

# Poly(*N,N'*-dichloro-*N*-ethyl-benzene-1, 3-disulfonamide) and *N,N,N',N'*-Tetrachlorobenzene-1,3-disulfonamide as Novel Catalytic Reagents for Synthesis of Bis-indolyl, Tris-indolyl, Di(bis-indolyl), Tri(bis-indolyl) and Tetra(bis-indolyl) Methanes under Solid-State, Solvent and Water Conditions

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Descreve-se a preparação fácil e rápida de bis-indolil, tris-indolil, di(bis-indolil), tri(bis-indolil) e tetra(bis-indolil) metanos a partir de indole com diferentes aldeídos e cetonas, sob diferentes condições reacionais, usando poly(*N,N'*-dicloro-*N*-etil-benzeno-1,3-disulfonamida), [PCBS], e *N,N,N',N'*-tetrachlorobenzeno-1,3-disulfonamida, [TCBDA], como novos catalizadores.

Easy and rapid preparation of bis-indolyl, tris-indolyl, di(bis-indolyl), tri(bis-indolyl) and tetra(bis-indolyl) methanes from indole with various aldehydes and ketones using poly (*N,N'*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] and *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide [TCBDA] as novel catalysts under various conditions are here described.

**Keywords:** TCBDA, PCBS, bis(indolyl)methanes, catalytic reagents

## Introduction

Indole derivatives are widely distributed in nature and are known to possess broad spectrum of biological and pharmaceutical activities.<sup>1</sup> Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism<sup>2</sup> and induce apoptosis in human cancer cell. Thus, the development of facile and environmental friendly synthetic methods for the preparation of these compounds constitutes an active area of investigation in pharmaceutical and organic synthesis.<sup>3-5</sup>

Synthetically the reaction of 1H-indole with aldehydes or ketones produces azafulvenium salts that react further with a second 1H-indole molecule to form bis(indol-3-yl)methanes.<sup>6</sup> In recent years, synthesis of this class of molecules under mild conditions have been reported, with promoters such as montmorillonite clay K-10,<sup>7</sup> trichloro-1,3,5-triazine,<sup>8</sup> AIPW<sub>12</sub>O<sub>40</sub>,<sup>9</sup> sodium dodecyl sulfate (SDS),<sup>10</sup> ZrCl<sub>4</sub>,<sup>11</sup> H<sub>2</sub>NSO<sub>3</sub>H,<sup>12</sup> I<sub>2</sub>,<sup>13</sup> zeolites,<sup>14</sup> bentonite,<sup>15</sup> In(OTf)<sub>3</sub>/ionic liquid,<sup>16</sup> CuBr<sub>2</sub>,<sup>17</sup> Dy(OTf)<sub>3</sub>/ ionic liquid,<sup>18</sup> HClO<sub>4</sub>-SiO<sub>2</sub>,<sup>19</sup> InCl<sub>3</sub>,<sup>20</sup> MW/ Lewis acids (FeCl<sub>3</sub>, BiCl<sub>3</sub>, InCl<sub>3</sub>, ZnCl<sub>2</sub>, CoCl<sub>2</sub>),<sup>21</sup> NaHSO<sub>4</sub> and Amberlyst-15,<sup>22</sup> sulfated zirconia,<sup>23</sup> ZrOCl<sub>2</sub>/SiO<sub>2</sub>,<sup>24</sup> silica sulfuric acid

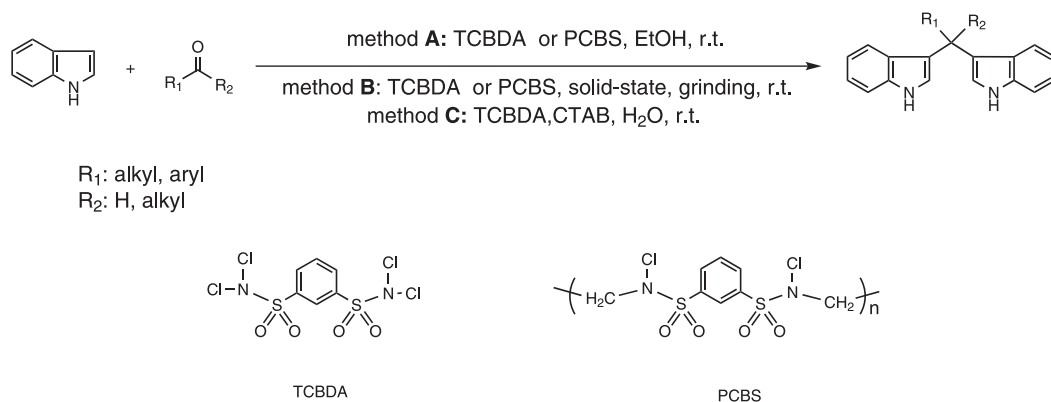
(SSA),<sup>25</sup> TiO<sub>2</sub>,<sup>26</sup> (NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>,<sup>27</sup> acidic ionic liquid,<sup>28</sup> NaBF<sub>4</sub>,<sup>29</sup> metal hydrogen sulfates,<sup>30</sup> tetrabutylammonium tribromide,<sup>31</sup> superacid SO<sub>4</sub><sup>2-</sup>/TiO<sub>2</sub>,<sup>32</sup> NaHSO<sub>4</sub>/ionic liquid,<sup>33</sup> NBS,<sup>34</sup> Ph<sub>3</sub>CCl,<sup>35</sup> H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>,<sup>36</sup> LiClO<sub>4</sub>,<sup>37</sup> Zr(DS)<sub>4</sub>,<sup>38</sup> and Bi(NO<sub>3</sub>)<sub>3</sub>·5H<sub>2</sub>O.<sup>39</sup>

## Result and Discussion

In continuation of our interest in the synthesis of *N*-halo sulfonamide and application of these reagents in organic synthesis,<sup>40-43</sup> we report the synthesis of poly (*N,N'*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] and *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide [TCBDA] as novel catalytic reagents in organic reactions (Scheme 1).

Many of the methods described above involve the use of expensive reagents, high catalyst loading, long reaction times and environmentally hazardous reagents. Therefore, we studied the use of poly (*N,N'*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) and *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide as novel catalysts in the electrophilic substitutions of indole with a variety of aldehydes and ketones under (i) solvent-free, (ii) solvent conditions (H<sub>2</sub>O and EtOH) to afford bis(indolyl)methanes (Scheme 1).

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Scheme 1.

Since TCBDA and PCBS contain chlorine atoms which are attached to nitrogen atoms, it is also possible that they release Cl<sup>+</sup> *in situ* which can act as Lewis acid to activate the carbonyl oxygen to form the bis-indole derivatives.

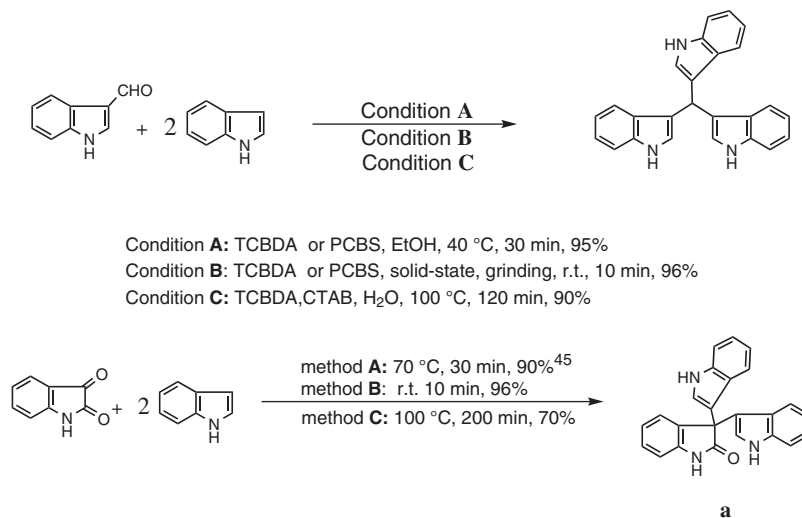
Initially, we carried out the reaction of indole with benzaldehyde in the presence catalytic amount of *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide (TCBDA) in EtOH at room temperature. After 5 min the reaction completed with good yield (96%).

The applicability of the present methodology is further extended by performing the reaction in an aqueous media. In this reaction, we also found that, water in the presence of 5 mol% CTAB (*N*-cetyl-*N,N,N*-trimethylammonium bromide) as surfactant is essential for this reaction using TCBDA at room temperature. However, this process is green, environmentally friendly, clean, and could be carried out easily at room temperature without undesirable side reactions.

In recent years, there has been an increasing interest in reactions that proceed in the absence of solvents due to




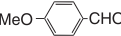
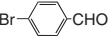
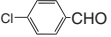


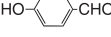
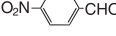
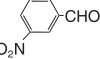
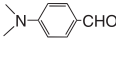
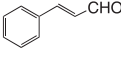



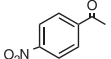

their reduced pollution, low cost, simplicity in process and handling. Therefore, we decided to test this reaction under solvent-free conditions (grinding) with these reagents. We found that the reaction could be rapid with excellent yield, (98%, entry 1) using *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide [TCBDA] (1 min) and using poly (*N,N'*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] (1.5 min). In comparison to the reported methods, TCBDA and PCBS under solvent-free conditions were found to be efficient catalysts in terms of handling, temperature, yield and reaction times.

These results promoted us to investigate the scope and the generality of these new protocols for various aldehydes and ketones under optimized conditions. As shown in Table 1, a series of aromatic, aliphatic and heterocyclic aldehydes underwent electrophilic substitution reaction with indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. The electron deficiency and nature of the substituents on the aromatic ring effect the conversion



Scheme 2.

