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Metal-free oxidative coupling of arylmethylamines with indoles: a simple, environmentally benign approach for the synthesis of 3,3′-bis(indolyl) methanes†

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The efficient metal-free oxidative coupling of arylmethylamines with indoles has been developed using molecular oxygen as a green oxidant. The present reaction provides a novel route towards the synthesis of 3,3′-bis(indolyl)methanes in excellent yields of up to 95% *via* C–C and C–N bond formation. This attractive and environmentally friendly one-pot protocol is a simple procedure that features inexpensive acetic acid as the catalyst and molecular oxygen as the sole oxidant, and it supports a wide substrate scope with the good tolerance of functional groups.

Introduction

The indole scaffold is the most ubiquitous nitrogen heterocycle and is present in various natural products, alkaloids, hormones, neurotransmitters, pharmaceuticals and agrochemicals.[1] This useful structural scaffold has been established as an essential component of heterocyclic compounds in pharmacology and medicinal chemistry.[2] Typically, along with various indole derivatives, bis(indolyl)methanes have been extensively recognized as a privileged class due to their presence in natural products[2] and their wide-ranging applications in pharmaceuticals.[1,3] In the last few years, a large number of bis(indolyl)methanes (BIMs) have been referred to as extremely privileged structures due to their presence in various terrestrial and marine natural sources, where they exhibit a wide range of biological applications.[4–7]

Biologically active bis(indolyl)methanes are depicted in Fig. 1. Simple 3,3′-bis(indolyl)methanes, such as arundine, have been used in cancer chemotherapy, while vibrindole A displays excellent antibacterial activity[8] and arsindoline A shows excellent antitumor activity towards various cancer cell lines.[9] Bis(indolyl)methanes are also efficacious at preventing cancer owing to their capability to modify established cancer-causing estrogen metabolites.[10] Recently, the M. Shiri group have reviewed the cancer chemotherapy effectiveness and various biological activities of BIMs.[11] Also, these compounds may normalize the anomalous cell growth that is related to cervical dysplasia.[12,13] Therefore, their preparation has generated additional interest from synthetic organic chemists and biologists.

Traditionally, 3,3′-bis(indolyl)methanes have been synthesized *via* the condensation of aldehydes with indoles in the presence of diverse catalysts and strong acids.[14–16] Alternatively, 3,3′-bis(indolyl) methanes can be synthesized from alkynes and indoles using ruthenium catalysts.[17] Also, a primary alcohol can undergo transfer hydrogenation in the presence of precious metal complexes, followed by condensation with indoles to furnish BIMs.[18–20] Then, Xiang *et al.* demonstrated the decarboxylative deamination of amino acids using an I_2/PTA catalyst, and the Zhang research group described the utility of a tetramethylethylenediamine (TMEDA) carbon source in the presence of $CuCl_2$ for BIM synthesis with indoles.[21,22] Previously, the Sankala research group reported the synthesis of 3,3′-benzylidenebis(1*H*-indole), using an iron(II) triflate catalyst, from benzylamine with indoles.[23] Furthermore, the platinum-catalyzed bisindolylation reaction of indoles and allenes has also led to the construction of 3,3′-bis(indolyl)methanes (Scheme 1).[24]

Although these methods are effective for 3,3′-bis(indolyl) methane synthesis, they all have at least one shortcoming, such as the use of toxic or precious metals, high catalyst loadings, expensive ligands, volatile solvents, large amounts of promoters, and/or hydrophobic oxidants; long reaction times; lower yields; tedious work-up procedures; and the formation of byproducts under microwave and ultrasound conditions. Moreover, removing metal impurities from the desired products is a highly challenging task for chemists and biologists. In this context, the versatile applications of BIMs have attracted great demand for the development of a new modified method. Herein, the present protocol provides a simple, attractive and environmentally friendly one-pot approach for the synthesis of functionalized bis(indolyl)methanes with the good tolerance of a wide range of functional groups.

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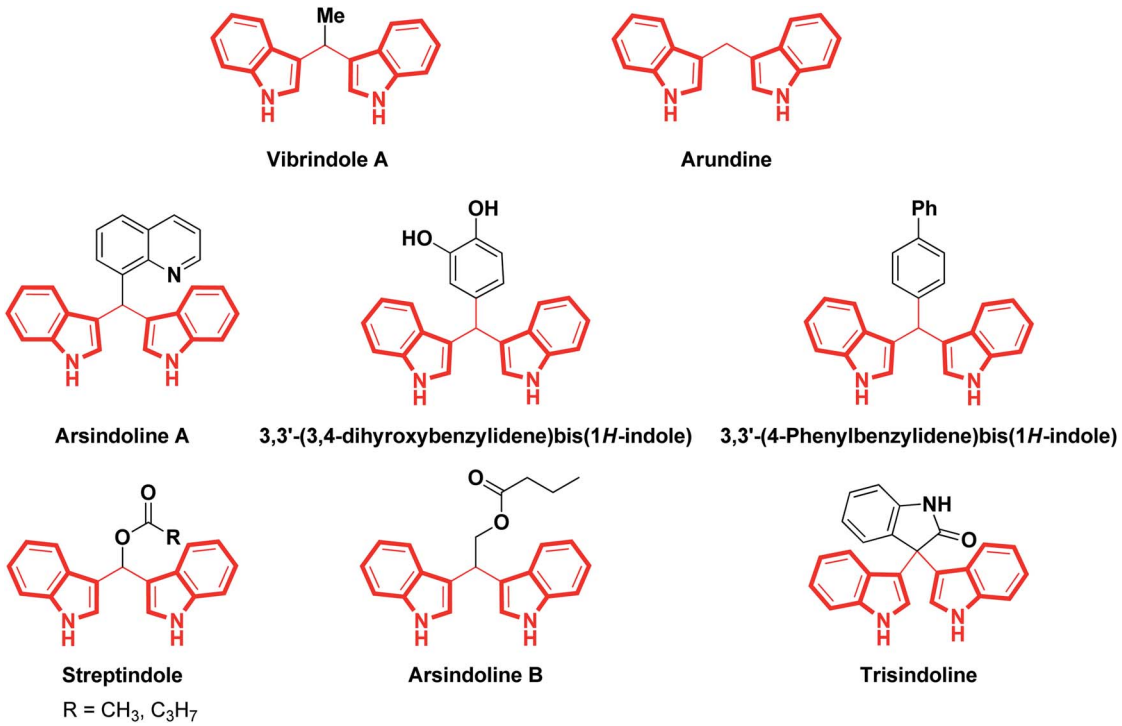


