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Ionic Liquid [DABCO-H][HSO_4] as a Highly Efficient and Recyclable Catalyst for Friedel–Crafts Alkylation in the Synthesis of Bis(naphthol)methane and Bis(indolyl)methane Derivatives

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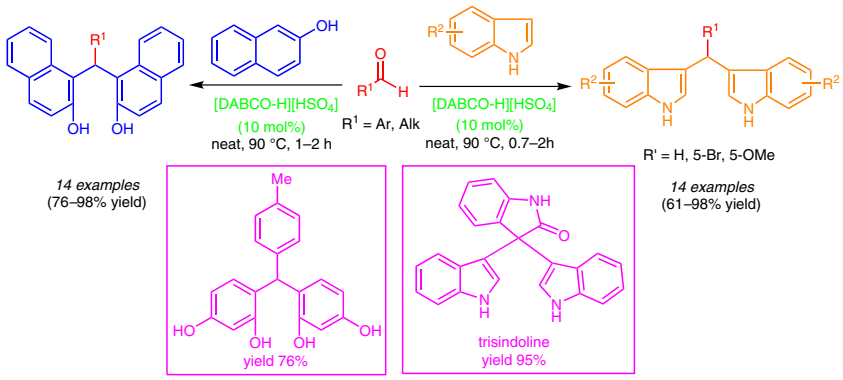

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Abstract A simple and highly efficient approach to the synthesis of bis(naphthol)methane (BNM) and bis(indolyl)methane (BIM) derivatives has been developed. In the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO)-based ionic liquid catalysts, which are environmental friendly, inexpensive, and recyclable, the reaction afforded the corresponding products in good to excellent yields within short times under solvent-free conditions. The catalysts can be easily recovered and reused several times without significant loss in activity.

Keywords ionic liquids, solvent-free, bis(naphthol)methanes, bis(indolyl)methanes, Friedel–Crafts alkylation

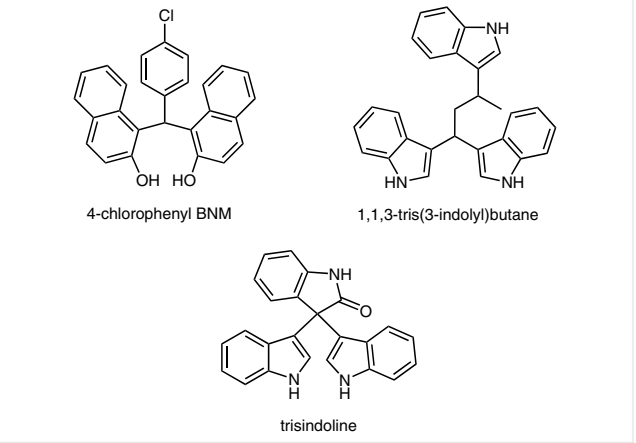


Figure 1 Significant structures of the BNMs and BIMs

Bis(naphthol)methanes (BNMs) have been reported as the key intermediates in many organic processes, such as in the synthesis of macrocyclic naphthacrowns,[1] benzofuran spirans,[2] and benzoxanthenes.[3] Some of these compounds show interesting antifugal activities.[4] BNMs are also known as a non-steroidal class of medication with anticancer, anti-inflammatory, and antianalgesic activity with good gastric tolerance.[5] The unique structural of BNM is shown in Figure 1. Chemists have particularly focused on the synthesis of xanthenes and benzoxanthenes because of their biological activity. However, reports on the synthesis of BNM intermediates are rare.[6] Furthermore, many disadvantages are associated with the few methods that are available, such as the requirement for high-pressure conditions, moisture-sensitive catalysts, low yields, and long reaction times, and most approaches afford a mixture of products.

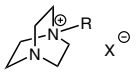
Indole and its derivatives are an important class of heterocyclic compounds. They have received significant attention because of their wide range of biological and anticancer activities.[7] Among them, bis(indolyl)methanes (BIMs) have attracted particular interest because of their biological and pharmacological activities, such as antimicrobial,[8] anti-inflammatory,[9] and antioxidant properties;[10] furthermore, BIMs are also effective in cancer chemotherapy,[11] whereby it can aid the inhibition of cancer cell growth through the induction of apoptosis and metastasis.[12] Significant examples of two marine-isolated BIM natural products are shown in Figure 1.[13] Various methods have been described for the synthesis of BIM derivatives, which involve condensation of indoles with carbonyl compounds catalyzed by different catalysts.[14] Ionic liquids (ILs), such as [Bmim][BF_4], [Bmim][PF_6],[15] [Bmim][$MeSO_4$],[16] guanidinium ILs,[17] and secondary amine-based ILs,[18] have also been employed in this transformation. However, despite their own merit, in

some cases, the reactions must be performed with an excess of catalyst, or under special conditions, such as microwave irradiation.

Therefore, the development of green and efficient procedures for the synthesis of both BNMs and BIMs is crucial in terms of both synthetic technology and environmental concerns. To our knowledge, no universal catalyst has been described that can promote the Friedel–Crafts reaction to synthesize both BNMs and BIMs with high yields under the same conditions.

In recent years, ILs have become increasingly important as environmentally friendly media in many chemical and biochemical transformations because of their unique physicochemical properties.[19] On the basis of these benefits, many functional ILs have been synthesized and utilized as recyclable catalysts for a range of reactions with good to excellent performance.[20–24] Recently, we have reported a series of ionic liquid catalysts based on the skeleton of 1,4-diazobicyclo[2.2.2]octane (DABCO) that have been shown to be very effective catalysts for Michael addition reaction,[25] Knoevenagel condensation,[26] Kabachnik–Fields reaction,[27] and tandem Knoevenagel–phospha-Michael reaction.[28] As part of our ongoing interest in IL-mediated organic reactions, here, we disclose the results of our study on the use of DABCO-based ILs as highly efficient catalysts for the synthesis of bis(naphthol)methane and bis(indolyl)methane derivatives through Friedel–Crafts alkylation.

