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Synthesis of novel benzimidazole-diindolylmethane hybrid compounds within the green chemistry context

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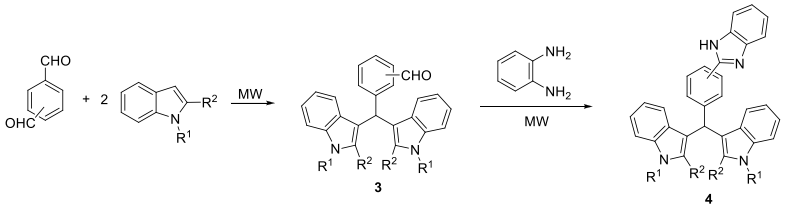
Abstract

The syntheses of novel hybrid 2-(3,3′-diindolylmethylphenyl)-1*H*-benzimidazole regioisomers under eco-friendly, solvent-less, catalyst-free conditions and using microwave energy with good to excellent yields in short reaction times were achieved.



Keywords: Benzimidazoles, diindolylmethanes, aryldialdehydes, *o*-phenylenediamine, microwave energy

Introduction

3,3'-Diindolylmethane (DIM, Figure **1A**), the major acid condensation product of indole-3-carbinol (I3C, Figure **1B**), is a promising antitumor agent derived from Brassica (Cruciferous) vegetables.[1] The anticarcinogenic effects of DIM have been shown in animal models of spontaneous, carcinogen-induced or transplanted tumors.[2,3] Because of their effectiveness and low toxicity, I3C and DIM have become widely used in adjunct therapies for recurrent respiratory papillomatosis (RRP), caused by some types of human papilloma viruses (HPVs).[4,5]

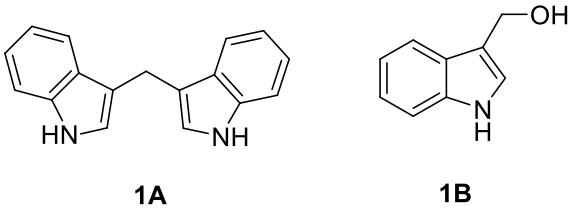


Figure 1. Structures of DIM (**1A**) and I3C (**1B**).

The benzimidazole pharmacophore is known to be an important structural core in medicinal chemistry that shows a broad spectrum of pharmacological activities. Several compounds containing the benzimidazole scaffold have been used as antiparasitic,[6] antimicrobial,[7] antitumor,[8] and antihistaminic agents.[9]

The main methodology to synthesize DIM and its derivatives is by a condensation reaction between an indole with either aliphatic or aromatic aldehydes or ketones employing Broensted-Lowry acids[10] or Lewis acids.[11] Some of these reactions have long reaction times[12] or low yields of products.[13] Benzimidazole derivatives have usually been synthesized by classical cyclocondensation of *o*-phenylenediamines with the corresponding carboxylic acids under harsh dehydrating reaction conditions[14] or from aldehydes under oxidative conditions. Some reagents such as nitrobenzene[15] and sodium metabisulfite,[16,17] have been employed for this last purpose.

On the other hand, microwave irradiation is well known to promote the syntheses of a great variety of compounds,[18-20] where chemical reactions are accelerated because of selective absorption of microwaves by polar molecules and the coupling of these two factors under solvent-free conditions has received notable attention.[21] A literature survey reveals examples of specific reactions, which do not occur under conventional heating, but could be possible by microwave irradiation.[22]

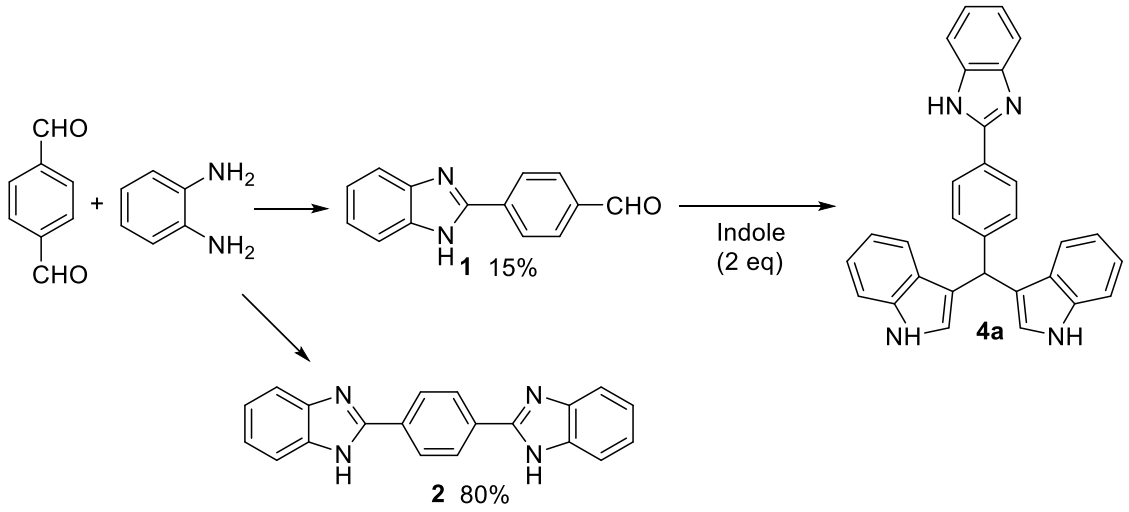
The synthesis of some DIM derivatives using catalysts such as silica sulfuric acid[23] under thermal conditions involved reactions that took a long time and provided low to moderate yields. In some cases, many by-products were formed when the reactions were carried out in aqueous medium and under controlled conditions at pH values of 1.0, 1.5, 2.5 and 7.2, respectively.[24] In recent years, diindolylmethane synthesis has taken a greener direction, such as: using infrared energy in solvent-less conditions and in presence of a bentonitic clay,[25] with ultrasound energy and aminosulfonic acid as catalyst,[26] under microwave solvent-free irradiation with Lewis acid-catalysis,[27] in ionic liquids,[28-30] with SBA-15-supported poly[4-styrenesulfonyl(perfluorobutylsulfonyl)imide] as heterogeneous Broensted-Lowry acid catalyst,[31] using Montmorillonite K-10 clay,[32,33] with nickel nanoparticles as a reusable catalyst under solvent-free conditions,[34] employing ion exchange resins,[35,36] with eutectic salts,[37] synthesis mediated by Zeokarb-225,[38] and with zeolites,[14,39] amongst others.

