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ORIGINAL PAPER

The first catalytic application of copper aluminate nanoparticles in C–C and C–O coupling reaction: green synthesis of some new α-lapachone derivatives

Bahareh Abdolpour Mori[1] · Saeed Khodabakhshi[2] · Sanaz Tajik[2] · Mojtaba Baghernejad[1] · Amir Yadegari[2]

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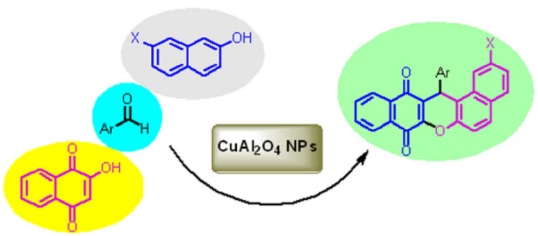
Abstract This is the first use of copper aluminate nanoparticles ($CuAl_2O_4$ NPs) as efficient catalyst for the multicomponent organic synthesis. The $CuAl_2O_4$ NPs was prepared and characterized by XRD, SEM, and TEM for this purpose and applied in the green synthesis of pyranonaphthoquinones (α-lapachone derivatives) under solvent-free conditions. The nanocatalyst can be recycled and reused for four times.

Graphical abstract



Keywords $CuAl_2O_4$ NPs · α-Lapachone · Nanocatalyst · Multicomponent · Solvent-free

Introduction

Polyheterocyclic compounds containing quinonoids are widely found in nature, and they possess a broad spectrum of biological activities. Synthesis of pyranonaphthoquinones such as α-lapachone [1] and pyranokunthone A and B [2, 3] has gained much attention because of their interesting pharmacological properties which result in manifestation of the following: anti-bacterial, anti-fungal, anti-trypanosomal, anti-malarial, and anti-tumor activities. (4*S*)-4-Hydroxy-α-lapachone and rhinacanthin A have been known as anti-tumor and mosquito cytochrome P450 enzyme inhibitor compounds, respectively [4] (Fig. 1).

Multicomponent reactions (MCRs) are known as useful methods to achieve a large number of heterocyclic scaffolds and drug-like compounds. In fact, they have become increasingly popular tools since they are economic, and they minimize waste, labor, time, and cost [5, 6].

Until now, several methods have been described in the literature for the synthesis of α-lapachone derivatives [7–12]. To the best of our knowledge, there are only two reports on the catalytic application of copper aluminate in organic reactions including catalytic decomposition of benzyl alcohol using bulk copper aluminate [13] and oxidation of benzyl alcohol using copper aluminate nanoparticles [14]. However, there is no report on the copper aluminate-catalyzed C–C and C–O coupling reactions. In continuation, we describe a three-component synthesis of α-lapachone derivatives in the presence of $CuAl_2O_4$ nanoparticles.

Result and discussion

As can be seen in Fig. 2a, the surface morphology of the prepared $CuAl_2O_4$ NPs was investigated by scanning electron microscopy (SEM). For further studies, the transmission

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✉ Saeed Khodabakhshi
saeidkhm@yahoo.com

[1] Department of Chemistry, Gachsaran Branch, Islamic Azad University, Gachsaran, Iran

[2] Department of Chemistry, Robatkarim Branch, Islamic Azad University, Robatkarim, Iran

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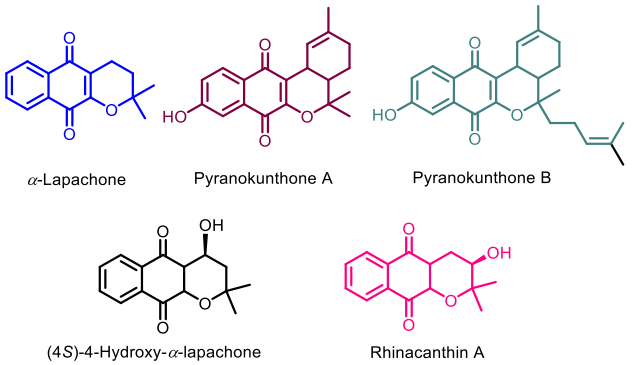


Fig. 1 Some biologically active pyranonaphthoquinones

electron microscopy (TEM) was also provided (Fig. 2b). The TEM image clearly shows the nanometric particles of the prepared $CuAl_2O_4$ with the diameters in the range of 10–30 nm. Figure 2c shows the XRD pattern of the as-synthesized $CuAl_2O_4$ NPs calcinated at 800 °C. The XRD pattern confirms the formation of the fully crystalline and single phase $CuAl_2O_4$. The six diffraction lines correspond to the $CuAl_2O_4$ phase having the perovskite crystal structure, and they are in agreement with the JCPDS values [15, 16].