**Table 1.** Synthesis of bis(indolyl)methanes by the reaction of indole with aldehydes and ketones in various conditions

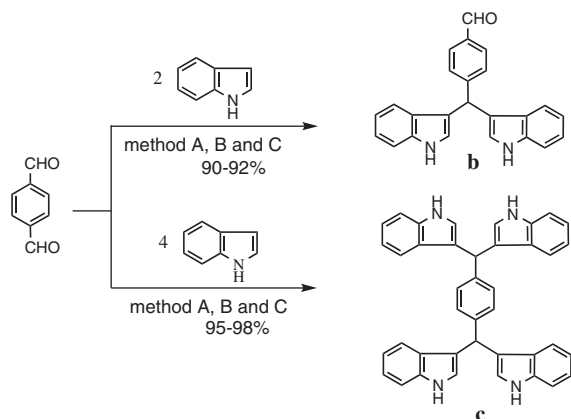
Entry	Carbonyl compound	TCBDA (method A)		PCBS (method A)		TCBDA (method B)		PCBS (method B)		TCBDA (method C)	
		time/min	yield (%) <sup>a</sup>	time/min	yield (%) <sup>a</sup>	time/min	yield (%) <sup>a</sup>	time/min	yield (%) <sup>a</sup>	time/h	yield (%) <sup>a</sup>
1		5	96	10	90	1	98	1.5	98	2	90 <sup>11</sup>
2		10	92	15	90	1.5	96	2	96	2.5	80 <sup>11</sup>
3		5	98	10	95	1	99	2	98	3	89 <sup>11</sup>
4		8	96	12	90	1	98	1.5	96	4	78 <sup>11</sup>
5		15	92	15	87	2	92	2	92	3.5	75 <sup>36</sup>
6		15	89	16	85	1.5	95	2.5	90	3.5	80 <sup>35</sup>
7		10	96	20	90	1	96	2	96	2	82 <sup>35</sup>
8		25	90	30	80	2.5	92	2.5	90	4	70 <sup>25a</sup>
9		15	92	20	90	1	96	2	96	2	79 <sup>11</sup>
10		20	90	30	85	1	98	2	96	5	70 <sup>35</sup>
11		25	90	30	85	2	97	2-3	97	4	70 <sup>35</sup>
12		30	78	40	75	2.5	96	3	96	5	75 <sup>13</sup>
13		25	95	35	90	2	95	4	94	4.5	72 <sup>11</sup>
14		2	92	5	90	1	98	2	96	2	82 <sup>36</sup>
15		70	85	85	80	4	90	6	90	6	70 <sup>13</sup>
16		120	80	120	75	4	90	6	90	9	65 <sup>36</sup>
17		100	85	100	85	4.5	85	5	80	7	75 <sup>11</sup>
18		110	78	120	70	5	80	6	80	6	70 <sup>11</sup>

<sup>a</sup> Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

rate; aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table 1, entries 10,11) react slower than electron-donating groups (Table 1, entries 4, 8, 9, 12). Furthermore, unsaturated aldehydes, such as cinnamaldehyde, give the corresponding bis(indolyl) methanes without polymerization or halogenation under the above reaction conditions. Ketones required longer reaction times, which is most probably due to the electron-donating and steric effects of the methyl group.

This reaction was further explored for the synthesis of tri-indolylmethane by the condensation of indol-3-carbaldehyde or isatin with two equivalents of indole under similar conditions with our methods in good to high yields (Scheme 2 and 3).

Selective condensation of a dialdehyde, *i.e.*, terephthalaldehyde to the corresponding bis-indolyl methane was achieved by controlling the molar ratio of indole (Scheme 3). The results showed that addition of 2



Scheme 3.

equivalents of indole to terephthalaldehyde, gives (**b**) in good yield under various conditions (Scheme 3). Treatment of 4 equivalents of indole with terephthalaldehyde gives the corresponding di(bis-indolyl methanes), (**c**) in excellent yield at room temperature under various conditions.<sup>38</sup>

This reaction was further explored for the synthesis of tri(bis-indolyl)methane (**e**) and tetra(bis-indolyl)methanes (**g, h**) as new triarylmethanes, by the condensation of aldehyde (**d**) with 6 equivalents indole and aldehydes (**f, h**) with 8 equivalents indole under similar condition (reflux in DMSO) in high yields (Scheme 4 and 5).

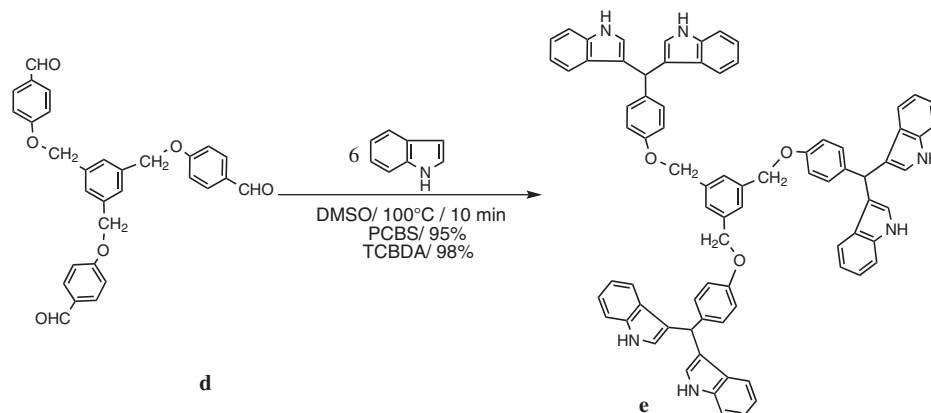
3-Substituted indoles were examined for this reaction under the above reaction conditions with aldehydes (Scheme 6). Since the more active site (C-3) in indole was blocked in this case electrophilic substitution took place at C-2 in indole giving the corresponding bis(indolyl)methane in high yield under various conditions. The results were summarized in Table 2.

Our experiments also indicated that TCBD and PCBS were reusable catalysts and after four runs, the catalytic activities of the reagents were almost the same as those of fresh catalysts. Thus, after the successful synthesis of

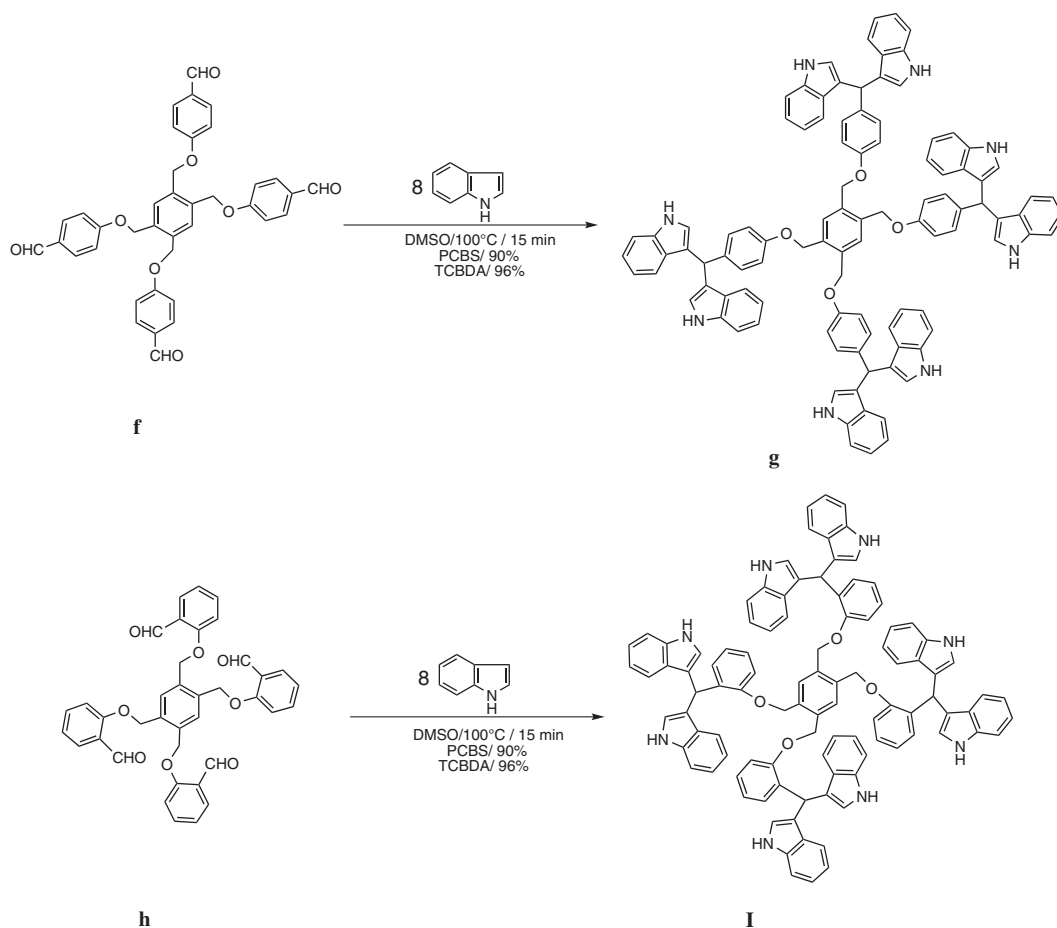
2-methoxyphenyl-3,3-bis(indolyl)methane in first run (in solvent condition), which gave the corresponding product in 98% isolated yield (Table 1, entry 3), the *N,N'*-dichlorobenzene-1,3-disulfonamide (TCBD) catalyst was subjected to a second run reaction from which it gave the product in 85% yield; the average chemical yield for four consecutive runs was 60%. The reusability of catalysts are shown in Figure 1.

The chemo selectivity of the present methods is also demonstrated by competitive reactions of indole with arylaldehydes in the presence of aliphatic ones and ketones. For example, when a 1:1 mixture of benzaldehyde and propionaldehyde was allowed to react with two equivalents of indole in the presence of TCBD and PCBS under various conditions, it was found that the arylaldehydes was chemo selectively converted to the corresponding bis(indolyl) methane but the aliphatic ones was converted slightly. Also, in an equimolar mixture arylaldehyde and ketone, only arylaldehyde was converted to the corresponding bis(indolyl)methane, whereas ketone remained (Scheme 7). The reaction was clean and the products were obtained in high yields without the formation of any side products such as *N*-alkylated products.

In conclusion, we have introduced the novel catalytic reagents poly (*N,N'*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] and *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide [TCBD] for the efficient preparation of bis-indolyl, tris-indolyl, di(bis-indolyl), tri(bis-indolyl) and tetra(bis-indolyl) methanes from indole with various aldehydes and ketones in ethanol, water and in solid-state conditions at room temperature with excellent yields. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic,  $\alpha,\beta$ -unsaturated, heterocyclic substrates, and ketones. In addition, efficiency, mild reaction conditions, easy work up, simplicity and chemoselectivity of this protocol provide a fast, green, and low cost procedure for the synthesis of these compounds.



Scheme 4.

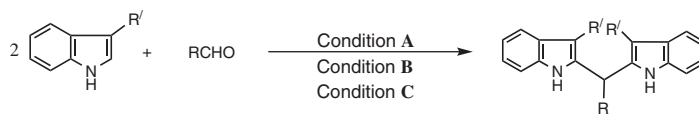


Scheme 5.