As a continuation of our interest in the syntheses of diindolylmethane derivatives, herein we report the synthesis of novel hybrid benzimidazole-diindolylmethane compounds using some principles of green chemistry such as the use of microwave energy source for the activation of reactions under solvent-free and catalyst-free conditions.

Results and Discussion

Following two previously established possible routes by us to synthesize 2-(4-(bis(1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole, we started with *o*-phenylenediamine and terephthalaldehyde to obtain **1** (Scheme 1), in order to generate compound **4a** by microwave irradiation but the main obtained product was **2** in 80% yield.

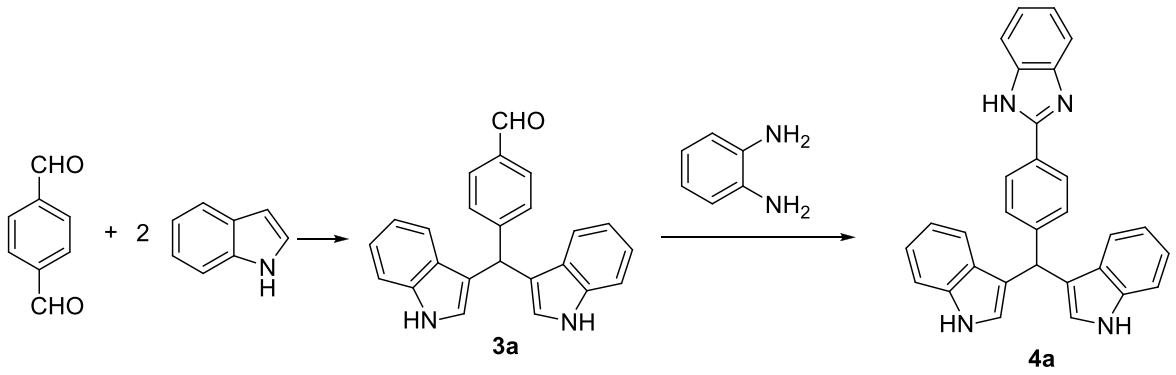
A second synthetic route, which used 1*H*-indole and terephthalaldehyde, was successful and we obtained the diindolylmethane **3a** in 96% yield in 8 min of reaction time by microwave irradiation (Scheme 2). Then, a mixture of *o*-phenylenediamine and 1 eq of **3a** were irradiated with microwave energy for 3 min and the product **4a** was generated in 88% reaction yield.



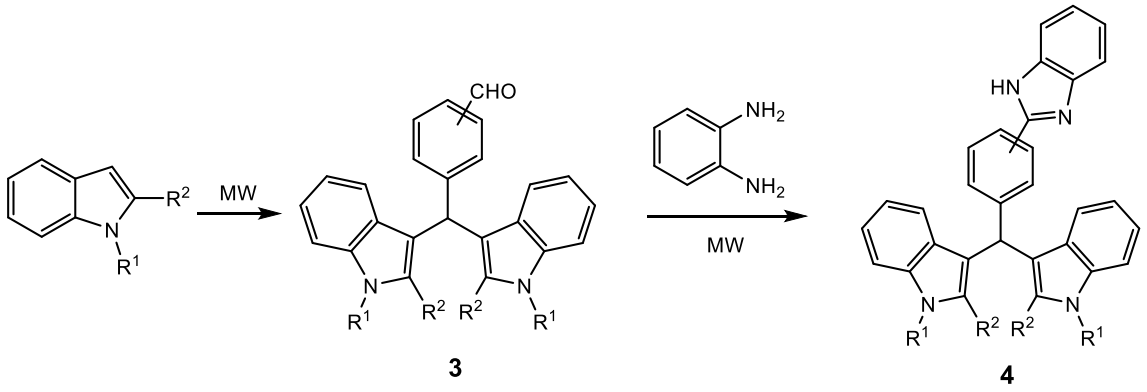
Scheme 1. Synthetic route A for **4a**.

Encouraged by this result, we realized the synthesis of **4a**-**4l** compounds, Table 1, using different indole derivatives and the 3 regioisomers of formylbenzaldehyde, according with the Scheme 3.

