Iodine-Catalyzed Oxidative Coupling between Indoles and Benzylamines: A Greener Method to Bis(indolyl)methanes

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Abstract

Metal-free synthesis of bis(indolyl)methanes involving oxidative coupling of indoles with benzylamines in the presence of iodine as a catalyst under an air atmosphere has been demonstrated. This method provides an attractive and efficient approach to a variety of functionalized bis(indolyl)methanes under mild conditions. Ostensibly, iodine promotes the electrophilic substitution of indoles with imines that were generated from benzylamines by self-coupling, to produce bis(indolyl)methane compounds. Previously, our laboratory also reported a first approach for the synthesis of bis(indolyl)methanes by iron-catalyzed oxidative coupling of benzylamines with indoles. The feasibility of a large-scale reaction was tested, and found that the reaction proceeds without any significant loss of its efficiency. Furthermore, the synthetic utility of the transformation was successfully demonstrated by preparing several biologically active compounds.

INTRODUCTION

In contemporary chemical syntheses, the development of novel methodologies with the insinuation of greener and sustainable catalytic systems has been invariably in practice to diminish harmful waste disposal and exploit catalytic efficiency.[1] Under this scenario, the construction of C-C bonds through selective oxidative C-H bond functionalization employing recyclable metallic[2] or non-metallic[3] catalysts is an exemplary approach for the synthesis of biologically and industrially important compounds. This approach is more attractive in recent years because it avoids the need for pre-functionalization of starting materials and proceeds through a shorter route and economy.[4]

In carbon–carbon bond-forming reactions, the Friedel–Crafts reaction is one of the breakthroughs for an acid-catalyzed alkylation or acylation of an aromatic ring system.[5] This has been the origin for the present chapter, synthesis of bis(indolyl)methanes through oxidative coupling of indoles with benzylamines. It has been evident that the C-3 position of indole is about 10^{13} times more reactive than benzene.[6] Indole ring system is one of the π-electron excessive nitrogen heterocycles[7] possessing significant properties in organic and medicinal chemistry.[8] The C-3 substituted indoles, in particular, act as free-radical scavengers,[9] HIV-1 integrase inhibitors[10] and exhibit a broad spectrum of antioxidant activity.[11]

Bis(indolyl)methanes (BIMs) are an important class of bioactive metabolites extensively found in terrestrial cruciferous plants[12] as well as marine sponge alkaloids.[13] Studies have reported that regular use of BIMs in the diet supplement maintains the estrogen and testosterone hormonal balance in the human body.[14] Moreover, scientists have also confirmed that BIMs regulate apoptosis in human cancer cells[15] and also govern abnormal cell growth linked with cervical dysplasia.[16] Subsequent investigations have revealed that BIMs and their ring-substituted bromo-derivatives induce cell death in MCF-7 and MDA-MB-231 breast cancer cells.[17] In addition, bis(indolyl)methane derivatives act as antifungal, antibacterial, anti-inflammatory, antibiotic, and analgesic properties (Figure 1).[18] Consequent to these, both natural and synthetic BIMs are versatile intermediates in organic synthesis.[19]

