Acid Catalyzed Efficient Syntheses of Aryl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14-(13*H*)-tetraones and 3,3-(Arylmethylene)bis(2-hydroxynaphthalene-1,4-diones) and *In Vitro* Evaluation of their Antioxidant Activity

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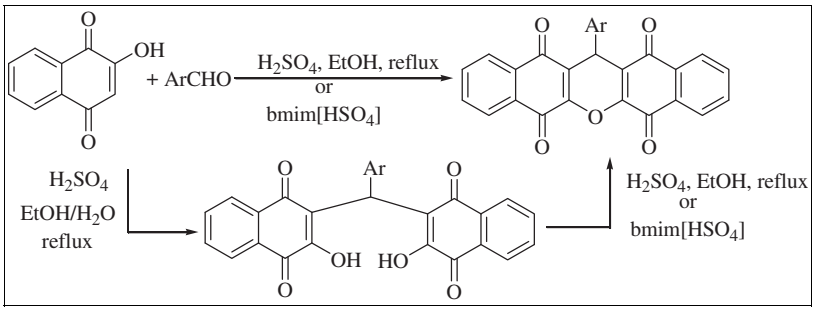

A simple and efficient synthesis of aryl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14-(13*H*)-tetraones and 3,3-(arylmethylene)bis(2-hydroxynaphthalene-1,4-diones) by the condensation of aromatic aldehydes and 2-hydroxy-1,4-naphthoquinone under extremely mild conditions using catalytic amount of H_2SO_4 or in the presence of acidic ionic liquid 1-butyl-3-methylimidazolium hydrogen sulphate, which could be recycled, has been reported. The radical scavenging capacity of the synthesized compounds has been examined towards the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), and the compounds **2** were found to scavenge DPPH free radical efficiently.

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INTRODUCTION

Molecules with the quinone structure constitute an interesting class of compounds in organic chemistry, because of their biological properties and industrial applications [1]. Among the quinones, naphthoquinones are considered as privileged structures in medicinal chemistry as they act as intermediates for the synthesis of biologically active heterocycles [2], which are employed for the treatment of various diseases [3]. They are usually colored, yellow or brown, and thus play important roles as dyes in pigmentation. 2-Hydroxy-1,4-naphthoquinone (Lawsone) is the principal natural dye in the leaves of henna (1.0–1.4%), *Lawsonia inermis* [4]. Henna has been used for more than 4000 years not only as a hair dye but also as body paint and tattoo dye. A series of related naphthoquinone pigments (streptocarpone, α-dunnione, dunniol, and dunnione) from *Streptocarpus dunnii* have been isolated and characterized [5,6].

The generation of free radicals during metabolic processes is responsible for human conditions such as aging, cancer, atherosclerosis, arthritis, viral infection, stroke, and myocardial infarction. Antioxidants act as a major defense against radical-mediated toxicity by inhibiting the free radicals. In recent years, compounds that exhibit 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity are receiving attention [7].

Considering the importance of naphthoquinone derivatives, development of new methods for the synthesis of naphthoquinone scaffolds is an interesting challenge. In continuation of our work on the synthesis of heterocycles [8], we have investigated the synthesis of 3,3-(arylmethylene)bis (2-hydroxynaphthalene-1,4-diones) and 13-aryl-5*H*-dibenzo [*b*,*i*] xanthene-5,7,12,14(13*H*)-tetraone derivatives under acidic conditions or by using task-specific ionic liquid, 1-butyl-3-methylimidazolium hydrogen sulphate (bmim[HSO_4]).

RESULTS AND DISCUSSION

In the present study, we report "one-pot" syntheses of aryl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14-(13*H*)-tetraones (**1a–i**) and 3,3-(arylmethylene)bis (2-hydroxynaphthalene-1,4-diones) (**2a–k**) by condensation of 2-hydroxynaphthalene-1,4-dione and aromatic aldehydes catalyzed by sulfuric acid in ethanol under reflux or in task-specific ionic liquid bmim[HSO_4] under different conditions. These compounds were also screened for their *in vitro* antioxidant activity by using DPPH radical scavenging assay.

The reaction conditions were optimized by attempting the condensation of 4-chlorobenzaldehyde (1.0 mmol) and 2-hydroxy-1,4-naphthoquinone (2.0 mmol) in the presence of acids such as HCl, H_2SO_4, HNO_3, and AcOH in different media and at different temperatures. The results are summarized in Table 1. The best yield of 13-(4-chlorophenyl)-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14 (13*H*)-tetraone (**1a**), which is 89%, was achieved when the reaction was carried out in ethanol in the presence of 0.20 mmol of

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Table 1

Optimization of reaction conditions.