Compounds **3a** and **3b** had been previously reported,[40-42] apparently as byproducts when trying to synthesize the corresponding 1,4-bis[bis(2-aryl-1*H*-indol-3-yl)methyl]benzene derivatives. According to our knowledge, the synthesis of all other (formylphenyl)ldiindolylmethane and (diindolylmethyl)phenyl-benzimidazole derivatives presented here have not been reported, hence another point in the novelty of this work.



Scheme 2. Synthetic route B for **4a**.



Scheme 3. Synthesis of compounds **3** and **4**.

Table 1. Synthesis of compounds **3** and **4** by microwave irradiation

Compound	Indole	Aldehyde	% **3**[a,b]	% **4**[c,b]
a	R^1= H R^2= H	terephthalaldehyde	96	88
b	R^1= Me R^2= H	terephthalaldehyde	93	92
c	R^1= H R^2= Me	terephthalaldehyde	94	94
d	R^1= H R^2= Ph	terephthalaldehyde	96	89
e	R^1= H R^2= H	Isophthalaldehyde	94	87
f	R^1= Me R^2= H	Isophthalaldehyde	94	90
g	R^1= H R^2= Me	Isophthalaldehyde	94	89
h	R^1= H R^2= Ph	Isophthalaldehyde	93	88
i	R^1= H R^2= H	Phthalaldehyde	94	89
j	R^1= Me R^2= H	Phthalaldehyde	93	87
k	R^1= H R^2= Me	Phthalaldehyde	91	86
l	R^1= H R^2= Ph	Phthalaldehyde	94	89

[a] 8 min at 850W. [b]: Yield of isolated products. [C]: 3 min at 850W.

The structures of all the synthesized compounds were established on the basis of IR, ^{1}HNMR, ^{13}C-NMR spectral data, and molecular weights were confirmed by high resolution mass spectrometry or elemental analysis.

As an example, the ^{1}H-NMR of compound **3b** showed a singlet at δ 3.69 integrating for 6 protons for the two methyl groups attached to nitrogen atoms; two singlets appeared at δ 5.95, integrating for one proton, and δ 6.54, integrating for two protons, are due to H_{10} and for hydrogens at position 2 of the indole structure, respectively. Two triplets appeared around δ 7.00 (*J* 7 Hz) and 7.24 (*J* 7 Hz) each integrating for two protons attached at H_5 and H_6, respectively. A multiplet around δ 7.29-7.37 integrating for 4 protons is assigned to aromatic protons H_4 and H_7. Two doublets at 7.53 (*J* 9 Hz) and 7.80 (*J* 9 Hz) are due to H_{12} and H_{13} respectively. Finally, a singlet at δ 9.98 integrating for one proton is assigned to C_{15}-H. Its ^{13}C-NMR spectra showed 15 signals which corresponds to all magnetically inequivalent carbons. At δ 32.8 and δ 40.4 assigned to C_1 and C_{10} respectively. The carbonyl carbon signal appeared at δ 192.2 and the aromatic carbons appeared between δ 109.3 and δ 151.9.

On the other hand, the ^{1}H-NMR of compound **4b** showed equivalent shifts, multiplicity and number of protons on each one signal for protons of methyl groups, H_2, H_{10}, H_{12} and H_{13} than compound **3b** and the signal for proton the aldehyde is not observed. A singlet at δ 5.31 is assigned to proton attached to nitrogen of the benzimidazole moiety and two multiplets around δ 6.70-7.40 are assigned for the other aromatic protons. Its ^{13}C-NMR spectra showed 18 signals which corresponds to all magnetically inequivalent carbons.

According to all of above, we think that our methodology to form compounds **3a-l** has important green advantages over some previous mentioned synthetic methodologies for DIM derivatives, such as not use of solvent on reactions, compared with the use of dichloromethane[11,23,29,30,33,35], chloroform[13,32], acetonitrile[12,38], ionic liquids[27,28,29], not use of Broensted-Lowry and Lewis acid catalyst[11,12,13,23,25,26,30,32,33,34,37,39], resins[31,35,36,38], inert atmosphere[26], and does not require long reaction times (7-10 h[29], 24 h[35], 12-36 h[13]), with the use of microwave energy for the activation of reactions. In addition, to obtain benzimidazole compounds **4a-l** we do not require any redox reagents, such as nitrobenzene[16], sodium metabisulfite[17], neither catalyst[16,18,22] or solvent.[18] In addition, all atomic economy values are excellent, 95.10-96.72%.

Conclusions

We present straightforward synthetic methodology to generate novel hybrid diindolylmethylphenyl-benzimidazole compounds. Because these reactions are conducted in the absence of solvents and catalysts and using microwave energy for the activation of the reactions, they provide the desired products under conditions that are within the context of green chemistry.

Experimental Section

General. Melting points were determined on a Buchi B-450 device and are uncorrected. The microwave monomode oven used was a Microwave Synthesis Reactor, Monowave 300, Anton Paar, employing sealed reaction vessels and the monitoring of the reaction mixture temperature was determined with an internal probe. The ^{1}H and ^{13}C NMR spectra were obtained from a Varian EM-390 (300 MHz) apparatus. Chemical shifts are given in ppm relative to TMS for $CDCl_3$ or ppm relative to DMSO-*d*6 (Sigma-Aldrich) as mentioned in the corresponding spectral data (According to Gottlieb et al., the signals for DMSO and H_2O present in DMSO- *d*6 appear at 2.55 and 3.33 ppm, respectively).[43] The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet. Mass spectrometry (MS) was performed on a JEOL JMS-SX102A spectrometer by EI + at an ionization potential of 70 eV and with FAB + techniques. IR spectra were

obtained with a Perkin-Elmer 283B spectrophotometer, using either KBr tablet or film techniques. The following starting materials were commercially available: 1*H*-indole, *N*-methylindole, 2-methylindole, 2-phenylindole, terephthalaldehyde, isophthalaldehyde, phthalaldehyde, o-phenylenediamine (all Sigma-Aldrich).