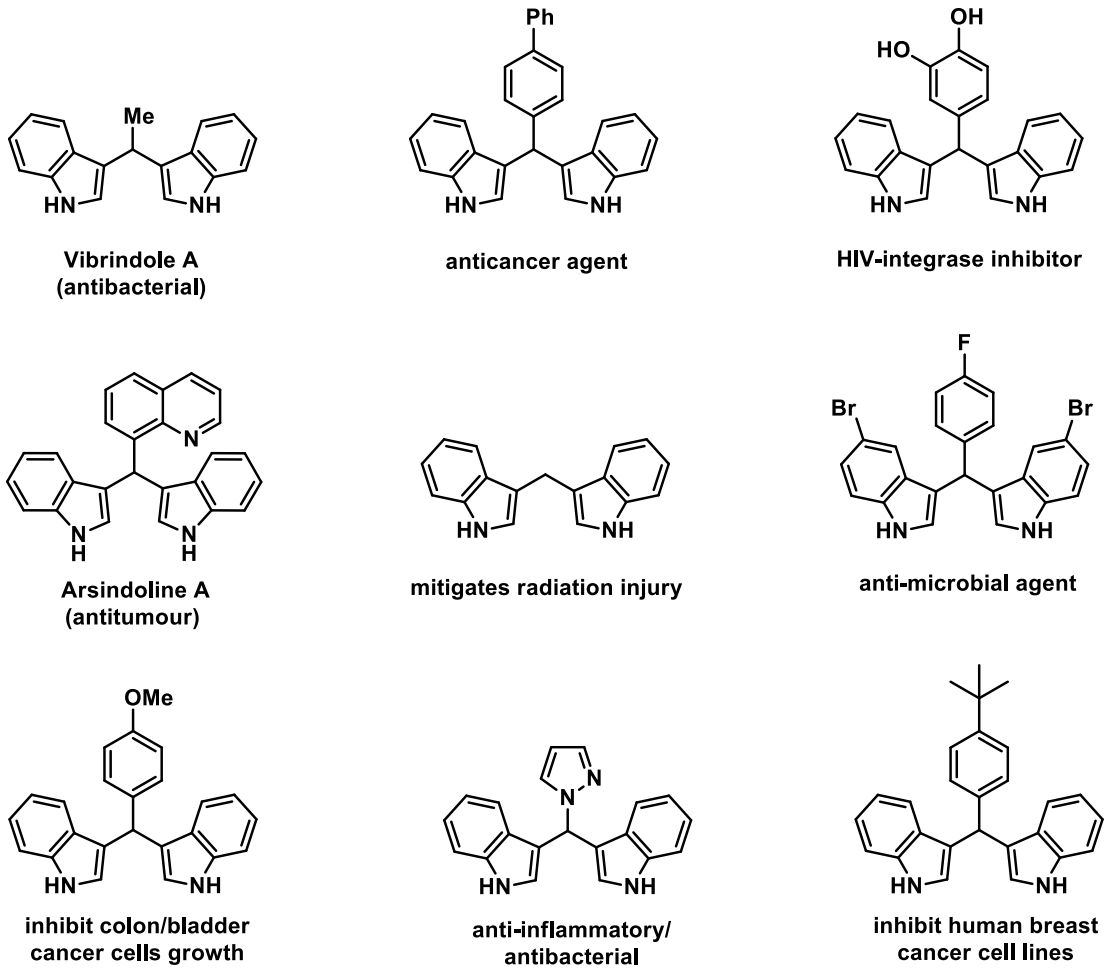


Figure 1: Selected examples of biologically important BIMs

In modern organic synthesis, molecular iodine is very often used as a catalyst in iodination, oxidation, as well as a Lewis acid.[20] It is very apparent in its nature as non-toxic, tolerance to air and moisture, cheap and ready availability for its use as a mild Lewis acid in carbon-carbon and carbon-heteroatom bond formations.[21]

Conventionally, synthesis of BIMs was performed by multicomponent condensation of two moles of indole as nucleophile with one mole of carbonyl compound using Brønsted or Lewis acids to accelerate the reaction. Numerous methods are reported in the literature with a variety of catalysts such as $HClO_4$-SiO_2,[22] $KHSO_4$,[23] $LiClO_4$,[24]Zr(IV) salts,[25] $InCl_3$,[26] $SbCl_3$,[27]Glycerin/$CeCl_3$. $7H_2O$,[28] SmI_3,[29]$InCl_3$/$In(OTf)_3$,[30] $Sc(OTf)_3$,[31]$La(NO_3)_3$. $6H_2O$,[32]and ionic liquids.[33] In addition, synthesis of BIMs was accomplished with aldehydes by means of some standard catalysts such as Br_2/H_2O;[34] Zn/4f cluster, Indion Ina 225H resin;[35] phosphate-impregnated titania catalyst;[36] $NH_4[NbO(C_2O_4)_2(H_2Ox)].nH_2O$;[37] Fe/Al pillared clay-425^oC;[38] Fe^{+3}-Montmorillonite K10;[39] Bakers' yeast;[40] TEBA(Triethylbenzylammonium chloride)/H_2O/reflux or MWI;[41] Polymethylhydrosiloxane (PMHS) – Tris(pentafluorophenyl)borane $[B(C_6F_5)_3]$;[42] tetramethyltetra-3,4-pyridinoporphyrazinato

copper(II) methyl sulfate [Cu(3,4-tmtppa)] $(MeSO_4)_4$;[43] $Dy(OTf)_3$ – [BMIM]BF_4: 1-butyl-3-methylimidazolium tetrafluoroborate.[44]

However, most of these methods suffer from certain impediments, such as the addition of catalysts in stoichiometric amounts, as some of them are highly toxic and expensive. Non-availability of reagents, toxic solvents, and tedious isolation procedures leads to inadequate yields. Subsequently, Li research group reported the synthesis of symmetrical and unsymmetrical BIMs by reaction of indoles with ethers through C-H bond oxidation and C-O bond cleavage using $FeCl_2$ as a catalyst and ditertiarybutylperoxide (DTBP) as oxidant in a one-pot procedure.[45] Subsequently, Yang et al. explored CuBr-catalyzed C-N bond cleavage by oxidative cross-dehydrogenative-coupling (CDC) between *N*-benzylamines and indoles in the presence of *tert*-butyl hydroperoxide (TBHP), forming a series of BIMs.[46] Wang and co-workers developed a rhenium-catalyzed method for the synthesis of *anti*-Markovnikov and Markovnikov BIM products by site-selective intermolecular addition of indoles to inactivated terminal alkynes under variable reaction conditions.[47]

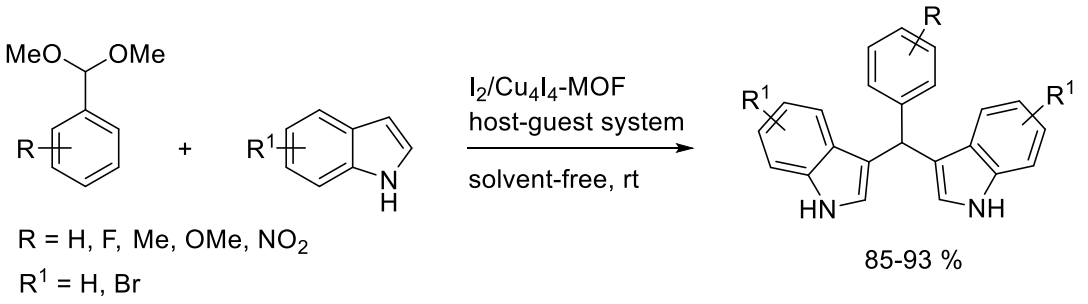
Later, Dong research group expounded a heterogeneous I_2/Cu_4I_4-MOF (metal-organic framework) composite host-guest catalytic system for Friedel–Crafts alkylation of indoles with acetals through a one-pot two-step procedure for the synthesis of a series of BIMs in high yields.[48]

In our previous report, we developed the synthesis of BIMs by oxidative coupling of benzylamines with indoles as the first example using catalytic amounts of iron(II) triflate under molecular oxygen, producing moderate to excellent yields.[18]

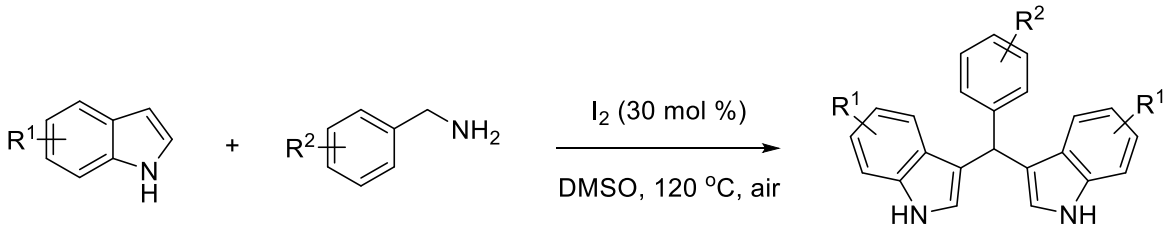
In continuation of our efforts, herein, we report the synthesis of C-3 substituted bis(indolyl)methanes by oxidative coupling of benzylamines and indoles using molecular iodine as a catalyst under an air atmosphere. The present method provides an attractive and efficient approach to a variety of biologically relevant functionalized BIMs in a simple and one-pot procedure (Scheme 1).

