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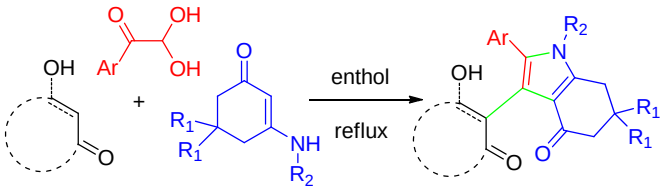

An Efficient Synthesis of Functionalized Dihydro-1*H*-indol-4(5*H*)-ones via One-Pot Three-Component Reaction under Catalyst-Free Conditions

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ABSTRACT: A facile and efficient one-pot procedure for the preparation of functionalized dihydro-1*H*-indol-4(5*H*)-ones by a catalyst-free, three-component reaction of 1,3-dicarbonyl compounds, arylglyoxal monohydrate and enaminones under mild conditions in excellent yield is reported. This synthesis was confirmed to follow the group-assisted-purification (GAP) chemistry process, which can avoid traditional purifications, chromatography and recrystllization.

KEYWORDS: functionalized dihydro-1*H*-indol-4(5*H*)-ones, multi-component reactions, group-assisted-purification (GAP) chemistry process.

Introduction

Multi-component reactions (MCRs) are chemical transformations in which three or more different starting materials combine together via a one-pot procedure to give a final complex product. Such reactions have emerged as powerful and bond-forming efficient tools in organic, combinatorial and medicinal chemistry for their facileness and efficiency as well as their economy and ecology in organic synthesis.[1] In the past decade, there have been tremendous developments in three- and four-component reaction and significant efforts continue to be made to develop new MCRs.[2]

The indole nucleus is probably the most well-known heterocyclic compound, a common and important feature of a variety of natural products and medicinal agents.[3] Compounds carrying the indole moiety exhibit antibacterial and antifungal activities.[4]

It is used as an important skeleton in organic synthesis[5] and is also utilized in other important fields, such as medicinal chemistry.[6] As a consequence, a number of methods have been reported for the construction of indoles.[7] Recently, some functionalized indoles have been synthesized by using different starting materials.[8]

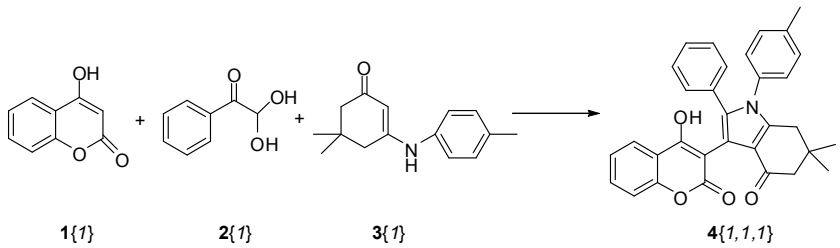
4-Hydroxycoumarins are a very important class of biologically active substances in nature and in medicine. They exhibit mainly anticoagulant activity and there are some drugs which are widely used as anticoagulants.[9] They exhibit cytotoxic[10] and antioxidant activities[11] as well as activity against HIV.[12] However, to the best of our knowledge, there have been few reports about the synthesis of coumarin-fused indole derivatives by multi-component reactions. Our interest in the synthesis of indole derivatives[13] guided by the observation that the presences of two or more different heterocyclic moieties in a single molecule often enhances remarkably the biological activity, we herein described a facile synthesis of 3-(4-hydroxycoumarin-3-yl)-dihydro-1*H*-indol-4(5*H*)-ones derivatives by a three-component reaction of 4-hydroxycoumarin, arylglyoxal monohydrates and enaminones in ethanol without any catalyst.

