (6H, m, *J* = 9.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.60, 154.91, 152.50, 145.38, 134.46, 132.97, 131.13, 129.09, 127.44, 119.32, 117.96, 117.29, 72.97, 55.40, 50.59, 41.85, 40.86, 38.88, 32.12, 29.56, 26.51, 21.74, 19.83, 18.98, 18.67, 17.03, 16.64, 12.51. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{37}ClO_4$ [M + Na]$^+$: 507.2278; found: 507.2178.

Compound **5d**: White solid; yield 83%; m.p. 135–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (1H, s), 7.46 (1H, d, *J* = 7.7 Hz), 7.13 (2H, d, *J* = 7.9 Hz), 5.40 (1H, d, *J* = 2.4 Hz), 5.18 (2H, m, *J* = 7.5 Hz), 2.47 (3H,

s), 2.08 (3H, m), 1.90 (2H, m), 1.74 (2H, m), 1.59 (6H, m), 1.34 (3H, m), 1.19 (1H, m), 1.01 (6H, d, *J* = 6.5 Hz), 0.90 (3H, t, *J* = 6.2 Hz), 0.85 (6H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.10, 155.87, 154.33, 146.95, 145.09, 134.49, 131.02, 128.16, 125.04, 116.61, 115.90, 114.62, 72.36, 55.36, 50.60, 41.81, 40.82, 38.94, 32.09, 29.56, 26.53, 21.72, 21.11, 19.81, 18.96, 17.04, 16.62, 12.49. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{40}O_4$ $[M + Na]^+$: 487.2819; found: 487.2827.

Compound **5f**: White solid; yield 85%; m.p. 171–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (1H, s), 7.51 (1H, d, *J* = 8.7 Hz), 6.91 (1H, m, *J* = 8.7, 2.4 Hz), 6.84 (1H, d, *J* = 2.3 Hz), 5.43 (1H, d, *J* = 2.4 Hz), 5.21 (2H, m, *J* = 7.5 Hz), 3.93 (3H, s), 2.11 (3H, m), 1.93 (2H, m), 1.72 (1H, m, *J* = 9.0 Hz), 1.63 (1H, s), 1.62 (6H, m), 1.35 (3H, m), 1.18 (1H, q, *J* = 9.5 Hz), 1.08 (6H, m), 0.93 (3H, t, *J* = 9.5 Hz), 0.89 – 0.82 (6H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.03, 162.28, 156.55, 155.96, 147.21, 134.54, 131.05, 129.67, 113.90, 112.54, 110.72, 99.40, 72.18, 55.43, 55.02, 50.68, 41.85, 40.86, 38.95, 32.13, 29.63, 26.56, 21.77, 19.84, 18.98, 18.67, 17.09, 16.65, 12.53. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{40}O_5$ $[M + Na]^+$: 503.2768; found: 503.2774.

Compound **5g**: White solid; yield 80%; m.p. 194–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (1H, d, *J* = 2.6 Hz), 8.53 (2H, m), 7.50 (1H, t, *J* = 8.8 Hz), 5.43 (1H, d, *J* = 2.4 Hz), 5.27 (2H, m), 2.10 (3H, m), 1.88 (2H, m), 1.62 (2H, d, *J* = 9.7 Hz), 1.61 (4H, m), 1.51 (3H, m), 1.31 (m, 12H), 1.06 (6H, m), 0.94 (2H, m), 0.81 (6H, m, *J* = 15.9, 8.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.01, 157.33, 153.81, 145.20, 143.19, 134.37, 131.14, 127.42, 124.18, 120.32, 116.98, 73.44, 55.32, 49.82, 41.81, 40.82, 38.82, 32.09, 29.49, 28.70, 26.47, 21.70, 19.82, 18.96, 18.64, 16.97, 16.62, 12.52. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{37}NO_6$ $[M + Na]^+$: 518.2513; found: 518.2517.

Compound **5h**: Yellow solid; yield 80%; m.p. 154–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (1H, s), 7.31 (1H, d, *J* = 9.1 Hz), 7.24 (1H, m, *J* = 9.1, 2.9 Hz), 7.01 (1H, d, *J* = 2.9 Hz), 5.44 (1H, d, *J* = 2.5 Hz), 5.21 (2H, m, *J* = 7.5 Hz), 3.90 (3H, s), 2.12 (3H, m), 1.91 (2H, m), 1.77 (1H, m), 1.64 (1H, s), 1.62 (6H, m), 1.34 (3H, m), 1.22 (1H, m), 1.05 (6H, d, *J* = 7.9 Hz), 0.96 (3H, m), 0.86 (6H, m, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.08, 155.79, 155.28, 148.74, 146.54, 134.52, 131.07, 121.37, 118.39, 117.24, 116.90, 109.73, 72.58, 55.41, 54.97, 50.63, 41.85, 40.87, 38.92, 32.13, 29.60, 26.55, 21.76, 19.84, 18.98, 18.67, 17.07, 16.65, 12.53. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{40}O_5$ $[M + Na]^+$: 503.2768; found: 503.2770.

Electronic Supplementary Information

The ESI is available through: http://ingentaconnect.com/content/stl/jcr/2017/00000041/00000012/art00002

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