Previous work:

I_2/Cu_4I_4-MOF host-guest catalytic synthesis of BIMs from acetals



This Work:

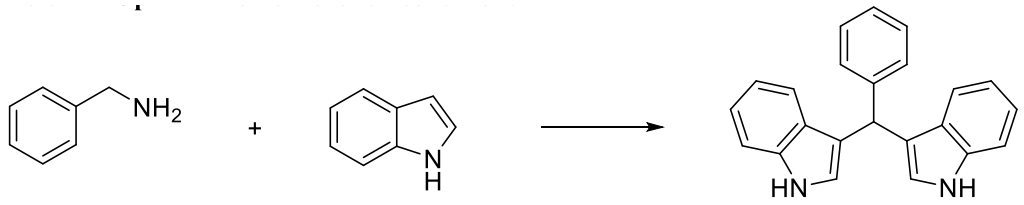


Scheme 1: I_2 catalyzed synthesis of BIMs by oxidative coupling via indoles

RESULTS AND DISCUSSION

Our preliminary investigation began by operating the reaction between benzylamine (1a) and indole (2a) in the presence of molecular iodine (1.0 equiv) in acetonitrile at refluxing temperature under a nitrogen atmosphere (Table 1). We were delighted to observe the formation of the desired product (**3a**), albeit in low yield (32%) (Table 1, entry 1). Then, we used DMSO as the solvent and repeated the reaction at 100 °C. The yield of **3a** was slightly increased to 40 % (Table 1, entry 2). Increasing the reaction temperature to 120 °C improved the yield of **3a** to 53% (Table 1, entry 3), but several other compounds were also formed along with the desired product. The yield of **3a** was not improved by altering the solvent to DMF, NMP, or amyl alcohol (Table 1, entries 4-6). Subsequently, the quantity of iodine was decreased from 100 mol% to 50 mol% and then to 30 mol%, leading to the formation of the desired product **3a** in 61 % and 67% yields, respectively (Table 1, entries 7 and 8). Further decrease of the catalyst loading resulted in a low yield of **3a** (Table 1, entry 9). Finally, when the reaction was conducted in an air atmosphere, surprisingly, the yield of **3a** was increased to 74 % (Table 1, entry 10). Thus, the optimized reaction conditions established involve the use of 30 mol% of iodine in DMSO at 120 °C under an air atmosphere.

Table 1. Optimization of reaction conditions.



1a **2a** **3a**

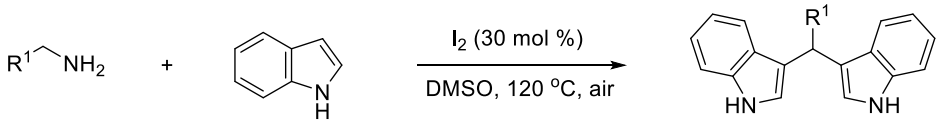
Entry	I_2 (mol %)	Solvent	Time (h)	Yield (%)[b]
1	100	CH_3CN	24	32
2[c]	100	DMSO	24	40
3[d]	100	DMSO	24	53
4[d]	100	DMF	24	48
5[d]	100	NMP	24	50
6[d]	100	amylalcohol	24	42
7[d]	50	DMSO	24	61
8[d]	30	DMSO	24	67
9[d]	20	DMSO	24	55
10[d,e]	30	DMSO	20	74

[a]Reaction conditions: **1a** (1.2 mmol), **2a** (2.0 mmol), iodine, solvent (2 mL), reflux, nitrogen atmosphere (N_2 balloon) unless otherwise noted. [b]Isolated yield. [c]100 ^oC. [d]120 ^oC. [e]air atmosphere.

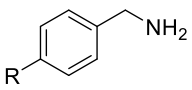
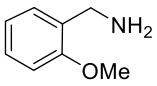
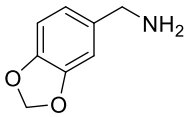
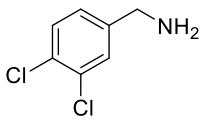
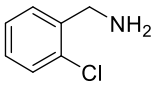
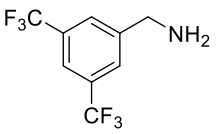
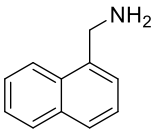
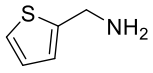
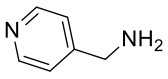
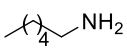
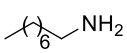
After optimizing the reaction conditions, we studied the scope of the reaction with a variety of benzylamines, and the obtained results are summarized in Table 2. Several substituted benzylamines tolerated well to afford the desired products in moderate to high yields (Table 2, entries 1-11). The electronic properties of the substituents on benzylamines had little effect on the reactivity. Electron-donating substituents (methyl, *tert*-butyl, hydroxy, methoxy, methylenedioxy) on benzylamines gave slightly higher yields than the latter bearing electron-withdrawing groups (fluoro and chloro) (Table 2, entries 1-9). The benzylamine having strongly electron-withdrawing groups such as $–CF_3$ at the *meta* positions gave the corresponding product **3k** in lower yield as compared with the other BIMs **3b-j** (Table 2, entry 10 *vs* entries 1-9). Bulky amine such as 1-naphthylmethylamine (**1l**) was also a good substrate for the oxidative coupling with indole, giving the desired product in 73% yield (Table 2, entry 11). Heteroarylmethylamines such as 2-thiophenemethylamine (**1m**) and 4-picolylamine (**1n**)

also reacted well with indole to produce the desired coupling products in good yields (Table 2, entries 12 and 13). Furthermore, aliphatic amines such as *n*-hexylamine (**1o**) and *n*-octylamine (**1p**) were used as substrates, giving the corresponding products, namely, 1,1-(3,3'-bis-indolyl)hexane (**3o**) and 1,1-(3,3'-bis-indolyl)octane (**3p**) in 45% and 48% yields, respectively (Table 2, entries 14 and 15).