Typical procedures

(Formylphenyl)diindolylmethanes derivatives 3a-3l. In a microwave tube indole (5.7141 mmol) and the dialdehyde (2.8570 mmol) were added; this mixture was mixed well and irradiated with microwave energy (195 °C at 850 W) for 8 min. Then, once the mixture reaction cooled at room temperature, the corresponding reaction products were extracted with acetone and the solvent was removed at reduced pressure. All products were purified by recrystallization with a mixture of ethanol/water.

(Benzimidazol-2-yl)-3,3'-diindolylmethanes 4a-4l. In a microwave tube were added a (formylphenyl) diindolylmethane (**3**) (1.4251 mmol) and *o*-phenylenediamine (1.4251 mmol). The reagents were well blended and then irradiate with microwave energy for 3 min (195 °C at 850 W). Microwave irradiation was performed at 1 minute intervals. The solids formed were dissolved in acetone and purified by preparative chromatography on silica gel using an eluting system of hexane/ethyl acetate (7:3). The products were scraped from the chromatographic plate and the solids were placed in a funnel. The silica gel was washed with hot ethanol, which was collected in a beaker in an ice bath; cold water was added for crystallization. In some cases, it was necessary to add a little cold acetone with water to achieve precipitation and the pure product was obtained as a sticky semisolid substance.

(4-Formylphenyl)(bis-(1*H*-indol-3-yl))methane (3a). (96%), colorless crystals, mp 253-256 °C (Lit[23]. 253-257 °C); IR (KBr) 3404, 3051, 2835, 1691, 1602, 1574, 1415, 1337, 783, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 5.96 (s, 1H), 6.66 (s, 2H), 6.97-7.04 (t, *J* 6 Hz, 2H), 7.25 (t, *J* 6 Hz, 2H), 7.36 (t, *J* 6 Hz, 2H), 7.50-7.52 (d, *J* 7 Hz, 2H), 7.78-7.81 (d, *J* 8 Hz, 2H), 7.97 (s, 2H, NH, D_2O), 8.01 (s, 2H) 9.97 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 40.4, 109.3, 117.1, 118.9, 119.8, 121.7, 123.6 , 127.2, 129.4, 129.9, 134.8, 137.5, 151.9, 192.2 ppm; MS(EI) *m/z* (%) 350 (M+, 100). ESI+ MS[1] Calc. 351.14943, Found 351.14995.

(4-Formylphenyl)(bis(1-methyl-1*H*-indol-3-yl))methane (3b). (93%), colorless crystals, *mp* 169-171 °C (Lit.[39] 170-172 °C); IR (KBr) 3047, 2910, 2878, 1698, 1468, 1610, 1546, 788, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 3.69 (s, 6H), 5.95 (s, 1H), 6.54 (s, 2H), 7.00 (t, *J* 7 Hz, 2H'), 7.24 (t, *J* 7 Hz, 2H), 7.29-7.37 (m, 4H), 7.53 (d, *J* 9 Hz, 2H), 7.80 (d, *J* 9 Hz, 2H), 9.98 (s, H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 32.8, 40.4, 109.3, 117.1, 118.9, 119.8, 121.7, 127.2, 128.3, 129.4, 129.9, 134.8, 137.5, 151.9, 192.2 ppm. MS (EI) *m/z* (%) 378 (M^+, 100). ESI+ MS[1] Calc. 379.18104, Found 379.18068.

(4-Formylphenyl)(bis(2-methyl-1*H*-indol-3-yl))methane (3c). (94%), colorless crystals, *mp* 127-128 °C; IR (KBr) 3400, 3302, 3052, 2920, 2853, 1684, 1458, 1601, 1573, 1302, 829, 811, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.08 (s, 6H), 6.05 (s, 1H), 6.83-6.95 (m, 4H), 7.05 (t, *J* 8.1 Hz, 2H), 7.26 (d, *J* 7.5 Hz, 2H), 7.43 (d, *J* 8.1 Hz, 2H), 7.76 (d, *J* 8.1 Hz, 2H), 7.80 (s, 2H, NH, D_2O), 9.98 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.4, 39.9, 110.2, 112.0, 119.0, 120.6, 128.7, 129.7, 129.8, 132.3, 134.5, 135.2, 151.9, 192.2 ppm; MS(EI) *m/z* (%) 378 (M^+, 100). ESI+ MS[1] Calc. 379.18104, Found 379.18073.