The ionic liquid catalysts that we have synthesized such as 1-butyl-1,4-diazabicyclo[2.2.2]octanylium bromide ([DABCO-C_4]Br), and 1,4-diazabicyclo[2.2.2]octane hydroacetate ([DABCO-H][AcO]), hydrogensulfate ([DABCO-H][HSO_4]), hydrochloride ([DABCO-H]Cl) and hydrotetrafluoroborate ([DABCO-H][BF_4]) are shown in Figure 2.[26]

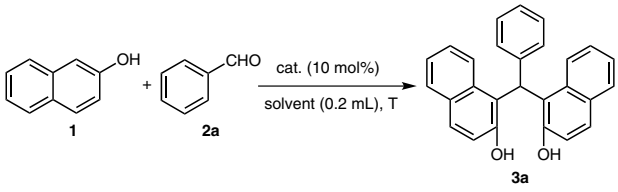


[DABCO-C_4]Br, X = Br, R = *n*-Bu
[DABCO-H][AcO], X = AcO, R = H
[DABCO-H][HSO_4], X = HSO_4, R = H
[DABCO-H]Cl, X = Cl, R = H
[DABCO-H][BF_4], X = BF_4, R = H

Figure 2 Structures of the DABCO-based ionic liquid catalysts

Initially, our studies were focused on optimizing the conditions for the synthesis of BNMs with 2-naphthol (2 mmol) and benzaldehyde (1 mmol) under different conditions (Table 1). The yields of BNM **3a** differed significantly when different DABCO-base IL catalysts were employed in the reaction in methanol at room temperature (entries 1–5). All the IL catalysts could promote the reaction, and better yield was obtained when [DABCO-H][HSO_4] was used under the same conditions (entry 3 vs. entries 1, 2, 4, and 5). However, the product **3a** could be obtained with a higher yield of 69% when the temperature was increased to 60 °C (entry 7). We then tried to raise the temperature of this reaction in other solvents, such as EtOH, MeCN, DCE and DMSO, but the product **3a** was only formed in poor yields even after long reaction times (entries 8–11). Finally, it was found that under neat conditions, **3a** was obtained in 87% yield at 90 °C within only one hour (entry 12). The solvent-free conditions allowed the reactions to be performed in a very simple, inexpensive, and green manner. Upon completion of the reaction, the mixture was washed with cold water to separate the catalyst from organic phase, then the water was evaporated under vacuum and the catalyst could be reused for the same reaction.

Table 1 Optimization of Reaction Conditions[a]



1 2a 3a

Entry	Cat (10 mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	[DABCO-C_4]Br	MeOH	r.t.	24	23
2	[DABCO-H]AcO	MeOH	r.t.	24	8
3	[DABCO-H][HSO_4]	MeOH	r.t.	24	43
4	[DABCO-H]Cl	MeOH	r.t.	24	31
5	[DABCO-H][BF_4]	MeOH	r.t.	24	27
6	[DABCO-H][HSO_4]	MeOH	40	6	55
7	[DABCO-H][HSO_4]	MeOH	60	3	69
8	[DABCO-H][HSO_4]	EtOH	75	6	46
9	[DABCO-H][HSO_4]	MeCN	80	6	19
10	[DABCO-H][HSO_4]	DCE	80	6	22
11	[DABCO-H][HSO_4]	DMSO	90	6	26
12	[DABCO-H][HSO_4]	neat	90	1	87

[a] Reaction conditions: 2-naphthol (**1a**; 2 mmol), benzaldehyde (**2a**; 1 mmol), DABCO-based catalyst (0.1 mmol).
[b] Isolated yield.

The efficiency and applicability of this method for the synthesis of **3a** are compared with those of other reported catalysts in Table 2. Under solvent-free conditions, the DABCO-based IL catalyst, which can be recovered and reused, is the most effective catalyst for the formation of BNM **3a** with a good yield in short times.

Having optimized the conditions, we next explored the generality of this method for the synthesis of BNMs with 2-naphthol and aldehydes in the presence of 10 mol% IL [DABCO-H][HSO_4] as catalyst. As shown in Table 3, the reaction of 2-naphthol and aldehydes proceeded smoothly to afford the corresponding BNMs in good to excellent yields (76–98%) within 1–2 hours. Especially, the BNM of **3c**, which has been reported to have interesting antifugal activities, was

Table 2 Comparison with Reported Catalysts for the Synthesis of **3a**

Entry	Catalyst (mol%)	Conditions	Time (h)	Yield (%)	Recyclable?	Ref.
1	$H_3[P(Mo_3O_{10})_4]\cdot nH_2O$	CH_2Cl_2, reflux	1	51	no	14
2	TfOH (10)	EtOH, 3 kbar, 60 °C	24	89	no	17b
3	concd HCl	AcOH, 0 °C	50	64	no	6f
4	$BF_3\cdot OEt_2$, AcOH	CH_2Cl_2, r.t.	1	85	no	6e
5	[DABCO-H][HSO_4]	neat, 90 °C	1	87	yes	this work

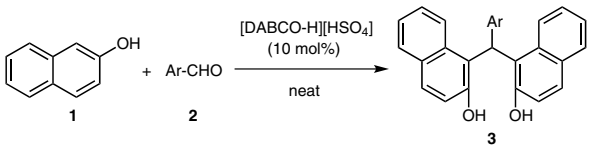
obtained in a good yield of 85% (entry 3). The products were often obtained in high yields when aromatic aldehydes with electron-withdrawing groups, such as a nitro group, were employed in the reaction (entries 4 and 11). When aromatic aldehydes have the same substituents, the reaction of *ortho*- or *meta*-substituted substrates required shorter reaction times, and afforded the corresponding BNMs in higher yields than the substrates with *para* substituents (entry 2 vs. 6, entry 3 vs. 7 and 8). When 2-naphthaldehyde was used in the reaction with 2-naphthol, the product, containing three units of naphthyl, BNM **3i** was isolated in a good yield of 76% (entry 9). 2-Naphthol with other substituents, such bromo and cyano, were also examined in the reaction, and afforded the corresponding products in good to excellent yields (entries 10–14).