Results and discussion

We initially evaluated the three-component reaction of the 4-hydroxycoumarin **1**{*1*}, phenylglyoxal monohydrate **2**{*1*}, and enaminone **3**{*1*}(Scheme 1). The reaction mixture, which was composed of a 1:1:1 mixture of **1**{*1*}, **2**{*1*} and **3**{*3*}, was tested under a variety of different conditions. The effects of solvent and temperature were evaluated for this reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out in water without any catalyst the yield of product was very low (Table 1, Entry 1). Chloroform and ethanol provided higher yields than those using other organic solvents (Table 1, Entry 5-6 *vs* Entries 2-4). Considering the volatility and toxicity of the chloroform, ethanol was chosen as the solvent for all further reactions. To identify the optimum reaction temperature, the reaction was carried out at r.t., 40ºC, 60ºC and reflux temperature, providing the product **4**{*1*,*1*,*1*} in yields of 34%, 52%, 80% and 94% (Table 1, Entries

7-9 and 6), respectively. The use of additives, such as *L*-proline, resulted in no significant improvement of the yield (Table 1, Entry 10). Thus, the optimum conditions tested were refluxing ethanol without any catalyst.

Scheme 1 . Model Reaction



1{*1*} **2**{*1*} **3**{*1*} **4**{*1,1,1*}

Table 1. **Optimizing the Reaction Conditions for the Synthesis of 4**{*1,1,1*}

Entry	Solvent	Temperature (°C)	Time (h)	Yield [a] (%)
1	H_2O	80	1.0	34
2	DMF	80	1.0	69
3	Acetone	reflux	1.0	78
4	CH_3CN	reflux	1.0	80
5	$CHCl_3$	reflux	1.0	92
6	EtOH	reflux	1.0	94
7	EtOH	r. t.	1.0	34
8	EtOH	40	1.0	52
9	EtOH	60	1.0	80
10	EtOH+*L*-proline (10 mol %)	reflux	1.0	90

[a] Yield was determined by HPLC-MS, if the precipitated solids were occurred during the reaction, acetonitrile should be added to dissolve the solids before determining the yield.

The optimized reaction conditions were then tested for library construction with eight 1,3-dicarbonyl compounds **1**{*1-8*}, five phenylglyoxal monohydrates **2**{*1-5*}, and sixteen enaminones **3**{*1-16*} (Figure 1). The corresponding functionalized indole derivatives **4** were obtained in good yields in catalyst free, refluxing ethanol. The results are summarized in Table 2. This protocol was efficient with 1,3-dicarbonyl compounds with either 1,3-diketones or *β*-keto esters. It was also found that *n*-butyl and phenyl groups, bearing either electron-withdrawing or electron-donating groups on the enaminone ring, were tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 94%). Moreover, this synthesis followed the GAP chemistry (group-assisted-purification chemistry)[14] process, which can avoid

traditional chromatography and recrystallization purifications. Pure products can be obtained by washing the solid, crude products with cold ethanol.

The structures of all products **4** were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS analysis. The structure of compound **4**{*1*,*1*,*1*} was further confirmed by X-ray diffraction analysis. The molecular structure of compound **4**{*1*,*1*,*1*} is shown in Figure 2.