(4-Formylphenyl)(bis(2-phenyl-1*H*-indol-3-yl))methane (3d). (96%), colorless crystals, *mp* 260-262 °C; IR (KBr) 3399, 3056, 3027, 1694, 1449,1602, 1575, 1553, 1336, 773, 733, 696 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$, TMS) δ 5.97 (s, 1H), 6.94-7.03 (m, 4H), 7.15-7.37 (m, 14H), 7.44 (t, *J* 9 Hz, 2H), 7.62-7.65 (d, *J* 9 Hz, 2H), 7.73-7.76 (d, *J* 9 Hz, 2H), 7.86 (s, 2H), 9.95 (s, 1H) ppm; ^{13}C NMR (75 MHz; $CDCl_3$, TMS) δ 39.9, 109.0, 109.2, 117.4, 118.8, 119.8, 121.6, 127.2, 127.5, 128.3, 128.9, 130.2, 134.9, 136.5, 137.5, 145.8, 192.7 ppm, MS(EI) *m/z* (%) 502 (M^+, 8). FAB+ Calc. 502.2045, Found 502.2049.

(3-Formylphenyl)(bis(1*H*-indol-3-yl))methane (3e). (94%), colorless crystals, *mp* 176-178 °C; IR (KBr) 3399, 3051, 2908, 1686, 1451, 1602, 1310, 843, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) 6.07 (s, 1H), 6.89 (t, *J* 5 Hz, 2H), 7.06 (t, *J* 6 Hz, 2H), 7.29-7.37 (m, 4H), 7.59 (d, *J* 3 Hz, 2H), 7.84 (d, *J* 9 Hz, 2H), 8.07-8.09 (d, *J* 6 Hz, 2H), 8.17 (s, 2H, NH, D_2O), 9.98 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 34.7, 108.5, 111.0, 117.4, 119.3, 119.5, 122.6, 123, 124.2, 126.5, 127.6, 130.9, 132.2, 136.5, 137.4, 192.2 ppm; MS(EI) *m/z* (%) 350 (M^+, 100). ESI+ MS[1] Calc. 351.4974, Found 351.14890.

(3-Formylphenyl)(bis(1-methyl-1*H*-indol-3-yl))methane (3f). (94%), colorless crystals, *mp* 139-142 °C; IR (KBr) 3050; 2931; 2910; 2838; 2821; 1687; 1469; 1687; 1610; 1582; 1546); 1327; 794; 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 3.70 (s, 6H, $2CH_3$), 5.97 (s, 1H), 6.53 (s, 2H'), 7.00 (t, *J* 6 Hz, 2H), 7.19-7.30 (m, 6H), 7.37 (t, *J* 6 Hz, 1H), 7.64 (d, *J* 6 Hz, 1H), 7.74 (d, *J* 6 Hz, 1H), 7.86 (s, 1H), 9.95 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 32.4, 40.3, 109.2, 109.4, 117.1, 118.9, 119.7, 121.3, 127.7, 128.4, 129.8, 134.7, 137.4, 144.5, 146.0, 192.0 ppm, MS(EI) *m/z* (%) 378 (M^+, 73). FAB+ Calc. 378.1732, Found 378.1729.

(3-Formylphenyl)(bis(2-methyl-1*H*-indol-3-yl))methane (3g). (94%), colorless crystals, *mp* 140-142 °C; IR (KBr), 3404, 3050, 2838, 1686, 1454, 1601, 1515, 1336, 792, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.12 (s, 6H, 2CH3), 6.00 (s, 1H), 6.80 (t, *J* 9 Hz, 3H), 6.90 (d, *J* 6 Hz, 2H), 6.98 (t, *J* 9 Hz, 3H), 7.23 (d, *J* 9 Hz, 2H), 7.40 (d, *J* 9 Hz, 2H), 7.70 (d, *J* 6 Hz, 2H), 9.93 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.4, 40.2, 110.2, 112.1, 119.3, 119.9, 120.6, 127.2, 128.2, 128.5, 129.2, 132.3, 134.5, 135.2, 136.8, 137.6, 192.2 ppm; MS(EI) *m/z* (%) 378 (M^+, 100). ESI+ MS[1] Calc. 379.18104, Found 379.18038.

(3-Formylphenyl)(bis(2-phenyl-1*H*-indol-3-yl))methane (3h). (93%), colorless crystals, *mp* 202-205 °C; IR (KBr) 3424, 3395, 3053, 1686, 1598, 1485, 1339, 1310, 843, 740, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 5.99 (s, 1H), 6.65-6.92 (m, *J* 6 Hz, 4H), 7.01 (t, *J* 6 Hz, 2H), 7.15-7.39 (m, 18H), 9.98 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 40.2, 109.0, 109.2, 119.8, 120.1, 121.2, 121.6, 127.2, 127.5, 128.2, 128.3, 128.9, 129.4, 129.6, 130.2, 134.9, 136.5, 137. 4, 137.4, 192.7 ppm; MS(EI) *m/z* (%) 502 (M^+, 7). ESI+ MS[1] Calc. 503.21234, Found 503.21105.

(2-Formylphenyl)(bis(1*H*-indol-3-yl))methane (3i). (94%), colorless crystals, *mp* 117-118 °C; IR (KBr) 3400, 3051, 2957, 2919, 1702, 1452, 1608, 1541, 1317, 875, 834, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 5.83 (s 1H), 6.56 (s, 2H), 6.96 (t, *J* 15 Hz, 2H'), 7.08-7.37 (m, 10H), 7.76 (s, 2H), 9.99 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 39.9, 109.9, 110.8, 116.6, 119.5, 119.7, 131.7, 123.4, 125.9, 126.8, 128.0, 128.5, 130.4, 137.7, 143.8, 193.4 ppm; MS(EI) *m/z* (%) 350 (M^+, 8). ESI+ MS[1] Calc. 350.14191, Found 350.14211.