This is a highly efficient method for the synthesis of BNMs, and some of the above BNM derivatives cannot be prepared by using the previous method. After the above success, to confirm the generality of the present approach, we then extended the method to the synthesis of BIMs through Friedel–Crafts alkylation with indoles. The results are summarized in Table 4. The reactions of indole (**4a**) and substituted benzaldehydes **4a**–**g** containing electron-withdrawing or -donating groups were converted into the corresponding products **5a**–**g** in good to excellent yields (74–98%) within 0.7–2 hours (entries 1–10). Heteroaromatic aldehydes, such as thiophene-2-carbaldehyde (**5k**) were also effective substrates in the Friedel–Crafts alkylation of indole with a good yield of 86% (entry 11). Other substituted indoles were found to be compatible with [DABCO-H][HSO_4] and gave the corresponding BIMs in good yields (entries 12 and 13). This catalytic system was also successfully applied for the reaction of aliphatic aldehydes, such as isobutyraldehyde, with indole and produced the desired BIM **5n** in a high yield of 92% within 1.5 hours (entry 14).

The recyclability of the catalyst was investigated for the synthesis of bis(indolyl)methane **5c**, which was carried out on a 5-mmol scale. Upon completion of the reaction, the reaction mixture was diluted with cold water. Once the organic phase had been separated from the mixture, the water was evaporated under vacuum, and the catalyst was used directly in the next recycling run under the same conditions. Friedel–Crafts alkylation of indole with 4-chlorobenzaldehyde gave the corresponding product **5c** in similar yields over six cycles (Figure 3).

Recycling of the catalyst [DABCO-H][HSO_4] for the synthesis of BIM **5c** was also investigated. Resorcinol dimers are the key intermediates in the synthesis of macrocyclic host molecules resorcin[4]arenes.[29] The synthetic procedures for these compounds often suffered from long reaction times, low yields, and the use of large quantities of volatile organic solvents. Under optimized reaction conditions, resorcinol dimer **7** was formed from the reaction of resorcinol and 4-methylbenzaldehyde with a good yield of 76% in only 1.5 hours (Scheme 1).

Table 3 Synthesis of Bis(naphthol)methanes by Friedel–Crafts Reactions from 2-Naphthol and Aldehydes Catalyzed by [DABCO-H][HSO_4][a]

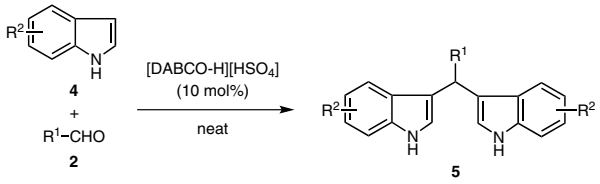


1 2 3

Entry	R	Ar	3	Time (h)	Yield (%)[b]
1	H	Ph	**3a**	1	87
2	H	4-MeC_6H_4	**3b**	2	83
3	H	4-ClC_6H_4	**3c**	2	85
4[c]	H	4-$O_2NC_6H_4$	**3d**	1	98
5	H	4-BrC_6H_4	**3e**	1	79
6	H	3-MeC_6H_4	**3f**	1.5	94
7	H	2-ClC_6H_4	**3g**	1	98
8	H	2,4-$Cl_2C_6H_3$	**3h**	1.5	91
9	H	2-naphthyl	**3i**	1	76
10	6-Br	Ph	**3j**	1.5	81
11	6-Br	4-$O_2NC_6H_4$	**3k**	1	92
12	6-Br	3-MeC_6H_4	**3l**	1	85
13	6-Br	2,4-$Cl_2C_6H_3$	**3m**	1	90
14	6-CN	Ph	**3n**	1	88

[a] Reaction conditions: 2-naphthol (**1**; 2 mmol), aldehyde (**2**; 1 mmol), [DABCO-H][HSO_4] (21 mg, 0.1 mmol), 90 °C.
[b] Isolated yield.
[c] Reaction temperature 120 °C.

Table 4 Synthesis of Bis(indolyl)methanes by Friedel–Crafts Reactions from Indoles and Aldehydes Catalyzed by [DABCO-H][HSO_4][a]



Entry	R^1	R^2	5	Time (h)	Yield (%)[b]
1	Ph	H	**5a**	2	91
2	4-MeC_6H_4	H	**5b**	1	79
3	4-ClC_6H_4	H	**5c**	0.7	97
4	4-BrC_6H_4	H	**5d**	1	81
5	4-O_2NC_6H_4	H	**5e**	1	98
6	4-MeOC_6H_4	H	**5f**	2	74
7	2-ClC_6H_4	H	**5g**	1	95
8	2,4-$Cl_2C_6H_3$	H	**5h**	0.7	98
9	2,5-$(MeO)_2C_6H_3$	H	**5i**	1	98
10	2-naphthyl	H	**5j**	1.5	96
11	2-thienyl	H	**5k**	2	86
12	4-ClC_6H_4	5-Br	**5l**	2	61
13	4-ClC_6H_4	5-OMe	**5m**	2	70
14	*i*-Pr	H	**5n**	1.5	92

[a] Reaction conditions: indole (**4**; 2 mmol), aldehyde (**2**; 1 mmol), [DABCO-H][HSO_4] (21 mg, 0.1 mmol), 90 °C.
[b] Isolated yield.

