An Efficient and Convenient Approach for the Synthesis of Novel 2-Hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones Using *p*-Toluenesulfonic acid in Ethanol and Ionic Liquid

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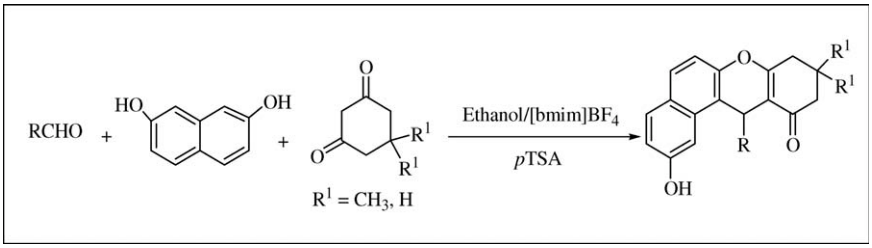

A novel series of 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones were synthesized by the one-pot multicomponent condensation of 2,7-dihydroxynaphthalene, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds in the presence of a catalytic amount of *p*-toluenesulfonic acid in ethanol and in ionic liquid butyl methyl imidazolium tetrafluroborate ([bmim]BF_4). The newly developed protocol is operationally convenient, widely applicable, and gives excellent yields of the diversely substituted title compounds in high purity by easy workup.

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INTRODUCTION

The development of multicomponent reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial, and medicinal chemistry [1–4]. One-pot MCR strategies offer significant advantages over conventional linear-type syntheses by virtue of their convergence, productivity, facile execution, and high yields [5,6]. In recent years, they have emerged as valuable tools for carbon-carbon and carbon-heteroatom bond formation during the synthesis of structurally diverse and important organic molecules in the search for novel lead structures [7,8]. Thus, the success of combinatorial chemistry in the drug discovery process is considerably dependent on further advances in heterocyclic MCR methodology.

Xanthenes and benzoxanthenes are important components of biologically active heterocycles. Although not widely found in nature, xanthenes and its compounds exhibit exceptional pharmaceutical activities such as antibacterial [9], anti-inflammatory [10], and antiviral [11]. Besides this they have been used as antagonists for paralyzing the action of zoxazolamine [12] and in photodynamic therapy [13]. Moreover, they also find application in industries such as dyes [14], pH-sensitive fluorescent materials to monitor changes in intracellular pH [15] and in laser technologies [16].

Thus, a broad utility range has made xanthenes prime synthetic candidates, thereby accentuating the need to synthesize a variety of novel xanthene heterocyclic molecules under milder and more practical conditions. Limited methods are reported in the literature for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives [17–21].

RESULTS AND DISCUSSION

Based on the green chemistry approach, this is the first report on the one-pot three-component synthesis of 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives (1) by cyclo-condensation of aldehydes, 2,7-dihydroxynaphthalene and cyclic 1,3-dicarbonyl compounds in the presence of catalytic amount of *p*-toluenesulfonic acid (*p*TSA) in refluxing ethanol and in ionic liquid butyl methyl imidazolium tetrafluroborate [bmim]BF_4 at 50°C. All our attempts to achieve double cyclo-condensation on separate benzene rings of naphthalene have been unsuccessful.

Initially, we investigated the condensation reaction of 4-chlorobenzaldehyde (1 mmol), 2,7-dihydroxynaphthalene (1 mmol), and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (1.2 mmol) using different acid catalysts such as *p*TSA, HCl, H_2SO_4, and CH_3COOH separately in ethanol under reflux. The corresponding xanthene derivative 12-(4-chlorophenyl)-2-hydroxy-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*] xanthen-11-one (**1a**) was formed in 94, 36, 40, and 26% yield, respectively. The *p*TSA was the most effective catalyst and the reactions

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Table 1

Solvent effect on the reaction of 4-chlorobenzaldehyde, 2,7 dihydroxynaphthalene, and 5,5-dimethylcyclohexane-1,3-dione.