Run	Reaction media	Temp. (°C)	Catalyst	mol%	Time (h)	Product (% Yield)
1	$CHCl_3$	60	H_2SO_4	15	5.0	**1a** (30)[b,c]
2	CH_3CN	80–85	H_2SO_4	15	5.0	**1a** (30)[b,c]
3	DMF	110	H_2SO_4	15	5.0	**1a** (25)[b,c]
4	EtOH	70–80	H_2SO_4	15	2.5	**1a** (78)
5	EtOH	70–80	H_2SO_4	20	2.0	**1a** (89)
6	EtOH + H_2O (1:1)	70–80	H_2SO_4	20	0.5	**2a** (93)
7	H_2O	100	H_2SO_4	20	7	**2a** (56)[b,c]
8	EtOH	70–80	H_2SO_4	25	2.0	**1a** (87)
9	EtOH	70–80	CH_3COOH	20	5.0	**1a** (30)[b,c]
10	EtOH	70–80	HNO_3	20	5.0	**1a** (20)[b,c]
11	EtOH	70–80	HCl	20	5.0	–[d]

[a]Molar ratio, 4-chlorobenzaldehyde:2-hydroxy-1,4-naphthoquinone, 1:2.
[b]Incomplete reaction.
[c]Yields after column chromatography.
[d]Number of spots on TLC.

H_2SO_4 (Table 1, entry 5) under reflux. We observed that the yields were affected by the amount of H_2SO_4 used, and optimum yield was obtained using 0.20 mmol of H_2SO_4. The reactions in the presence of HCl, AcOH, and HNO_3 and in solvents such as MeCN, $CHCl_3$, and DMF were sluggish and incomplete. Interestingly, when the reaction was performed in EtOH–H_2O (1:1, v/v), in the presence of 0.20 mmol of H_2SO_4 under reflux, it resulted in the formation of the intermediate product 3,3-(4-chlorophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (**2a**) in 93% yield in 30 min (Table 1, entry 6), which did not undergo further cyclization under these conditions. However, this condensation reaction was not complete even after 7 h when attempted in water, although it resulted in the formation of **2a** (56%). It is thus obvious that the course of the reaction can be controlled by changing the solvent system (Scheme 1).

Subsequently, reactions of various aromatic aldehydes containing electron-withdrawing and electron-donating substituents showed equal ease towards condensation with 2-hydroxy-1,4-naphthoquinone and resulted in the formation of **1** using H_2SO_4 as catalyst in ethanol under reflux (method A, Table 2) and **2** using H_2SO_4 as catalyst in ethanol–H_2O (1:1, v/v) under reflux (Table 3) in high yields.

The condensation of 4-chlorobenzaldehyde and 2-hydroxy-1,4-naphthoquinone was also attempted in the presence of task-specific ionic liquid, bmim[HSO_4]. The condensation could be achieved successfully at 70°C by using 20 mol%

Scheme 1

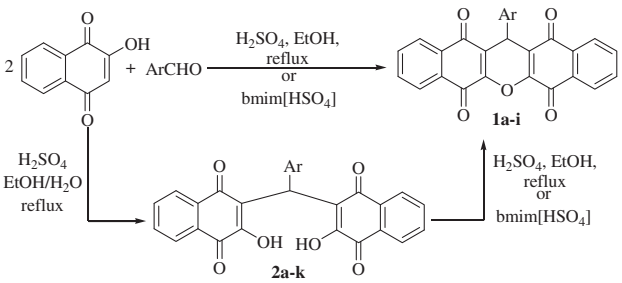

Table 2

Synthesis of aryl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14-(13*H*)-tetraones (**1**).

		Method A		Method B		Method C			
Product	Ar	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (min)	Yield (%)	mp (°C) (Obsd.)	mp (°C) (Lit.)
1a	4-ClC_6H_4	2.0	89	1.5	86	30	91	330–332	330–332[9]
1b	4-BrC_6H_4	2.5	87	2.0	84	35	93	328–330	333–335[9]
1c	4-$CH_3OC_6H_4$	2.5	90	1.0	88	25	94	320–322	–
1d	C_6H_5	3.0	88	2.0	88	40	91	300–302	305–307[9]
1e	4-$CH_3C_6H_4$	2.5	91	1.5	84	30	88	304–306	304–307[9]
1f	2-ClC_6H_4	2.0	86	1.0	85	35	90	304–306	307–309[9]
1g	4-$CF_3C_6H_4$	2.5	89	2.0	85	40	91	324–326	–
1h	4-FC_6H_4	3.0	85	2.0	86	45	92	276–278	270–272[9]
1i	2-BrC_6H_4	2.0	88	1.0	89	30	93	290–292	283–285[10]

Method A: H_2SO_4, EtOH, reflux.
Method B: bmim[HSO_4], 70°C.
Method C: H_2SO_4, EtOH, reflux, cyclization of **2**.