Table 2. Substrate scope of Benzylamines.[a]



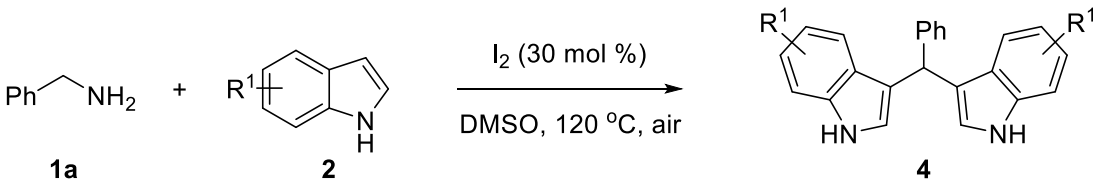
1 **2a** **3**

Entry	Amine **1**			Reaction Time (h)	Product **3**	Yield (%)[b]
1		R = F	**1b**	24	**3b**	70
2		R = Me	**1c**	21	**3c**	79
3		R = *t*-Bu	**1d**	24	**3d**	77
4		R = OH	**1e**	20	**3e**	82
5		R = OMe	**1f**	20	**3f**	86
6			**1g**	23	**3g**	78
7			**1h**	21	**3h**	81
8			**1i**	24	**3i**	73
9			**1j**	24	**3j**	68
10			**1k**	24	**3k**	59
11			**1l**	22	**3l**	73
12			**1m**	24	**3m**	63
13			**1n**	24	**3n**	65
14			**1o**	24	**3o**	45
15			**1p**	24	**3p**	48

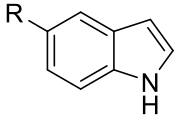
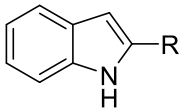
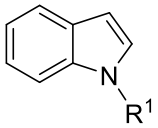
[a]Reaction conditions: amine **1** (1.2 mmol), indole **2a** (2.0 mmol), I_2 (30 mol %), DMSO (2 mL), 120 °C, air atmosphere. [b] Isolated yield.

In order to widen the scope of this protocol, a broad range of indoles were employed to react with benzylamine under the optimized reaction conditions (Table 3). Delightfully, several functionalized indoles underwent the oxidative coupling smoothly and produced the desired products in high yields. Electron-withdrawing and electron-donating groups such as nitro, halogen, methoxy, benzyloxy, phenyl, and methyl, at C-5 and C-2 positions of indole, were not detrimental to the efficiency of the reaction (Table 3, entries 1-6). In addition, *N*-aryl and *N*-alkyl protected indoles (**2h-2k**) were favourable with the reaction, generating the corresponding products in good yields (Table 3, entries 7-10).

Table 3. Substrate scope of Indoles[a]

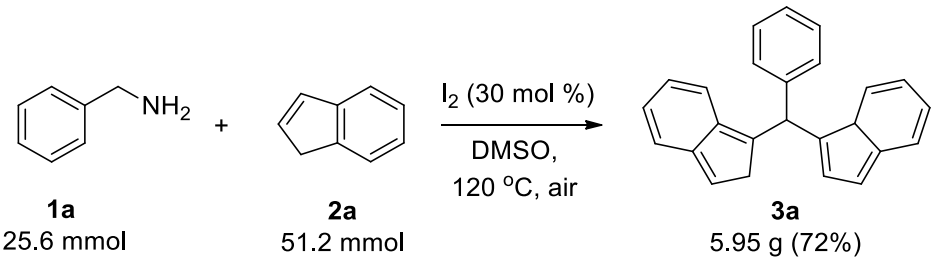


1a **2** **4**

Entry	Indole **2**			Reaction Time (h)	Product **4**	Yield (%)[b]
1		R = NO_2	**2b**	24	**4a**	75
2		R = Br	**2c**	24	**4b**	79
3		R = OMe	**2d**	19	**4c**	84
4		R = OCH_2Ph	**2e**	15	**4d**	85
5		R = Ph	**2f**	24	**4e**	78
6		R = Me	**2g**	24	**4f**	81
7		R = Ph	**2h**	18	**4g**	84
8		R = CH_2Ph	**2i**	18	**4h**	87
9		R = Me	**2j**	20	**4i**	83
10		R = Et	**2k**	20	**4j**	83