Entry	Solvent	Catalyst	Temperature	Time (h)	Yield (%)
1	CH_3CN	*p*TSA	Reflux	8	10
2	CH_2Cl_2	*p*TSA	Reflux	8	36
3	$CHCl_3$	*p*TSA	Reflux	8	34
4	Toluene	*p*TSA	80°C	8	56
5	DMF	*p*TSA	80°C	8	51
6	None	*p*TSA	120°C	2.5	48
7	C_2H_5OH	*p*TSA	Reflux	2.5	94

in the presence of acids other than *p*TSA were sluggish and incomplete even after 12 h. Moreover, we observed that 2 mol% of *p*TSA was sufficient to catalyze the reaction efficiently. Excessive amount of catalyst did not affect the yields significantly. Reactions at room temperature and in the absence of the catalyst did not yield any product.

Reactions carried out in different solvents (Table 1, entries 1–5) and under solvent-free conditions (Table 1, entry 6) using *p*TSA as catalyst gave poor yields of xanthene derivative **1a**. Thus, condensation using *p*TSA in ethanol under reflux appeared to be the optimized condition (Table 1, entry 7).

Subsequently, the applicability of the reaction was extended to a variety of electronically divergent aromatic aldehydes. All these aldehydes underwent smooth reaction with 2,7-dihydroxynaphthalene and 5,5-dimethylcyclohexane-1,3-dione (dimedone) to give excellent yields of the novel xanthene derivatives (Table 2, method A, entries 1–14) (Scheme 1). Replacement of 5,5-dimethylcyclohexane-1,3-dione (dimedone) by cyclohexane-1,3-dione also led to successful condensation under similar conditions, to afford novel xanthene derivatives in high yields (Table 2, method A, entries 15–23).

None of the reaction showed the formation of any bis-condensation product. Even reactions using double molar ratio concentration of aldehydes and dimedone did not show formation of bis-condensation products. Reactions of initially formed **1** with aldehyde and

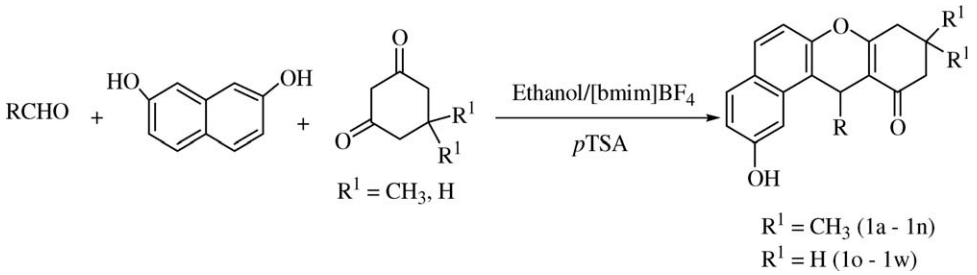
Table 2

Synthesis of novel 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives *via* multi-component condensation reaction.

			Method A		Method B		
Entry	R	Product	Time (h	Yield (%)	Time (h)	Yield (%)	Mp. (°C)
1	4-ClC_6H_4	**1a**	2.5	94	2	94	>300 (decom.)
2	C_6H_5	**1b**	4.0	89	1.5	87	>300 (decom.)
3	4-BrC_6H_4	**1c**	2.5	92	2.5	91	290–292 (decom.)
4	4-$CH_3C_6H_4$	**1d**	3.5	86	1.5	89	286–288 (decom.)
5	4-$CH_3OC_6H_4$	**1e**	4.0	91	1.5	92	282–284 (decom.)
6	4-$O_2NC_6H_4$	**1f**	3.0	88	3.5	88	288–290 (decom.)
7	4-FC_6H_4	**1g**	2.5	96	2	93	278–280 (decom.)
8	3-$O_2NC_6H_4$	**1h**	3.0	86	1	92	>300 (decom.)
9	3-BrC_6H_4	**1i**	3.0	88	1.5	93	>300 (decom.)
10	3,4-$(CH_3O)_2C_6H_3$	**1j**	4.0	84	1	92	256–258
11	1-Naphthyl	**1k**	4.0	90	2.5	90	>300 (decom.)
12	2-Naphthyl	**1l**	3.5	92	2	90	272–274
13	9-Anthrayl	**1m**	4.0	88	6	—	295–297 (decom.)
14	4-$Me_2CHC_6H_4$	**1n**	3.5	93	1.5	91	250–252
15	C_6H_5	**1o**	4.0	88	3	88	>300 (decom.)
16	4-$CH_3C_6H_4$	**1p**	4.0	84	2.5	90	286–288 (decom.)
17	4-$CH_3OC_6H_4$	**1q**	4.0	87	2	92	255–257
18	4-$O_2NC_6H_4$	**1r**	3.5	86	3	89	>300 (decom.)
19	4-BrC_6H_4	**1s**	3.0	86	2	88	>300 (decom.)
20	4-FC_6H_4	**1t**	3.0	88	2	90	292–294 (decom.)
21	4-(OH),3-$(CH_3O)C_6H_3$	**1u**	4.0	85	3.5	91	>300 (decom.)
22	2-Naphthyl	**1v**	3.5	89	1.5	92	286–288 (decom.)
23	4-$Me_2CHC_6H_4$	**1w**	4.0	90	2.5	89	258–260