In continuation of the foregoing discussion and our previous studies on the use of nanocatalysts in organic reactions [17–19], the as-synthesized $CuAl_2O_4$ NPs was used as a nanocatalyst in the synthesis of some pyranonaphthoquinones **4** (α-lapachone derivatives) through a three-component reaction of aromatic aldehydes **1**, 2-hydroxy-1,4-naphthoquinone (**2**), and β-naphthols **3** under solvent-free conditions (Scheme 1).

What is widely known to make a sustainable green process is synthesizing using no solvent. To explore and ascertain the feasibility of the above-mentioned reaction, the reaction of benzaldehyde (**1a**), **2**, and β-naphthol (**3a**) was initially chosen as a model. Firstly, solvent effect on the reaction was explored and some solvents such as MeOH, EtOH, H_2O, and CH_2Cl_2 at 110 °C were tested. By setting the reaction under solvent-free conditions, however, the best yield of the corresponding product was afforded (Table 1). In another variation, the effect of catalyst amount on the reaction rate and product yield was also investigated (Table 1). Besides, the temperature played a key role because there was no product formation at room temperature under solvent-free conditions while the reaction led to the desired product in 92 % yield at 110 °C. As a matter of fact, increasing the temperature markedly affects the reaction (Table 1).

After screening, it was found that the condensation reaction can be efficiently performed by adding 0.07 mmol of the catalyst at 110 °C under solvent-free conditions in a short time span of 70 min. Encouraged by these results, as shown in Table 2, we investigated the reaction scope for the synthesis of compounds **4**.

A variety of aldehydes **1** were reacted with **2** and **3** under standard conditions. Regardless of the electronic nature and the substitution on the aromatic rings of **1** and **3**, the reaction afforded corresponding pyranonaphthoquinones **4** in good to excellent yields.

A mechanistic rationale for the formation of compounds **4** in the presence of metal oxides is proposed in Scheme 2.

It is conjectured that the reaction takes place in three steps. The initial event involves the Knovenagel coupling of aldehyde with naphthol. Next, the Michael addition of naphthoquinone to the intermediate and intramolecular cyclization followed by dehydration leads to the final product.

Having in mind increasing pollution and decreasing resources, one major goal of green chemistry is the development of efficient routes to synthesize fine chemical under cost-effective and safe conditions. To make our catalytic reaction in agreement with green chemistry criteria, we concentrated on the catalyst recycling experiment. As can be seen in Fig. 3, after recycling, the $CuAl_2O_4$ NPs exhibited remarkable activity for the first three consecutive runs while a little decrease was observed during fourth run. However, the decrease in the product yield for the fourth run is likely to be because of handling loss of catalyst.

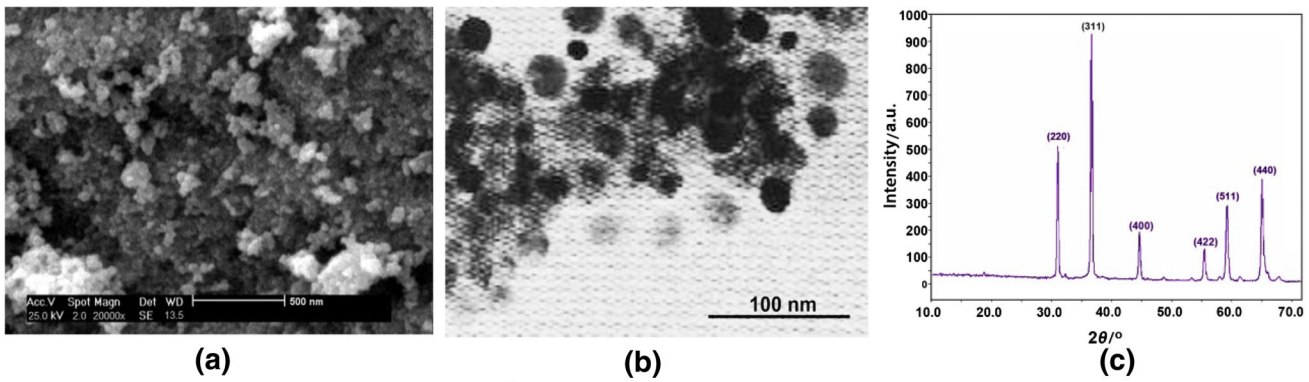


Fig. 2 SEM image (**a**), TEM image (**b**), and XRD patterns (**c**) for $CuAl_2O_4$ NPs