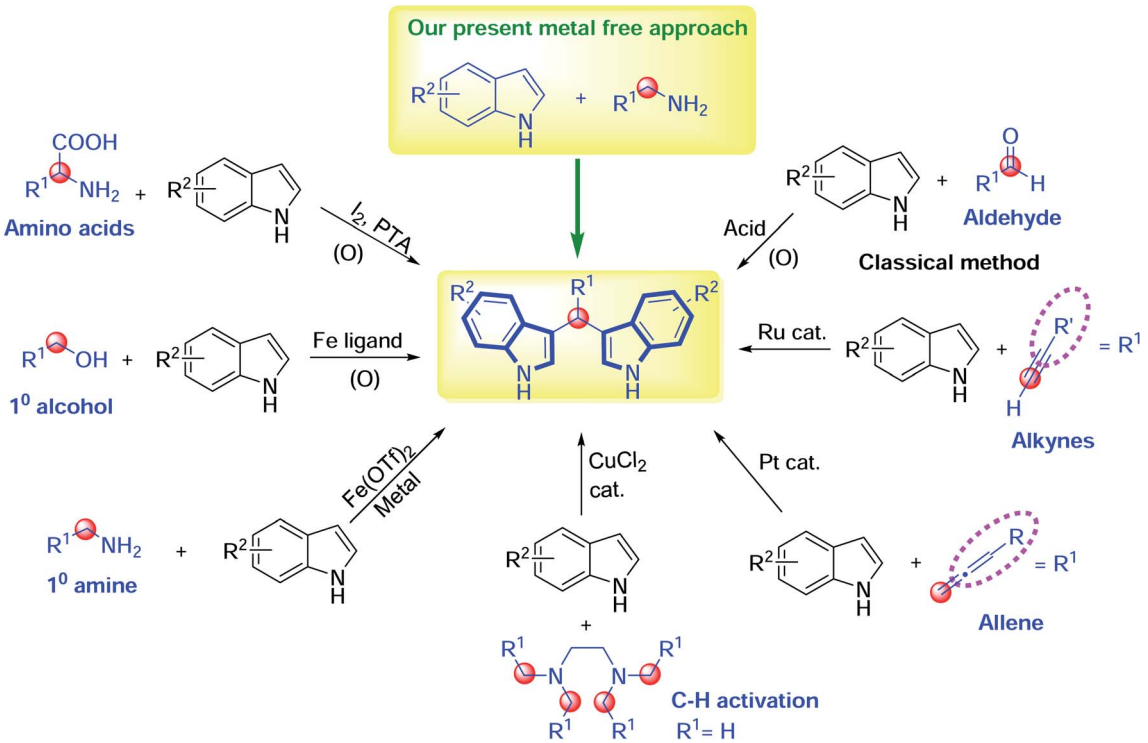
Fig. 1 Some biologically active bis(indolyl)methanes.

Results and discussion

We commenced our investigation with benzylamine **1a** (1.1 mmol) and indole **2a** (2 mmol) as model substrates to optimize the reaction parameters, as depicted in Table 1.

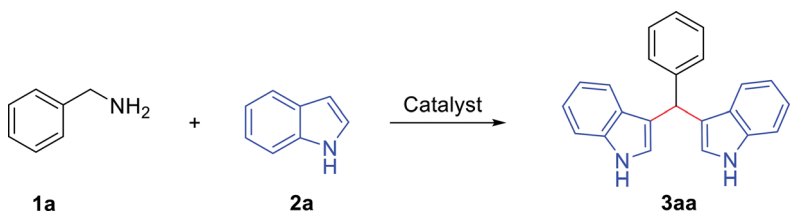
Initially, a series of toluene-mediated acid systems was tested. For this, benzylamine **1a** (1.1 mmol) and indole **2a** (2 mmol) were studied in the presence of trifluoroacetic acid (TFA) (30 mol%) and toluene (1 mL) at 120 °C for 12 h under an O_2 atmosphere; this gratifyingly afforded the 3,3′-bis(indolyl) methane **3aa** in 62% yield (Table 1, entry 1). Then, reaction optimization was carried out with different acids, such as MsOH, TfOH, AcOH and PivOH, under similar reaction conditions; the desired product **3aa** was obtained and yields are reported in Table 1 (entries 2–5). All the toluene/acid systems promoted 3,3′-bis(indolyl)methane **3aa** formation, and the AcOH/toluene combination was observed to be most effective (yield of **3aa**: 71%; entry 4). For further yield improvements, the reaction conditions were optimized using the polar solvents ethylene glycol and DMF in AcOH (30 mol%) at 120 °C, but 3,3′-bis(indolyl)methane **3aa** was procured in low yields of 25% and 31%, respectively (Table 1, entries 6 and 7). Then, the transformation was accelerated in the non-polar solvent chlorobenzene and, significantly, the anticipated product 3,3′-bis(indolyl) methane **3aa** was produced in 91% yield (Table 1, entry 8). After that, neat reaction conditions were tested, and the yield of product **3aa** shifted from 91% to 75% (Table 1, entry 9). Subsequently, we attempted various catalyst loading levels from 30 mol% to 10 mol% to further optimize the reaction conditions (Table 1, entries 10–11). A lesser amount of AcOH catalyst (10 mol%) secured the same yield (92%) of product **3aa**. However, further lowering the amount of AcOH catalyst (5 mol%) reduced the yield of product **3aa** from 92% to 79%. Also, the reaction was executed under atmospheric air, and this furnished **3aa** in 81% yield (Table 1, entry 12). Next, the reaction was performed under a nitrogen atmosphere, and this afforded a 35% yield of the desired product **3aa** (Table 1, entry 13). After that, a decrease in the reaction temperature from 120 °C to 80 °C was also studied, and this resulted in a lower yield of **3aa** (Table 1, entry 14). Overall, the optimal conditions were identified as: **1a**: 1.1 mmol; **2a**: 2.0 mmol; AcOH: 10 mol%; toluene: 1 mL; 120 °C; and under an O_2 atmosphere.

