Chapter 3

Persulfate Mediated Synthesis of Diindolylmethanes from Coupling of Arylacetic Acids with Indoles

3. Persulfate Mediated Synthesis of Diindolylmethanes from Coupling of Arylacetic Acids with Indoles

3.1 Introduction

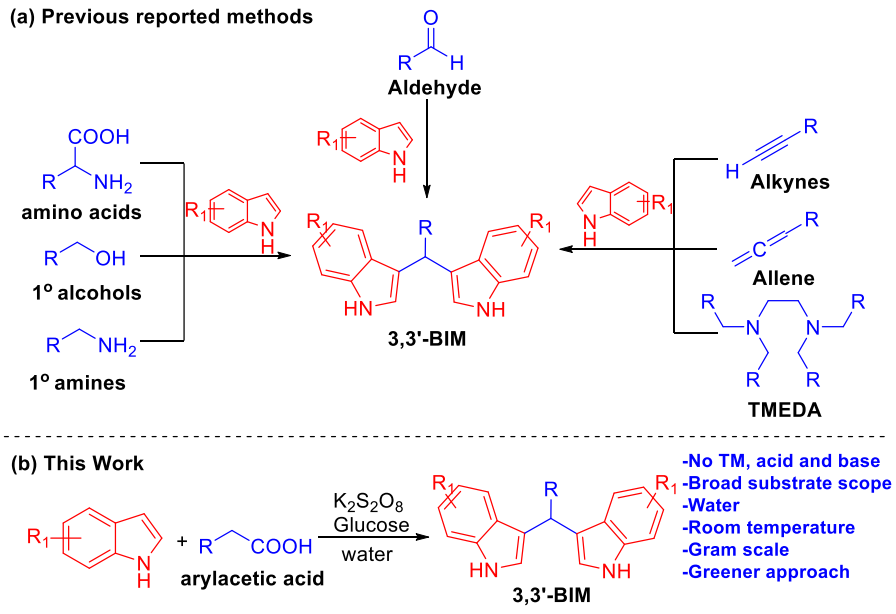
Among the various structural indole alkaloids, 3,3′-bis(indolyl)methane (3,3′-BIM) skeletons are the most common and frequently occur in terrestrial[1–4] and marine[5,6] resources. BIMs exhibit a wide range of biological applications such as anticancer,[7–13], antimicrobial,[14], antileishmanial,[15] antioxidant,[16] and anti-inflammatory[17] agents. Owing to their prevalence in natural resources and versatile biological activity, great attention has been made towards BIMs synthesis.

There are several reports for synthesis of 3,3′-BIMs using indoles with various coupling partners as depicted in scheme 3.1. The general synthetic route for the synthesis of 3,3′-BIMs involves the condensation of aldehydes/ketones with indoles using appropriate catalysts.[18–23] Alternatively, 3,3′-bis(indolyl)methanes can be synthesized from indoles using alkyne,[24] and allene[25] substrates in the presence of rhenium and platinum catalysts, respectively. There are few methods on metal based oxidative coupling of alcohols and indoles to generate BIMs.[26–31] Xiang *et al.* described I_2/phosphotungstic acid catalysed decarboxylative deaminative dual-coupling of amino acids with indoles for BIM synthesis.[32] Li *et al.* demonstrated tetramethylethylenediamine (TMEDA) as a carbon source in the presence of $CuCl_2$ in synthesis of BIM with indoles.[33] Gopalaiah *et al.* developed the synthesis of BIMs from benzylamine and indoles using iron(II) triflate catalyst.[34] Kadu *et al.* developed metal-free AcOH catalysed synthesis of 3,3′-BIM from benzylamines and indoles using chlorobenzene as a reaction medium.[35] The Same research group used Oxone in ethanol for conversion of benzylamines and indoles in to 3,3′-BIM.[36] As is evident from the available studies, most of these methods involve the use of transition metals, application of high

temperatures, and use of organic solvents as reaction media. Thus, a sustainable and environmentally friendly process to yield BIMs is highly desirable.

Potassium persulfate ($K_2S_2O_8$) is an inexpensive and commercially available, oxidative agent for various organic transformations.[37–41]. Laha *et al.* used glucose as the persulfate activator at room temperature for synthesis of diverse heterocycles.[42] Recently, we have used $K_2S_2O_8$-glucose system for synthesis of BIMs by *in situ* conversion of alcohols to their corresponding carbonyls and their subsequent condensation with indoles at room temperature in water.[40] Our group also reported $K_2S_2O_8$-glucose mediated oxidative trifluoromethylation using Langlois' reagent on the C2 position of indoles.[38] Kandasamy research group performed $K_2S_2O_8$-glucose mediated synthesis of (3)-S-arylthioindoles from Indole and thiophenols in water.[43] In continuation of our previous work in this field, we explored here the $K_2S_2O_8$-glucose mediated decarboxylative coupling of aryl acetic acid with indoles in water at room temperature. Finally, a possible mechanism is proposed for the synthesis.