(2-Formylphenyl)(bis(1-methyl-1*H*-indol-3-yl))methane (3j). (93%), colorless crystals, *mp* 179-181 °C; IR (KBr) 3050, 3019, 2928, 2879, 2841, 1473, 1539, 1344, 1317, 866, 828, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 3.69 (s, 6H, 2CH3), 5.95 (s, 1H), 6.53 (s, 2H), 7.00 (t, *J* 6 Hz, 2H), 7.25-7.33 (m, 6H), 7.52 (d, *J* 9 Hz, 2H), 7.78 (d, *J* 9 Hz, 2H), 9.98 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 30.9, 39.6, 110.2, 112.2, 117.6, 119.0, 120.6, 126.9, 127.6, 128.3, 129.1, 130.2, 134.5, 135.2, 137.1, 138.9, 191.8 ppm; MS(EI) *m/z* (%) 378 (M^+, 5). ESI+ MS[1] Calc. 379.18104, Found 379.17955.

(2-Formylphenyl)(bis(2-methyl-1*H*-indol-3-yl))methane (3k). (91%), colorless crystals, *mp* 218-220 °C; IR (KBr) 3279, 3050, 2931, 2870, 2827, 1687, 1468, 1609, 1583, 1327, 794, 767, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.96 (s, 6H, 2CH3), 6.00 (s, 1H), 6.87 (s, 1H), 6.93 (t, *J* 7.5 Hz, 1H), 7.13 (t, *J* 7.8 Hz, 2H), 7.33 (d, *J* 7.8 Hz, 1H), 7.40 (d, *J* 8.1 Hz, 1H), 7.53 (d, *J* 8 Hz, 2H), 7.71-7.89 (m, 6H), 9.94 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.4, 31.3, 110.6, 112.8, 118.7, 121.3, 122.8, 126.5, 127.9, 129.3, 132.2, 134.9, 136.4, 138.2, 139.1, 141.9, 191.5 ppm; MS(EI) *m/z* (%) 378 (M^+, 100). ESI+ MS[1] Calc. 378.17321, Found 378.17222.

(2-Formylphenyl)(bis(2-phenyl-1*H*-indol-3-yl))methane (3l). (94%), colorless crystals, *mp* 100-103 °C; IR (KBr) 3413, 3387, 3335, 3057,3028, 1684, 1595, 1575, 1425, 1342, 765, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 5.52 (s, 1H), 6.85 (t, *J* 9 Hz, 2H), 7.07 (t, *J* 9 Hz, 2H), 7.19-7.42 (m, 16H), 7.54 (d, *J* 9 Hz, 2H), 7.98 (s, 2H), 9.90 (s,

1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 42.9, 108.9, 111.1, 118.9, 119.9, 121.6, 123.3, 126.3, 127.5, 127.5, 128.2, 129.3, 129.8, 131.2, 133.3, 134.2, 135.2, 137.5, 138.8, 191.7 ppm; MS(FAB+) m/z (%) 503 (M^++1, 4). ESI+ MS[1] Calc. 503.21234, Found 503.21120.

2-(4-(Bis(1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole. (88%), colorless crystals, *mp* 206-208 °C; IR (KBr) 3410, 3051, 2955, 2918, 2850, 1704, 1454, 1247, 1610, 1337, 868, 805, 738 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 5.81 (s 1H), 6.39-7.27(m, H12) 7.86-8.04 (d, *J* 6 Hz, 2H), 8.01-8.29 (m 2H), 8.59 (s, 2H), 10.67 (s, 1H, NH), 10.72 (d, 1H, NH), 10.82 (s, 1H, NH), ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 41.0, 111.1, 112.1, 115.2, 118.6, 119.0, 121.6, 123.2, 125.4, 127.3, 129.4, 131.7, 136.3, 138.2, 141.5, 152.2 ppm; MS(EI) *m/z* (%) 438 (M^+, 13). ESI+ MS[1] Calc. 439.19227, Found 439.19143.

2-(4-(Bis(1-methyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4b). (92%), colorless crystals, *mp* 108-111 °C. IR (KBr) 3054, 3011, 3011, 2960, 2907, 2877, 2851, 1698, 1437, 1280, 1615, 1567, 1319, 846, 738 cm^{-1}; ^{1}H NMR (300 MHz, DMSO- d_6, ref. DMSO- d_6) δ 3.73 (s, 6H), 5.31 (s, 1H, NH), 5.94 (s, 1H), 6.38 (t, *J* 3 o 6 Hz, 2H), 6.73 (q, *J* 6 Hz, 2H), 6.88-6.97 (m, 4H), 7.33-7.50 (m, 6H), 7.89-7.92 (d, *J* 9 Hz, 2H), 8.13 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 32.7, 56.1, 108.0, 110.1, 114.9, 116.5, 117.7, 118.8, 119.6, 121.6, 127.2, 128.4, 129.0; 134.9, 135.4, 136.1, 148.4, 155.9 ppm; MS(EI) *m/z* (%) 466 (M^+, 7). FAB+ Calc. 467.2236, Found 467.2228.