With the optimized conditions in hand, we investigated the scope of amines as coupling partners (Table 2). To our delight, a wide range of amines (**1a–1r**), with electron-donating and electron-withdrawing groups, furnished the desired products (**3aa–3ra**) without any difficulties under the optimized reaction conditions. Moreover, a variety of functional groups, such as methoxy, methyl, halogen, trifluoromethyl, naphthyl and thiophene, could be significantly maintained under the optimized reaction conditions. Electronic factors slightly influenced the yields of the desired products. Benzylamines with electron-donating groups at the *para* position (**1b–1e**) furnished the corresponding 3,3′-BIMs in slightly higher yields than benzylamines with electron-withdrawing groups (**1f–1g**). Furthermore, benzylamines with halogen substituents also afforded the desired products in good to moderate yields. Sterically hindered benzylamines (**1i–1n**), such as those with 2-chloro, 2-methoxy, 4-chloro-2-fluoro, 2-chloro-4-fluoro, and 2,3-dichloro



Scheme 1 Approaches for the synthesis of 3,3′-bis(indolyl)methanes.

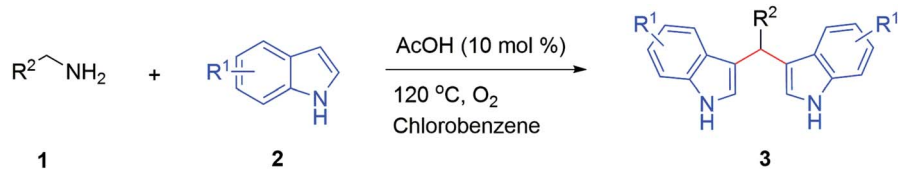
Table 1 Optimization of the reaction conditions[a]

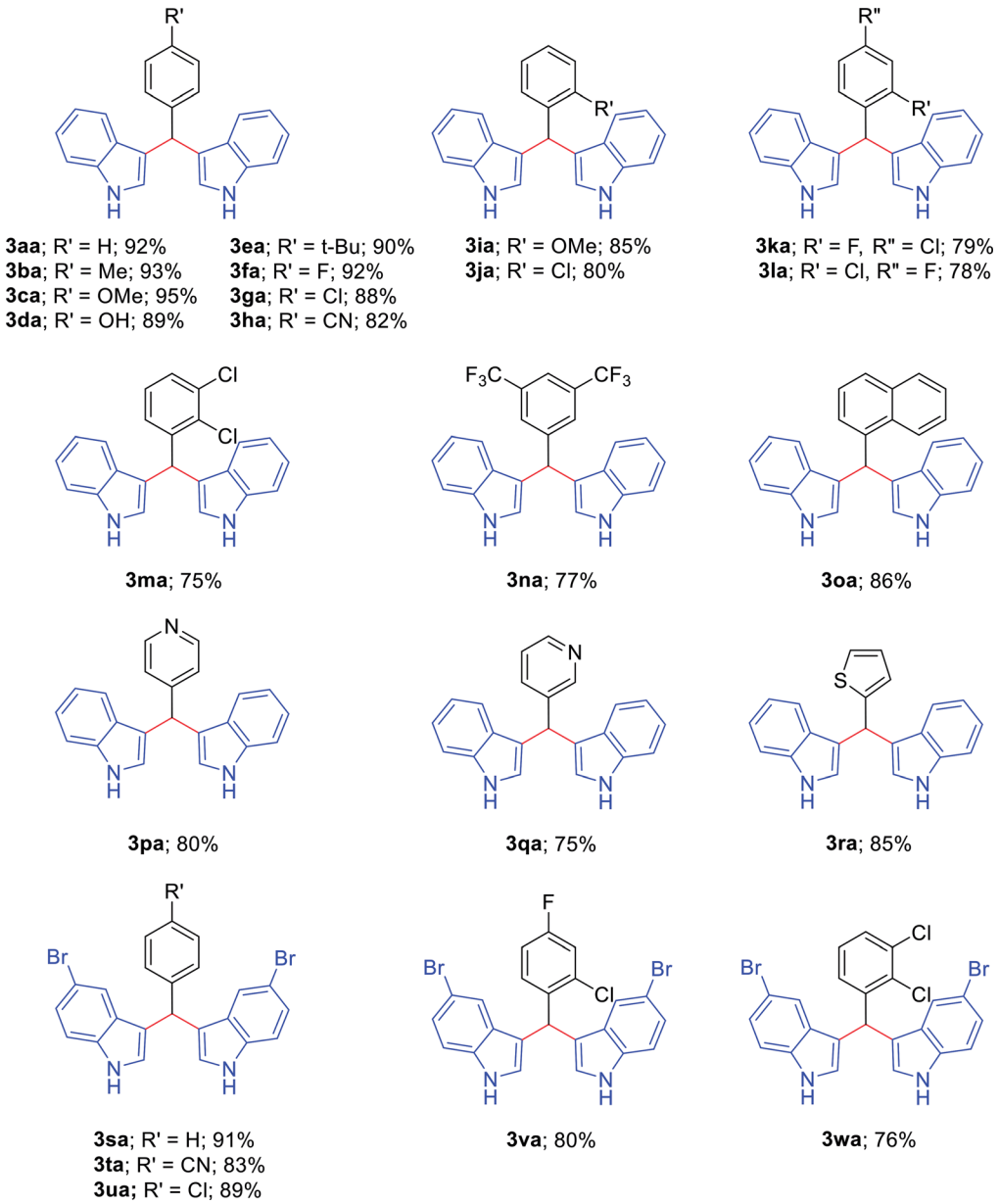


Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	TFA	Toluene	12	62
2	MsOH	Toluene	12	50
3	TfOH	Toluene	12	35
4	AcOH	Toluene	12	71
5	PivOH	Toluene	12	65
6	AcOH	Ethylene glycol	12	25
7	AcOH	DMF	12	31
8	AcOH	Chlorobenzene	9	92
9	AcOH	—	9	75
10[c]	AcOH	Chlorobenzene	9	92
11[d]	AcOH	Chlorobenzene	9	79
12[c,e]	AcOH	Chlorobenzene	9	81
13[c,f]	AcOH	Chlorobenzene	12	35
14[c,g]	AcOH	Chlorobenzene	12	76

[a] Reaction conditions: **1a** (1.1 mmol), **2a** (2.0 mmol), catalyst (30 mol%), solvent (1 mL), at 120 °C, under an O_2 balloon unless otherwise mentioned. [b] Isolated yield. [c] 10 mol% of catalyst was used. [d] 5 mol% catalyst was used. [e] Under atmospheric air. [f] Under N_2. [g] Reaction was carried out at 80 °C.