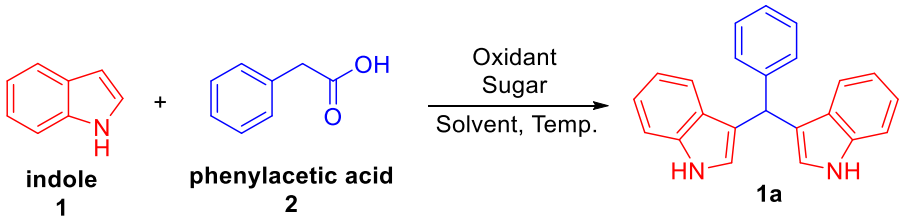
Scheme 3.1: (a) previous reported methods for synthesis of 3,3'-BIM. (b) current synthetic approach for synthesis of 3,3'-BIM.



3.2 Results and Discussion

At the outset, the reaction parameter was optimized employing indole (**1**) and phenyl acetic acid (**2**) as model substrates (Table 3.1). **1** (1 mmol) was reacted with **2** (1 mmol) in the presence of $K_2S_2O_8$ (1.2 equiv.) at room temperature in water for 12 h, which did not result in the formation of **1a** (entry 1). However, the addition of glucose (0.6 equiv.) under the same conditions gave **1a** in 54% yield (entry 2), indicating glucose as the persulfate activator. The amount of the $K_2S_2O_8$ was then increased to 2 equiv., and as a result, the yield of **1a** was improved to 78% (entry 3). However, a further increase in $K_2S_2O_8$ (3 equiv.) resulted deterioration in the yield of **1a** (entry 4). Changing the sugar from glucose to galactose, mannose, maltose or starch gave **1a** with 52-64% yields (entries 5-8). Further, we investigated the reaction with other oxidants. Ammonium persulfate [$(NH_4)_2S_2O_8$] provided **1a** in a comparatively lower yield (entry 9). The desired product **1a** was not formed with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (entry 10), and Oxone (entry 11).

Table 3.1. Optimization of the reaction condition for synthesis of BIM.[a]



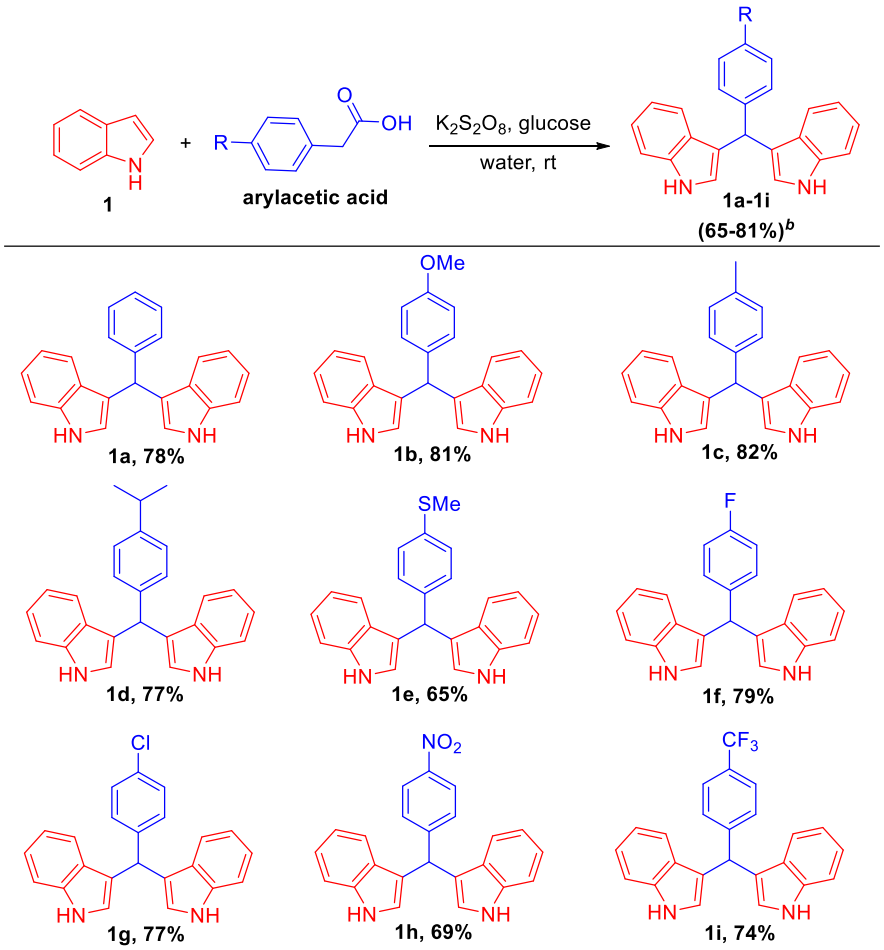
S. No.	Oxidant (equiv.)	Sugar	Solvent	%Yield[b]
1	$K_2S_2O_8$ (1.2)	-	Water	0
2	$K_2S_2O_8$ (1.2)	Glucose	Water	54
3	$K_2S_2O_8$ (2.0)	Glucose	Water	78
4	$K_2S_2O_8$ (3.0)	Glucose	Water	62
5	$K_2S_2O_8$ (2.0)	Galactose	Water	64

6	$K_2S_2O_8$ (2.0)	Mannose	Water	61
7	$K_2S_2O_8$ (2.0)	Maltose	Water	58
8	$K_2S_2O_8$ (2.0)	Starch	Water	52
9	$(NH_4)_2S_2O_8$ (2.0)	Glucose	Water	68
10[c]	DDQ (2.0)	-	ACN	N.R.[d]
11[c]	$KHSO_5$ (2.0)	-	ACN	N.R.[d]

[a]Reaction conditions: indole (1 mmol), phenyl acetic acid (1 mmol), oxidant, sugar (0.6 equiv.), solvent (4 mL), room temp. [b]Isolated yield (%). [c] 80 ^oC. [d]N.R.= no reaction.