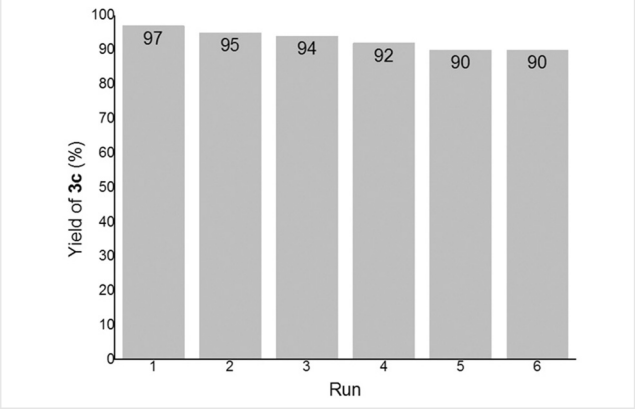
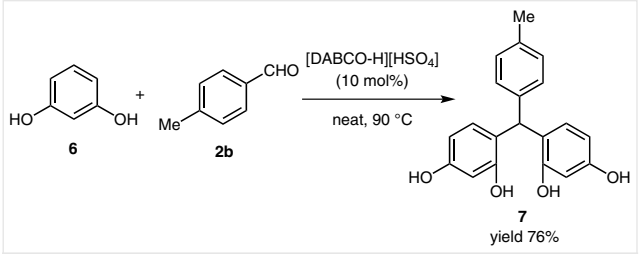
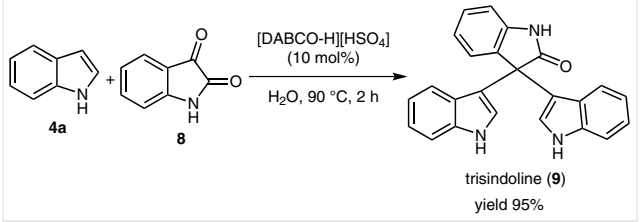


Figure 3

It is of interest to further extend the application of this IL catalysis to other potential bioactive skeleton synthesis. Thus, we selected a marine natural product trisindoline as the target compound, which was synthesized with a high yield of 95% in the presence of 10 mol% [DABCO-H][HSO_4] with water as solvent at 90 °C (Scheme 2).



Scheme 1 Synthesis of the resorcinol dimer



Scheme 2 Synthesis of the marine-isolated natural product trisindole

In summary, it was demonstrated that the readily available, economical, DABCO-based ionic liquids could be used as a recyclable and highly efficient catalyst for the synthesis of bis(naphthol)methanes and bis(indolyl)methanes through Friedel–Crafts alkylation. The reactions, which were performed under solvent-free conditions, allowed a very simple, clean synthesis of both bis(naphthol)methanes and bis(indolyl)methanes with good to excellent yields in short times. By using the ionic liquid catalyst, other potential bioactive skeleton compounds, such as the natural product trisindoline, were also synthesized with excellent yields. The catalyst was easily isolated from the reaction mixture and could be reused six times without loss of activity. Further investigations on the applications of these ionic liquid catalysts are in progress in our laboratory.

All chemicals were purchased from commercial suppliers and were used without further purification. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were determined with an X-4 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer with DMSO-d_6 and $CDCl_3$ as the solvent. Chemical shifts are reported relative to TMS as internal standard. The ^{1}H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constant in hertz, and number of protons. HRMS were obtained on an IonSpec FT-ICR mass spectrometer with ESI resource.

Synthesis of Bis(naphthol)methanes; Typical Procedure for 3a

A 25 mL round-bottomed flask was charged with 2-naphthol (**1**; 288 mg, 2 mmol), aldehyde **2a** (1 mmol), and [DABCO-H][HSO_4] (21 mg, 0.1 mmol). The reaction mixture was well stirred and heated to 90 °C for the appropriate time under air. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with cold water (5 mL) and CH_2Cl_2 (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL), the

organic phase was washed with brine (5 mL), and dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was subjected to chromatography on a silica gel (200–300 mesh) column (petroleum ether–EtOAc, 3:1) to afford **3a**.

1,1′-(Phenylmethylene)bis(naphthalen-2-ol) (3a)[2]

White solid; yield: 328 mg (87%); mp 194–196 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.02 (d, *J* = 7.2 Hz, 2 H, ArH), 7.06 (s, 1 H, CH), 7.11–7.23 (m, 9 H, ArH), 7.69 (d, *J* = 8.8 Hz, 2 H, ArH), 7.73 (d, *J* = 7.6 Hz, 2 H, ArH), 8.12 (d, *J* = 8.0 Hz, 2 H, ArH), 9.70 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.83, 119.36, 120.76, 122.55, 124.44, 125.40, 126.22, 128.11, 128.63, 128.83, 128.96, 129.09, 134.68, 144.52, 153.11.