Method A: Reaction carried out in ethanol under reflux.
Method B: Reaction carried out in $[bmim]BF_4$ at 50°C.

Scheme 1



dimedone to give bis-condensation products were also unsuccessful. Our efforts to prepare similar novel series of xanthene derivatives starting from 1,6- and 1,7-dihydroxynaphthalenes have been unsuccessful.

Further, we decided to investigate the reaction in ionic liquids too. The condensation of 4-chlorobenzaldehyde (1 mmol), 2,7-dihydroxynaphthalene (1 mmol) and dimedone (1.2 mmol) was attempted in different ionic liquids at room temperature as well as under heating in the presence of *p*TSA. In [bmim]BF_4, at 50°C, 94% of the corresponding xanthene derivative **1a** was obtained after 2 h using *p*TSA as a catalyst. Reactions in other ionic liquids gave inferior yields of the desired product. Therefore, [bmim]BF_4 appeared to be the most suitable medium for successive reactions. Other aromatic aldehydes also underwent condensation successfully in [bmim]BF_4 using *p*TSA as a catalyst at 50°C and the corresponding xanthene derivatives were obtained in high yields (Table 2, method B, entries 1–14). Also, on replacing dimedone with cyclohexane-1,3-dione, the reaction underwent successful completion in [bmim]BF_4 (Table 2, method B, entries 15–23). Again, all attempts to achieve bis-condensation under these conditions also were unsuccessful. A plausible mechanism for the formation of 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one derivatives (**1a–w**) in the presence of *p*TSA is proposed in Scheme 2.