Scheme 1

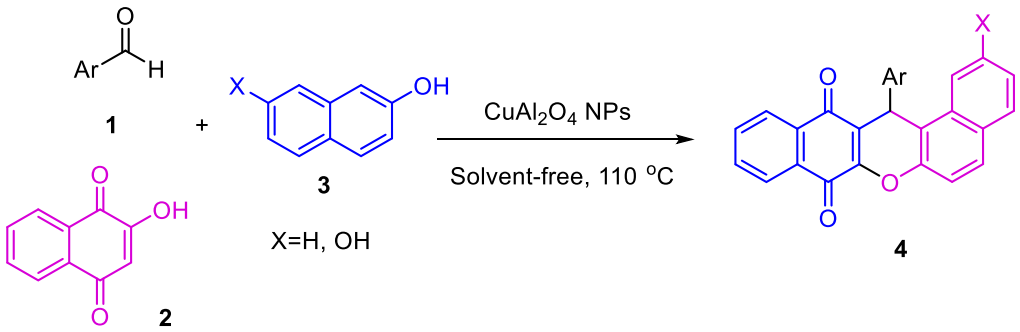


Table 1 Optimization of the reaction conditions in the synthesis of **4a** at 110 °C. Reaction time: 70 min

Entry	Solvent (10 cm^3)	Catalyst amount/ %	Temperature/ °C	Yield/ %
1	MeOH	10 %	65	40
2	EtOH	10 %	78	45
3	H_2O	10 %	100	15
4	CH_2Cl_2	10 %	40	–
5	Free	10 %	110	91
6	Free	–	110	25
7	Free	3 %	110	55
8	Free	7 %	110	92
9	Free	15 %	110	90
10	Free	7 %	80	35
11	Free	7 %	50	Trace
12	Free	7 %	25	Trace

Table 2 Synthesis of α-lapachone derivatives using $CuAl_2O_4$ NPs under solvent-free conditions (Scheme 1)