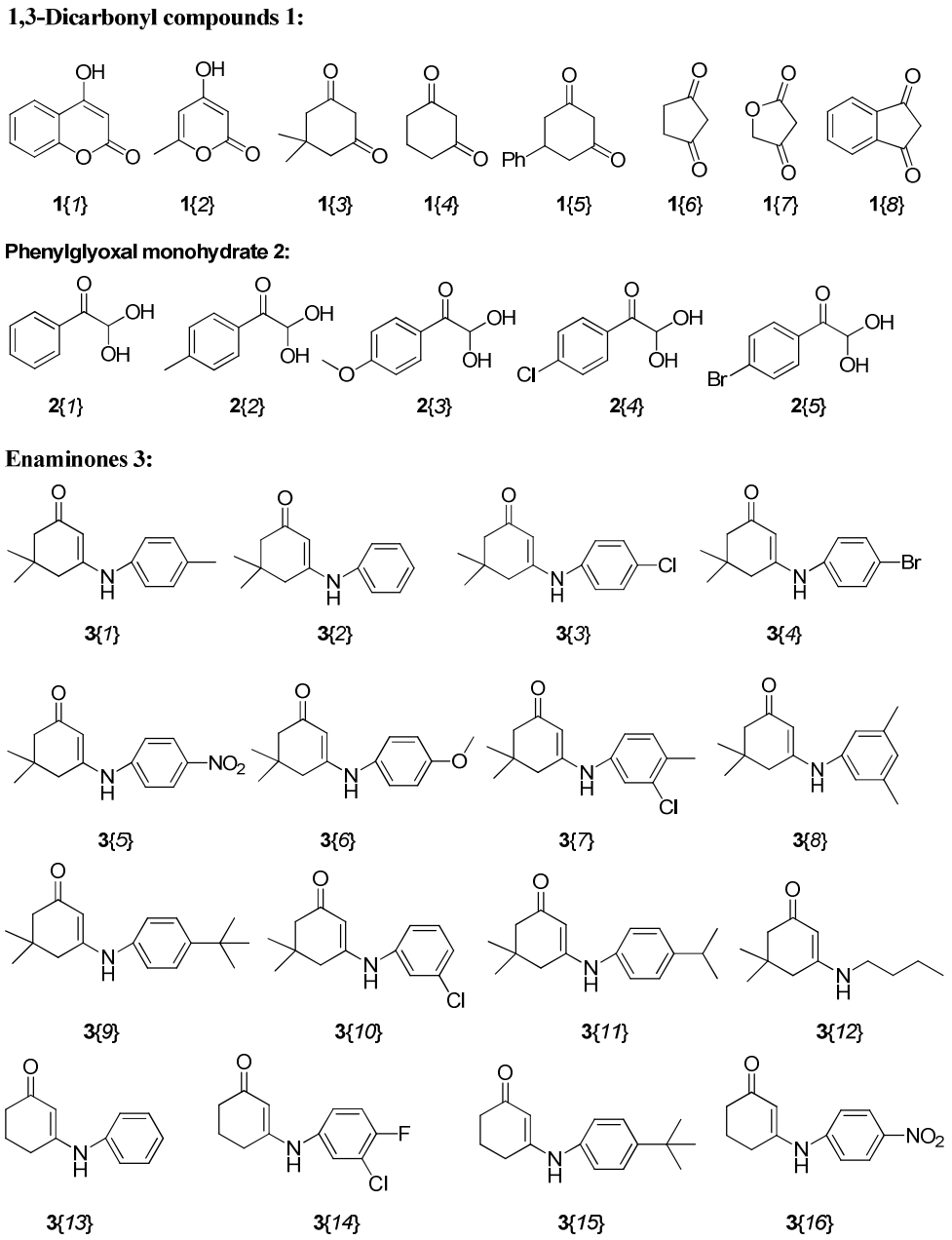
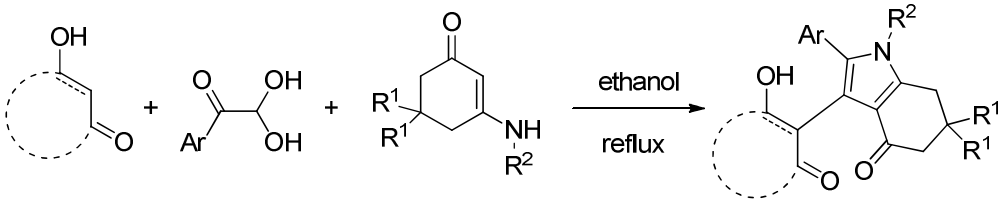


Figure 1 . Diversity of reagents.