**Table 2.** The reaction of aromatic aldehydes with 3-substituted indoles under various conditions

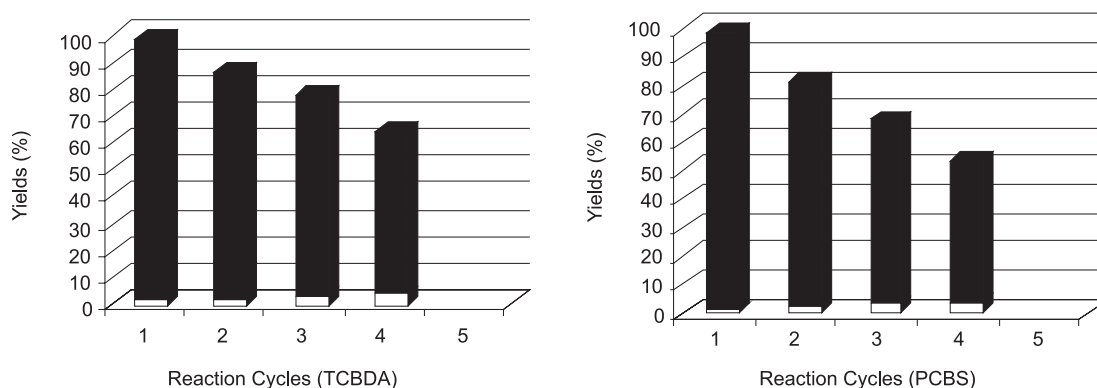
Entry	Carbonyl compound	Indole	Product	Condition A		Condition B		Condition C	
				time/min	yield (%) <sup>a</sup>	time/min	yield (%) <sup>a</sup>	time/min	yield (%) <sup>a</sup>
1				30	95	10	96	120	90 <sup>13</sup>
2				30	92	10	90	150	80 <sup>13</sup>
3				25	96	5	90	100	85 <sup>25</sup>
4				60	75	10	70	180	50 <sup>44</sup>

<sup>a</sup> Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods

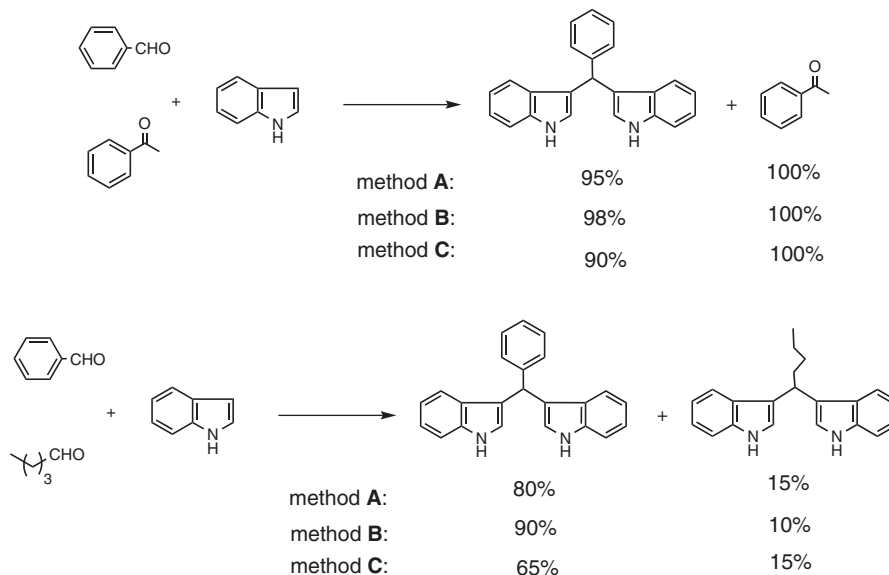


Condition A: TCBDA or PCBS, EtOH  
 Condition B: TCBDA or PCBS, solid-state, grinding, r.t.  
 Condition C: TCBDA, CTAB, H<sub>2</sub>O, 100 °C

Scheme 6.



**Figure 1.** Reusability of catalysts. Conditions: TCBDA (0.1 mmol) or PCBS (0.1 g), indole (4 mmol), 2-methoxybenzaldehyde (2 mmol), EtOH (5 mL) and time (10 min).



Scheme 7.

## Experimental

*Procedure for the preparation of poly (N,N'-dichloro-N-ethyl-benzene-1,3-disulfonamide) [PCBS] and N,N,N',N'-tetrachlorobenzene-1,3-disulfonamide [TCBDA]*

A sample of white finely powdered poly (*N*-ethyl-benzene-1,3-disulfonamide) (1 g) or benzene-1,3-disulfonamide (1 g) was dissolved in a solution of NaOCl

(50 mL, 14%), at 25 °C for 30 min. The color of the solution did not change. After this time, acetic acid (20 mL, 50%) was added to the solution. The insoluble chlorinated reagent was removed by filtration and washed with water (5 mL).

*Analytical data for N,N,N',N'-tetrachlorobenzene-1,3-disulfonamide*

White solid, mp: 145-147 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3050, 2950, 2900, 1570, 1462, 1417, 1377, 1304, 1167, 1082,

807, 776, 675.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95-8.09 (m, CH aromatic, 1H), 8.11-8.58 (m, CH aromatic, 2H), 8.79 (s, CH aromatic, 1H). m/e: 374 ( $[\text{M}+\text{H}]^+$ ), 339, 337, 321, 319, 305, 303, 272, 269, 267, 156, 154, 139, 125, 120, 104, 91, 77, 63. Anal. Calc. for  $\text{C}_6\text{H}_4\text{N}_2\text{S}_2\text{O}_4\text{Cl}_4$ : C, 19.25; H, 1.06; N, 7.48; S, 17.11. Found: C, 19.05; H, 1.16; N, 6.94; S, 16.28.

*Analytical data for poly (N,N'-dichloro-N-ethyl-benzene-1,3-disulfonamide)*

White solid, mp: 175-178 °C, IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3050, 2950, 2900, 1578, 1462, 1418, 1377, 1303, 1168, 1081, 809, 779, 674, 603, 570.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56-8.48 (b, CH aromatic).

*Synthesis of bis(indolyl)methanes in ethanol catalyzed by TCBDA or PCBS (method A)*

A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol) and catalyst [PCBS (0.05 g) or TCBDA (0.05 mmol, 0.04 g)] in EtOH (3 mL) was stirred at room temperature for the appropriate time (Table 1). The progress of the reaction was monitored by TLC (4:1, n-hexan/acetone). After completion of reaction, the organic solvent was concentrated in vacuo and then  $\text{CH}_2\text{Cl}_2$  (10 mL) was added, and the catalyst was removed by filtration. Evaporation of the solvent under reduced pressure gave the products. Further purification was achieved by recrystallization from ethanol-water to afford pure products.

*Synthesis of bis(indolyl)methanes in solid-state catalyzed by TCBDA or PCBS (method B)*

A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol) and catalyst [PCBS (0.05 g) or TCBDA (0.05 mmol, 0.04 g)] were added to a mortar and the mixture was pulverized with a pestle. A spontaneous reaction took place (1-6 min, Table 1, monitored by TIC, 4:1, hexane/acetone). After completion of the reaction,  $\text{CH}_2\text{Cl}_2$  (10 mL) was added, and insoluble reagents were removed by filtration. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by recrystallization from ethanol-water to afford pure products.

*Synthesis of bis(indolyl)methanes in  $\text{H}_2\text{O}$  catalyzed by TCBDA and TBAB (method C)*

A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol), TCBDA (0.05 mmol, 0.04 g) and CTAB (5 mol%) in water (3 mL) was stirred at room temperature for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the solid which separated was filtered and then recrystallized from ethanol-water to afford pure products.

*Synthesis of tri(bis-indolyl)methanes in DMSO catalyzed by TCBDA or PCBS*

A mixture of indole (6.0 mmol), aldehyde, (**d**), (1.0 mmol) and catalyst PCBS (0.05 g) or TCBDA (0.05 mmol, 0.04 g) in DMSO (5 mL) was heated in an oil bath until 100 °C. The reaction mixture was filtered after 10 min. The residue was washed with EtOH (5 mL). Then, water (30 mL) was added to the filtrate, and the product was precipitated and filtered. The product was purified by washing with cold EtOH (2  $\times$  5 mL).

*Synthesis of tetra(bis-indolyl)methanes in DMSO catalyzed by TCBDA or PCBS*

A mixture of indole (8.0 mmol), aldehyde, (**f** or **h**), (1.0 mmol), and catalyst PCBS (0.05 g) or TCBDA (0.05 mmol, 0.04 g) in DMSO (5 mL) was heated in an oil bath until 100 °C. The reaction mixture was filtered after 15 min. The residue was washed with EtOH (5 mL). Then, water (30 ml) was added to the filtrate, and the product was precipitated and filtered. The product was purified by washing with cold EtOH (2  $\times$  5 mL).

*Analytical data for compound e*

Light red solid, mp 208-210 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3421, 2950, 2900, 1635, 1506, 1457, 1377, 1216, 1173, 1082, 742.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta_{\text{H}}$  (ppm) 5.01 (s,  $\text{CH}_2$  benzylic, 6H), 5.72 (s, CH, 3H), 6.74-7.50 (m, CH aromatic, 46H), 10.71 (s, NH, 6H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta_{\text{C}}$  (ppm) 40.08, 69.48, 111.85, 114.67, 115.24, 118.54, 118.82, 119.58, 121.25, 123.87, 127.05, 129.66, 137.03, 137.73, 138.15, 156.91. Anal. Calc. for  $\text{C}_{78}\text{H}_{60}\text{N}_6\text{O}_3$ : C, 82.95; H, 5.35; N, 7.44. Found: C, 82.52; H, 5.21; N, 7.36.

*Analytical data for compound g*

Red solid, mp 250-251 °C d. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3417, 2926, 2854, 1609, 1506, 1456, 1413, 1338, 1218, 1172, 1127, 1012, 743.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta_{\text{H}}$  (ppm) 5.08 (s,  $\text{CH}_2$  benzylic, 8H), 5.76 (s, CH, 4H), 6.82-7.65 (m, CH aromatic, 60H), 10.70 (s, NH, 8H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta_{\text{C}}$  (ppm) 41.05, 70.40, 111.45, 114.52, 115.12, 117.85, 118.85, 119.26, 120.85, 122.82, 126.65, 129.26, 136.76, 137.43, 138.63, 157.43. Anal. Calc. for  $\text{C}_{102}\text{H}_{78}\text{N}_8\text{O}_4$ : C, 82.79; H, 5.31; N, 7.57. Found: C, 82.12; H, 5.20; N, 7.35.