Table 2 Substrate scope[a,b]



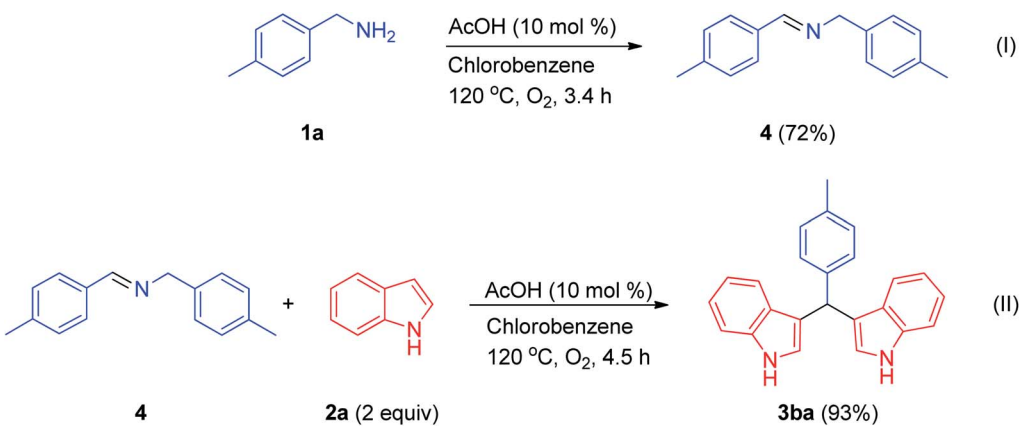


[a] Reaction conditions: **1** (1.1 mmol), **2** (2.0 mmol), AcOH (10 mol%), chlorobenzene (1 mL), at 120 °C, under an O_2 balloon unless otherwise mentioned. [b] Isolated yield.

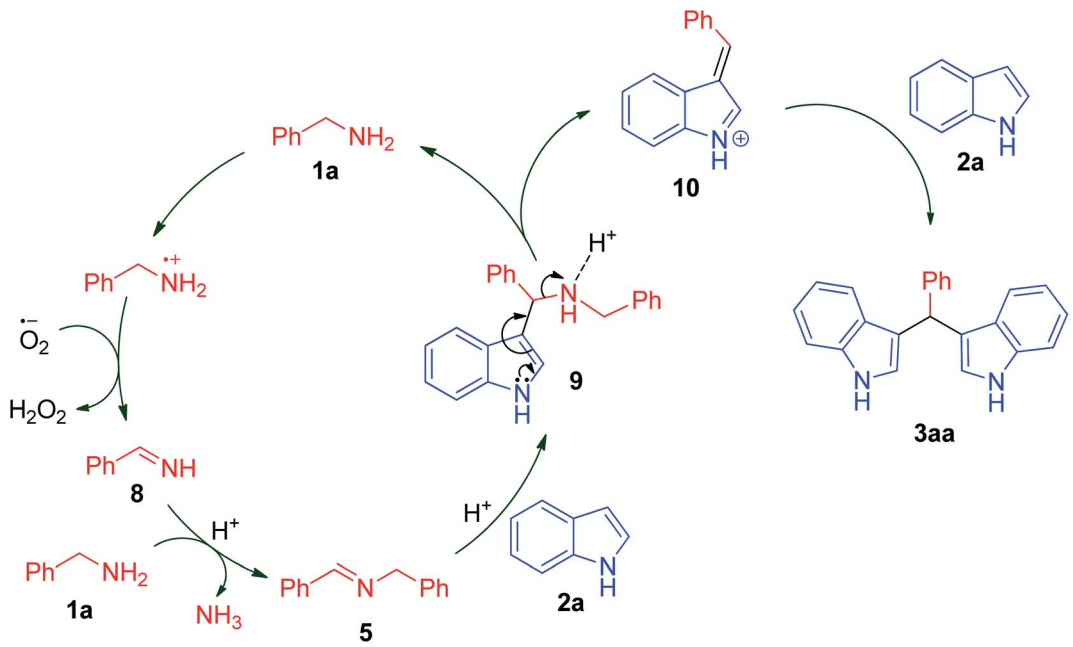
substituents on the benzene rings, also imparted the corresponding 3,3′-BIMs with up to 85–75% yields (**3ia–3ma**,Table 2).

Excitingly, having a strong electron-withdrawing group at the *meta* position of 3,5-bis(trifluoromethyl)benzylamine (**1n**) also resulted in 3,3′-[3,5-bis(trifluoromethyl)-benzylidene]bis(1*H*-indole) (**3na**) in good yield.

To expand the scope of the reaction, heteroaryl methylamines, such as 4-picolylamine, 3-picolylamine and 2-



Scheme 2 Control experiments.



Scheme 3 The proposed reaction mechanism.

thiophene-methylamine, were further investigated, and the desired products (**3pa–3ra**) could be obtained with notable yields of 80%, 75%, and 85%, respectively. In addition, 5-bromo indole (**2b**) tolerated various substituted arylmethylamines well and furnished 3,3′-BIMs (**3sa–3wa**) in good to high yields of 91%, 83%, 89%, 80%, and 76%, respectively.