Table 2 . Synthesis of functionalized dihydro-1*H*-indol-4(5*H*)-one derivatives 4



1{*1-8*} **2**{*1-5*} **3**{*1-16*} **4**{**1**{*1-8*},**2**{*1-5*},**3**{*1-16*}}

Entry	Products	Time (h)	Isolated Yield (%)	M.P. (ºC)
1	**4**{*1,1,1*}	1.0	89	162-163
2	**4**{*1,1,2*}	1.0	91	308-310
3	**4**{*1,1,3*}	2.0	88	170-172
4	**4**{*1,1,4*}	1.5	90	176-178
5	**4**{*1,1,5*}	4.0	77	185-186
6	**4**{*1,1,6*}	0.7	90	270-271
7	**4**{*1,1,7*}	1.0	94	152-154
8	**4**{*1,1,8*}	1.0	87	294-295
9	**4**{*1,1,9*}	1.0	88	268-269
10	**4**{*1,1,10*}	1.5	82	278-280
11	**4**{*1,1,12*}	1.0	81	114-116
12	**4**{*1,1,13*}	1.0	87	282-284
13	**4**{*1,1,14*}	1.5	90	172-174
14	**4**{*1,1,15*}	1.0	94	278-279
15	**4**{*1,1,16*}	5.0	72	167-170
16	**4**{*1,2,3*}	1.5	83	250-251
17	**4**{*1,2,11*}	1.0	90	172-174
18	**4**{*1,3,1*}	1.5	85	264-265
19	**4**{*1,3,3*}	1.5	92	172-173
20	**4**{*1,4,1*}	1.5	89	> 300
21	**4**{*1,4,3*}	1.5	94	> 300
22	**4**{*1,5,3*}	1.5	92	> 300
23	**4**{*1,5,11*}	1.0	93	> 300

24	**4**{*2*,*1*,*1*}	1.0	81	268-270
25	**4**{*2*,*1*,*3*}	3.0	88	282-283
26	**4**{*2*,*1*,*6*}	0.7	85	142-144
27	**4**{*2*,*1*,*12*}	1.0	80	279-281
28	**4**{*3*,*1*,*1*}	1.0	80	196-198
29	**4**{*3*,*1*,*6*}	0.7	82	183-184
30	**4**{*4*,*1*,*1*}	1.0	75	174-175
31	**4**{*5*,*1*,*1*}	1.0	77	137-138
32	**4**{*5*,*1*,*3*}	1.5	88	154-156
33	**4**{*6*,*1*,*1*}	1.0	84	293-295
34	**4**{*6*,*1*,*3*}	1.5	89	290-292
35	**4**{*7*,*1*,*1*}	1.0	76	142-144
36	**4**{*8*,*1*,*1*}	1.5	82	239-240
37	**4**{*8*,*1*,*3*}	1.0	85	224-226