2-(4-(Bis(2-methyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4c). (94%), colorless crystals, *mp* 235-237 °C; IR (KBr) 3379, 3051, 2955, 2918, 2850, 1652, 1462, 1248, 1560, 1409, 1342, 918, 869, 738 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 2.13 (s, 6H), 4.41 (s, 1H),6.40 (d, *J* 6 Hz, 2H), 6.53 (d, *J* 6 Hz, 2H), 6.71-6.74 (d, *J* 9 Hz, 2H), 6.90 (t, *J* 9 Hz, 2H), 7.21-7.23 (d, *J* 6 Hz, 3H), 7.58-7.91 (m, 4H), 8.09 (d, *J* 6 Hz, 2H), 10.75 (s, 1H, NH), 10.84 (s 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 12.8, 41.6, 110.8, 112.1, 115.2, 115.3, 118.4, 119.6, 121.3, 123.5, 125.2, 127.4, 129.4, 131.0, 131.3, 141.1, 153.9 ppm; MS(EI) *m/z* (%) 466 (M^+, 18). ESI+ MS[1] Calc. 467.22357, Found 467.22209.

2-(4-(Bis(2-phenyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4d). (89%), colorless crystals, *mp* 150-152 °C; IR (KBr) 3464, 3390, 3049, 2980, 2832, 1600, 1487, 1450, 822, 739, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 5.58 (s, 1H), 6.97-7.10 (m, 4H), 7.21-7.41 (m, 10H), 7.53-7.71 (m, 4H), 7.87 (m, 2H), 8.11-8.23 (m, 2H), 8.32 (d, *J* 9 Hz, 2H), 8.66 (d, *J* 6 Hz, 2H), 11.38 (s, 2H, NH), 11.46 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz; DMSO-d_6, ref. DMSO-d_6) δ 41.4, 108.1, 111.4, 115.8, 118.4, 118.6, 119.7, 121.7, 123.3, 125.0, 127.9, 128.8, 129.5, 129.8, 131.3, 133.1, 136.8, 138.5, 141.6, 153.1 ppm; MS(EI) *m/z* (%) 590 (M^+, 2). Elemental analysis: Calc. C, 85.40; H, 5.12; N, 9.48, Found. C, 85.38; H, 5.10; N, 9.43.

2-(3-(Bis(1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4e). (87%), colorless crystals, *mp* 195-197 °C; IR (KBr) 3512, 3383, 3361, 2955, 2918, 2850, 1620, 1590, 1466, 1248, 1210, 869, 804, 722 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 4.42 (s brd, 2H, NH), 5.75 (s, 1H), 6.36-6.39 (m, 2H), 6.49-6.52 (m, 4H), 6.88 (d, *J* 6 Hz, 2H), 7.13 (d, *J* 6 Hz, 2H), 7.20 (d, *J* 6 Hz, 2H), 7.39-7.49 (m, 4H),7.80 (d, *J* 6 Hz, 1H), 8.09 (s, 1H), 10.65 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 60.1, 110.4, 110.8, 112.7, 118.1, 119.1, 119.9, 121.6, 123.1, 126.3, 126.4, 128.6, 130.0, 132.2, 135.1, 136.7, 137.9, 144.2, 152.1 ppm; MS(EI) *m/z* (%) 438 (M^+, 2). ESI+ MS[1] Calc. 439.19227, Found 439.19143.

2-(3-(Bis(1-methyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4f). (90%), colorless crystals, *mp* 139-142 °C; IR (KBr) 3330, 3054, 3006, 2962, 2631, 2880, 2823, 1708, 1638, 1599, 1474, 1370, 883 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 3.63 (s, 3H), 3.72 (s, 3H), 5.14 (s, 1H, NH), 5.76 (s, 1H), 6.00 (d, *J* 3 Hz, 2H), 6.69 (s, 2H), 6.87-6.97 (m, 3H), 7.11-7.27 (m, 3H), 7.38 (t, *J* 9 Hz, 2H), 7.50 (s, 2H), 7.71-7.85 (m, 2H), 7.90 (s, 1H), 8.05 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 32.7, 56.1, 108.5, 110.0, 111.7, 114.9, 116.6, 117.0, 117.6, 118.4, 118.8, 119.5, 119.6, 121.3, 121.7, 122.1, 126.3, 127.3, 128.1, 128.5, 137.2, 144.6 ppm; MS(EI) *m/z* (%) 466 (M^+, 58). ESI+ MS[1] Calc. 467.22357, Found 467.22322.

2-(3-(Bis(2-methyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4g). (89%), colorless crystals, *mp* 114-116 °C; IR (KBr) 3390; 3053, 2914, 2746, 1696, 1607, 1575, 1454, 1437, 1338, 845, 802, 730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 2.10 (s, 6H), 5.17 (s, 1H, NH), 5.95 (d, *J* 9 Hz, 2H), 6.43 (s, 2H), 6.60-6.68 (q, *J* 9 Hz, 2H), 6.87 (t, *J* 9 Hz, 2H), 7.00-7.09 (m, 2H), 7.17-7.26 (m, 3H), 7.33-7.40 (m, 2H), 8.72 (d, *J* 12 Hz, 2H), 10.87 (s, 1H, NH), 10.93 (d, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 22.0, 41.6, 111.1, 112.1, 115.2, 118.6, 119.7, 121.3, 123.1, 127.4, 128.6, 129.2, 129.7, 130.2, 136.2, 137.4, 138.4, 141.3, 153.0 ppm; MS(FAB+) *m/z* (%) 467 (M^++1, 4). FAB+ Calc. 467.2236, Found 467.2228.