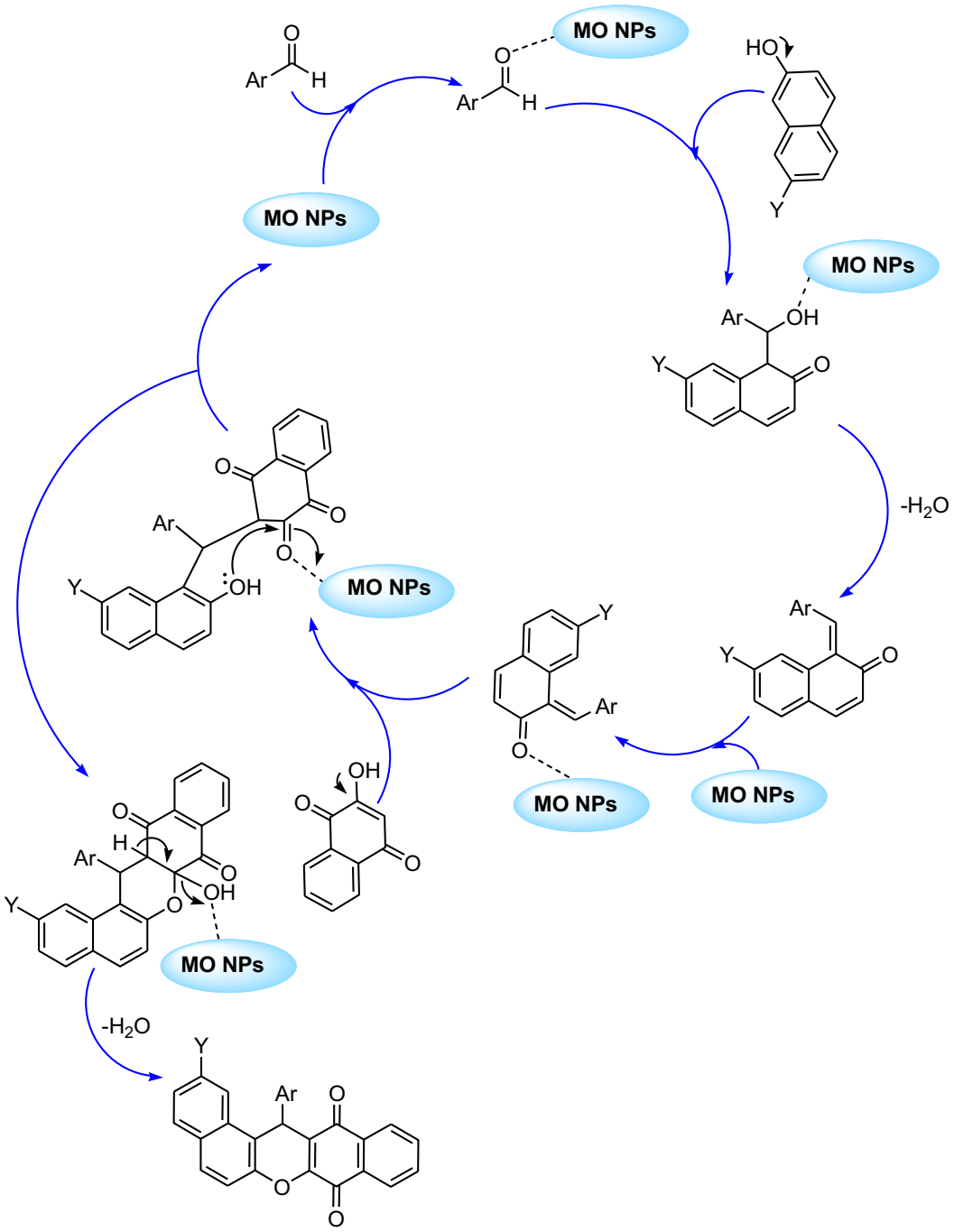
Entry	X	Ar	Time/ min	Yield[a]/ %	M.p./ °C (reported)
4a	H	Ph	70	92	318–320 (>300 [8])
4b	OH	3-OH-Ph	75	85	310–312
4c	H	4-CN-Ph	60	88	318–320
4d	H	1-Naphthyl	90	82	270–272
4e	H	2-MeO-Ph	65	95	390–392
4f	OH	4-Benzyloxy-Ph	75	90	295–297
4g	OH	(1,4-Phenylene)bis	110	82	247–249
4h	H	2-Naphthyl	85	90	282–284 (>300 [8])
4i	H	3-NO_2-Ph	80	85	300–302 (>300 [8])
4j	H	4-Cl-Ph	80	88	305–306 (>300 [8])

[a] Isolated yield

Table 3 demonstrates the merits of the present method for the synthesis of pyranonaphthoquinones compared to some previously ones. As can be seen, we believe that these reactions can be efficiently carried out under our suggested conditions in terms of the reaction time and product yield.

In conclusion, $CuAl_2O_4$ NPs has been prepared and successfully used for the first time in the one-pot, three-component synthesis of α-lapachone derivatives. The present method possesses several advantages such as high atom economy and product yields, using a stable, environmentally benign, and renewable nanocatalyst, simplicity of the procedure, and avoidance of solvent. It is hoped this strategy to be used by the synthetic organic community for the scale-up synthesis.

Scheme 2



Experimental

Chemicals were purchased from Merck and Aldrich and used without further purification. Powder X-ray diffraction measurements were made on a Philips X'pertdiffractometer, using filtered Cukα radiation. A Philips XL30 instrument was used to record SEM micrographs. The images of $CuAl_2O_4$ nanocrystals were obtained with JEDL-JFM-1200 EX transmission electron microscopy (TEM). IR spectra were recorded on a FT-IR JASCO-680. ^{1}H (400 and 500 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were recorded on a Bruker Avance II model. The varioEl CHNS was also used for elemental analysis. The compounds **4a** and **4 h–4j** have been previously reported in the literature [8].