1,1′-(*p*-Tolylmethylene)bis(naphthalen-2-ol) (3b)[2]

Yield: 324 mg (83%); white solid; mp 164–165 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3 H, CH_3), 6.91 (d, *J* = 7.6 Hz, 2 H, ArH), 6.98 (d, *J* = 7.6 Hz, 2 H, ArH), 7.02 (s, 1 H, CH), 7.13–7.23 (m, 6 H, ArH), 7.68 (d, *J* = 8.8 Hz, 2 H, ArH), 7.72 (d, *J* = 7.6 Hz, 2 H, ArH), 8.12 (d, *J* = 8.4 Hz, 2 H, ArH), 9.64 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.08, 41.54, 119.42, 120.90, 122.56, 124.42, 126.25, 128.56, 128.82, 128.85, 128.93, 129.12, 134.26, 134.70, 141.35, 153.16.

1,1′-[(4-Chlorophenyl)methylene]bis(naphthalen-2-ol) (3c)[2]

Yield: 349 mg (85%); white solid; mp 191–193 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00–7.02 (m, 3 H, CH and ArH), 7.15–7.23 (m, 8 H), 7.68 (d, *J* = 8.8 Hz, 2 H, ArH), 7.72 (d, *J* = 8.0 Hz, 2 H, ArH), 8.12 (d, *J* = 8.4 Hz, 2 H, ArH), 9.84 (s, 2 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.37, 119.37, 120.39, 122.64, 124.30, 126.36, 127.93, 128.88, 129.09, 129.16, 129.84, 130.48, 134.56, 143.92, 153.02.

1,1′-[(4-Nitrophenyl)methylene]bis(naphthalen-2-ol) (3d)[6g]

Yield: 413 mg (98%); yellow solid; mp 141–143 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.17–7.24 (m, 7 H, ArH and CH), 7.29 (d, *J* = 8.8 Hz, 2 H, ArH), 7.73 (d, *J* = 8.8 Hz, 4 H, ArH), 8.10 (d, *J* = 8.8 Hz, 2 H, ArH), 8.18 (d, *J* = 8.4 Hz, 2 H, ArH), 10.06 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.62, 118.85, 119.23, 122.32, 122.83, 123.65, 126.09, 126.55, 128.48, 128.67, 129.04, 129.26, 134.00, 145.11, 152.54.

1,1′-[(4-Bromophenyl)methylene]bis(naphthalen-2-ol) (3e)[30]

Yield: 359 mg (79%); yellow solid; mp 191–192 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.99 (d, *J* = 8.4 Hz, 2 H, ArH), 7.03 (s, 1 H, CH), 7.18–7.26 (m, 6 H, ArH), 7.38 (d, *J* = 8.4 Hz, 2 H, ArH), 7.72 (t, *J* = 8.8 Hz, 4 H, ArH), 8.15 (d, *J* = 8.4 Hz, 2 H, ArH), 9.92 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.94, 117.80, 118.91, 119.82, 122.16, 123.79, 125.89, 128.40, 128.59, 128.69, 130.36, 130.44, 134.08, 143.93, 152.58.

1,1′-(*m*-tolylmethylene)bis(naphthalen-2-ol) (3f)[31]

Yield: 367 mg (94%); white solid; mp 123–125 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.16 (s, 3 H, CH_3), 6.78 (d, *J* = 7.6 Hz, 1 H, ArH), 6.88 (s, 1 H, ArH), 6.93 (d, *J* = 7.2 Hz, 1 H, ArH), 7.02 (s, 1 H, CH), 7.06 (d, *J* = 7.6 Hz, 1 H, ArH), 7.12–7.23 (m, 6 H, ArH), 7.69–7.73 (m, 4 H, ArH), 8.11 (d, *J* = 8.0 Hz, 2 H, ArH), 9.67 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.19, 41.30, 118.89, 120.34, 122.07, 123.91, 125.30, 125.76, 127.58, 128.35, 128.45, 128.59, 128.77, 134.20, 136.34, 143.98, 152.64.

1,1′-[(2-Chlorophenyl)methylene]bis(naphthalen-2-ol) (3g)[2]

Yield: 402 mg (98%); white solid; mp 133–135 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.03–7.16 (m, 8 H, ArH and CH), 7.27 (t, *J* = 8.4 Hz, 2 H, ArH), 7.37 (d, *J* = 7.6 Hz, 1 H, ArH), 7.63 (d, *J* = 8.4 Hz, 1 H, ArH), 7.71 (m, 3 H, ArH), 7.95 (d, *J* = 7.6 Hz, 1 H, ArH), 8.31 (s, 1 H, ArH), 9.59 (s, 1 H, OH), 10.10 (s, 1 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.00, 118.24, 118.39, 118.88, 120.79, 121.96, 122.10, 122.89, 124.43, 125.60, 126.01, 126.20, 126.76, 128.31, 128.39, 128.45, 128.63, 128.70, 130.57, 133.43, 133.98, 134.13, 142.23, 152.14, 153.07.

1,1′-[(2,4-Dichlorophenyl)methylene]bis(naphthalen-2-ol) (3h)[2]

Yield: 404 mg (91%); white solid; mp 153–155 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.95 (d, *J* = 8.4 Hz, 1 H, ArH), 7.01 (s, 1 H, CH), 7.02 (d, *J* = 8.4 Hz, 1 H, ArH), 7.12–7.19 (m, 4 H, ArH), 7.22–7.28 (m, 2 H, ArH), 7.49 (d, *J* = 2.0 Hz, 1 H, ArH), 7.66–7.73 (m, 3 H, ArH), 7.88 (d, *J* = 8.8 Hz, 1 H, ArH), 8.25 (s, 1 H, ArH), 9.67 (s, 1 H, OH), 10.18 (s, 1 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.60, 117.75, 118.17, 118.84, 120.32, 122.06, 122.17, 122.67, 124.27, 125.70, 126.17, 126.36, 127.71, 128.43, 128.49, 128.62, 128.93, 130.30, 131.71, 133.85, 133.93, 134.18, 141.69, 152.13, 152.98.