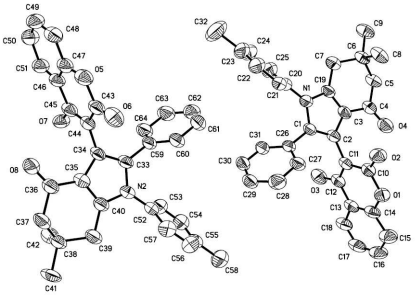
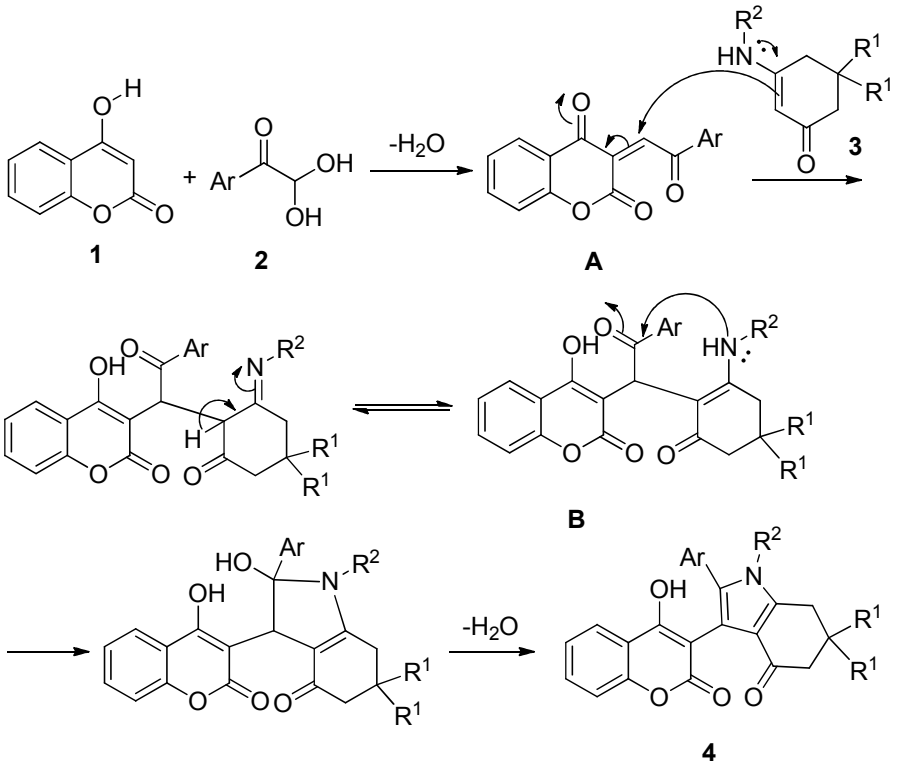


Figure 2 . **Crystal structure of compound 4**{*1*,*1*,*1*}

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of compound **4** could be explained by the reaction sequence in Scheme 2. First, a Knoevenagel condensation of 1,3-dicarbonyl compounds **1** with phenylglyoxal **2** is proposed to give intermediate **A**. Michael addition of enaminone **3** to intermediate **A** then occurs to provide intermediate **B**, which undergoes intramolecular cyclization and dehydration to form the desired product **4**.

Scheme 2 . Proposed Mechanism for the synthesis of 4



Conclusion

The new GAP synthesis of functionalized dihydro-1*H*-indol-4(5*H*)-one derivatives has been achieved by three-component reaction of 1,3-dicarbonyl compounds, arylglyoxal monohydrates and enaminones under mild conditions without any catalyst. Good chemical yields have been achieved without the use of the traditional purifications, chromatography and recrystallization.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR and ^{13}C NMR were determined on Varian Invoa-400 MHz or Invoa-300 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS analyses were carried out using Bruker micrOTOF-Q instrument or TOF-MS instrument.

General Procedure for the Synthesis of 4. A dry 25 mL flask was charged with 1,3-dicarbonyl compounds **1** (1 mmol), phenylglyoxal monohydrate **2** (1 mmol),

enaminones **3** (1 mmol) and ethanol (5 mL). The mixture was stirred at refluxing temperature for 0.7-5 h. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The crystalline solids were collected and washed with little cold ethanol to give the pure products **4**.

Compound 4{*1*,*1*,*1*}: White powder; IR (KBr, *v*, cm^{-1}): 3430, 3280, 3058, 2956, 2869, 1729, 1694, 1665, 1624, 1515, 1492, 1451, 1408, 1366, 1270, 1194, 1103, 1044, 1020, 961, 897, 837, 757, 699; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.81 (s, 1H, OH), 7.77 (d, J = 8.0 Hz, 1H, ArH), 7.54 (t, J = 7.6 Hz, 1H, ArH), 7.31-7.24 (m, 2H, ArH), 7.19 (d, J = 7.6 Hz, 2H, ArH), 7.09-6.99 (m, 7H, ArH), 2.56 (d, J = 16.4 Hz, 1H, CH_2), 2.47-2.45 (m, 1H, CH_2), 2.30-2.26 (m, 4H, CH_2+CH_3), 2.16 (d, J = 15.6 Hz, 1H, CH_2), 1.04 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 192.80, 162.17, 161.17, 152.78, 144.37, 138.06, 135.37, 134.90, 132.36, 131.41, 130.19, 130.02, 129.77, 128.26, 127.96, 127.65, 124.25, 123.86, 118.27, 116.45, 109.36, 100.34, 52.62, 36.85, 35.38, 28.91, 28.38, 21.07; HRMS calcd for $C_{32}H_{27}NNaO_4$ $[M+Na]^+$: 512.1838, found: 512.1842.