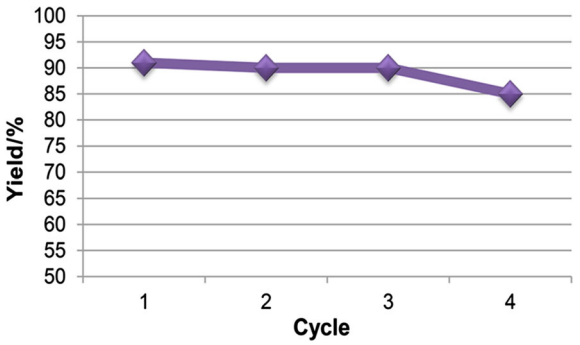


Fig. 3 Recyclability study of $CuAl_2O_4$ NPs catalyst (10 mol %) for the synthesis of **4a**. Reaction conditions: 110 °C, solvent-free, 70 min

Table 3 Comparison of the present method with some previously reported ones

Entry	Catalyst	Time/ min/ yield/ %	References
1	Silica chloride	45/88	[7]
2	AcOH	300/93	[8]
3	*p*-TSA	600/88	[9]
4	Polystyrene-supported $GaCl_3$	89/120	[10]
5	[bmim]HSO_4	30/91	[11]
6	$HClO_4$-SiO_2	–/92	[12]
7	$CuAl_2O_4$ NPs	70/92	Present work

Preparation of nanocatalyst

Typically, a solution of $Al_2(SO_4)_3$ (10 mmol), Cu_2SO_4 (5 mmol), and $Mg(OH)_2$ (35 mmol) in 100 cm^3 deionized water was stirred and heated at 80 °C for 24 h. The resulting suspension was filtered and dried at 100 °C for 2 h followed by heating at 900 °C for 5 h to acquire the nanosized $CuAl_2O_4$ particles.

Synthesis of pyranonaphthoquinones 4

A mixture of β-naphtol or 2,7-dihydroxynaphthalene (1 mmol; 2 mmol for **4 g**), aromatic aldehyde (1 mmol), lawsone (1 mmol; 2 mmol for **4 g**), and $CuAl_2O_4$ (7 mol %) was stirred and heated at 110 °C in a preheated oil bath for an appropriate time. After completion of the reaction as monitored by TLC (AcOEt/hexane), the reaction mixture was dissolved in hot EtOH. Then, the catalyst was separated by simple filtration, washed with hot EtOH, and dried at 90 °C to reuse. The solvent was removed and the corresponding product purified by recrystallization from EtOH.

2-Hydroxy-14-(3-hydroxyphenyl)-13H-dibenzo[a,i]xanthene-8,13(14H)-dione (**4b**, $C_{27}H_{16}O_5$)
M.p.: 310–312 °C; IR (KBr): $\bar{\nu}$ = 3410, 2925, 1690, 1634, 1593, 1518, 1452, 1378, 1290, 1245, 1215 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (s, 1H), 9.29 (s, 1H), 8.21 (1H, d, J = 7.6 Hz), 7.99 (d, 1H, J = 7.6 Hz), 7.90 (t, 2H, J = 7.6 Hz), 7.81 (d, 1H, J = 7.6 Hz), 7.69 (t, 1H, J = 7.6 Hz), 7.50 (d, 1H, J = 8.4 Hz), 7.26 (s, 1H), 7.05–7.0 (m, 2H), 6.81 (s, 1H), 6.70 (s, 1H), 6.50 (dd, 1H, J = 7.6, 2.4 Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.7, 177.5, 157.3, 156.6, 156.3, 147.3, 144.74, 135.0, 132.2, 131.3, 130.3, 130.1, 129.1, 128.4, 125.83, 124.3, 119.2, 117.6, 115.2, 114.8, 113.67, 113.62, 105.3, 34.6 ppm.

14-(4-Cyanophenyl)-13H-dibenzo[a,i]xanthene-8,13(14H)-dione (**4c**, $C_{28}H_{15}NO_3$)
M.p.: 318–320 °C; IR (KBr): $\bar{\nu}$ = 3073, 2227, 1703, 1664, 1635, 1590, 1369, 1238, 1214 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27 (d, 1H, J = 8.8 Hz), 8.09 (t, 2H, J = 7.6 Hz), 7.99 (t, 2H, J = 7.6 Hz), 7.92 (t, 1H, J = 8.8 Hz), 7.80 (d, 1H, J = 8.8 Hz), 7.23 (d, 1H, J = 7.2 Hz), 7.69 (d, 2H, J = 8.4 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.57–7.48 (m, 2H), 5.93 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.6, 177.3, 156.5, 148.9, 146.8, 144.4, 135.0, 132.3, 131.6, 131.4, 130.5, 130.1, 129.7, 128.7, 128.4, 127.6, 125.6, 124.5, 123.4, 118.5, 117.7, 117.4, 115.6, 114.5, 109.4, 35.0 ppm.