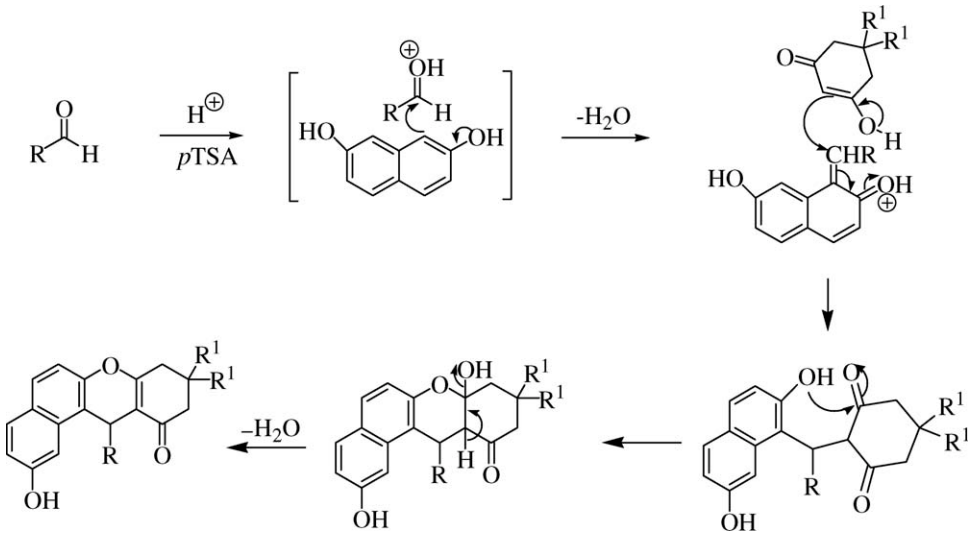
CONCLUSION

In conclusion, we have described a highly efficient synthetic route to novel 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones based on the three-component cyclo-condensation reaction of aromatic aldehydes, 2,7-dihydroxynaphthalene and 5,5-dimethylcyclohexane-1,3-dione/cyclohexane-1,3-dione. Further investigations to expand the scope of these xanthene derivatives are under progress.

EXPERIMENTAL

All the chemicals used in the synthesis were purchased from Sigma-Aldrich and used as received. Thin layer chromatography was used to monitor reaction progress. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin Elmer FTIR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin spectrometer at 300 MHz. The chemical shift

Scheme 2



values are recorded on δ scale and the coupling constants (*J*) are in Hertz. Mass spectra were recorded on JEOL-AccuTOF JMS–T100 mass spectrometer having a DART source.

General procedure for the synthesis of 2-hydroxy-12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives (1a–w). ***Method A*** A mixture of aldehyde (1.0 mmol), 2,7-dihydroxynaphthalene (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione/1,3-cyclohexanedione (1.2 mmol), *p*TSA (2 mol% or 0.02 mmol) and 10 mL of ethanol was placed in 50 mL round-bottomed flask and stirred under reflux for an appropriate time as mentioned in Table 2. After completion of the reaction as monitored by TLC (petroleum ether : ethyl acetate), the reaction mixture was allowed to cool to room temperature. The precipitate formed was collected by filtration at pump, washed with ethanol, and dried to obtain pure xanthen-11-one derivatives.

Method B A mixture of aldehyde (1.0 mmol), 2,7-dihydroxynaphthalene (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione/1,3-cyclohexanedione (1.2 mmol), and *p*TSA (2 mol% or 0.02 mmol) were taken in a 25 mL round-bottomed flask containing 0.5 mL of [bmim]BF_4. The mixture was stirred at 50°C for an appropriate time as mentioned in Table 2. After completion of the reaction as monitored by TLC, the mixture was allowed to cool to room temperature and quenched with water (~5 mL). The precipitate formed was collected by filtration at pump, washed with ethanol, and dried to obtain pure xanthen-11-one derivatives. The filtrate was concentrated under reduced pressure and dried at 100°C to recover the ionic liquid for subsequent use. Marginal loss in the yield of the products were observed in first three runs (94, 90, and 85%), whereas in fourth and fifth runs the yields were quite low.

Representative analytical data. ***12-(4-Chlorophenyl)-2-hydroxy-9,9-dimethyl-8,9,10,12 tetrahydrobenzo[a]xanthen-11-one (1a)*** White solid; m.p. >300°C (decom.), ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.29 (s, 1H, OH), 7.67–7.62 (m, 2H, Ar—H), 7.31–7.24 (m, 3H, Ar—H), 7.14–7.09 (m, 3H, Ar—H), 7.02–6.99 (m, 1H, Ar—H), 5.50 (s, 1H, CH), 2.57 (s, 2H, CH_2) 2.33 (d, J = 16.2 Hz, 1H), 2.24 (d, J = 16.2 Hz, 1H), 1.12 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 199.4, 166.18, 156.30, 147.96, 142.95, 132.87, 132.04, 130.39, 129.87, 129.04, 128.42, 126.49, 117.39, 115.45, 113.87, 105.86, 50.40, 34.45, 32.51, 29.32, 27.05. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3194, 2929, 1631, 1594, 1381, 1235. MS (ESI): m/z = 405$(M + H)^+$.