*Analytical data for compound I*

Red solid, mp 255-257 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3420, 2912, 2860, 1612, 1510, 1435, 1403, 1327, 1218, 1170, 1118, 735.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta_{\text{H}}$  (ppm) 5.10 (s,  $\text{CH}_2$  benzylic, 8H), 5.71 (s, CH, 4H), 6.75-7.85 (m, CH



aromatic, 60H), 10.65 (s, NH, 8H).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta_c$  (ppm) 42.10, 70.41, 111.43, 114.60, 115.10, 117.88, 118.86, 119.36, 120.01, 120.85, 122.09, 122.90, 126.65, 129.25, 136.82, 137.45, 138.70, 157.45. Anal. Calc. for  $\text{C}_{102}\text{H}_{78}\text{N}_8\text{O}_4$ : C, 82.79; H, 5.31; N, 7.57. Found: C, 82.35; H, 5.18; N, 7.42.

## Supplementary Information

Supplementary characterization data and  $^1\text{H}$  NMR spectra are available, free of charge at <http://jbcbs.sbj.org.br>, as a PDF file

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**Poly (*N,N'*-dichloro-*N*-ethyl-benzene-1, 3-disulfonamide) and *N,N,N',N'*-Tetrachlorobenzene-1,3-disulfonamide as Novel Catalytic Reagents for Synthesis of Bis-indolyl, Tris-indolyl, Di(bis-indolyl), Tri(bis-indolyl) and Tetra(bis-indolyl) methanes under Solid-State, Solvent and Water Conditions**

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*3,3'*-Bisindolyl-phenylmethane (Table 1, entry 1)

Solid, mp 124-125 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3402, 3050, 2986, 1615, 1600, 1455, 1112. <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  (ppm) 5.88 (s, 1H), 6.68 (s, 2H), 7.13-7.45 (m, ArH, 13H), 7.95 (br s, NH, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  (ppm) 31.6, 110.9, 111.9, 118.4, 119.5, 1121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2. MS: (MS-EI) *m/z* 322.

*3,3'*-Bisindolyl-4-methylphenylmethane (Table 1, entry 2)

Solid, mp 97-98 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3452, 3112, 3045, 2950, 1604, 1523, 1210, 1052, 765. <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  (ppm) 2.38 (s, 3H), 5.85 (s, 1H), 6.70-7.55 (m, ArH, 14H), 7.85 (br s, NH, 2H). MS: (MS-EI) *m/z* 336. Anal. Calc. for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.45; H, 5.88; N, 8.14.

*3,3'*-Bisindolyl-2-methoxyphenylmethane (Table 1, entry 3)

Red solid, mp 134-136 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3408, 3056, 2932, 1597, 1486, 1450, 1335, 1102, 745. <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  (ppm) 3.82 (s, 3H), 6.32 (s, 1H), 6.61 (s, 2H), 6.81-7.40 (m, ArH, 12H), 7.80 (br s, NH, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  (ppm) 32.3, 56.0, 110.0, 110.8, 111.1, 119.2, 119.8, 120.2, 120.6, 121.9, 123.7, 127.2, 129.9, 132.5, 136.9, 157.1. Anal. Calc. for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.24; H, 5.45; N, 7.86.

*3,3'*-Bisindolyl-4-methoxyphenylmethane (Table 1, entry 4)

<sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  (ppm) 3.84 (s, 3H), 5.90 (s, 1H), 6.64-7.65 (m, ArH, 14H), 7.80 (br s, NH, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  (ppm) 39.7, 55.6, 111.5, 114.0, 119.6, 120.4, 120.4, 122.3, 123.9, 127.5, 130.0, 136.7, 137.1, 158.3.

*3,3'*-Bisindolyl-4-bromophenylmethane (Table 1, entry 5)

Pink solid, mp 110-112 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3410, 3054, 1487, 1455, 1089. <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  (ppm) 6.66 (s, 2H), 7.02-7.45 (m, ArH, 12H), 7.85 (br s, NH, 2H). MS: (MS-EI) *m/z* 361.

*3,3'*-Bisindolyl-4-chlorophenylmethane (Table 1, entry 6)

mp 75-76 °C, FT-IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3409, 2958, 1456, 1488. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>)  $\delta$  (ppm) 5.90 (s, 1H), 6.82 (s, 2H), 6.89-7.39 (m, 12H), 9.99 (s, 2H, N-H). <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>)  $\delta$  (ppm) 40.8, 112.1, 119.2, 120.1, 120.3, 121.9, 124.5, 128.1, 129.2, 138.0, 143.4.

*3,3'*-Bisindolyl-2-chlorophenylmethane (Table 1, entry 7)

<sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 7.89 (br s, 2H), 7.07-7.51 (m, 12H), 6.53 (s, 2H), 6.36 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 36.9, 110.1, 111.3, 119.3, 119.8, 122.0, 124.0, 126.7, 127.0, 128.3, 30.4, 130.7, 135.3, 136.7, 141.5.

*3,3'*-Bisindolyl-2-furylmethane (Table 1, entry 8)

<sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 7.74 (br s, 2H), 7.32-7.63 (m, 9H), 7.09 (s, 2H), 6.21-6.35 (m, 2H), 5.82 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 41.2, 102.1, 110.3, 111.8, 112.6, 119.4, 120.3, 121.5, 122.6, 131.0, 136.4, 141.2, 152.0.

*3,3'*-Bisindolyl-4-hydroxyphenylmethane (Table 1, entry 9)

mp 212-213 °C, FT-IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3420, 3239, 1455, 1511, 1616. <sup>1</sup>H NMR (90 MHz, DMSO)  $\delta$  (ppm) 7.58 (br s, 2H), 6.69-7.24 (m, 13H), 6.67 (s, 2H), 5.85 (s, 1H). <sup>13</sup>C NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 31.12, 111.89, 115.28, 118.58, 119.19, 119.71, 121.30, 123.89, 127.17, 129.66, 135.71, 136.93, 137.10, 155.79.

*3,3'*-Bisindolyl-4-nitrophenylmethane (Table 1, entry 10)

<sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 8.19 (d, 2H, *J* 7.81), 7.76 (br s, 2H), 7.40-7.58 (m, 10H), 7.03 (s, 2H), 6.05 (s,

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1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 44.5, 110.0, 112.1, 119.6, 119.8, 120.9, 121.3, 121.9, 130.2, 133.8, 136.2, 143.1, 145.2

*3,3'-Bisindolyl-3-nitrophenylmethane* (Table 1, entry 11)

$^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 8.46 (br s, 2H), 7.02-7.87 (m, 12H), 6.61 (s, 2H), 5.34 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 34.9, 111.5, 111.6, 119.5, 120.7, 121.9, 122.2, 124.3, 126.8, 129.6, 131.2, 132.6, 134.2, 136.8, 149.7.

*3,3'-Bisindolyl-4-(N,N-dimethyl)phenylmethane* (Table 1, entry 12)

$^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 3.28 (s, 6H), 5.75 (s, 1H), 6.76-7.84 (m, ArH, 14H), 7.82 (br s, NH, 2H). MS: (MS-EI)  $m/z$  365.

*3,3'-Bisindolyl-1-(2-phenylethylene)methane* (Table 1, entry 13)

$^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 5.92-6.07 (m, 2H), 5.76 (m, 1H), 6.71 (s, 2H), 6.89-7.68 (m, 15H), 8.02 (br s, 2H, NH). MS: (MS-EI)  $m/z$  348.

*3,3'-Bisindolyl-[2]thienylmethane* (Table 1, entry 14)

Brown solid, mp 185-186 °C. IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3412, 1715, 1452, 1260, 1105 cm $^{-1}$ .  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 6.18 (s, 1H), 6.87 (s, 2H), 6.92-7.48 (m, ArH, 11H), 7.98 (br s, NH, 2H). Anal. Calc. for  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{S}$ : C, 76.80; H, 4.91; N, 8.53. Found: C, 76.52; H, 5.10; N, 8.35.

*3,3'-Bisindolyl-1-butylmethane* (Table 1, entry 15)

$^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 0.80 (t,  $J$  6.7 Hz, 3H), 1.25-1.29 (m, 6H), 4.62 (t,  $J$  6.7 Hz, 1H), 6.80 (d,  $J$  2.5 Hz, 2H), 6.89-7.68 (m, 8H), 8.12 (br s, 2H, NH). MS: (MS-EI)  $m/z$  302.

*3,3'-Bisindolyl-1-methyl-1-phenylmethane* (Table 1, entry 16)

mp 165-167 °C.  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 2.40 (s, 3H), 6.67 (s, 2H), 6.95-7.43 (m, 13H), 7.91 (br s, 2H, NH). MS:  $m/z$  336.

*3,3'-Bisindolyl-1-methyl-1-(4-nitro)phenylmethane* (Table 1, entry 17)

$^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 2.46 (s, 3H), 6.78 (s, 2H), 6.79-7.68 (m, 12H), 7.98 (br s, 2H, NH). MS: (MS-EI)  $m/z$  381.

*3,3'-Bisindolyl-[1,1]cyclohexane* (Table 1, entry 18)

Red solid, mp 115-116 °C. IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3478, 3020, 2935, 1603, 1522, 1421, 1335, 1216, 1099, 1017,

758, 699 cm $^{-1}$ .  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.56 (m, 6H), 2.48 (m, 4H), 6.81 (s, 2H), 7.03-7.65 (m, 8H), 7.84 (br s, NH, 2H).

*Analytical data for compound Tri-indolylmethane*

Yellow solid, mp 243-245 °C.  $^1\text{H}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 9.67 (br s, 2H), 6.24 (s, 3H), 6.27-6.87 (m, 12H), 5.47 (s, 1H). IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3403, 3043, 2918 cm $^{-1}$ . MS: (MS-EI)  $m/z$  361.

*Analytical data for compound (a)*

Yellow solid, mp 243-245 °C.  $^1\text{H}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 9.98 (br s, 2H), 9.81 (br s, 1H), 6.45 (m, 2H), 6.52-6.93 (m, 12H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 200.8, 160.5, 137.4, 136.8, 125.5, 124.4, 123.9, 121.0, 120.5, 118.3, 117.7, 117.0, 113.9, 111.7, 111.5. MS: (MS-EI)  $m/z$  364.