14-(1-Naphthyl)-13H-dibenzo[a,i]xanthene-8,13(14H)-dione (**4d**, $C_{31}H_{18}O_3$)
M.p.: 270–272 °C; IR (KBr): $\bar{\nu}$ = 3055, 2932, 1700, 1635, 1590, 1368, 1288, 1237, 1215 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1H), 8.25 (d, 1H, J = 7.6 Hz), 7.96 (d, 1H, J = 7.6 Hz), 7.91–7.89 (m, 3H), 7.84–7.75 (m, 4H), 7.68 (t, 1H, J = 7.6 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.48–7.39 (m, 3H), 7.34 (d, 1H, J = 2 Hz), 6.99 (dd, 1H, J = 8.8, 2 Hz), 5.73 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.7, 177.4, 156.6, 156.2, 147.3, 140.8, 135.0, 132.6, 131.7, 131.3, 130.3, 130.2, 130.1, 129.3, 128.4, 127.9, 127.6, 127.2, 127.0, 126.6, 126.1, 125.8, 124.4, 117.5, 115.4, 114.5, 113.7, 105.3, 35.2 ppm.

14-(3-Methoxyphenyl)-13H-dibenzo[a,i]xanthene-8,13(14H)-dione (**4e**, $C_{28}H_{18}O_4$)
M.p.: 390–392 °C; IR (KBr): $\bar{\nu}$ = 2920, 1668, 1637, 1590, 1575, 1365, 1290, 1246, 1235, 1215 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.26 (d, 1H, J = 7.6 Hz), 8.10 (d, 1H, J = 7.6 Hz), 7.97–7.85 (m, 3H), 7.78 (d, 1H, J = 7.6 Hz), 7.68–7.64 (m, 2H), 7.54 (t, 1H, J = 8.0 Hz), 7.40–7.38 (m, 2H), 7.18 (d, 1H, J = 8.0 Hz), 7.07 (t, 1H, J = 7.6 Hz), 6.90 (t, 1H, J = 7.6 Hz), 5.80 (s, 1H), 3.69 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.5, 178.2, 155.1, 147.1, 144.3, 141.7, 138.1, 137.0, 135.3, 134.9, 133.6, 130.3, 127.2, 127.0, 126.8, 125.3, 124.9, 124.4, 123.9, 123.4, 121.0, 118.9, 118.2, 113.6, 112.4, 111.7, 52.2, 35.7 ppm.

14-(4-Benzyloxyphenyl)-13H-dibenzo[a,i]xanthene-8,13(14H)-dione (**4f**, $C_{34}H_{22}O_5$)
M.p.: 295–297 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.20$ (s, 1H), 7.96 (d, 1H, $J = 8.0$ Hz), 7.87 (d, 1H, $J = 7.6$ Hz), 7.60 (t, 1H, $J = 7.2$ Hz), 7.55 (d, 1H, $J = 8.8$ Hz), 7.48 (d, 1H, $J = 8.8$ Hz), 7.39 (t, 1H, $J = 7.6$ Hz), 7.17–7.10 (m, 9 H), 6.85 (dd, 1H, $J = 8.4$, 2.4 Hz), 6.58 (d, 2H, $J = 8.4$ Hz), 5.49 (s, 1H), 4.73 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 180.6$, 165.3, 160.6, 157.7, 151.0, 150.1, 150.0, 140.1, 138.1, 135.4, 135.3, 133.9, 133.7, 133.5, 133.4, 123.4, 120.4, 120.0, 119.4, 116.6, 115.4, 111.5, 110.4, 104.4, 89.2, 58.5, 33.2 ppm.

14,14′-(1,4-Phenylene)bis(2-hydroxy-13H-dibenzo[a,i]xanthene-8,13(14H)-dione) (**4g**, $C_{48}H_{26}O_8$)
M.p.: 247–249 °C; IR (KBr): $\bar{\nu} = 3438$, 2933, 1698, 1579, 1633, 1457, 1381, 1289, 1215 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.88$ (s, 2H), 7.93–7.88 (m, 10 H), 7.81–7.88 (m, 6H), 7.59 (d, 4H, $J = 8.0$ Hz), 7.25 (s, 2H), 5.67 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 192.2$, 192.4, 156.5, 149.8, 147.2, 135.0, 134.7, 132.1, 131.5, 130.4, 130.3, 129.9, 129.6, 129.3, 128.4, 125.8, 124.4, 117.6, 114.7, 113.9, 113.7, 105.18, 105.12, 35.30 ppm.

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