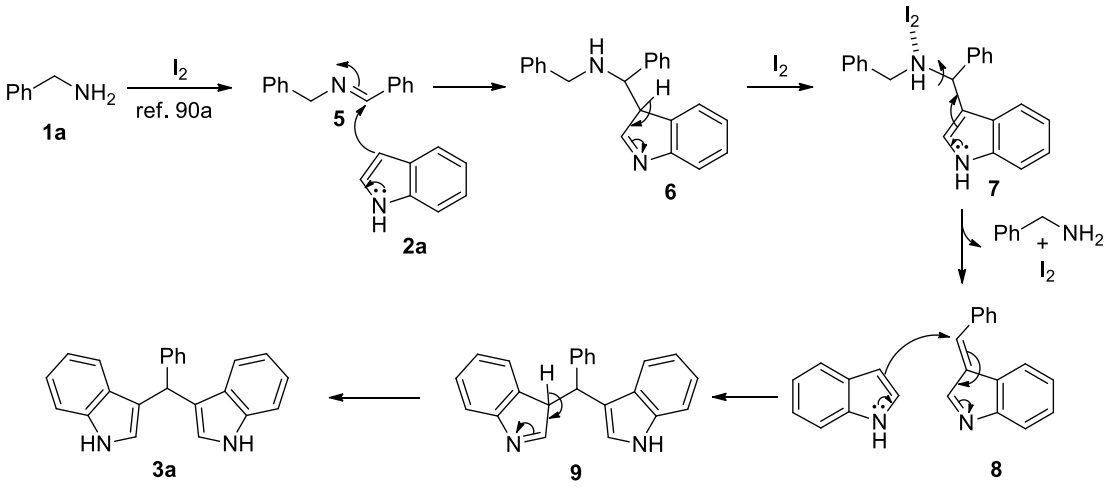
[a] Reaction conditions: amine **1a** (1.2 mmol), Indole **2** (2.0 mmol), I_2 (30 mol %), DMSO (2 mL), 120 °C, air atmosphere. [b] Isolated yield.

To test the practicability of a large-scale reaction, the reaction between benzylamine (**1a**, 25.6 mmol) and indole (**2a**, 51.2 mmol) was examined. The reaction afforded 5.95 g of **3a** in 72% yield, which suggests the large-scale efficiency of the reaction protocol (Scheme 2). Therefore, the present scheme could be applied as a practical method to synthesize a wide variety of BIM products.



Scheme 2: Large-scale reaction of benzylamine and indole for BIM formation

Based on our previous report[18] and available relevant literature,[49] a plausible mechanistic route is proposed in Scheme 3. Primarily, the oxidative addition of iodine to **1a** leads to the formation of imine **5**. Imine **5** on subsequent reaction with **2a** generates intermediate **6**. Intermediate **6,** on further reaction with I_2 in the presence of O_2, forms iodine-coordinated indole complex **7**, which eventually converts to 3-benzylideneindole intermediate **8** by consequent removal of benzylamine and I_2. The generated intermediate **8**, as an electrophile, undergoes nucleophilic addition with a second molecule of indole giving the desired product BIM **3a**.



Scheme 3: Plausible mechanistic route for BIM formation

CONCLUSIONS

In summary, we have explored a versatile metal-free iodine-catalyzed oxidative coupling reaction of benzylamines with indoles for the synthesis of a wide variety of functionalized BIMs in a simple and one-pot procedure. Molecular iodine is inexpensive, readily available, and non-toxic in the reaction protocol. The reaction was performed under air as an oxidant, which makes the transformation very economical and environmentally green. The present method is efficient, practical, and amenable to gram-scale synthesis.

EXPERIMENTAL SECTION

Every reaction was carried out with oven-dried round-bottom flasks and Schlenk tubes using dry solvents under a molecular oxygen balloon unless mentioned otherwise. Iodine was obtained from Sigma-Aldrich and used as received. The rest of the chemicals were used as received from commercial sources. Progress of the reactions was monitored by TLC on 0.25-mm Merck silica gel plates (60 F_{254}) with UV light for visualization. Purification was performed with column chromatography using silica gel 100-200 mesh. Melting points were recorded on Büchi melting point equipment and were uncorrected. IR spectra were recorded on an RX1 FT-IR spectrophotometer. NMR spectra were recorded on a JEOL ECX-400P spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz), with DMSO-d_6 or $CDCl_3$, or CD_3COCD_3 as the solvent by fixing TMS as the internal standard. Mass was recorded on a 6530 Accurate-Mass Q-TOF LC/MS using Agilent Technologies.

General Procedure for the Synthesis of Bis(indolyl)methanes

To a Schlenk tube, benzylamine **1** (1.2 mmol), indole **2** (2.0 mmol), I_2 (30 mol%), and dry DMSO (2.0 mL) were added. The tube was outfitted with an air balloon, and the reaction mixture was constantly stirred at 120 °C until complete consumption of indole with benzylamine, which was monitored by TLC. After completion of the reaction, the contents of the reaction mixture were cooled to room temperature, and diluted with CH_2Cl_2 (10 mL), followed by washings with water (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the resultant residue was purified by silica gel-packed column chromatography using hexane/ethyl acetate as eluents to obtain the corresponding bis(indolyl)methane compounds **3** and **4**.

Characterization of Products

3,3'-Bis(indolyl)phenylmethane **(3a).** Yield: 74%, pink solid, M.P: 149-151 ºC (Lit. 151-152 ºC);[23] IR: 3418, 3060, 2926, 1604, 1457, 1336, 1215, 1095, 746, 702, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (br s, 2H, NH), 7.40-7.32 (m, 5H), 7.25 (t, *J* = 6.8 Hz, 3H), 7.23-7.12 (m, 3H), 6.98 (t, *J* = 7.4 Hz, 2H), 6.63 (s, 2H), 5.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 136.7, 128.5, 128.7, 128.3, 127.1, 126.0, 123.5, 121.8, 121.9, 119.8, 119.7, 119.5, 119.2, 119.0, 111.1, 40.3

3,3'-Bis(indolyl)-4-fluorophenylmethane **(3b).** Yield: 70%, orange solid, M.P: 82-84 ºC (Lit. 80-82 ºC);[23] IR: 3414, 3057, 2927, 1604, 1506, 1455, 1216, 1093, 864, 745, 584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (br s, 2H, NH), 7.31 (d, *J* = 8.4 Hz, 4H), 7.24-7.18 (m, 2H), 7.10 (t, *J* = 6.8 Hz, 2H), 6.95-6.88 (m, 4H), 6.57 (d, *J* = 2.4 Hz, 2H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 136.7, 130.2, 130.1, 126.8, 123.6, 122.1, 119.7, 119.5, 119.2, 115.1, 114.7, 111.1, 39.2.