2-Hydroxy-9,9-dimethyl-12-phenyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1b) White solid; m.p. >300°C (decom.), ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.87 (s, 1H, OH), 7.77–7.72 (m, 2H, Ar—H), 7.26–7.17 (m, 6H, Ar—H), 7.09–7.04 (m, 1H, Ar—H), 6.98–6.94 (m, 1H, Ar—H), 5.34 (s, 1H, CH), 2.69 and 2.58 (AB system, J = 17.4 Hz, 2H, $CH_aCH_bC(CH_3)_2$), 2.35 (d, J = 16.2 Hz, 1H), 2.13 (d, J = 16.2 Hz, 1H), 1.05 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 195.87, 163.88, 156.39, 147.63, 144.65, 132.46, 130.19, 128.72, 128.07, 128.04, 126.14, 125.45, 117.10, 115.44, 113.52, 113.28, 105.13, 50.06, 34.12, 31.85, 28.81, 26.14. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3182, 2959, 1630, 1596, 1379, 1227, 1182. MS (ESI): m/z = 371 $(M + H)^+$.

2-Hydroxy-9,9-dimethyl-12-(3-nitrophenyl)-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1h) White solid; m.p. >300°C (decom.), ^{1}H NMR (300 MHz, DMSO-d6): δ_H 9.93 (s, 1H, OH), 8.11 (s, 1H, Ar—H), 7.99–7.96 (m, 1H, Ar—H), 7.82–7.75 (m, 2H, Ar—H), 7.67 (d, J = 7.8 Hz, 1H, Ar—H), 7.54 (t, J = 7.8 Hz, 1H, Ar—H), 7.25–7.16 (m, 2H, Ar—H), 6.98–6.95 (m, 1H, Ar—H) 5.50 (s, 1H, CH), 2.72 and 2.62 (AB system, J = 17.7 Hz, 2H, $CH_aCH_bC(CH_3)_2$), 2.37 (d, J = 16.2 Hz, 1H), 2.16 (d, J = 16.2 Hz, 1H), 1.05 (s, 3H, CH_3), 0.84 (s, 3H, CH_3). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 195.99, 164.44, 156.67, 147.76, 147.53, 146.62, 134.66, 132.22, 130.37, 129.75, 129.43, 125.49, 122.52, 121.47, 117.30, 113.95, 113.51, 112.29, 104.90, 49.94, 34.20, 31.90, 28.66, 26.15. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3182, 2962, 1625, 1594, 1526, 1382, 1350, 1224. MS (ESI): m/z = 416 $(M + H)^+$.

12-(3-Bromophenyl)-2-hydroxy-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1i) White solid; m.p. >300°C (decom.) ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.93 (s, 1H, OH), 7.80 (t, J = 7.8 Hz, 2H, Ar—H), 7.42 (s, 1H, Ar—H), 7.30–7.13 (m, 5H, Ar—H), 7.00–6.96 (m, 1H, Ar—H), 5.34 (s, 1H, CH), 2.70 and 2.61 (AB system, J = 17.4 Hz, 2H, $CH_aCH_bC(CH_3)_2$), 2.36 (d, J = 16.2 Hz, 1H), 2.16 (d, J = 16.2 Hz, 1H), 1.05 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 195.93, 164.24, 156.57, 147.68, 147.18, 132.31, 130.70, 130.38, 130.31, 129.19, 129.13, 127.09, 125.46, 121.36, 117.24, 114.52, 113.50,112.68, 104.95, 50.00, 33.96, 31.90, 28.72, 26.12. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3157, 2957, 1624, 1593, 1384, 1227, 1170. MS (ESI): m/z = 449 $(M + H)^+$.