Table 3

Synthesis of 3,3-(arylmethylene)bis(2-hydroxynaphthalene-1,4-dione) derivatives (2) by condensation of aldehydes and 2-hydroxy-1,4-naphthoquinone in EtOH/H_2O (1:1) using H_2SO_4 as the catalyst.

Product	Ar	Time (min)	Yield (%)	mp (°C) (Obsd.)	mp (°C) (Lit.)
2a	4-ClC_6H_4	30	93	188–190	180–182[11]
2b	4-BrC_6H_4	25	90	214–216	216–218[11]
2c	4-$CH_3OC_6H_4$	20	86	220–222	220–222[11]
2d	C_6H_5	15	90	202–204	202–204[11]
2e	4-$CH_3C_6H_4$	20	94	174–176	170–172[11]
2f	2-ClC_6H_4	20	89	218–220	215–217[9]
2g	4-$CF_3C_6H_4$	25	91	188–190	–
2h	4-FC_6H_4	30	87	190–192	193–195[9]
2i	2-BrC_6H_4	20	89	210–212	–
2j	2-$CH_3OC_6H_4$	15	91	212–214	–
2k	3-ClC_6H_4	30	89	224–226	231–233[9]

of bmim[HSO_4] and led to the formation of **1a** in 86% yield. However, the reaction at room temperature remained incomplete and gave a mixture of **1a** and **2a**. Other substituted aldehydes also underwent condensation successfully under these conditions, and the corresponding aryl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraones (**1a–i**) were obtained in high yields (Table 2, method B). The recovered ionic liquid could be recycled for three cycles before losing activity (Fig. 1). Synthesis of xanthene derivatives (**1a–i**) could also be achieved by dehydration of the initially formed **2a–i** in ethanol under reflux using H_2SO_4 as a catalyst or in the presence of bmim[HSO_4] at 70°C (Table 2, method C). Both the methods gave comparative yields. However, the yields reported in Table 2, method C, are those obtained using H_2SO_4 as catalyst under reflux.

Hydroxyl naphthoquinone and its alkylated derivatives are reported to show high antioxidant activity [12]. Therefore, we screened *in vitro* antioxidant activity of naphthoquinone-based compounds **1** and **2**. Radical scavenging activity of 3,3-(arylmethylene)bis(2-hydroxynaphthalene-1,4-diones) (**2a–k**) were measured at different concentrations (Fig. 2) by using DPPH assay and compared with butylated hydroxy toluene (BHT) as standard. The antioxidant activities of compounds **1a–i** could not be performed as these compounds showed little solubility in the solvent system (methanol–acetone). The compounds **2a–i** showed good to moderate radical scavenging activity, as compared with the standard BHT (Table 4). The IC_{50} (μM) values of the compounds **2a**, **2c**, **2d**, **2e**, **2g**, and **2k** were found to be 61.00, 62.41, 35.01, 62.99, 80.93, and 60.86 respectively, which were comparable with the standard (BHT) (Fig. 3). Among them, compound **2d** exhibited promising radical scavenging activity. The variation exhibited in DPPH scavenging capacity could be attributed to the effect of different substituents, and the results are summarized in Table 4.

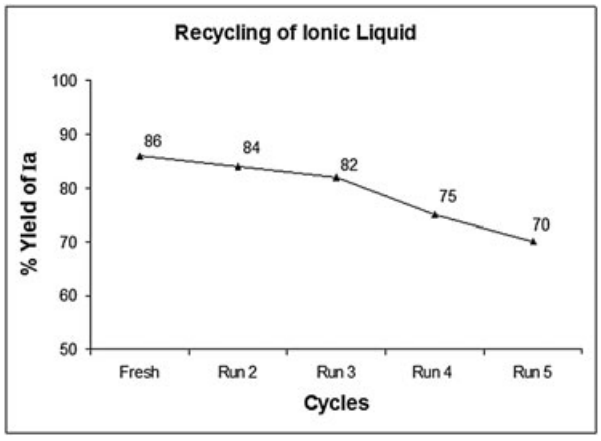

Figure 1. Recycling yields. Reactions of 2-hydroxy-1,4-naphthoquinone and 4-chloro benzaldehyde and bmim[HSO_4] (20 mol%).