2-(3-(Bis(2-phenyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4h). (88%), colorless crystals, *mp* 221-224 °C; IR (KBr) 3409, 3052, 2975, 1602, 1485, 1449, 800, 739, 695 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 5.73 (s, 1H), 6.71 (t, *J* 6 Hz, 2H), 6.96 (t, *J* 6 Hz, 6H), 7.09 (m, 6H), 7.23 (d, *J* 6 Hz, 9H), 7.3 (s, 1H), 7.38-7.41 (d, *J* 9 Hz, 2H), 11.31 (s, 1H, NH), 11.41 (d, 1H, NH), 11.47 (s, 1H, NH), ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 56.4, 108.0, 111.6, 115.0, 117.3, 119.3, 121.0, 121.3, 127.2, 127.3, 128.4, 128.6, 130.1, 133.0, 134.3, 135.3, 136.6, 137.2, 146.7 ppm; MS(EI) *m/z* (%) 590 (M^+, 11). Elemental analysis: Calc. C, 85.40; H, 5.12; N, 9.48, Found. C, 85.37; H, 5.01; N, 9.44

2-(2-(Bis(1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4i). (89%), colorless crystals, *mp* 179-181 °C; IR (KBr) 3392, 3051, 2955, 2914, 2850, 1652, 1463, 1248, 1209, 804, 739 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 6.09 (s, 1H), 6.87 (t, *J* 6 Hz, 4H), 6.97-7.05 (m, 5H), 7.29-7.48 (m, 5H), 7.71 (s, 2H), 7.93 (s, 2H), 10.51 (s, 1H, NH), 11.27 (s, 1H, NH), 11.60 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 41.2, 110.6, 112.2, 115.4, 118.7, 119.9, 120.4, 121.4, 123.1, 127.4, 128.5, 129.6, 130.4, 136.1, 136.8, 138.4, 141.5, 153.4 ppm; MS(EI) *m/z* (%) 438 (M^+, 1). FAB+ Calc. 438.1844, Found 438.1835.

2-(2-(Bis(1-methyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4j). (87%), colorless crystals, *mp* 148-151 °C; IR (KBr) 3052, 2932, 2880, 1697, 1468, 1424, 1370, 1328, 790, 741 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 3.36 (s, 6H), 6.90 (s, 1H), 6.98-7.13 (t, *J* 6 Hz, 3H), 7.29-7.34 (t, *J* 6 Hz, 2H), 7.40-7.44 (t, *J* 3 Hz, 2H), 7.46-7.56 (m, 6H), 7.87 (d, *J* 6 Hz, 3H), 11.53 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 33.2, 41.4, 109.4, 112.3, 115.3, 118.4, 119.4, 120.4, 121.4, 123.1, 126.4, 127.5, 128.2, 129.3, 130.1, 136.2, 137.4, 138.2, 141.6, 153.1 ppm; MS(EI) *m/z* (%) 466 (M^+, 13). ESI+ MS[1] Calc. 467.22357, Found 467.22253.

2-(2-(Bis(2-methyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4k). (86%), colorless crystals, *mp* 225-227 °C; IR (KBr) 3436, 3385, 3357, 3225, 3051, 2921, 1627, 460, 1320, 927, 812, 739 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 2.09 (s, 6H), 5.75 (s, 1H), 6.87-6.93 (m, 4H), 7.13-7.24 (m, 9H), 7.41-7.44 (m, 3H), 10.65 (s, 2H, NH), 10.79 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 12.2, 41.4, 111.3, 112.5, 115.0, 118.8, 119.6, 120.2, 121.6, 123.7, 127.2, 128.2, 129.4, 130.6, 131.0, 136.2, 138.4, 141.2, 152.8 ppm; MS(FAB+) *m/z* (%) 467 (M^++1, 12). ESI+ MS[1] Calc. 467.22357, Found 467.22235.

2-(2-(Bis(2-phenyl-1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole (4l). (89%), colorless crystals, *mp* 127-129 °C; IR (KBr) 3327, 3059, 2975, 1745, 1604, 1486, 1450, 796, 764, 746 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ref. DMSO-d_6) δ 4.43 (s, 1H, NH), 5.85 (s, 1H), 6.39 (t, *J* 3 Hz, 2H), 6.52 (t, *J* 3 Hz, 2H), 6.70-6.80 (m, 5H), 6.84-6.92 (m, 10H), 7.02 (d, *J* 6 Hz, 2H), 7.19-7.21 (m, 5H), 10.82 (s, 1H, NH), 10.85 (d, 1H', NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, ref. DMSO-d_6) δ 41.6, 108.8, 111.1, 115.3, 118.9, 119.6, 120.3, 121.1, 123.3, 127.4, 127.7, 128.2, 128.8, 129.3, 129.6, 130.7, 133.0, 136.0, 136.8, 138.2, 141.6, 153.5 ppm; MS(FAB+) *m/z* (%) 591 (M^++1, 1). Elemental analysis: Calc. C, 85.40; H, 5.12; N, 9.48, Found. C, 85.40; H, 4.99; N, 9.37.

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Supplementary Material

Structure of synthesized compounds and IR, MS, ^{1}H NMR, ^{13}C NMR Spectra

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