2-Hydroxy-9,9-dimethyl-12-(1-naphthyl)-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1k) White solid; m.p. >300°C (decom.), ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.66 (s, 1H, OH), 9.00 (brs, 1H, Ar—H), 7.85 (d, J = 8.1 Hz, 1H, Ar—H), 7.74–7.63 (m, 4H, Ar—H), 7.54 (t, J = 7.5 Hz ,1H, Ar—H), 7.31–7.21 (m, 3H, Ar—H),7.06 (s, 1H, Ar—H), 6.94 (d, J = 8.7 Hz, 1H, Ar—H), 6.11 (s, 1H, CH), 2.70 and 2.59 (AB system, J = 17.4 Hz, 2H, $CH_aCH_bC(CH_3)_2$), 2.29 (d, J = 16.2 Hz, 1H), 2.03 (d, J = 16.2 Hz, 1H), 1.01 (s, 3H, CH_3), 0.77 (s, 3H, CH_3). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 196.08, 163.72, 156.20, 147.72, 142.41, 133.08, 132.94, 130.34, 130.08, 128.67, 128.28, 127.33, 126.93, 125.99, 125.50, 124.74, 117.17, 117.01, 114.32, 113.70, 105.70, 50.12, 34.47, 31.67, 28.80, 26.08. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3152, 2956, 1620, 1589, 1366, 1217, 1170. MS (ESI): m/z = 421 $(M + H)^+$.

2-Hydroxy-12-phenyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1o) White solid; m.p. >300°C (decom.), ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.86 (s, 1H, OH), 7.76–7.72 (m, 2H, Ar—H), 7.25–7.16 (m, 6H, Ar—H), 7.08–7.04 (m, 1H, Ar—H), 6.97(d, J = 9 Hz, 1H, Ar—H), 5.37 (s, 1H, CH), 2.71–2.69 (m, 2H, CH_2), 2.41–2.25 (m, 2H, CH_2), 1.99–1.94 (m, 1H), 1.83–1.79 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 196.14, 165.76, 156.38, 147.70, 144.97, 132.46, 130.18, 128.70, 128.15, 128.07, 126.13, 125.45, 117.10, 115.45, 114.57, 113.48, 105.13, 36.40, 34.06, 26.90, 19.91. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3200, 2966, 1625, 1593, 1382, 1230, 1194. MS (ESI): m/z = 343 $(M + H)^+$.

12-(4-Bromophenyl)-2-hydroxy-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1s) White solid; m.p. >300°C (decom.), ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.89 (s, 1H, OH), 7.78–7.73 (m, 2H, Ar—H), 7.41 (d, J = 8.4 Hz, 2H, Ar—H), 7.21–7.13 (m, 4H, Ar—H), 6.99–6.95 (m, 1H, Ar—H), 5.35 (s, 1H, CH), 2.73–2.69 (m, 2H, CH_2), 2.37–2.26 (m, 2H, CH_2), 1.99–1.93 (m, 1H), 1.86–1.83 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 196.19, 165.90, 156.49, 147.65, 144.27, 132.33, 131.06, 130.32, 130.28, 128.99, 125.44, 119.28, 117.16, 114.70,

113.96, 113.46, 105.01, 36.36, 33.70, 26.90, 19.88. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3196, 2944, 1626, 1597, 1379, 1231, 1197. MS (ESI): m/z = 421 $(M + H)^+$.

2-Hydroxy-12-(4-hydroxy-3-methoxyphenyl)-8,9,10,12 tetrahydrobenzo[a]xanthen-11-one (1u) White solid; m.p. >300°C (decom.), ^1H NMR (300 MHz, DMSO-d_6): δ_H 9.89 (s, 1H, OH), 8.80 (s, 1H, OH), 7.75 (d, J = 8.7 Hz, 2H, Ar—H), 7.25–7.16 (m, 2H, Ar—H), 6.99–6.91 (m, 2H, Ar—H), 6.59–6.46 (m, 2H, Ar—H) 5.29 (s, 1H, CH), 3.71 (s, 3H, OCH_3), 2.76–2.70 (m, 2H, CH_2), 2.35–2.28 (m, 2H, CH_2), 1.99–1.95 (m, 1H), 1.85–1.83 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ_C 196.34, 165.46, 156.28, 147.63, 146.96, 144.89,136.10, 132.56, 130.14, 128.46, 125.43, 120.26, 117.04, 115.85, 115.25, 114.88, 113.47, 112.76, 105.32, 56.03, 36.46, 33.41, 26.90, 19.96. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3536, 3119, 2938, 1621, 1591, 1512, 1450, 1382, 1233, 1200. MS (ESI): m/z = 389 $(M + H)^+$.

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