To gain more insight into the reaction mechanism, we conducted some control experiments (Scheme 2). Initially, *N*-4-methyl-*N*-(4-methylbenzylidene)benzylamine was prepared from 4-methylbenzylamine at 120 °C in chlorobenzene under a molecular oxygen atmosphere using acetic acid (10 mol%) (I). Afterwards, this intermediate was treated with two equivalents of indole, furnishing a bis(indolyl)methane (II) (Scheme 2); this was also achieved using 1.5 mmol of benzylamine and 2.0 mmol of indole. From previous literature reports and the above control experiments, we propose a tentative reaction mechanism for the synthesis of a bis(indolyl)methane from benzylamine **1a** and indole **2a** under metal-free conditions (Scheme 3). At first, an oxidative process involving benzylamine **1a** results in the formation of the corresponding aldimine **8**. Then, this aldimine **8** undergoes further transamination with another molecule of amine to furnish the corresponding homo-coupled product *N*-benzylidinebenzylamine **5**. In the next step, indole **2a** undergoes a Mannich reaction with *N*-benzylidine-benzylamine **5** to afford the C-3 alkylated intermediate **9**, which undergoes further oxidation resulting in the formation of the azafulvene intermediate **10**. In the final step, azafulvene **10** reacts with another molecule of indole **2a**, resulting in the formation of the desired product 3,3′-bis(indolyl)methane **3aa**. For testing the practicability of the reaction on a large scale, the reaction of benzylamine (**1a**, 19.5 mmol) and indole (**2a**, 30 mmol) was investigated, and it afforded 4.59 g of **3aa** in 91%

yield, showing no major loss of efficiency. As a result, this protocol has utility as a practical process for preparing bis(indolyl)methanes.

Additionally, we studied the ability of our methodology to synthesize some biologically active bis(indolyl)methanes, such as 3,3′-(4-methoxybenzylidene)bis(1*H*-indole) (**3ca**), 3,3′-(4-hydroxybenzylidene)bis(1*H*-indole) (**3da**), and 3,3′-(4-*tert*-butylbenzylidene)bis(1*H*-indole) (**3ea**) (Table 2). The compounds **3ca** and **3da** induce nuclear NR4A1-dependent apoptosis and inhibit the growth of colon, bladder, lung and pancreatic cancer cells[25–27] through the activation or deactivation of receptors. Compound **3ea** inhibits the proliferation of the invasive estrogen receptor-negative MDA-MB-231 and MDA-MB-453 human breast cancer cell lines.[28]

Conclusions

In summary, we have developed a simple AcOH-catalyzed novel metal-free oxidative coupling reaction between benzylamines and indoles to synthesize a diverse range of functionalized bis(indolyl)methanes. The synthesis of bis(indolyl)methanes involves aerobic oxidative addition, cleavage, and sequential coupling in a one-pot procedure using green molecular oxygen as the oxidant, making the transformation very economical and environmentally benign.

Experimental section

General information

All reactions were carried out in oven-dried glassware using dry solvents under a molecular oxygen atmosphere, unless stated otherwise. Iron salts were purchased from Sigma-Aldrich and were used as received. All other chemicals were used as received from commercial sources. Reactions were monitored *via* TLC on 0.25 mm Merck silica gel plates (60 F_{254}) using UV light for visualization. Column chromatography purification was performed using silica gel (100–200 mesh). Melting points were measured using Büchi melting point apparatus and are uncorrected. IR spectra were recorded using a Spectrum FT-IR spectrophotometer. NMR spectra were recorded using a Bruker 400 MHz spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz), using DMSO-d_6 or $CDCl_3$ as the solvent with TMS as the internal standard at room temperature. Mass spectra were recorded using a 6530 Accurate-Mass Q-TOF LC/MS (Agilent Technologies).

General procedure for the synthesis of bis(indolyl)methanes (3)

Benzylamine **1** (1.1 mmol), indole **2** (2.0 mmol), AcOH (10 mol%), and dry chlorobenzene (2 mL) were added to a 25 mL round bottom flask. The round bottom flask was equipped with an O_2 balloon, and the reaction mixture was stirred at 110 °C until the complete consumption of indole **2** occurred, as monitored *via* TLC. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and washed with water (2 × 10 mL). The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the resulting residue was purified *via* silica gel column chromatography using a hexane/ethyl acetate mixture to afford the corresponding bis(indolyl)methane products **3**.

Characterization data from the pure bis(indolyl)methanes products

Synthesis of 4-methyl-*N*-(4-methylbenzylidene)benzylamine (4). 4-Methylbenzylamine (**1a**) (350 mg, 2.89 mmol), AcOH (10 mol%), and dry chlorobenzene (2 mL) were added to a 25 mL round bottom flask. The round bottom flask was equipped with an O_2 balloon, and the reaction mixture was stirred at 110 °C for 3.4 h. The reaction mixture was cooled to room temperature and adsorbed on basic alumina. It was purified *via* column chromatography over basic alumina using a hexane/ethyl acetate (9 : 1) mixture as the eluent to afford 4-methyl-*N*-(4-methylbenzylidene)benzylamine (**4**) (232 mg, 72% yield) as a pale yellow solid.

IR (cm^{-1}): 3022, 2923, 2853, 1646, 1514, 1174, 1021, 811, 711; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.07–7.26 (m, 8H, ArH), 4.5 (d, J = 5.6 Hz, 2H), 2.35 (s, 3H), 2.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 137.5, 134.5, 129.6, 129.5, 129.3, 129.2, 127.8, 126.9, 41.97, 21.1 ppm; ^{13}C NMR DEPT-135 (100 MHz, $CDCl_3$): 160.9 (=CH, up), 129.6, 129.5, 127.8, 126.9, 41.9 (CH_2, down), 21.1 (2 × CH_3, up) ppm.

Synthesis of 3,3′-benzylidenebis(1*H*-indole) (3aa). Yield: 296 mg (92%) as a pink solid; mp: 148–151 °C (lit.[29] 151–152 °C); IR (cm^{-1}): 3416, 3058, 2924, 1601, 1456, 1337, 1217, 1093, 745, 701, 597; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (br s, 2H, NH), 7.45–7.24 (m, 9H, ArH), 7.22 (t, J = 8.4 Hz, 2H), 7.05 (t, J = 8.0 Hz, 2H), 6.64 (s, 2H), 5.93 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 137.7, 128.8, 128.3, 127.1, 126.2, 123.7, 121.9, 120.0, 119.2, 111.0, 40.2 ppm; ^{13}C NMR DEPT-135 (100 MHz, $CDCl_3$): 128.8, 128.3, 126.2, 123.7, 121.9, 120.0, 119.2, 111.09 (up, =CH, sp^2), 40.2 (up, CH, sp^3) ppm.