After optimization of the protocol, we investigated the scope of aryl acetic acid as coupling partners (scheme 3.2). Aryl acetic acid substituted with electron-donating (-OMe, -Me, -*i*Pr, and -SMe) and electron-withdrawing (-F, -Cl, $-NO_2$, and $-CF_3$) groups, furnished the desired BIMs products (**1b–1i, 65-81%**) without any difficulties under the optimized reaction conditions. Electronic factors slightly influenced the yields of the desired products. Aryl acetic acids with electron-donating groups at the *para* position (**1b-1e**) resulted in the corresponding 33'-BIMs in slightly higher yields than those with electron-withdrawing groups (**1f–1i**).

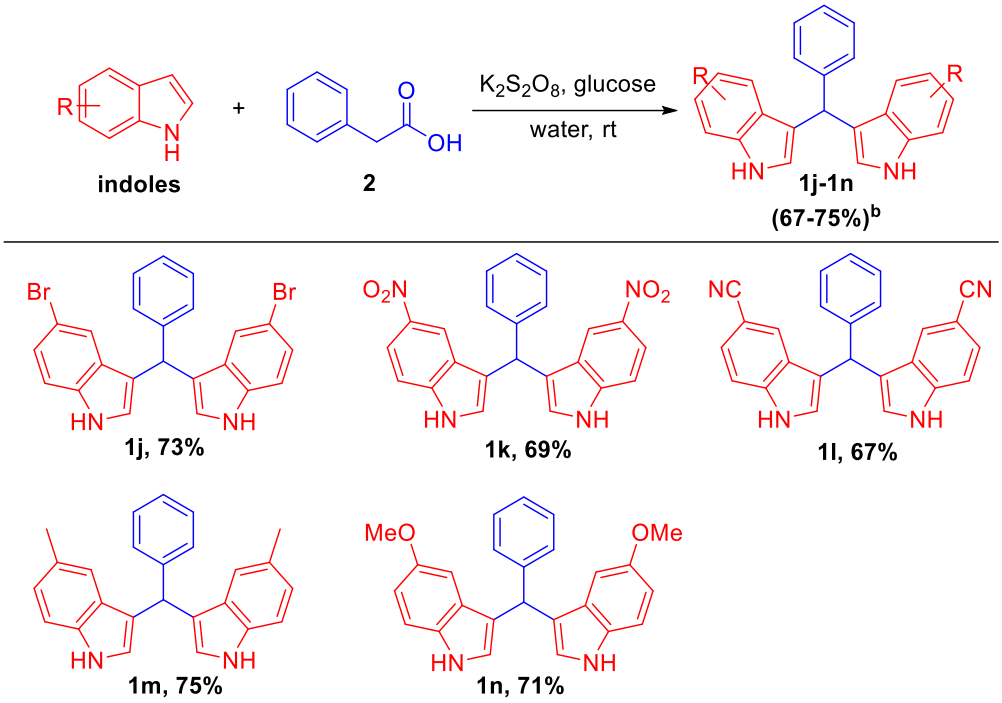
Scheme 3.2: Substrate scope with aryl acetic acids.[a]



[a]Reaction conditions: indole (1 mmol), phenyl acetic acid (1 mmol), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.), water (4 mL), room temp., 12 h. [b]Isolated yield (%).

Further, we explored the synthesis of BIMs with phenyl acetic acid and functionalized indoles under optimized conditions. Indoles bearing electron withdrawing groups (-Br, -NO_2, -CN) and electron donating groups (-Me and -OMe) were well tolerated under optimized reaction conditions with phenyl acetic acid, which resulted BIMs **1j**-**1n** (67-75%, scheme 3.3).