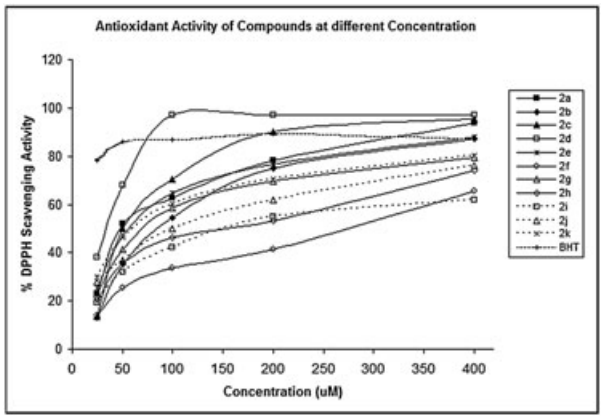

Figure 2. Graphical representation of % DPPH radical scavenging activity of compounds **2a**-**k** and BHT as a function of concentration.

CONCLUSION

In conclusion, we have reported an efficient acid catalyzed synthesis of aryl-5*H*-benzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraones and 3,3-(arylmethylene)bis(2-hydroxy naphthalene-1,4-diones). The synthesis of aryl-5*H*-benzo

Table 4

Antioxidant activity of the test compounds and standard using DPPH scavenging method – % DPPH radical scavenging activity.

	% DPPH scavenging activity*					
Compound	25 μ*M*	50 μ*M*	100 μ*M*	200 μ*M*	400 μ*M*	IC_{50} (μ*M*)
2a	22.95	52.07	62.82	78.23	93.64	61.00
2b	13.02	35.25	54.44	74.90	87.15	89.00
2c	13.47	49.81	70.64	90.1	95.32	62.41
2d	38.00	67.98	97.11	97.11	97.11	35.01
2e	25.34	47.03	64.61	76.59	88.16	62.99
2f	14.11	25.36	33.41	41.17	65.49	278.08
2g	22.62	41.42	58.49	69.54	79.61	80.93
2h	20.31	38.58	46.29	53.27	74.13	184.79
2i	19.27	31.93	42.06	54.96	61.85	167.20
2j	28.00	36.84	49.91	61.84	76.01	96.29
2k	30.80	46.27	60.02	70.54	80.46	60.86
BHT	78.42	85.92	86.79	89.19	87.43	11.93

*Each experiment was performed in triplicate, and the standard deviation was less than 10% of the mean.

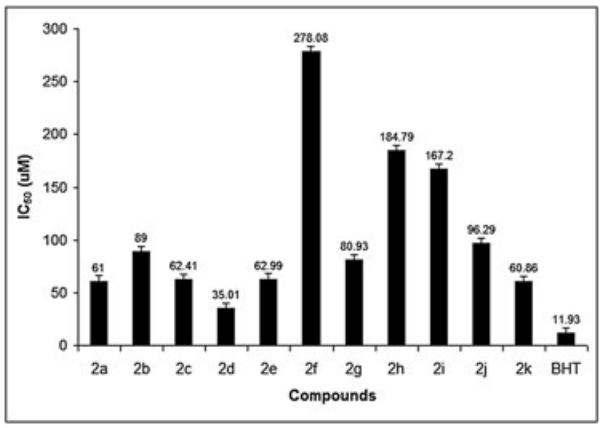

Figure 3. IC_{50}: concentration needed for reducing DPPH absorption by 50% at 517 nm. Values are average of 3 independent measurements for each compound.

[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraones has also been reported with the task-specific ionic liquid bmim[HSO_4], which acts as an effective catalyst and media for this transformation. The antioxidant activity of the synthesized compounds was screened by DPPH method, and IC_{50} (μ*M*) values of the compounds **2a**, **2c**, **2d**, **2e**, **2g**, and **2k** were found comparable with the standard (BHT).