Synthesis of 3,3′-(4-methylbenzylidene)bis(1*H*-indole) (3ba). Yield: 313 mg (93%) as a pink solid; mp: 95–96 °C (lit.[29] 94–96 °C); IR (cm^{-1}): 3414, 3055, 2920, 2850, 1618, 1456, 1417, 1216, 1093, 776, 744, 598; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (br s, 2H, NH), 7.32 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 6.8 Hz, 2H), 7.08 (t, J = 6.8 Hz, 2H), 7.00 (d, J = 7.6 Hz, 2H), 6.92 (t, J = 6.8 Hz, 2H), 6.58 (d, J = 1.6 Hz, 2H), 5.77 (s, 1H), 2.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 136.6, 135.4, 128.9, 128.5, 127.0, 123.5, 121.8, 119.9, 119.8, 119.1, 111.0, 39.7, 21.0 ppm.

Synthesis of 3,3′-(4-methoxybenzylidene)bis(1*H*-indole) (3ca). Yield: 334 mg (95%) as a light orange solid mp: 187–190 °C (lit.[30] 187–189 °C); IR (cm^{-1}): 3408, 1609, 1507, 1455, 1416, 1337, 1300, 1242, 1173, 1124, 1092, 1027, 813, 793, 740; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (br s, 2H, NH), 7.41 (d, J = 7.6 Hz, 2H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.28 (d, J = 6.6 Hz, 2H, ArH), 7.19 (t, J = 7.8 Hz, 2H, ArH), 7.03 (t, J = 7.5 Hz, 2H, ArH), 6.84 (d, J = 6.8 Hz, 2H, ArH), 6.68 (s, 2H, ArH), 5.87 (s, 1H), 3.81 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 136.6, 136.2, 129.6, 127.1, 123.5, 121.9, 120.0, 119.9, 119.2, 113.5, 111.0, 55.2, 39.3 ppm.

Synthesis of 3,3′-(4-hydroxybenzylidene)bis(1*H*-indole) (3da). Yield: 300 mg (89%) as a pink solid; mp: 214–216 °C (lit.[14] 210–212 °C); IR (cm^{-1}): 3412, 2924, 2853, 1611, 1510, 1456, 1338, 1217, 1093, 786, 744, 598; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (br s, 2H, NH), 7.37–7.32 (m, 4H), 7.19–7.12 (m, 4H), 6.98 (t, J = 6.8 Hz, 2H), 6.72 (d, J = 11.2 Hz, 2H), 6.63 (t, J = 1.2 Hz, 2H), 5.81 (s, 1H), 4.80 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 136.6, 135.5, 129.4, 126.9, 123.5, 121.3, 119.7, 118.6, 114.8, 110.9, 60.2 ppm.

Synthesis of 3,3′-(4-*tert*-butylbenzylidene)bis(1*H*-indole) (3ea). Yield: 340 mg (90%) as a yellow solid; mp: 88–91 °C (lit.[23] 86–89 °C); IR (cm^{-1}): 3412, 2959, 2923, 2852, 1457, 1419, 1338, 1217, 1092, 1010, 795, 742, 600; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (br s, 2H, NH), 7.49–7.46 (m, 2H), 7.37–7.32 (m, 6H), 7.24–7.20 (m, 2H), 7.09–7.04 (m, 2H), 6.60 (s, 2H), 5.92 (s, 1H), 1.37 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 140.8, 136.6, 128.2, 127.1, 125.0, 123.5, 121.7, 119.9, 119.8, 119.0, 111.0, 39.5, 34.3, 31.4 ppm.

Synthesis of 3,3′-(4-fluorobenzylidene)bis(1*H*-indole) (3fa). Yield: 313 mg (92%) as an orange solid; mp: 72–74 °C (lit.[14] 71–73 °C); IR (cm^{-1}): 3413, 3056, 2926, 1603, 1506, 1456, 1217, 1094, 863, 744, 582; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 2H, NH), 7.30 (d, J = 8.4 Hz, 4H), 7.23–7.19 (m, 2H), 7.11 (t, J = 6.8 Hz, 2H), 6.96–6.87 (m, 4H), 6.58 (d, J = 2.4 Hz, 2H), 5.80 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 136.7, 130.1, 130.0, 126.9, 123.5, 122.0, 119.8, 119.6, 119.3, 115.0, 114.8, 111.0, 39.4 ppm.

Synthesis of 3,3′-((4-chlorophenyl)methylene)bis(1*H*-indole) (3ga). Yield: 313 mg (88%) as a pink solid; mp: 78–80 °C (lit.[14] 77–79 °C); IR (cm^{-1}): 3411, 3055, 2923, 2848, 1617, 1417, 1337, 1089, 1013, 743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 1H, Ar-CH), 6.63 (s, 2H, Ar-H), 6.97 (t, 2H, Ar-H), 7.02 (t, 2H, Ar-H), 7.14–7.36 (m, 8H, Ar-H), 7.91 (br, s, 2H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 136.7, 131.9, 130.0, 128.3, 126.9, 123.4, 122.1, 119.8, 119.4, 119.2, 111.0, 39.6 ppm.

Synthesis of 4-(di(1*H*-indol-3-yl)methyl)benzonitrile (3ha). Yield: 284 mg (82%) as a pink solid; mp: 209–211 °C (lit.[14] 209–210 °C); IR (cm^{-1}): 3396, 3165, 2940, 2253, 1602, 1407, 757; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (br s, 2H, NH), 7.56 (d, J = 8.18 Hz, 2H, Ar-H), 7.44 (d, J = 8.18 Hz, 2Ar-H), 7.1–7.5 (m, 8H, Ar-H), 6.63 (s, 2H, Ar-CH), 5.92 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 136.7, 132.2, 129.5, 126.7, 123.7, 122.3, 119.6, 119.5, 119.2, 118.2, 111.2, 110.0, 40.4 ppm.

Synthesis of 3,3′-(2-methoxybenzylidene)bis(1*H*-indole) (3ia). Yield: 299 mg (85%) as a white solid; mp: 136–137 °C (lit.[14] 136–138 °C); IR (cm^{-1}): 3414, 3057, 2933, 1597, 1489, 1456, 1338, 1243, 1092, 1028, 743, 600; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (br s, 2H, NH), 7.39 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.15–7.11 (m, 4H), 6.97 (t, J = 6.8 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.79 (t, J = 8.0 Hz, 1H), 6.63 (s, 2H), 6.34 (s, 1H), 3.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 136.7, 132.3, 129.7, 127.2, 127.1, 123.5, 121.7, 120.4, 120.0, 119.6, 119.0, 110.9, 110.6, 55.7, 32.0 ppm.