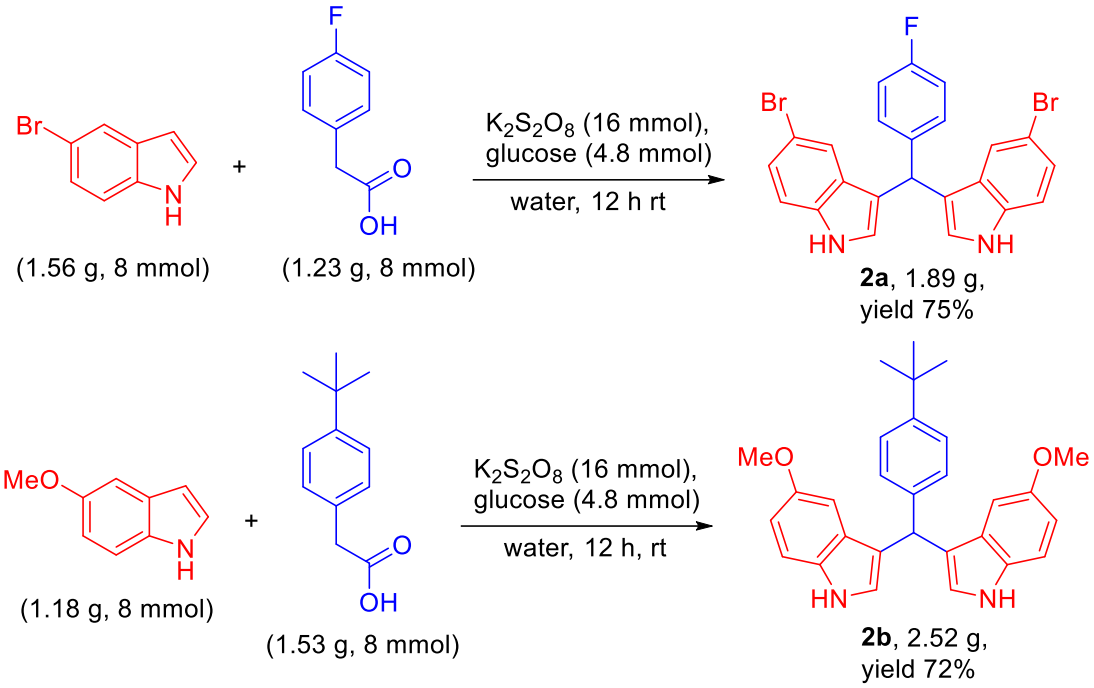
Scheme 3.3: Substrates scope with various substituted indoles.[a]



[a]Reaction conditions: indole (1 mmol), phenyl acetic acid (1 mmol), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.), water (4 mL), room temp., 12 h. [b]Isolated yield (%).

In literature, compound **2a** has been reported for anti-leishmanial activity on *Leishmania donovani* promastigotes.[15] Compound **2b** has been reported as a potent inhibitor of S. aureus, and resistant bacterial strain.[14] We have successfully demonstrated the practical application of our method in gram-scale synthesis of **2a** and **2b**. The yields of compounds **2a** and **2b** were found to be 75% and 72%, respectively (scheme 3.4).

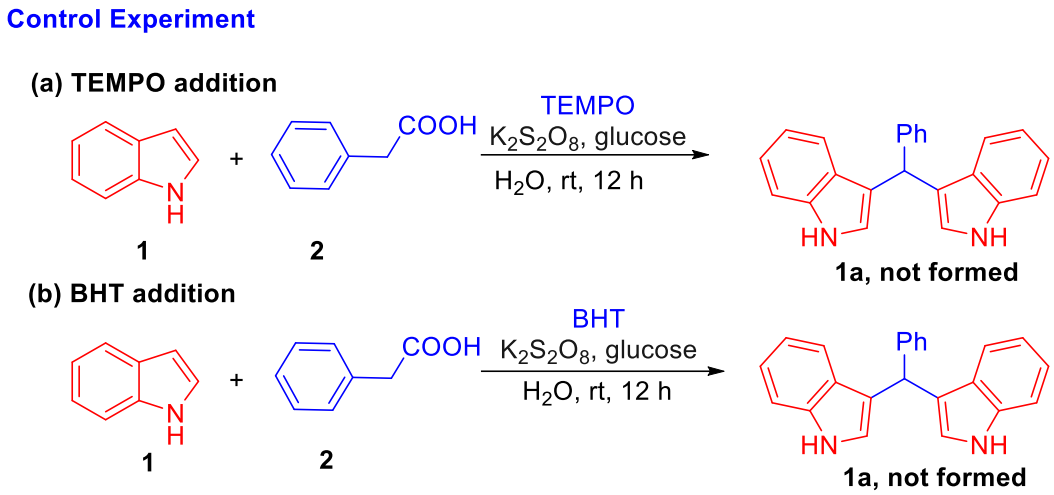
Scheme 3.4: Gram scale experiment.



[a]Reaction Conditions: indole (8 mmol), 4-fluorophenyl acetic acid (8 mmol), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.), water, room temp., 12 h. [b] indole (8 mmol), 4-*t*-butylphenyl acetic acid (8 mmol), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.), water, room temp., 12 h.

After developing the substrate scope, control experiments were performed to affirm the reaction mechanism. Compound **1a** was not formed when *2,2,6,6*-tetramethylpiperidinooxy (TEMPO) or *2,6*-di*tert*-butyl-4-methylphenol (BHT) was added to optimized reaction conditions (scheme 3.5). These results indicate that a radical mechanism is involved for synthesis of BIMs. In literature, Bhat *et al.* showed sulfate radical anion convert phenyl acetic acid to benzaldehyde via benzyl radical.[44] In our previous report, we have shown the involvement of sulfate radical anion in synthesis of bisindolylmethane from indole and aldehyde.[40]