3,3'-Bis(indolyl)-4-methylphenylmethane **(3c).** Yield: 79%, pink solid, M.P: 95-97 ºC (Lit. 94-96 ºC);[24] IR: 3416, 3057, 2921, 2851, 1619, 1457, 1418, 1217, 1094, 775, 743, 596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (br s, 2H, NH), 7.31 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 6.8 Hz, 2H), 7.07 (t, *J* = 6.8 Hz, 2H), 7.01 (d, *J* = 7.4 Hz, 2H), 6.91 (t, *J* = 6.8 Hz, 2H), 6.57 (d, *J* = 1.4 Hz, 2H), 5.76 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 136.5, 135.3, 128.8, 128.4, 127.1, 123.4, 121.7, 119.8, 119.7, 119.0, 111.0, 39.6, 21.1.

3,3'-Bis(indolyl)-4-tert-butylphenylmethane **(3d).** Yield: 77%, yellow solid, M.P: 85-88 ºC; IR: 3413, 2958, 2924, 2851, 1456, 1418, 1337, 1216, 1093, 1011, 794, 743, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (br s, 2H, NH), 7.49-7.47 (m, 2H), 7.34-7.31 (m, 6H), 7.24-7.20 (m, 2H), 7.09-7.05 (m, 2H), 6.60 (s, 2H), 5.92 (s, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 140.9, 136.7, 128.4, 127.2, 125.2, 123.7, 121.9, 120.1, 119.9, 119.2, 111.2, 39.7, 34.5, 31.6.

3,3'-Bis(indolyl)-4-hydroxyphenylmethane **(3e).** Yield: 82%, pink solid, M.P. 211-213 ºC (Lit. 210-211 ºC);[29] IR: 3413, 2925, 2854, 1612, 1511, 1457, 1339, 1218, 1094, 787, 745, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (br s, 2H, NH), 7.38-7.33 (m, 4H), 7.19-7.13 (m, 4H), 6.99 (t, *J* = 6.8 Hz, 2H), 6.73 (d, *J* = 11.4 Hz, 2H), 6.64 (t, *J* = 1.4 Hz, 2H), 5.82 (s, 1H),

4.81 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 136.7, 135.6, 129.5, 126.9, 123.6, 121.4, 119.6, 118.8, 114.9, 110.8, 60.3.

3,3'-Bis(indolyl)-4-methoxyphenylmethane **(3f).** Yield: 86%, light orange solid, M.P. 186-188 ºC (Lit. 187-189 ºC);[34] IR: 3411, 3005, 2932, 1611, 1507, 1456, 1337, 1245, 1091, 1041, 745, 584 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 2H, NH), 7.38 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 2.4 Hz, 2H), 7.16 (t, *J* = 8.4 Hz, 2H), 6.98 (t, *J* = 8.4 Hz, 2H), 6.83-6.81 (m, 2H), 6.64 (s, 2H), 5.84 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 136.6, 136.1, 129.5, 126.9, 123.4, 121.7, 119.9, 119.8, 119.0, 113.4, 110.9, 55.2, 39.3.

3,3'-Bis(indolyl)-2-methoxyphenylmethane **(3g).** Yield: 78%, white solid, M.P. 135-137 ºC (Lit. 134-136 ºC);[37] IR: 3415, 3058, 2932, 1596, 1488, 1455, 1337, 1244, 1093, 1029, 745, 601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (br s, 2H, NH), 7.38 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.14-7.12 (m, 4H), 6.96 (t, *J* = 6.6 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.78 (t, *J* = 8.0 Hz, 1H), 6.64 (s, 2H), 6.35 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 136.6, 132.4, 129.8, 127.1, 127.0, 123.4, 121.6, 120.5, 120.1, 119.5, 119.0, 110.8, 110.5, 55.6, 32.2.

3,3'-Bis(indolyl)-3,4-methylenedioxyphenylmethane **(3h).** Yield: 81%, brick red solid, M.P. 87-89 ºC (Lit. 89-91 ºC);[42] IR: 3414, 3054, 2892, 1617, 1485, 1455, 1243, 1093, 1036, 926, 786, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 2H, NH), 7.38 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 6.6 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.66 (t, *J* = 1.2 Hz, 2H), 5.88 (s, 2H), 5.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 145.9, 138.2, 136.5, 126.8, 123.4, 121.8, 121.5, 119.8, 119.6, 119.1, 111.0, 109.2, 107.8, 100.6, 39.7.

3,3'-Bis(indolyl)-3,4-dichlorophenylmethane **(3i).** Yield: 73%, red solid, M.P.151-154 ºC (Lit. 153-154 ºC);[43] IR: 3415, 3012, 2922, 2850, 1617, 1468, 1457, 1418, 1337, 1215, 1095, 746, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 2H, NH), 7.36 (d, *J* = 1.6 Hz, 1H), 7.32-7.28 (m, 4H), 7.17 (s, 1H), 7.13-7.08 (m, 3H), 6.94 (t, *J* = 6.8 Hz, 2H), 6.57 (d, *J* = 1.6 Hz, 2H), 5.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 136.6, 132.1, 130.5, 130.2, 130.1, 128.2, 126.6, 123.5, 122.1, 119.5, 119.4, 118.4, 111.1, 39.4.

3,3'-Bis(indolyl)-2-chlorophenylmethane **(3j).** Yield: 68%, pink solid, M.P. 71-73 ºC (Lit. 72-74 ºC);[43] IR: 3414, 3056, 2925, 1617, 1455, 1336, 1215, 1094, 1037, 744, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 2H), 7.35-7.29 (m, 5H), 7.19-7.01 (m, 5H), 6.95 (t, *J* = 6.8 Hz, 2H), 6.58 (d, *J* = 1.6 Hz, 2H), 6.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 136.6, 133.8, 130.2, 129.3, 127.4, 126.8, 126.5, 123.6, 121.9, 119.7, 119.2, 118.2, 110.9, 36.5.