1,1′-(Naphthalen-2-ylmethylene)bis(naphthalen-2-ol) (3i)[6e]

Yield: 324 mg (76%); white solid; mp 126–129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.33 (m, 7 H, CH and ArH), 7.39–7.48 (m, 4 H, ArH), 7.63 (d, *J* = 8.0 Hz, 1 H, ArH), 7.80–7.84 (m, 5 H, ArH), 7.89 (d, *J* = 8.0 Hz, 1 H, ArH), 8.30 (d, *J* = 8.4 Hz, 2 H, ArH), 9.87 (s, 2 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.94, 119.16, 120.33, 122.36, 124.12, 125.06, 125.18, 125.77, 126.07, 127.02, 127.40, 127.49, 128.39, 128.62, 128.87, 131.63, 133.23, 134.46, 142.38, 152.96.

1,1′-(Phenylmethylene)bis(6-bromonaphthalen-2-ol) (3j)

Yield: 431 mg (81%); white solid; mp 212–215 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.98–7.01 (m, 3 H, ArH and CH), 7.13–7.19 (m, 5 H, ArH), 7.29 (d, *J* = 8.8 Hz, 2 H, ArH), 7.69 (d, *J* = 8.8 Hz, 2 H, ArH), 7.97 (d, *J* = 8.8 Hz, 2 H, ArH), 7.99 (s, 2 H, ArH), 9.93 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.19, 114.92, 119.88, 120.51, 125.19, 126.68, 127.83, 128.12, 128.18, 129.93, 132.76, 143.47, 153.31.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{19}Br_2O_2^+$: 532.9752; found: 532.9749.

1,1′-[(4-Nitrophenyl)methylene]bis(6-bromonaphthalen-2-ol) (3k)[6g]

Yield: 531 mg (92%); yellow solid; mp 145–148 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.07 (s, 1 H, CH), 7.23 (d, *J* = 8.4 Hz, 2 H, ArH), 7.24 (d, *J* = 8.4 Hz, 2 H, ArH), 7.31 (d, *J* = 2.0 Hz, 1 H, ArH), 7.33 (d, *J* = 2.0 Hz, 1 H, ArH), 7.34 (d, *J* = 8.8 Hz, 2 H, ArH), 7.98–8.02 (m, 4 H, ArH), 8.10 (d, *J* = 8.4 Hz, 2 H, ArH), 10.25 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.35, 115.24, 119.30, 119.93, 122.96, 126.03, 128.43, 128.67, 129.21, 129.97, 130.13, 132.46, 145.22, 152.73, 153.11.

1,1′-(*m*-Tolylmethylene)bis(6-bromonaphthalen-2-ol) (3l)

Yield: 464 mg (85%); white solid; mp 204–206 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.15 (s, 3 H, CH_3), 6.76 (d, *J* = 7.6 Hz, 1 H, ArH), 6.86 (s, 1 H, CH), 6.95 (d, *J* = 7.2 Hz, 1 H, ArH), 6.98 (s, 1 H, ArH), 7.07 (t, *J* = 7.6 Hz, 1 H, ArH), 7.18 (d, *J* = 8.8 Hz, 2 H, ArH), 7.30 (d, *J* = 9.2 Hz, 2 H, ArH), 7.69 (d, *J* = 8.8 Hz, 2 H, ArH), 7.98 (d, *J* = 9.2 Hz, 2 H, ArH), 7.99 (s, 2 H, ArH), 9.90 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.16, 41.16, 114.92, 119.88, 120.61, 125.29, 126.00, 126.69, 127.79, 128.17, 128.73, 129.92, 132.78, 136.59, 143.45, 153.32.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{21}Br_2O_2^+$: 546.9908; found: 546.9903.

1,1′-[(2,4-Dichlorophenyl)methylene]bis(6-bromonaphthalen-2-ol) (3m)

Yield: 543 mg (90%); white solid; mp 176–179 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.91 (d, *J* = 8.8 Hz, 1 H, ArH), 6.97 (s, 1 H, CH), 7.09 (d, *J* = 8.8 Hz, 1 H, ArH), 7.22 (dd, *J* = 8.4, 2.0 Hz, 1 H, ArH), 7.28 (dd, *J* = 9.2, 1.6 Hz, 1 H, ArH), 7.36 (t, *J* = 8.0 Hz, 2 H, ArH), 7.54 (d, *J* = 2.0 Hz, 1 H, ArH), 7.65 (d, *J* = 8.4 Hz, 1 H, ArH), 7.77 (t, *J* = 8.8 Hz, 2 H, ArH), 7.96 (d, *J* = 2.0 Hz, 1 H, ArH), 8.01 (d, *J* = 2.0 Hz, 1 H, ArH), 8.16 (d, *J* = 8.8 Hz, 1 H, ArH), 9.79 (s, 1 H, OH), 10.47 (s, 1 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.89, 115.08, 115.23, 117.93, 119.38, 119.97, 120.29, 124.99, 126.42, 126.57, 127.89, 127.96, 128.45, 128.50, 128.86, 129.99, 130.14, 130.19, 130.62, 131.47, 132.41, 134.20, 140.89, 152.74, 153.44.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{16}Br_2Cl_2NaO_2^+$: 622.8792; found: 622.8795.