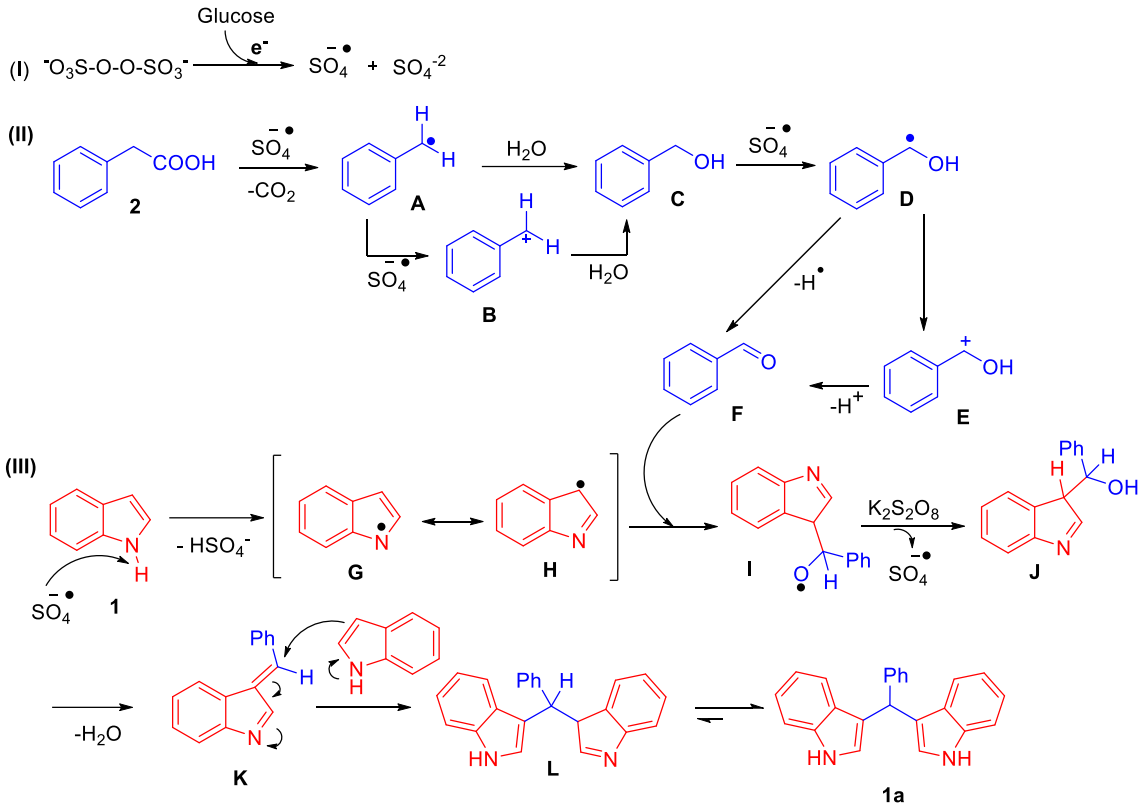
Scheme 3.5: Control experiments.



Reaction conditions: (a) 1 (1 mmol), 2 (1 mmol), TEMPO (3 equiv.), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.), water (4 mL), room temp. 12h; (b) 1 (1 mmol), 2 (1 mmol), BHT (3 equiv.), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.), water (4 mL), room temp. 12 h.

Based on inference drawn from literature report.[40,44] and control experiment, we proposed a plausible reaction mechanism as depicted in scheme 3.6. Glucose transfers one electron to potassium persulfate which generate $SO_4^{\cdot-}$ radical by cleavage at peroxy linkage (I, scheme 3.6). Sulfate radical anion reacted with **2,** which generates benzyl radical (**A**) by carbon dioxide elimination. $SO_4^{\cdot-}$ further oxidizes **A** to benzyl carbocation (**B**) via one electron oxidation. This reactive species reacts with water to form benzyl alcohol (**C**). Persulfate further oxidizes **C** to benzaldehyde (**F**) via intermediates **D** and **E** (**II,** scheme 3.6). Also, $SO_4^{\cdot-}$ attacks the **1** to form nitrogen radical **G**. 1,3-*H* shift and isomerization in **G** forms carbon radical **H**, which reacts with **F** to generate oxygen radical **I**. Intermediate **I** can react with persulfate and water to generate **J**. β-elimination of **J** generates intermediate **K**. Another molecule of **1** then reacts with **K** to form **L** that gradually isomerizes to give final product **1a** (III, scheme 3.6).[14]

Scheme 3.6: Possible reaction mechanism.



3.3 Conclusion

Herein, we have reported an efficient and ecologically sound method for the preparation of 3,3′-bis(indolyl)methanes from indoles and aryl acetic acids. Aryl acetic acids were converted to corresponding benzyl alcohols in presence of $K_2S_2O_8$ / glucose in water, which then underwent oxidation to the benzaldehyde and condensation with indoles to produce bisindolylmethanes. The reaction has been carried out at ambient temperatures in metal-free conditions, yielding a wide range of BIM derivatives with fair yields. This method shows versatile functional group tolerance and mechanistic exploration led to the finding that this method involved the occurrence of a radical pathway.