EXPERIMENTAL

All the chemicals used were purchased from Sigma-Aldrich (Missouri, USA) and used as received. Silica gel 60 F_{254} (precoated aluminium plates) from Merck (Mumbai, India) was used to monitor reaction progress. Melting points were determined on a Tropical Labequip apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin-Elmer FTIR spectrophotometer, and the values are expressed as ν_{max} cm^{-1}. Absorbance measurements were made using Analytikjena Specord 250 Spectrophotometer. Mass spectral data were recorded on JEOL-AccuTOF mass spectrometer having a DART source. The ^1H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 MHz, using TMS as an internal standard. The chemical shift values are recorded on δ scale, and the coupling constants (*J*) are in Hertz. Ionic liquid bmim[HSO_4] was synthesized according to a reported procedure [13]. The spectral data of the known compounds are comparable with those reported in the literature.

General procedure for the synthesis of aryl-5*H*-dibenzo[*b*,*i*] xanthene-5,7,12, 14(13*H*)-tetraones (1a–i).

Method A. A mixture of aldehyde (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (2.0 mmol), H_2SO_4 (0.20 mmol), and 10 mL of EtOH was placed in a 50 mL round-bottomed flask and stirred under reflux. After completion of the reaction, as monitored by TLC using $CHCl_3$ as eluent (Table 2, method A), the reaction was allowed to cool at room temperature, and the precipitate formed was collected by filtration under vacuum. The solid was washed with ethanol and dried to obtain pure aryl-5*H*-dibenzo[*b*,*i*] xanthene-5,7,12,14(13*H*)-tetraone derivatives.

Method B. Aldehyde (1.0 mmol) and 2-hydroxy-1,4-naphthoquinone (2.0 mmol) were mixed thoroughly and placed in a 50 mL round-bottomed flask containing 1 mL of bmim[HSO_4]. The mixture was stirred at 70°C for the appropriate time as mentioned in Table 2, method B. After completion of the reaction as monitored by TLC using $CHCl_3$ as solvent, the mixture was allowed to cool at room temperature and quenched with water (5–7 mL). The precipitate thus formed was collected by filtration at pump and washed with water and then with EtOH to afford pure aryl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraone derivatives.

The filtrate was concentrated under reduced pressure and dried at 100°C to recover the ionic liquid for subsequent use. The ionic liquid thus obtained was reused for successive reactions for three more times without losing significant catalytic activity.

Method C. 3,3-(Arylmethylene)bis(2-hydroxy naphthalene-1,4-dione) (**2a–i**) (1 mmol), H_2SO_4 (0.20 mmol), and EtOH (10 mL) were placed in a 50 mL round-bottomed flask. The mixture was refluxed for appropriate time as mentioned in Table 2, method C. The precipitate formed was filtered at pump and washed with EtOH to yield pure aryl-5*H*-dibenzo[*b*,*i*] xanthene-5,7,12,14(13*H*)-tetraone derivatives. The aforementioned condensation could also be effected in the presence of task-specific ionic liquid bmim[HSO_4] (1 mL) instead of H_2SO_4 by heating at 70°C.

General procedure for the synthesis of 3,3-(arylmethylene) bis(2-hydroxy naphthalene-1,4-dione) (2a–k). A mixture of aldehyde (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (2.0 mmol), H_2SO_4 (0.20 mmol), and 10 mL of EtOH–H_2O (1:1, v/v) was stirred magnetically under reflux in a 50 mL round-bottomed flask for an appropriate time as mentioned in Table 3. The progress of the reaction was monitored by TLC using ethyl acetate–petroleum ether (60:40, v/v) as eluent. After completion, the reaction mixture was allowed to cool at room temperature. The precipitate, thus formed, was collected by filtration at pump and washed with water followed by ethanol to yield pure 3,3-(arylmethylene) bis(2-hydroxynaphthalene-1,4-dione) derivatives.

2,2-Diphenyl-1-picrylhydrazyl free radical scavenging assay. Methanolic solution of DPPH was used as a reagent for the spectrophotometric assay with modifications [14]. Solutions of different concentration of synthesized compounds (i.e., 25–400 μ*M*) were prepared using a mixture of methanol–acetone (1:1). We added 1 mL of 0.1 m*M* methanolic solution of DPPH to a 3 mL solution of the compounds, and the mixture was shaken vigorously using vortex mixer. Absorbance was read against a blank at 517 nm after incubation of the reaction mixtures for 60 min in dark at room temperature. BHT was used as a reference compound. The radical scavenging activities were expressed as the inhibition percentage and were calculated using the following formula:

$$\text{Radical scavenging activity}(\%) = [(A_0 - A_1)/A_0) \times 100],$$

where A_0 is the absorbance of the control (blank, without compound) and A_1 the absorbance of the compound. All the tests were carried out in triplicate, and the results were averaged.

Spectral data of some representative products are given in the succeeding text.