Synthesis of 3,3′-(2-chlorobenzylidene)bis(1*H*-indole) (3ja). Yield: 284 mg (80%) as an orange solid; mp: 72–74 °C (lit.[14] 72–73 °C); IR (cm^{-1}): 3413, 3057, 2924, 1618, 1456, 1337, 1216, 1093, 1038, 743, 599; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (br s, 2H), 7.36–7.28 (m, 5H), 7.16–7.01 (m, 5H), 6.94 (t, J = 6.8 Hz, 2H), 6.57 (d, J = 1.6 Hz, 2H), 6.27 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 136.7, 133.9, 130.3, 129.4, 127.5, 127.0, 126.6, 123.7, 122.0, 119.8, 119.3, 118.3, 111.0, 36.6 ppm.

Synthesis of 3,3′-((4-chloro-2-fluorophenyl)methylene) bis(1*H*-indole) (3ka). Yield: 295 mg (79%) as a light orange solid; mp: 187–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (br s, 2H, NH), 7.41–7.39 (m, 4H, ArH), 7.21 (m, 2H, ArH), 7.16 (m, 2H, ArH), 7.07–6.99 (m, 3H, ArH), 6.73 (d, J = 1.2 Hz, 2H, ArH), 6.19 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 136.7, 132.6, 131.2, 129.8, 126.7, 124.3, 124.2, 123.6, 122.2, 119.7, 117.7, 116.2, 111.1, 60.4 ppm.

Synthesis of 3,3′-((2-chloro-4-fluorophenyl)methylene) bis(1*H*-indole) (3la). Yield: 292 mg (78%) as a faint pink solid; mp: 98–99 °C; IR (cm^{-1}): 3407, 3060, 1603, 1484, 1456, 1417, 1337, 1260, 1216, 1124, 1093, 1035, 1010, 903, 858, 795; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (br s, 2H, NH), 7.40 (d, J = 8.4 Hz, 4H, ArH), 7.342–7.19 (m, 4H, ArH), 7.07–7.03 (m, 2H, ArH), 6.86 (t, J = 8.4 Hz, 1H, ArH), 6.64 (d, J = 2.4, 2H, ArH), 6.30 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 159.7, 137.3, 137.2, 136.7, 134.4, 134.3, 131.2, 131.1, 126.8, 123.7, 122.1, 119.8, 119.4, 118.2, 116.8, 116.6, 113.8, 113.6, 111.1, 36.2 ppm; HRMS: m/z $[M + H]^+$ calcd for $C_{23}H_{16}ClFN_2$: 374.0986, found: 374.1039.

Synthesis of 3,3′-((2,3-dichlorophenyl)methylene)bis(1*H*-indole) (3ma). Yield: 293 mg (75%) as a violet-pink solid; mp: 110–113 °C; IR (cm^{-1}): 3408, 1455, 1416, 1337, 1216, 1176, 1154, 1124, 1092, 1040, 1010, 794, 769, 738, 711, 686; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (br s, 2H, NH), 7.41–7.36 (m, 4H, ArH), 7.09–7.03 (m, 3H, ArH), 7.23–7.15 (m, 3H, ArH), 6.66 (d, J = 1.2 Hz, 2H, ArH), 5.32 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 136.6, 133.0, 132.2, 128.4, 128.4, 126.9, 126.8, 123.8, 122.1, 119.7, 119.4, 117.8, 111.1, 37.8 ppm; HRMS: m/z $[M + H]^+$ calcd for $C_{23}H_{16}Cl_2N_2$: 391.2925, found: 391.3125.

Synthesis of 3,3′-[3,5-bis(trifluoromethyl)benzylidene] bis(1*H*-indole) (3na). Yield: 353 mg (77%) as a dark red solid; mp: 64–66 °C (lit.[23] 65–67 °C); IR (cm^{-1}): 3415, 2923, 2852, 1620, 1458, 1373, 1278, 1171, 1133, 901, 745, 682; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br s, 2H, NH), 7.81 (s, 2H), 7.75 (s, 1H), 7.38–7.33 (m, 4H), 7.20 (t, J = 7.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 2H), 6.62 (d, J = 1.6 Hz, 2H), 6.01 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 136.7, 131.5, 131.2, 128.7, 126.5, 124.8, 123.7, 122.4, 122.1, 120.5, 119.6, 119.4, 117.9, 111.3, 40.0 ppm; HRMS: m/z $[M + H]^+$ calcd for $C_{25}H_{16}F_6N_2$: 457.1145, found: 457.1129.

Synthesis of 3,3′-(1-naphthylmethylene)bis(1*H*-indole) (3oa). Yield: 391 mg (86%) as a brown solid; mp: 218–221 °C (lit.[31] 218–220 °C); IR (cm^{-1}): 3414, 3052, 2923, 1618, 1452, 1341, 1255, 1217, 1094, 778, 744; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.63 (br s, 2H), 8.13 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.38–7.21 (m, 5H), 7.15 (d, J = 7.6 Hz, 2H), 6.96 (t, J = 7.6 Hz, 2H), 6.76 (t, J = 7.6 Hz, 2H), 6.63 (d, J = 1.2 Hz, 2H), 6.52 (s, 1H), 5.53 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.9, 137.3, 134.3, 131.9, 129.3, 127.4, 127.2, 126.7, 126.2, 126.0, 124.9, 124.4, 121.9, 119.6, 119.2, 118.5, 112.4, 55.3 ppm.

Synthesis of 3,3′-(4-pyridylmethylene)bis(1*H*-indole) (3pa). Yield: 258 mg (80%) as a brown solid; mp: 158–161 °C (lit.[32] 160–162 °C); IR (cm^{-1}): 3408, 3169, 3056, 2975, 2922, 1597, 1456,

1416, 1339, 1242, 1012, 801, 743; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 10.18 (br s, 2H, NH), 8.50 (t, J = 5.2 Hz, 2H), 7.46–7.42 (m, 4H), 7.04–6.98 (m, 7H), 6.75–6.71 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3): δ 156.3, 149.7, 138.2, 128.2, 125.7, 122.3, 121.8, 119.1, 112.2, 49.0 ppm.