3.4 Experimental Section

3.4.1 General procedure for the synthesis of bisindolylmethanes 1a-1n: indoles (1 mmol), phenyl acetic acid (2, 1 mmol), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.) and water (4 mL) were added to the reaction vessel equipped with a magnetic stirrer bar, and the reaction vessel was carried out at room temperature for 12 h. TLC monitored the progress of the reaction. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude residue, which was then purified by column chromatography on silica gel (60-120 mesh) using hexane/ethyl acetate as an eluent to afford the product.

3.4.2 Gram-scale procedure for the synthesis of compound 2a: 5-bromo indole (8 mmol), 4- fluoro phenyl acetic acid (8 mmol), $K_2S_2O_8$ (16 mmol.), glucose (4.8 mmol) and water (30 mL) were added to a reaction vessel equipped with a magnetic stirrer bar, and the reaction vessel was carried out at room temperature for 12 h. TLC monitored the progress of the reaction. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude residue, which was then purified by column chromatography on silica gel (60-120 mesh) using hexane/ethyl acetate as an eluent to afford **2a** (1.89 g, 75%).

3.4.3. Gram-scale procedure for the synthesis of compound 2b: 5-bromo indole (8 mmol), 4- isopropyl phenyl acetic acid (8 mmol), $K_2S_2O_8$ (16 mmol.), glucose (4.8 mmol) and water (30 mL) were added to an oven-dried reaction vessel equipped with a magnetic stirrer bar, and the reaction vessel was carried out at room temperature for 12 h. TLC monitored the progress of the reaction. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The organic phase was dried over

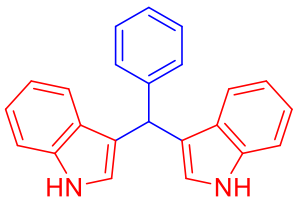
anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude residue, which was then purified by column chromatography on silica gel (60-120 mesh) using hexane/ethyl acetate as an eluent to afford **2b** (2.52 g, 72%).

3.4.4. Control experiments

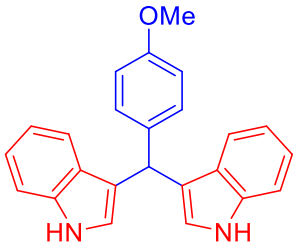
***3.4.4.1 TEMPO addition in the general procedure*:** A screw cap vial was charged with indole (1 mmol), phenyl acetic acid (1 equiv.), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.) and TEMPO (3 equiv.) in water (4 mL). The resulting solution was stirred at room temperature for 12 h. We have not observed formation of product **1a**.

***3.4.4.2 BHT addition in the general procedure*:** A screw cap vial was charged with indole (1 mmol), phenyl acetic acid (1 equiv.), $K_2S_2O_8$ (2 equiv.), glucose (0.6 equiv.) and BHT (3 equiv.) in water (4 mL). The resulting solution was stirred at room temperature for 12 h. We have not observed formation of product **1a**.

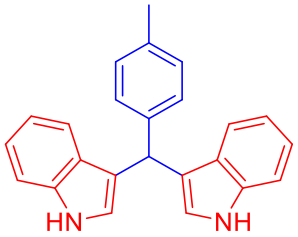
3.5. Analytical Data of synthesized compounds



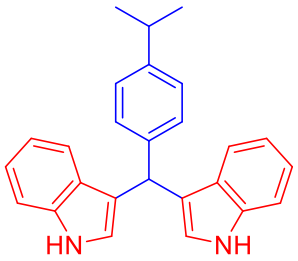
3,3'-(Phenylmethylene)bis(1H-indole) (**1a**): Brown solid (mp: 146–148 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 2H), 7.44–7.19 (m, 11H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.64 (s, 2H), 5.92 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 136.7, 128.7, 128.2, 127.1, 126.2, 123.7, 121.9, 119.9, 119.7, 119.2, 111.1, 40.2. HRMS (EI) m/z: [M-H$^+$] calculated for $C_{23}H_{17}N_2$: 323.1386, and found 323.1394.



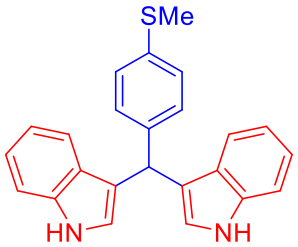
3,3′-((4-Methoxyphenyl)methylene)bis(1H-indole) (**1b**): Reddish brown amorphous solid (mp: 187–189 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 1H), 7.22 (s, 1H), 7.15 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 2H), 6.99 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 2H), 6.85–6.70 (m, 2H), 6.70–6.59 (m, 2H), 5.82 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 136.7, 136.2, 129.6, 127.1, 123.6, 121.9, 120.0, 119.9, 119.2, 113.6, 111.0, 55.2, 39.3. HRMS (ESI): calculated for $C_{24}H_{20}N_2O$ $[M + H]^+$ 353.1578, found 353.1576.