5,5′-(Phenylmethylene)bis(6-hydroxy-2-naphthonitrile) (3n)

Yield: 375 mg (88%); white solid; mp 237–239 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.02 (d, *J* = 7.2 Hz, 2 H, ArH), 7.08 (s, 1 H, CH), 7.15–7.24 (m, 3 H, ArH), 7.30 (d, *J* = 8.8 Hz, 2 H, ArH), 7.48 (d, *J* = 8.8 Hz, 2 H, ArH), 7.88 (d, *J* = 8.8 Hz, 2 H, ArH), 8.09 (d, *J* = 9.2 Hz, 2 H, ArH), 8.39 (s, 2 H, ArH), 10.42 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.18, 104.06, 119.49, 120.21, 120.59, 125.50, 125.64, 125.72, 127.44, 128.05, 128.13, 129.58, 134.74, 135.87, 142.94, 156.01.

HRMS: *m*/*z* [M – H]$^+$ calcd for $C_{29}H_{17}N_2O_2^+$: 425.1290; found: 425.1296.

Synthesis of Bis(indolyl)methanes; Typical Procedure for 5a

A 25 mL round-bottomed flask was charged with indole (**4a**; 234 mg, 2 mmol), aldehyde (**2a**; 106 mg, 1 mmol), and [DABCO-H][HSO_4] (21 mg, 0.1 mmol). The reaction mixture was well stirred and heated to 90 °C for the appropriate time under air. Upon completion of the reaction (monitored by TLC), the reaction mixture was diluted with cold water (5 mL) and CH_2Cl_2 (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL), the organic phase was washed with brine (5 mL), and dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was subjected to chromatography on a silica gel (200–300 mesh) column (petroleum ether–EtOAc, 4:1) to afford **5a**.

3,3′-(Phenylmethylene)bis(1*H*-indole) (5a)[14h]

Yield: 294 mg (91%); pink solid; mp 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (s, 1 H), 6.35 (s, 2 H), 6.87 (t, *J* = 7.6 Hz, 2 H), 7.02 (t, *J* = 7.6 Hz, 2 H), 7.07–7.14 (m, 5 H), 7.19 (d, *J* = 6.8 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.46 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.07, 110.04, 118.11, 118.43, 118.81, 120.79, 122.60, 125.07, 125.95, 127.16, 127.64, 135.53, 142.97.

3,3′-(*p*-Tolylmethylene)bis(1*H*-indole) (5b)[14h]

Yield: 265 mg (79%); red solid; mp 95–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 5.82 (s, 1 H), 6.59 (s, 2 H), 6.98 (t, *J* = 7.6 Hz, 2 H), 7.06 (d, *J* = 7.6 Hz, 2 H), 7.13 (t, *J* = 7.2 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.78 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.09, 39.79, 111.03, 119.2, 119.91, 119.98, 121.88, 123.57, 127.13, 128.59, 128.94, 135.5, 136.71, 141.02.

3,3′-[(4-Chlorophenyl)methylene]bis(1*H*-indole) (5c)[14h]

Yield: 345 mg (97%); red solid; mp 77–78 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (s, 1 H), 6.59 (s, 2 H), 7.02 (t, *J* = 7.6 Hz, 2 H), 7.16 (t, *J* = 7.2 Hz, 2 H), 7.20–7.26 (m, 4 H), 7.33 (t, *J* = 8.0 Hz, 4 H), 7.84 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.64, 119.21, 119.38, 119.84, 122.11, 123.63, 126.90, 128.39, 130.10, 131.81, 136.70, 142.58.

3,3′-[(4-Bromophenyl)methylene]bis(1*H*-indole) (5d)[17b]

Yield: 324 mg (81%); red solid; mp 113–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (s, 1 H), 6.64 (s, 2 H), 7.04 (t, *J* = 7.6 Hz, 2 H), 7.18–7.24 (m, 4 H), 7.36–7.41 (m, 6 H), 7.97 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.69, 111.16, 119.08, 119.38, 119.82, 119.94, 122.1, 123.65, 126.88, 130.52, 131.33, 136.69, 143.11.

3,3′-[(4-Nitrophenyl)methylene]bis(1*H*-indole) (5e)[14h]

Yield: 360 mg (98%); red solid; mp 228–230 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98 (s, 1 H), 6.67 (s, 2 H), 7.02 (t, *J* = 7.2 Hz, 2 H), 7.19 (t, *J* = 7.6 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 8.00 (br s, 2 H), 8.13 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.22, 111.26, 118.16, 119.56, 119.62, 122.36, 123.62, 126.67, 129.52, 136.71, 151.84.

3,3′-[(4-Methoxyphenyl)methylene]bis(1*H*-indole) (5f)[14h]

Yield: 260 mg (74%); red solid; mp 188–190 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (s, 1 H), 6.52 (s, 2 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 6.93 (t, *J* = 7.2 Hz, 2 H), 7.09 (t, *J* = 7.2 Hz, 2 H), 7.17 (d, *J* = 7.6 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.74 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.35, 55.24, 111.07, 113.6, 119.2, 120, 120.03, 121.9, 123.57, 127.09, 129.63, 136.27, 136.72, 157.92.

3,3′-[(2-Chlorophenyl)methylene]bis(1*H*-indole) (5g)[14g]

Yield: 338 mg (95%); red solid; mp 105–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (s, 1 H), 6.57 (s, 2 H), 7.07–7.15 (m, 3 H), 7.19–7.29 (m, 4 H,), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.46–7.50 (m, 3 H), 7.74 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.67, 111.20, 118.30, 119.37, 119.88, 122.07, 123.90, 126.72, 127.02, 127.60, 129.55, 130.39, 134, 136.73, 141.37.

3,3′-[(2,4-Dichlorophenyl)methylene]bis(1*H*-indole) (5h)[14g]

Yield: 382 mg (98%); red solid; mp 100–102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (s, 1 H), 6.57 (s, 2 H), 6.99–7.06 (m, 4 H), 7.10–7.18 (m, 4 H), 7.32–7.36 (m, 4 H), 7.89 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.36, 111.24, 117.78, 119.46, 119.74, 122.20, 123.85, 126.82, 126.99, 129.30, 131.20, 132.45, 134.62, 136.73, 140.09.