*Analytical data for compound (c)*

Pink solid, mp 194-195 °C. FT-IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3405, 3049, 1622, 1455, 1216 cm $^{-1}$ .  $^1\text{H}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 5.75 (s, CH, 1H), 6.29 (s, 4H), 7.05-7.40 (m, CH aromatic, 20H), 7.31 (br s, NH, 4H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 142.5, 136.7, 128.1, 126.8, 123.6, 120.9, 119.2, 118.4, 118.3, 111.5, 29.1. MS: (MS-EI)  $m/z$  566.200.

*Analytical data for compound (Table2, entry 1)*

$^1\text{H}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 10.68 (br s, 2H), 8.53 (br s, 2H), 6.75-7.55 (m, 12H), 6.35 (s, 1H), 4.12 (s, 3H), 2.55 (t, 2H), 2.23 (t, 2H), 1.78 (m, 2H).. Anal. Calc. for  $\text{C}_{32}\text{H}_{32}\text{N}_2\text{O}_5$ : C, 73.26; H, 6.15; N, 5.34. Found: C, 72.86; H, 6.18; N, 5.23. MS: (MS-EI)  $m/z$  524.

*Analytical data for compound (Table2, entry 2)*

$^1\text{H}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 10.59 (br s, 2H), 8.86 (br s, 2H), 6.92-7.62 (m, 12H), 6.22 (s, 1H), 5.22 (s, 4H), 2.30 (s, 3H). Anal. Calc. for  $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_4$ : C, 74.32; H, 5.35; N, 6.19. Found: C, 73.92; H, 5.12; N, 5.79. MS: (MS-EI)  $m/z$  452.

*2,2'-Bisindolyl-phenylmethane* (Table2, entry 3)

$^1\text{H}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 7.94 (br s, 2H), 7.22-7.66 (m, 13H), 6.04 (s, 1H), 2.23 (s, 6H). Anal. Calc. for  $\text{C}_{25}\text{H}_{22}\text{N}_2$ : C, 85.68; H, 6.33; N, 7.99. Found: C, 85.43; H, 5.95; N, 7.68. MS: (MS-EI)  $m/z$  350.

*2,2'-Bisindolyl-4-methoxyphenylmethane* (Table2, entry 4)

$^1\text{H}$  NMR (90 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 7.90 (br s, 2H), 7.06-7.66 (m, 12H), 6.12 (s, 1H), 3.73 (s, 3H), 2.30 (s, 6H). Anal. Calc. for  $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}$ : C, 82.07; H, 6.36; N, 7.36. Found: C, 81.67; H, 6.14; N, 7.03. MS: (MS-EI)  $m/z$  380.

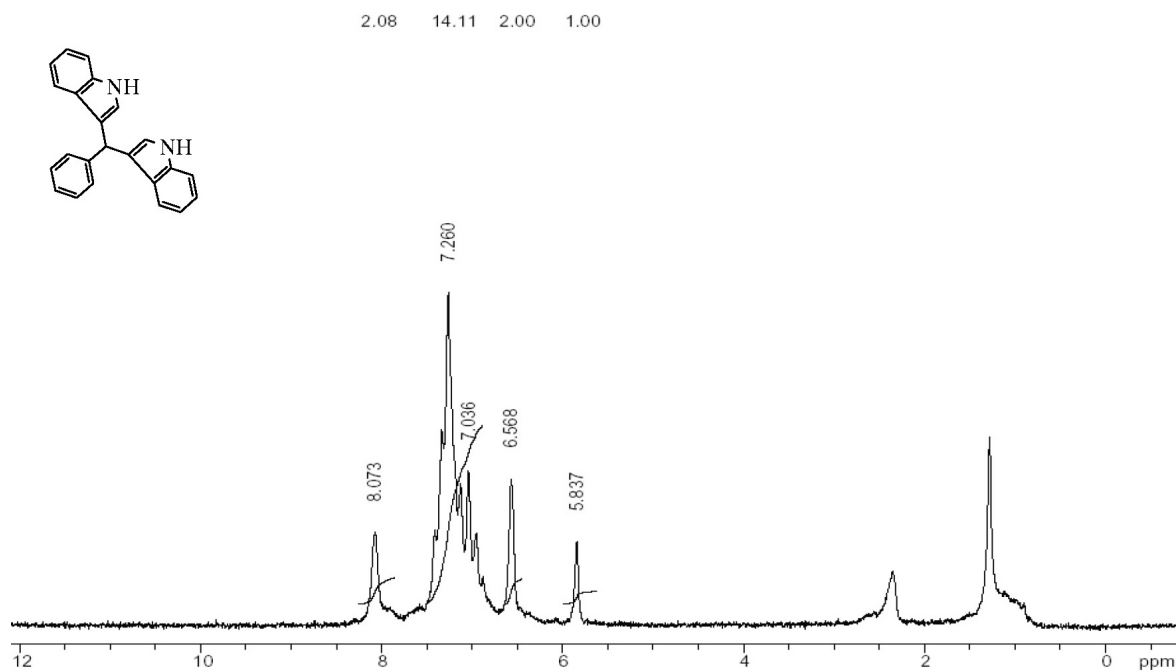


Figure S1.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) spectrum of 3,3'-bisindolyl-phenylmethane (Table 1, entry 1).

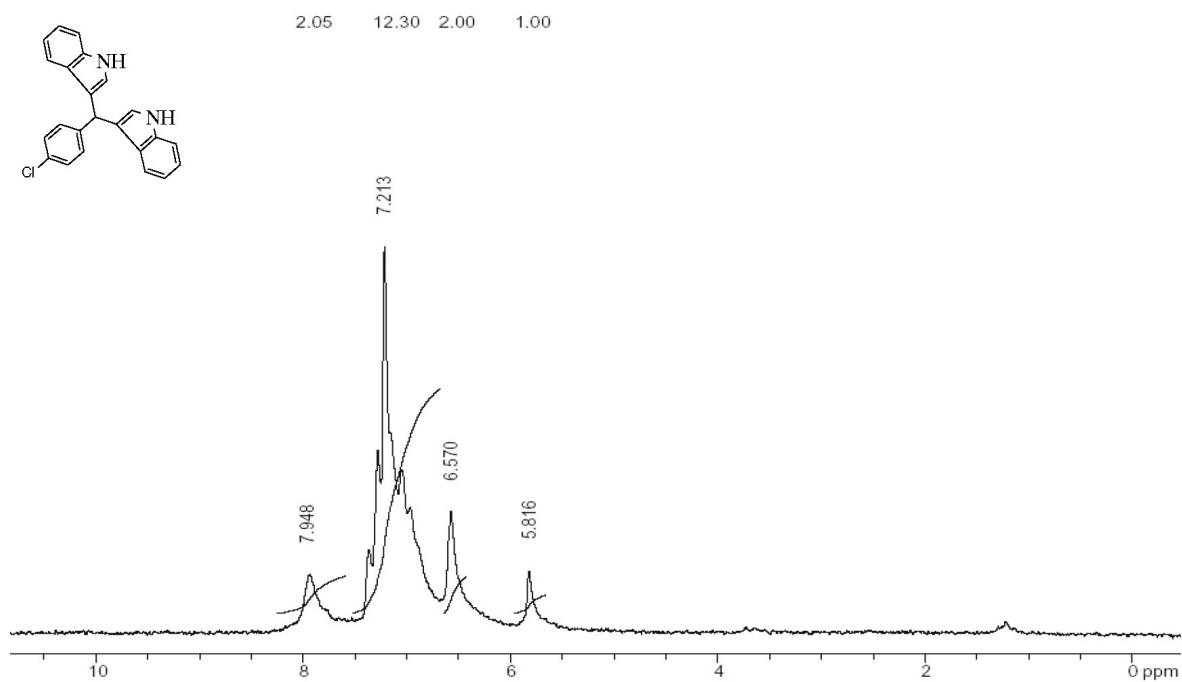


Figure S2.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) spectrum of 3,3'-bisindolyl-4-chlorophenylmethane (Table 1, entry 6).

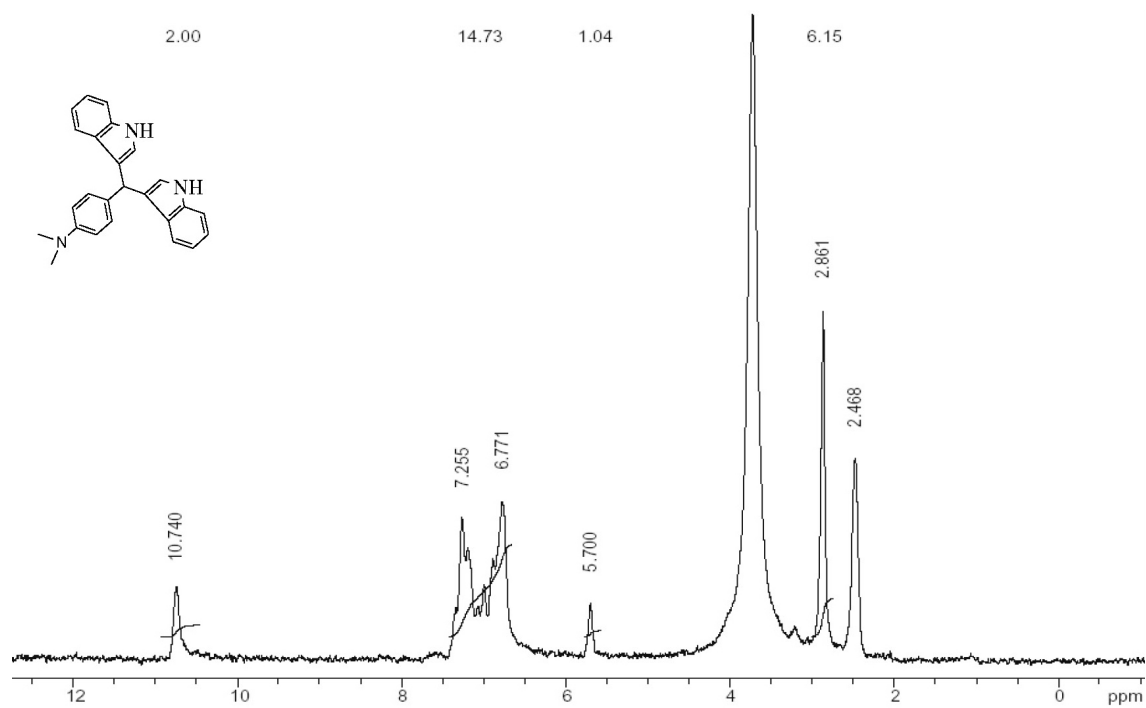


Figure S3. <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum of 3,3'-bisindolyl-4-(*N,N*-dimethyl)phenylmethane (Table 1, entry 12).