3,3'-Bis(indolyl)-3,5-bis(trifluoromethyl)phenylmethane **(3k).** Yield: 59%, dark red solid, M.P. 64-66 ºC; IR: 3416, 2924, 2851, 1621, 1457, 1372, 1276, 1172, 1132, 902, 744, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (br s, 2H, NH), 7.80 (s, 2H), 7.76 (s, 1H), 7.37-7.32 (m, 4H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 2H), 6.61 (d, *J* = 1.6 Hz, 2H), 6.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 136.6, 131.6, 131.3, 128.6, 126.6, 124.7, 123.8, 122.3, 122.0, 120.4, 119.5, 119.3, 117.8, 111.2, 40.1; HRMS: *m*/*z* $[M - H]^+$ calcd for $C_{25}H_{16}F_6N_2$: 457.1145; found: 457.1130.

3,3'-Bis(indolyl)(naphthalene-1-yl)methane **(3l).** Yield: 73%, brown solid, M.P. 217-220 ºC (Lit. 218-220 ºC);[44] IR: 3415, 3053, 2924, 1617, 1451, 1342, 1256, 1216, 1093, 779, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.62 (br s, 2H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.37-7.20 (m, 5H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.75 (t, *J* = 7.6 Hz, 2H), 6.62 (d, *J* = 1.2 Hz, 2H), 6.52 (s, 1H), 5.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.8, 137.2, 134.2, 131.8, 129.2, 127.3, 127.1, 126.6, 126.1, 126.0, 124.8, 124.3, 121.8, 119.5, 119.1, 118.4, 112.3, 55.2.

3,3'-Bis(indolyl)(thiophen-2-yl)methane **(3m).** Yield: 63%, red solid, M.P. 182-184 ºC (Lit. 185-188 ºC);[44] IR: 3415, 2924, 2853, 1457, 1339, 1218, 1095, 1011, 854, 743, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 2H, NH), 7.42 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.29-7.27 (m, 3H), 7.09 (t, *J* = 7.6 Hz, 2H), 6.86-6.83 (m, 2H), 6.76 (s, 2H), 6.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 137.9, 137.1, 128.8, 128.7, 128.3, 127.9, 127.4, 126.5, 119.8, 119.4, 109.8, 49.9, 40.3.

3,3'-Bis(indolyl)(pyridine-4-yl)methane **(3n).** Yield: 65%, brown solid, M.P. 159-161 ºC (Lit. 160-162 ºC);[44] IR: 3407, 3168, 3057, 2974, 2923, 1596, 1457, 1417, 1338, 1241, 1013, 802, 744 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ 10.19 (br s, 2H, NH), 8.51 (t, *J* = 5.2 Hz, 2H), 7.47-7.43 (m, 4H), 7.05-6.99 (m, 7H), 6.76-6.72 (m, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 156.4, 149.8, 138.3, 128.3, 125.8, 122.4, 121.9, 119.2, 112.3, 49.1.

3,3'-Bis(indolyl)hexane **(3o).** Yield: 45%, white solid, M.P. 69-71 ºC (Lit. 70-72 ºC);[24] IR: 3413, 2925, 2854, 1740, 1453, 1343, 1217, 1092, 1010, 740cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (br s, 2H, NH), 7.68 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.22-7.18 (m, 2H), 7.13-7.09 (m, 2H), 6.87 (d, *J* = 2.0 Hz, 2H), 4.52 (t, *J* = 7.2 Hz, 1H), 2.68-2.63 (m, 2H), 2.29-2.20 (m, 2H), 1.46-1.33 (m, 2H), 1.14-1.11 (m, 2H), 0.94 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 129.5, 128.4, 127.0, 121.4, 120.1, 119.4, 118.7, 111.0, 45.8, 35.7, 33.7, 31.8, 27.8, 22.5, 14.0.

3,3'-Bis(indolyl)octane **(3p).** Yield: 48%, yellow solid, M.P. 118-120 ºC (Lit. 119.8-120.6 ºC);[54] IR: 3415, 2925, 2854, 1629, 1455, 1337, 1221, 1095, 1012, 742cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 2H, NH), 7.53 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 6.4 Hz, 2H), 6.98-6.93 (m, 4H), 4.39 (t, *J* =7.6 Hz, 1H), 2.17-2.06 (m, 2H), 1.22-1.16 (m, 10H), 0.79 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 127.2, 121.7, 121.5, 120.6, 119.7, 118.9, 111.1, 35.9, 34.0, 32.0, 29.8, 29.4, 28.4, 22.7, 14.2.

3,3'-Bis(5-nitro-indolyl)phenylmethane **(4a).** Yield: 75%, pale yellow, M.P. 294-296 ºC (Lit. 295-297 ºC);[54] IR: 3306, 2923, 1623, 1514, 1471, 1322, 1088, 738, 698 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 10.91 (br s, 2H, NH), 8.37 (m, 2H), 8.02-8.00 (m, 2H), 7.59 (d, *J* = 9.2 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25-7.19 (m, 1H), 7.12 (m, 2H), 6.24 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 144.3, 141.8, 140.9, 129.2, 128.3, 127.3, 127.0, 121.8, 117.6, 117.1, 112.6, 40.2.

3,3'-Bis(5-bromo-indolyl)phenylmethane **(4b).** Yield: 79%, white solid, M.P. 244-246 ºC (Lit. 246-248 ºC);[37] IR: 3247, 2919, 2849, 1609, 1462, 1260, 1097, 884, 797, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (br s, 2H, NH), 7.39 (s, 2H), 7.21-7.13 (m, 9H), 6.57 (s, 2H), 5.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 135.4, 128.6, 128.5, 128.2, 126.3, 124.8, 124.5, 121.8, 118.6, 112.7, 112.2, 38.8.