Synthesis of 3,3′-(pyridin-3-ylmethylene)bis(1*H*-indole) (3qa). Yield: 242 mg (75%) as a reddish brown solid; mp: 137–139 °C (lit. 138–140 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, 1H, J = 7.6 Hz, ArH), 8.18 (brs, 2H, NH), 7.40–7.03 (m, 11H, ArH), 6.69 (s, 2H, ArH), 5.89 (s, 1H, Ar-CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 147.0, 140.2, 136.5, 135.5, 126.3, 123.6, 123.2, 121.0, 118.8, 118.2, 117.1, 111.5, 54.8 ppm.

Synthesis of 3,3′-(2-thienylmethylene)bis(1*H*-indole) (3ra). Yield: 278 mg (85%) as a red solid; mp: 180–182 °C (lit.[31] 185–188 °C); IR (cm^{-1}): 3414, 2923, 2852, 1456, 1338, 1217, 1094, 1010, 853, 742, 592; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (br s, 2H, NH), 7.45 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.18–7.13 (m, 3H), 7.02 (t, J = 7.6 Hz, 2H), 6.92–6.89 (m, 2H), 6.82 (s, 2H), 6.15 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 136.5, 126.7, 126.4, 125.1, 123.6, 123.1, 122.0, 119.7, 119.6, 119.3, 111.1, 35.3 ppm.

Synthesis of 3,3′-benzylidenebis(5-bromo-1*H*-indole) (3sa). Yield: 437 mg (91%) as a red solid; mp: 243–247 °C (lit.[30] 246–248 °C); IR (cm^{-1}): 3248, 2920, 2850, 1610, 1463, 1261, 1098, 885, 798, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (br s, 2H, NH), 7.38 (s, 2H), 7.20–7.12 (m, 9H), 6.56 (s, 2H), 5.66 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 135.3, 128.5, 128.4, 128.1, 126.2, 124.9, 124.4, 121.9, 118.5, 112.6, 112.1, 38.7 ppm.

Synthesis of 4-(bis(5-bromo-1*H*-indol-3-yl)methyl) benzonitrile (3ta). Yield: 419 mg (83%) as a dark red solid; mp: 230–232 °C; IR (cm^{-1}): 3444, 3393, 3332, 3053, 2922, 2852, 2230, 1651, 1604, 1562, 1488, 1457, 1416, 1336, 1315, 1303, 1242, 1220, 1207, 1173, 1134, 1100, 1043, 1019, 933, 885, 863, 852, 825, 790, 774, 762, 744, 726, 700, 683, 667; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.35 (dd, J = 5.2 and 3.6 Hz, 4H), 7.20–7.17 (m, 4H), 6.59 (d, J = 2 Hz, 2H), 5.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 135.5, 132.2, 129.4, 128.3, 125.2, 124.7, 121.6, 119.1, 116.9, 113.0, 112.4, 110.1, 40.2 ppm.

Synthesis of 3,3′-((4-chlorophenyl)methylene)bis(5-bromo-1*H*-indole) (3ua). Yield: 457 mg (89%) as a red solid; mp: 110–112 °C; IR (cm^{-1}): 3397, 3053, 2923, 2852, 1656, 1617, 1562, 1487, 1459, 1418, 1338, 1302, 1219, 1165, 1133, 1091, 1014, 925, 882, 867, 791, 744, 726, 700, 675, 653; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.46 (t, J = 1.2 Hz, 2H), 7.28–7.21 (m, 8H), 6.63 (dd, J = 2.4 & 0.8 Hz, 2H), 5.74 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 135.3, 132.2, 129.9, 128.6, 128.5, 125.1, 124.8, 122.2, 118.5, 112.8, 112.7, 39.3 ppm; HRMS: m/z calculated: 511.9291, found: 512.9225 $[M + H]^+$.

Synthesis of 3,3′-((2-chloro-4-fluorophenyl)methylene)bis(5-bromo-1*H*-indole) (3va). Yield: 426 mg (80%) as an orange solid; mp: 98–100 °C; IR (cm^{-1}): 3429, 1682, 1596, 1579, 1484, 1457, 1417, 1394, 1338, 1318, 1260, 1215, 1165, 1095, 1060, 1041, 903, 883, 861, 791, 768, 747, 682, 653; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.46 (t, J = 0.8 Hz, 2H), 7.30–7.20 (m, 5H), 7.09 (dd, J = 8.8 & 6.4 Hz, 1H), 6.88–6.83 (m, 1H), 6.61 (d, J = 1.6 Hz, 2H), 6.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 159.9, 136.4, 136.3, 135.4, 134.5, 134.4, 130.8, 130.7, 128.4, 125.2, 124.8, 122.1, 117.5, 117.2, 116.9, 114.0, 113.8, 112.8, 112.7, 35.5 ppm; HRMS: m/z calculated: 53.6301, found: 533.6301 $[M + H]^+$.

Synthesis of 3,3′-((2,3-dichlorophenyl)methylene)bis(5-bromo-1*H*-indole) (3wa). Yield: 417 mg (76%) as an orange red solid; mp: 220–222 °C; IR (cm^{-1}): 3431, 3415, 3075, 1708, 1614, 1580, 1564, 1458, 1449, 1413, 1339, 1318, 1292, 1256, 1268, 1213, 1176, 1154, 1133, 1095, 1041, 964, 903, 881, 864, 835, 802, 786, 780, 767, 749, 736, 714, 701, 668, 657; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H), 7.47 (s, 2H), 7.46–7.381 (m, 1H), 7.30–7.24 (m, 4H), 7.08–7.03 (m, 2H), 6.62 (d, J = 1.6 Hz, 2H), 6.22 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 135.3, 133.4, 132.3, 128.8, 128.4, 128.0, 127.0, 125.2, 124.9, 122.0, 117.2, 112.9, 112.7, 37.4 ppm; HRMS: m/z calculated: 546.8909 $[M + H]^+$, found 546.8886 $[M + H]^+$.

Conflicts of interest

There are no conflicts to declare.

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