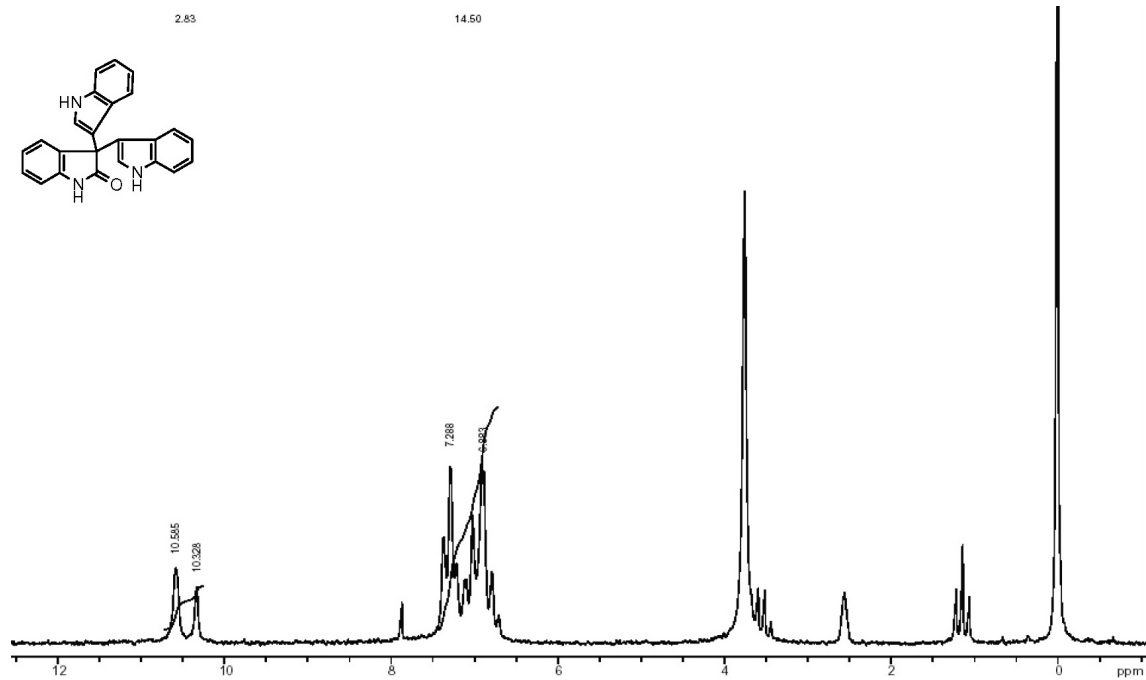


Figure S4. <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum of compound (a).

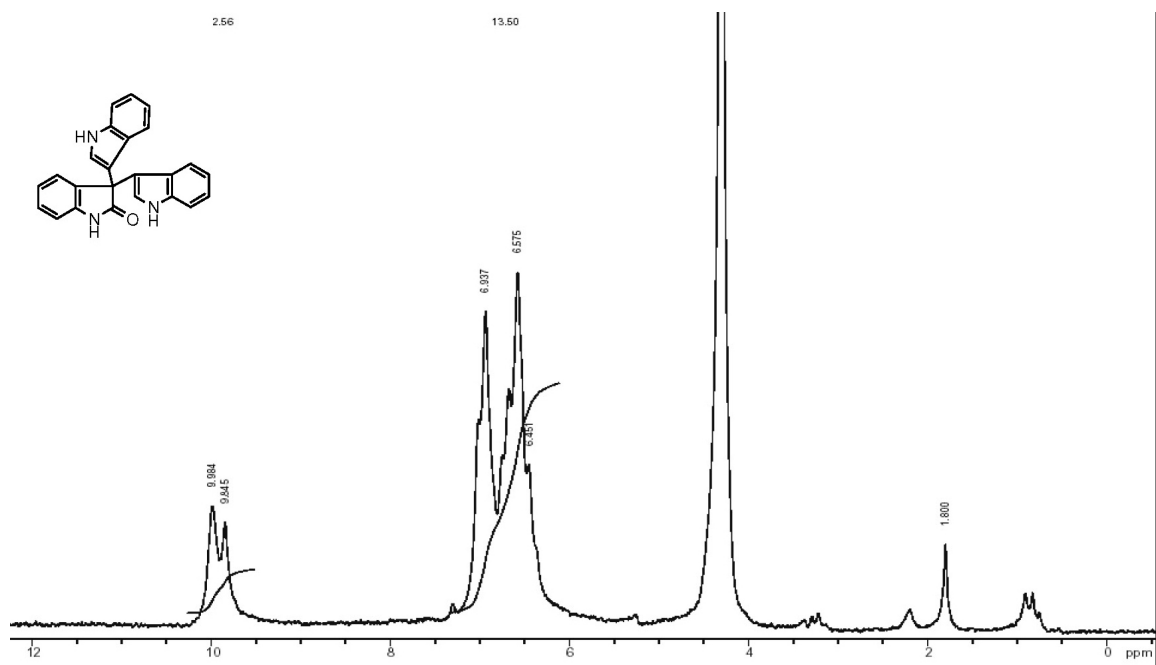


Figure S4. <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum of compound (a). Same compound? Different spectrum? Again S4 ?

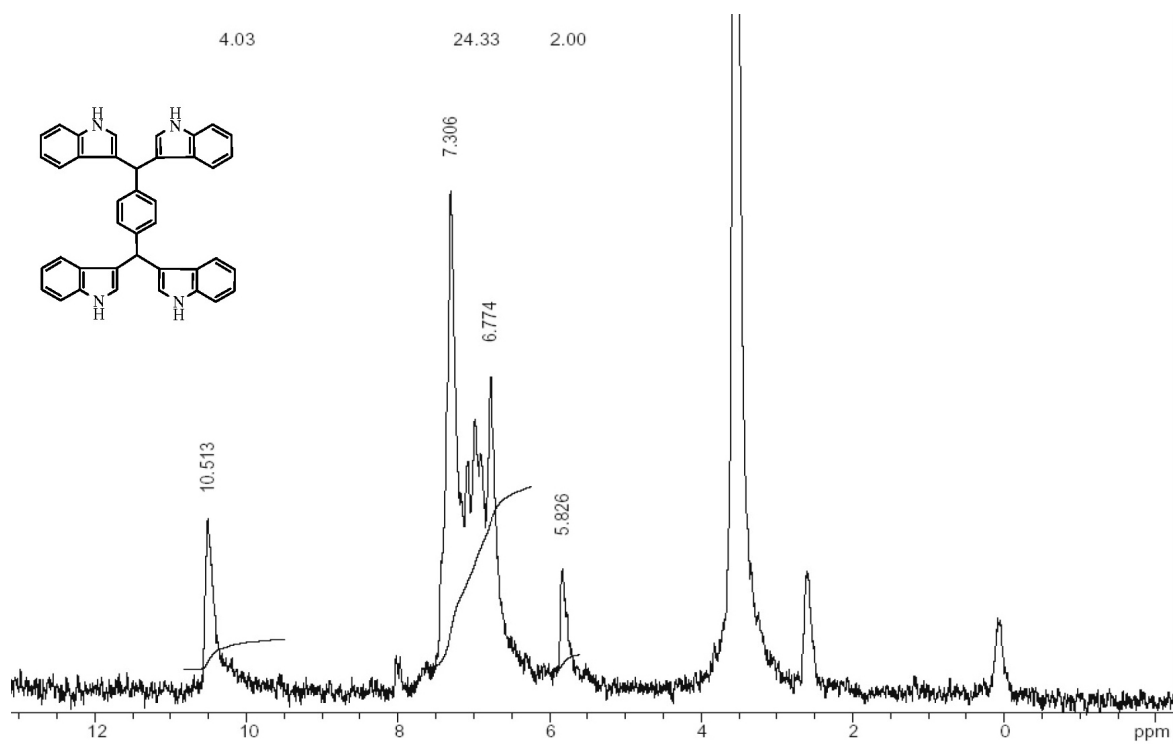


Figure S5. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) spectrum of compound (c).



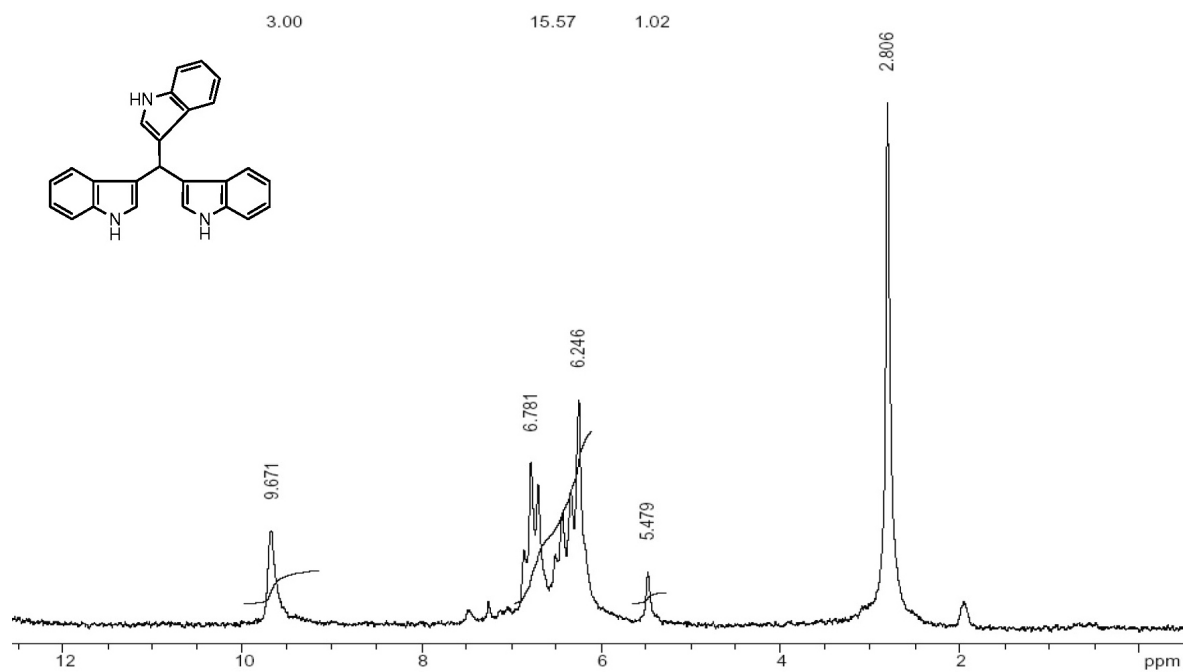


Figure S6. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) spectrum of compound tri-indolylmethane.