3,3′-[(2,5-Dimethoxyphenyl)methylene]bis(1*H*-indole) (5i)[14g]

Yield: 374 mg (98%); red solid; mp 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (s, 3 H), 3.75 (s, 3 H), 6.30 (s, 1 H), 6.54 (s, 2 H), 6.68–6.74 (m, 2 H), 6.84–6.86 (d, *J* = 8.0 Hz, 1 H), 6.98 (t, *J* = 7.2 Hz, 2 H), 7.12 (t, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.77 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.17, 55.51, 56.61, 110.63, 110.95, 111.82, 116.84, 119.03, 119.35, 119.97, 121.74, 123.52, 127.23, 134.07, 136.72, 151.43, 153.45.

3,3′-(Naphthalen-2-ylmethylene)bis(1*H*-indole) (5j)[14e]

Yield: 357 mg (96%); red solid; mp 108–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (s, 1 H), 6.59 (s, 2 H), 6.96 (t, *J* = 8.0 Hz, 2 H), 7.14 (t, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.37–7.41 (m, 4 H), 7.49 (dd, *J* = 1.6, 8.4 Hz, 1 H), 7.66–7.68 (m, 1 H), 7.72 (t, *J* = 4.4 Hz, 2 H), 7.77–7.80 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.32, 111.08, 119.30, 119.53, 119.96, 121.98, 123.82, 125.30, 125.71, 126.76, 127.12, 127.59, 127.77, 127.93, 132.38, 133.62, 136.72, 141.63.

3,3′-(Thiophen-2-ylmethylene)bis(1*H*-indole) (5k)[32]

Yield: 282 mg (86%); red solid; mp 147–149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.13 (s, 1 H), 6.76 (s, 1 H), 6.77 (s, 1 H), 6.89 (m, 2 H), 7.01 (t, *J* = 7.2 Hz, 2 H), 7.11–7.17 (m, 3 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.84 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.34, 111.16, 119.37, 119.69, 119.77, 122.02, 123.22, 123.62, 125.15, 126.44, 126.77, 136.59, 148.69.

3,3′-[(4-Chlorophenyl)methylene]bis(5-bromo-1*H*-indole) (5l)[32]

Yield: 312 mg (61%); red solid; mp 163–165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.69 (s, 1 H), 6.56 (s, 2 H), 7.16–7.24 (m, 8 H), 7.43 (s, 2 H), 7.97 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.3, 112.77, 118.48, 122.13, 124.82, 125.13, 128.46, 128.63, 129.9, 132.22, 135.34, 141.63.

3,3′-[(4-Chlorophenyl)methylene]bis(5-methoxy-1*H*-indole) (5m)[33]

Yield: 291 mg (70%); red solid; mp 156–158 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 6 H), 5.77 (s, 1 H), 6.63 (s, 2 H), 6.81 (d, *J* = 2.4 Hz, 2 H), 6.86 (d, *J* = 2.4 Hz, 1 H), 6.88 (d, *J* = 2.4 Hz, 1 H), 7.24–7.30 (m, 6 H), 7.88 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.68, 55.91, 101.88, 111.85, 111.97, 118.71, 124.51, 127.32, 128.38, 130.09, 131.76, 131.88, 142.51, 153.75.

3,3′-(2-Methylpropane-1,1-diyl)bis(1*H*-indole) (5n)[34]

Yield: 265 mg (92%); red solid; mp 58–60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3 H), 2.67–2.76 (m, 1 H), 4.32 (d, *J* = 8.4 Hz, 1 H), 6.80 (s, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 7.19–7.27 (m, 4 H), 7.33 (s, 2 H), 7.80 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.06, 33.12, 41.28, 111.4., 119.13, 119.58, 119.77, 121.71, 121.98, 127.70, 136.28.

4,4′-(*p*-Tolylmethylene)bis(benzene-1,3-diol) (7)

Yield: 245 mg (76%); white cream.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3 H, CH_3), 5.76 (s, 1 H, CH), 6.11 (dd, *J* = 2.0, 8.0 Hz, 2 H, ArH), 6.27 (d, *J* = 2.0 Hz, 2 H, ArH), 6.42 (d, *J* = 8.4 Hz, 2 H, ArH), 6.84 (d, *J* = 7.6 Hz, 2 H, ArH), 7.02 (d, *J* = 7.6 Hz, 2 H, ArH), 8.98 (s, 2 H, OH), 9.01 (s, 2 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.74, 40.62, 103.50, 106.50, 117.60, 122.70, 129.46, 129.92, 131.25, 135.12, 156.51, 157.32.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}O_4^+$: 323.1283; found: 323.1285.

Trisindoline (9)[13a]

Yield: 345 mg (95%); white solid; mp 277–280 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.79 (t, *J* = 7.6 Hz, 2 H, ArH), 6.86 (d, *J* = 2.0 Hz, 2 H, -C_4HNH), 6.91 (t, *J* = 7.6 Hz, 1 H, ArH), 6.99 (t, *J* = 8.0 Hz, 3 H, ArH), 7.18–7.27 (m, 4 H, ArH), 7.34 (d, *J* = 8.0 Hz, 2 H, ArH), 10.58 (s, 1 H, NH), 10.92 (s, 2 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 52.53, 109.52, 111.50, 114.27, 118.13, 120.75, 120.83, 121.34, 124.21, 124.82, 125.66, 127.70, 134.57, 136.88, 141.28, 178.74.

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Supporting Information

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