3,3'-Bis(5-methoxy-indolyl)phenylmethane **(4c).** Yield: 84%, white solid, M.P. 213-216 ºC (Lit. 218-220 ºC);[37] IR: 3414, 2925, 1622, 1583, 1483, 1451, 1208, 1170, 1041, 926, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br s, 2H, NH), 7.27-7.25 (m, 2H), 7.21-7.11 (m, 5H), 6.75 (d, *J* = 2.8 Hz, 1H), 6.72-6.71 (m, 3H), 6.57 (s, 2H), 5.68 (s, 1H), 3.59 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 143.9, 131.9, 128.7, 128.2, 127.5, 126.1, 124.5, 119.3, 111.9, 111.7, 102.0, 55.9, 40.3.

***3,3'-Bis(5-benzyloxy-indolyl)phenylmethane* (4d).** Yield: 85%, Pink solid, M.P. 68-70 ºC; IR: 3424, 3031, 2924, 1622, 1584, 1482, 1454, 1217, 1186, 1028, 800, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (br s, 2H, NH), 7.38-7.20 (m, 18H), 6.91-6.89 (m, 3H), 6.58 (d, *J* = 2.4 Hz, 2H), 5.71 (s, 1H), 4.92 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 143.9, 137.6, 132.0, 128.7, 128.6, 128.5, 128.3, 127.7, 127.5, 126.2, 124.6, 119.2, 112.6, 111.8, 103.5, 70.9, 40.3; HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{30}N_2O_2$: 535.2380; found: 535.2369.

***3,3'-Bis(2-phenyl-indolyl)phenylmethane* (4e).** Yield: 78%, white solid, M.P. 271-273 ºC (Lit. 272-274 ºC);[24] IR: 3405, 2925, 2854, 1603, 1453, 1308, 1030, 745, 700 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ 10.42 (br s, 2H), 7.44-7.37 (m, 6H), 7.29-7.20 (m, 11H), 7.08-7.02 (m, 4H), 6.73 (t, *J* = 7.2 Hz, 2H), 6.17 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 146.9, 137.7, 136.6, 134.2, 130.0, 129.8, 129.2, 129.1, 128.1, 126.9, 122.4, 122.1, 119.7, 115.9, 111.8, 41.3.

***3,3'-Bis(2-methyl-indolyl)phenylmethane* (4f).** Yield: 81%, dark pink solid, M.P. 244-246 ºC (Lit. 246-248 ºC).[29] IR: 3401, 3057, 2924, 2855, 1619, 1460, 1302, 1219, 1020, 745, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (br s, 2H, NH), 7.22-7.14 (m, 7H), 6.97 (t, *J* = 6.8 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 2H), 5.94 (s, 1H), 1.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 135.1, 131.9, 129.1, 128.8, 128.1, 125.8, 120.4, 119.2, 119.0, 113.2, 109.8, 39.1, 12.3.

***3,3'-Bis(1-phenyl-indolyl)phenylmethane* (4g).** Yield: 84%, white solid, M.P. 182-183 ºC; IR: 3056, 2925, 1598, 1501, 1457, 1377, 1215, 1137, 1029, 741, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.45-7.42 (m, 9H), 7.33-7.18 (m, 8H), 7.07 (t, *J* = 7.6 Hz, 2H), 6.88 (s, 2H), 5.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 139.9, 136.5, 129.5, 128.8, 128.5, 128.4, 127.4, 126.4, 126.1, 124.2, 122.5, 120.5, 120.3, 119.8, 110.4, 40.5; HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{26}N_2$: 475.2169; found: 475.2150.

***3,3'-Bis(1-benzyl-indolyl)phenylmethane* (4h).** Yield: 87%, white solid, M.P. 135-137 ºC; IR: 3058, 3028, 2924, 1611, 1481, 1465, 1354, 1333, 1172, 1014, 797, 741, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.28 (m, 4H), 7.20-7.10 (m, 12H), 7.02 (t, *J* = 7.2 Hz, 2H), 6.94 (d, *J* = 6.4 Hz, 3H), 6.90 (t, *J* = 6.8 Hz, 2H), 6.57 (s, 2H), 5.84 (s, 1H), 5.13 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 137.7, 137.1, 128.6, 128.5, 128.1, 127.8, 127.7, 127.2, 126.3,

126.0, 121.5, 120.1, 118.8, 118.7, 109.6, 49.8, 40.1; HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{30}N_2$: 503.2482; found: 503.2460.

3,3'-Bis(1-methyl-indolyl)phenylmethane **(4i).** Yield: 83%, white solid, M.P. 201-204 ºC (Lit. 204-206 ºC);[42] IR: 2924, 2853, 1613, 1469, 1453, 1372, 1329, 1118, 738, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.33 (m, 4H), 7.29-7.17 (m, 7H), 6.98 (t, *J* = 6.8 Hz, 2H), 6.52 (s, 2H), 5.87 (s, 1H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 144.3, 137.2, 128.5, 128.1, 128.0, 127.3, 126.0, 121.3, 120.0, 118.5, 118.1, 109.1, 39.9, 32.5.

3,3'-Bis(1-ethyl-indolyl)phenylmethane **(4j).** Yield: 83%, white solid, M.P. 163-165 ºC; IR: 3055, 2977, 2934, 1613, 1469, 1355, 1219, 1156, 1015, 739, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.18 (m, 11H), 6.99 (t, *J* = 7.6 Hz, 2H), 6.59 (s, 2H), 5.88 (s, 1H), 4.06 (q, *J* = 7.6 Hz, 4H), 1.36 (t, *J* = 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 136.3, 128.7, 128.0, 127.6, 126.6, 125.9, 121.1, 120.1, 118.4, 118.2, 109.0, 40.7, 40.2, 15.4; HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{26}N_2$: 379.2169; found: 379.2155.

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Conflict of Interest:

The authors declare no conflict of interest.

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