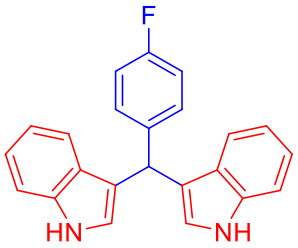
3,3′-(p-Tolylmethylene)bis(1H-indole) (**1c**): Orange amorphous solid (mp: 96–97 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.18–7.11 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.99 (td, *J* = 7.1, 3.5 Hz, 2H), 6.61 (dd, *J* = 2.2, 0.7 Hz, 2H), 5.83 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 136.7, 135.5, 128.9, 128.6, 127.1, 123.6, 121.9, 119.9, 119.9, 119.2, 111.0, 39.8, 21.1. HRMS (ESI): calculated for $C_{24}H_{21}N_2$ $[M + H]^+$ 338.1694, found 338.1705.



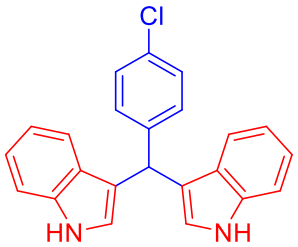
3,3′-((4-Isopropylphenyl)methylene)bis(1H-indole) (1d): Red solid (mp: 154–156 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.20–7.15 (m, 4H), 7.04–7.02 (m, 2H), 6.67 (d, *J* = 1.8 Hz, 2H), 5.89 (s, 1H), 2.94–2.87 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 141.2, 136.7, 128.5, 127.1, 126.2, 123.6, 121.9, 120.0, 120.1, 111.0, 39.7, 33.7, 24.1. HRMS (EI) m/z: [M-H^+] calculated for $C_{26}H_{23}N_2$: 363.1856, and found 363.1880.



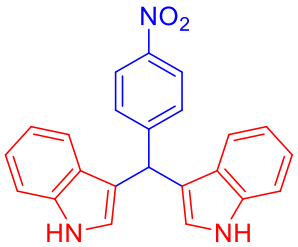
3,3′-((4-(Methylthio)phenyl)methylene)bis(1H-indole) (**1e**): Orangish brown amorphous solid (mp: 108–110 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 1.6 Hz, 1H), 7.24 (s, 1H), 7.16 (dt, *J* = 7.2, 3.3 Hz, 4H), 7.00 (dd, *J* = 7.9, 7.1 Hz, 2H), 6.61 (s, 2H), 5.83 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 136.7, 135.5, 129.3, 127.0, 126.7, 123.6, 122.0, 119.9, 119.5, 119.3, 111.1, 39.7, 16.0. HRMS (ESI): calculated for $C_{24}H_{20}N_2S$ $[M + H]^+$ 369.1414, found 369.1425.



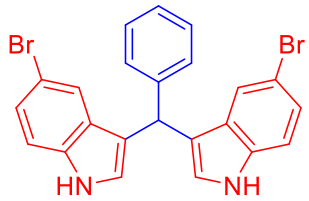
3,3′-((4-Fluorophenyl)methylene)bis(1H-indole) (**1f**): Dark brown amorphous solid (mp: 108–110 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.34 (dd, *J* = 11.5, 8.1 Hz, 4H), 7.29–7.25 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 2H), 6.96–6.89 (m, 2H), 6.63–6.57 (m, 2H), 5.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, J^1 = 243.5 Hz), 139.7 (d, J^4 = 3.0 Hz), 136.7, 130.1 (d, J^3 = 7.8 Hz), 126.9, 123.6, 122.1, 119.9, 119.6, 114.9 (d, J^2 = 21.2 Hz), 111.1, 39.5. HRMS (ESI): calculated for $C_{23}H_{17}FN_2$ $[M+H]^+$ 341.1409, found 341.1454.



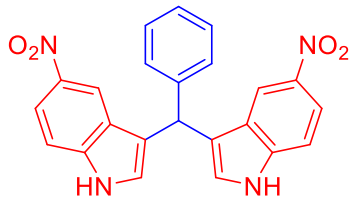
3,3′-((4-Chlorophenyl)methylene)bis(5-bromo-1H-indole) (1g): Maroon semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.45 (d, *J* = 0.7 Hz, 2H), 7.26–7.19 (m, 8H), 6.62 (d, *J* = 1.4 Hz, 2H), 5.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 135.3, 132.2, 129.9, 128.6, 128.4, 125.1, 124.7, 122.1, 118.5, 112.8, 112.6, 39.3. HRMS (ESI): calculated for $C_{23}H_{16}N_2ClBr_2$ $[M+ H]^+$ 512.9324, found 512.9369.



3,3′-((4-Nitrophenyl)methylene)bis(6-chloro-1H-indole) (1h): Brown semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 17.5, 10.7 Hz, 4H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.37 (s, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.98 (dd, *J* = 8.5, 1.3 Hz, 2H), 6.65 (d, *J* = 2.0 Hz, 2H), 5.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 146.7, 137.0, 129.4, 128.4, 125.1, 124.2, 123.8, 120.5, 120.3, 118.1, 111.3, 40.0. HRMS (ESI): calculated for $C_{23}H_{17}N_3O_2$ $[M + H]^+$ 368.1394, found 368.1396.