13-(4-Methoxyphenyl)-5,7,12,14-tetrahydrodibenzo[b,i]xanthene-5,7,12,14(13H)-tetraone (1c). Red solid; IR (KBr, cm^{-1}) ν_{max}: 2928, 1688, 1671, 1591, 1213; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.09–8.04 (m, 2H, Ar), 7.98–7.96 (m, 1H, Ar), 7.94–7.89 (m, 2H, Ar), 7.86–7.83 (m, 2H, Ar), 7.71–7.67 (m, 1H, Ar), 7.32 (d, J = 8.72 Hz, 2H), 6.77 (d, J = 8.44 Hz, 2H), 5.02 (s, 1H, ArCH), 3.69 (s, 3H, OCH_3); MS (ESI) *m/z* calcd. for $C_{28}H_{16}O_6$: 448.09, found: 449.12 [M^+ + H].

13-(4-Trifluoromethylphenyl)-5,7,12,14-tetrahydrodibenzo[b,i] xanthene-5,7,12,14 (13H)-tetraone (1g). Red solid; IR (KBr, cm^{-1}) ν_{max}: 2940, 1689, 1668, 1592, 1218; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.14–8.11 (m, 2H, Ar), 8.04–8.02 (m, 2H, Ar), 7.97–7.90 (m, 4H, Ar), 7.78–7.72 (m, 1H, Ar), 7.54–7.48 (m, 2H, Ar), 7.29–7.25 (m, 1H, Ar), 5.31 (s, 1H, ArCH); MS (ESI) *m/z* calcd. for $C_{28}H_{13}F_3O_5$: 486.07, found: 489.10 [M^+ + H].

3,3-(4-Chlorophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (2a). Yellow solid; IR (ν_{max} cm^{-1}) (KBr): 3332, 1673, 1651, 1365, 1298; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99 (d, J = 7.32 Hz, 2H, Ar), 7.92 (d, J = 7.32 Hz, 2H, Ar), 7.88–7.75 (m, 4H, Ar), 7.33–7.30 (m, 2H, Ar), 7.20–7.14 (m, 2H, Ar), 6.07 (s, 1H, ArCH), 4.06 (bs, OH, overlap with DMSO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.22, 181.02, 156.40, 138.36, 134.78, 133.22, 132.76, 132.01, 130.47, 129.84, 128.56, 127.54, 126.56, 126.09, 125.67, 122.03, 36.27; MS (ESI) *m/z* calcd. for $C_{27}H_{15}ClO_6$: 470.06, found: 471.10 [M^+ + H], 473.10 [M^+ + H + 2].

3,3-(4-Trifluromethylphenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (2g). Yellow solid; IR (KBr, cm^{-1}) ν_{max}: 3340, 1651, 1594, 1348, 1300; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.99–7.97 (m, 2H, Ar), 7.93 (d, J = 7.32 Hz, 2H, Ar), 7.87–7.63 (m, 4H, Ar), 7.54 (d, J = 7.8 Hz, 2H, Ar), 7.46–7.45 (m, 2H, Ar), 6.06 (s, 1H, ArCH), 4.44 (bs, OH, overlap with DMSO); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 183.90, 181.66, 157.17, 146.67, 135.18, 133.63, 132.62, 130.40, 129.32, 126.55, 126.12, 122.65, 38.01; MS (ESI) *m/z* calcd. for $C_{28}H_{15}F_3O_6$: 504.08, found: 505.15 [M^+ + H].

3,3-(2-Bromophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (2i). Yellow solid; IR (KBr, cm^{-1}) ν_{max}: 3330, 1672, 1545, 1360, 1254; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.99 (d, J = 7.32 Hz, 2H, Ar), 7.92 (d, J = 7.32 Hz, 2H, Ar), 7.86–7.75 (m, 4H, Ar), 7.51 (d, J = 7.8 Hz, 1H, Ar), 7.32 (d, J = 7.32 Hz, 1H, Ar), 7.22–7.18 (m, 1H, Ar), 7.12–7.08 (m, 1H, Ar), 6.02 (s, 1H, ArCH), 3.98 (bs, OH, overlap with DMSO); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 183.72, 181.53, 156.88, 140.46, 135.31, 133.76, 132.49, 132.40, 131.22, 130.34, 128.35, 127.60, 126.18, 124.24, 122.66, 39.34; MS (ESI) *m/z* calcd. for $C_{27}H_{15}BrO_6$: 514.01, found: 515.05 [M^+ + H], 5.17.05 [M^+ + H + 2].

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