Compound 4{*2*,*1*,*1*}: Light red powder; IR (KBr, *v*, cm^{-1}): 3427, 3063, 3035, 2938, 2867, 2735, 2691, 1662, 1637, 1576, 1515, 1492, 1447, 1404, 1367, 1279, 1233, 1209, 1107, 1125, 1081, 1050, 1000, 934, 923, 828, 804, 766, 726, 699, 650; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.64 (s, 1H, OH), 7.17-6.97 (m, 9H, ArH), 5.91 (s, 1H, =CH), 2.50-2.45 (m, 2H, CH_2), 2.25-2.18 (m, 5H, CH_2+CH_3), 2.10 (s, 3H, CH_3), 1.00 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 192.46, 166.34, 164.14, 160.89, 143.64, 137.88, 134.96, 134.27, 131.88, 130.18, 129.67, 128.19, 127.91, 127.33, 118.14, 110.74, 100.51, 97.07, 52.75, 36.89, 35.19, 28.67, 28.59, 21.05, 19.75; HRMS calcd for$C_{29}H_{27}NO_4$ $[M]^+$: 453.1940, found: 453.1929.

Compound 4{*3*,*1*,*6*}: White powder ; IR (KBr, *v*, cm^{-1}): 3588, 3425, 3056, 3030, 2957, 2892, 2644, 1670, 1585, 1562, 1513, 1486, 1451, 1367, 1299, 1257, 1211, 1166, 1148, 1046, 1028, 1013, 921, 845, 807, 775, 718, 702; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.63 (s, 1H, OH), 7.08-7.03 (m, 5H, ArH), 6.92-6.89 (m, 4H, ArH), 3.71 (s, 3H, OCH_3), 2.46-1.96 (m, 8H, 4×CH_2), 1.09-0.87 (m, 12H, 4×CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 196.51, 192.26, 170.40, 158.83, 143.57, 133.94,

132.17, 130.50, 129.71, 129.32, 127.92, 126.99, 118.32, 114.69, 112.19, 109.66, 56.49, 55.72, 52.88, 36.93, 35.17, 32.06, 28.77, 28.29, 19.02; HRMS calcd for $C_{31}H_{33}NO_4$ $[M]^+$: 483.2410, found: 483.2398.

Compound 4{*4,1,1*}: White powder ; IR (KBr, *v*, cm^{-1}): 3431, 3059, 3033, 2952, 2875, 2620, 1664, 1578, 1515, 1491, 1448, 1422, 1381, 1334, 1280, 1209, 1183, 1160, 1117, 1071, 1049, 985, 923, 833, 811, 769, 730, 697, 649; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.76 (s, 1H, OH), 7.15-6.90 (m, 9H, ArH), 2.47-1.70 (m, 13H, CH_3+5×CH_2), 0.98 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 192.36, 143.35, 137.63, 135.27, 133.55, 132.12, 130.10, 129.61, 129.53, 128.07, 127.95, 127.89, 126.92, 118.40, 112.67, 110.82, 52.88, 36.98, 36.95, 35.16, 28.67, 21.04, 20.91, 19.01; HRMS calcd for $C_{29}H_{28}NO_3$ $[M-H]^+$: 438.2069, found: 438.2073.