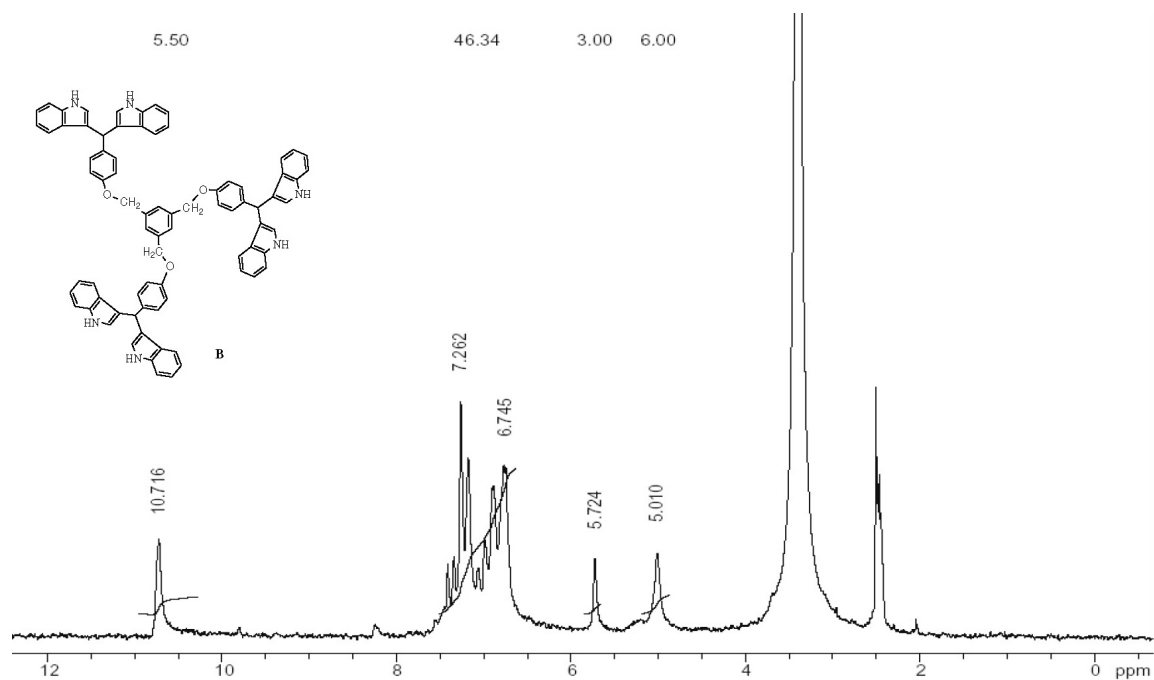
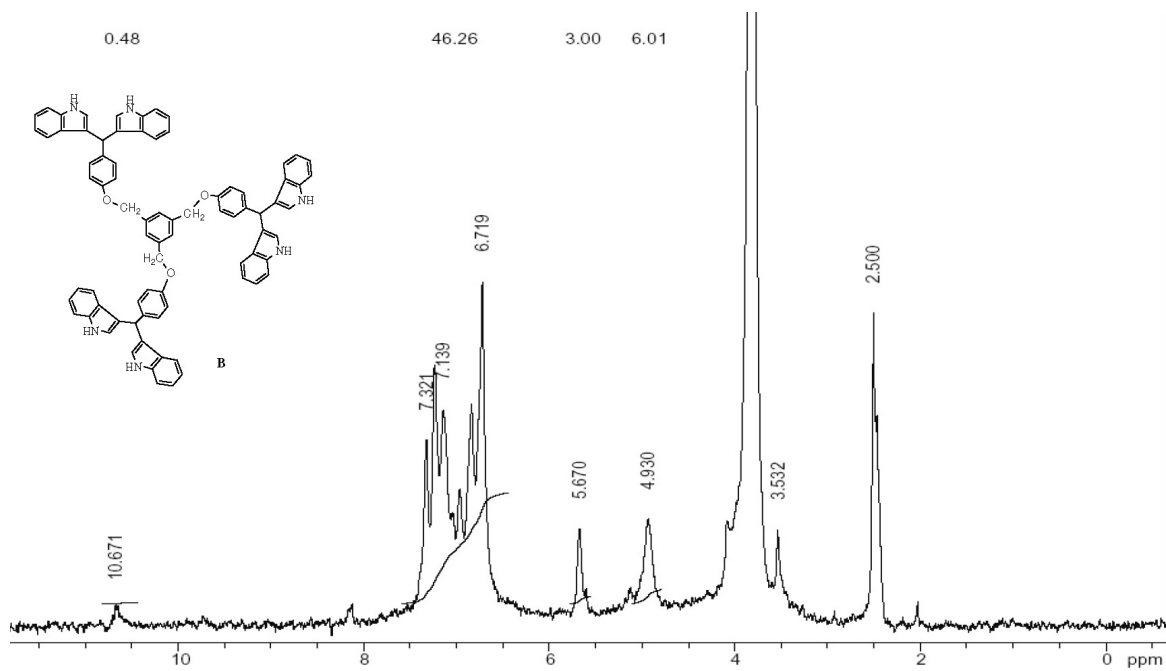


Figure S7. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) spectrum of compound (e).



**Figure S8.**  $^1\text{H}$  NMR ( $\text{DMSO-}d_6 + \text{D}_2\text{O}$ ) spectrum of compound (e).

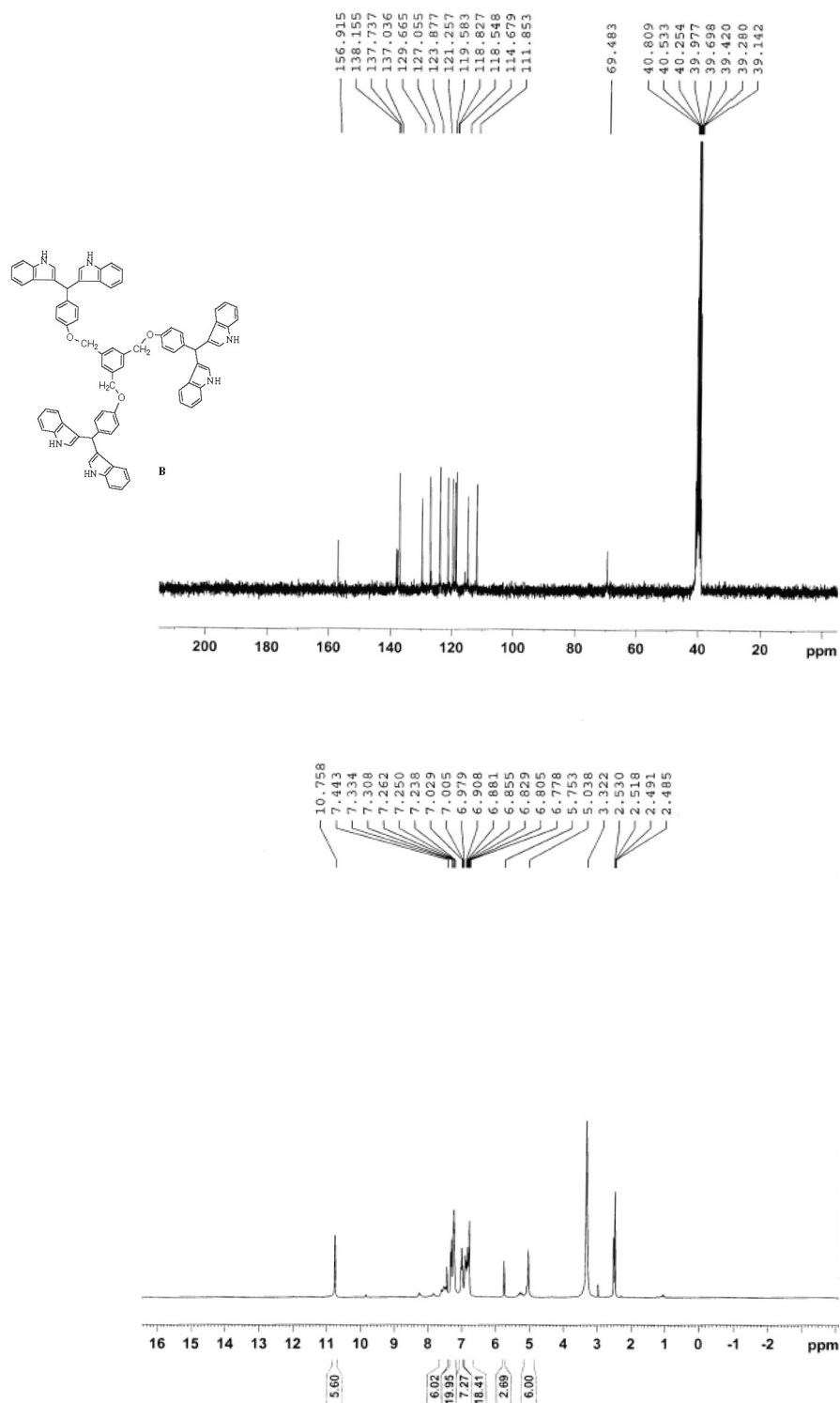


Figure S9. <sup>1</sup>H NMR and <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) spectrum of compound (e).