Compound 4{*5,1,3*}: White powder; IR (KBr, *v*, cm^{-1}): 3432, 3089, 3028, 2955, 2892, 1049, 1620, 1578, 1448, 1417, 1383, 1363, 1244, 1116, 1091, 1069, 1050, 1014, 923, 888, 843, 760, 724, 649; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.04 (s, 1H, OH), 7.04-6.93 (m, 14H, ArH), 3.35-3.10 (m, 1H, CH), 2.61-2.19 (m, 8H, 4×CH_2), 0.99 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 192.57, 192.44, 144.09, 143.95, 143.47, 143.42, 136.71, 133.81, 133.56, 132.83, 131.86, 131.74, 130.00, 129.70, 129.65, 129.02, 128.96, 128.22, 128.19, 127.33, 127.15, 118.59, 112.84, 112.79, 110.51, 110.42, 52.90, 52.84, 38.87, 38.53, 36.86, 35.22; 31.14, 28.67; HRMS calcd for $C_{34}H_{30}ClNO_3$ $[M]^+$: 535.1914, found: 535.1907.

Compound 4{*6,1,1*}: White powder; IR (KBr, *v*, cm^{-1}): 3427, 3031, 2955, 2932, 2869, 2590, 1665, 1576, 1515, 1487, 1410, 1313, 1208, 1116, 1045, 1018, 924, 840, 802, 771, 721, 699, 665, 649; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 11.36 (s, 1H, OH), 7.15-6.95 (m, 9H, ArH), 2.47-1.93 (m, 11H, CH_3+4×CH_2), 0.97 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 192.42, 143.61, 137.88, 135.07, 134.15, 133.95, 132.03, 131.87, 130.21, 129.73, 128.08, 127.92, 127.18, 118.32, 112.52, 110.16, 52.88, 36.95, 36.87, 35.12, 28.66, 28.58, 21.06; HRMS calcd for $C_{28}H_{26}NO_3$ $[M-H]^+$: 424.1913, found: 424.1940.

Compound 4{*7,1,1*}: Grey powder; IR (KBr, *v*, cm^{-1}): 3427, 3001, 2958, 2869, 1755, 1663, 1578, 1515, 1490, 1423, 1281, 1117, 1045, 1014, 924, 831, 768, 728, 698, 649;

^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 11.82 (s, 1H, OH), 7.14-7.03 (m, 9H, ArH), 4.57-4.00 (m, 2H, CH_2), 2.49-2.23 (m, 7H, CH_3+2×CH_2), 0.98 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 192.58, 174.58, 173.84, 143.84, 138.07, 134.88, 134.81, 131.43, 130.25, 129.89, 128.25, 127.92, 127.52, 118.34, 107.80, 95.79, 67.08, 52.73, 36.86, 35.17, 28.63, 28.41, 21.05; HRMS calcd for$C_{27}H_{24}NO_4$ $[M-H]^+$: 426.1705, found: 426.1714.

Compound 4{*8*,*1*,*1*}: Yellow powder; IR (KBr, v, cm^{-1}): 3433, 3001, 2955, 2869, 1751, 1651, 1516, 1490, 1465, 1445, 1417, 1367, 1321, 1246, 1206, 1154, 1114, 1040, 1014, 924, 886, 843, 778, 764, 746, 701, 649; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.88 (s, 4H, ArH), 7.20-7.15 (m, 7H, ArH), 7.07 (d, J = 7.6 Hz, 2H, ArH), 4.45 (s, 1H, CH), 2.47 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.05 (s, 2H, CH_2), 0.90 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 198.95, 193.07, 144.01, 142.27, 138.21, 137.54, 135.54, 134.56, 130.50, 130.27, 129.98, 128.83, 128.26, 127.87, 122.98, 116.47, 110.78, 53.86, 51.35, 36.46, 35.53, 28.47, 21.04; HRMS calcd for$C_{32}H_{26}NO_3$ $[M-H]^+$: 472.1913, found: 472.1923.

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Supporting Information Available. Experimental details and spectroscopic characterization for compounds **4**, and the X-ray crystallographic information for compound **4**{*1*,*1*,*1*}. This information is available free of charge via the Internet at http://pubs.acs.org/.

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