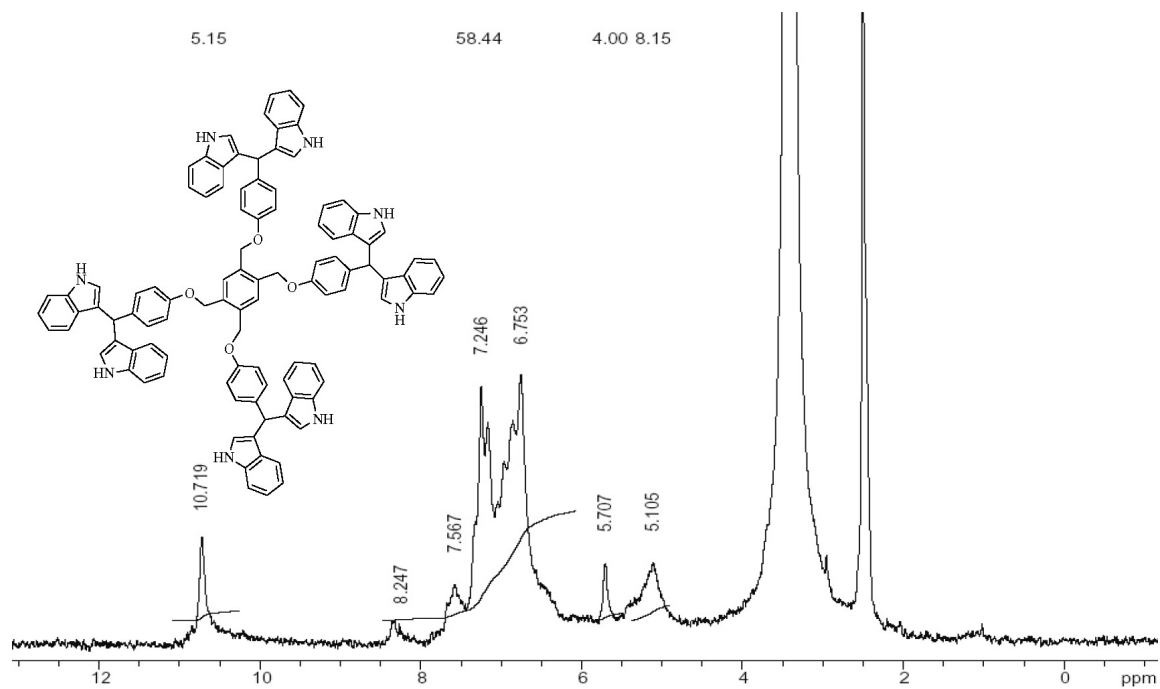


Figure S10. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) spectrum of compound (g).

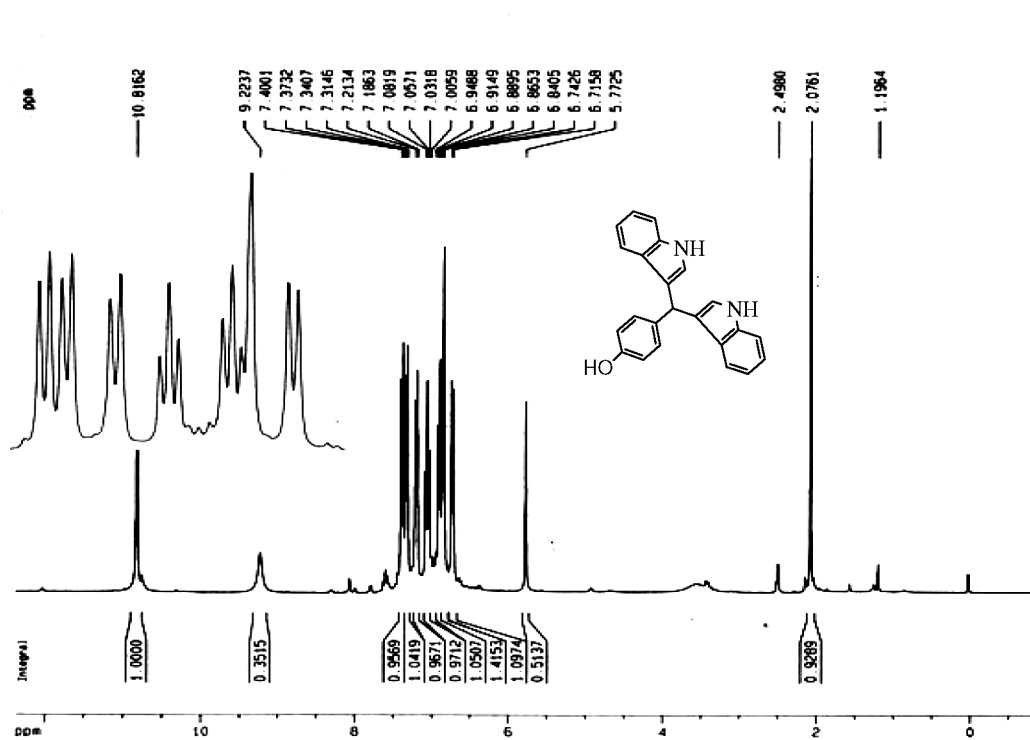


Figure S11. <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum of compound 3,3'-bisindolyl-4-hydroxyphenylmethane (Table 1, entry 9).

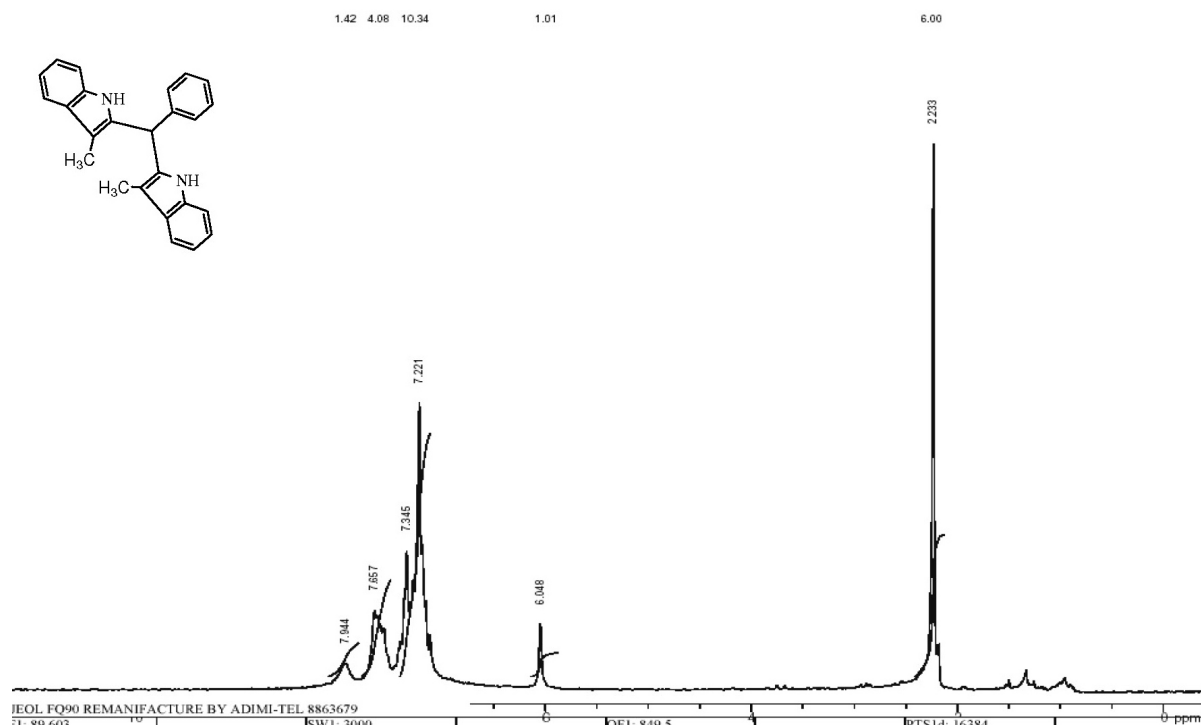


Figure S12. <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum of compound 2,2'-bisindolyl-phenylmethane (Table2, entry 3).

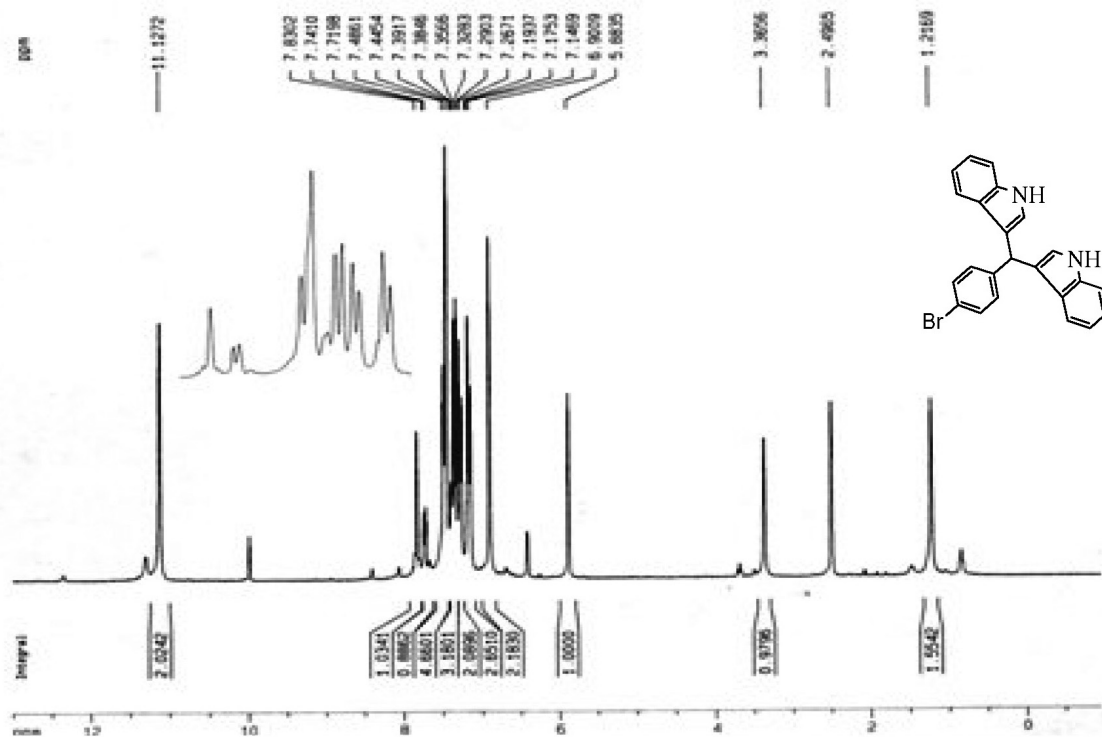


Figure S13. <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum of compound 3,3'-bisindolyl-4-bromophenylmethane (Table 1, entry 5).