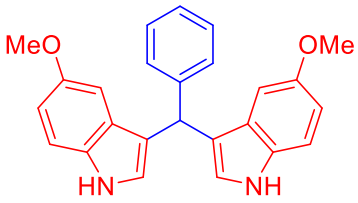


3,3′-(Phenylmethylene)bis(5-bromo-1H-indole) (1j): Red solid (mp: 232–234 °C) ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.08 (d, *J* = 2.0 Hz, 2H), 7.42 (d, *J* = 1.5 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.32–7.28 (m, 4H), 7.22–7.16 (m, 3H), 6.88 (d, *J* = 2.5 Hz, 2H), 5.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 140.4, 133.5, 133.3, 131.41, 130.4, 128.8, 126.4, 126.3, 122.8, 118.9, 116.2, 44.2. HRMS (EI) m/z: $[M\text{-}H^+]$ calculated for $C_{23}H_{15}Br_2N_2$: 476.9597, and found 476.9604.

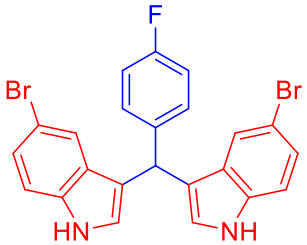


3,3′-(Phenylmethylene)bis(5-nitro-1H-indole) (1k): Yellow solid (mp: 277–279 °C). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 11.69 (s, 2H), 8.31 (d, *J* = 2 Hz, 2H), 7.99–7.96 (m, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.33–7.30 (m, 2H), 7.23–7.20 (m, 1H), 7.13 (d, *J* = 1.5 Hz, 2H), 6.19 (s, 1H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ

144.2, 140.6, 140.2, 128.9, 128.6, 128.0, 126.9, 126.2, 121.0, 117.1, 116.7, 112.6, 38.9. HRMS (EI) m/z: [M-H$^+$] calculated for $C_{23}H_{15}N_4O_4$: 411.1088, and found 411.1093.

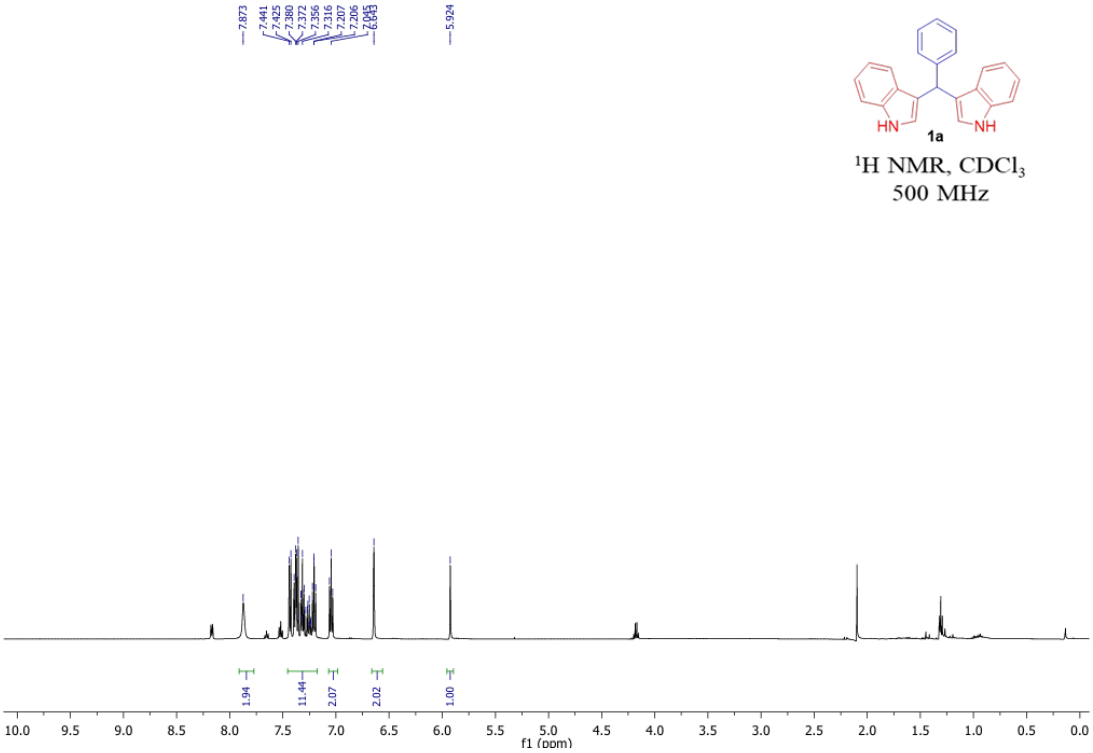


3,3′-(Phenylmethylene)bis(5-methoxy-1H-indole) (1n): Red solid (mp: 216–218 °C). ^{1}H NMR (500 MHz, DMSO- d_6) δ 10.61 (s, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.27–7.23 (m, 4H), 7.17–7.14 (m, 1H), 6.81 (d, J = 2.0 Hz, 2H), 6.70–6.68 (m, 4H), 5.71 (s, 1H), 3.57 (s, 6H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 153.1, 145.3, 132.2, 128.7, 128.5, 127.4, 126.3, 124.7, 118.1, 112.6, 111.0, 101.9, 55.7, 40.07. HRMS (EI) m/z: [M-H$^+$] calculated for $C_{25}H_{21}N_2O_2$: 381.1598, and found 381.1603.

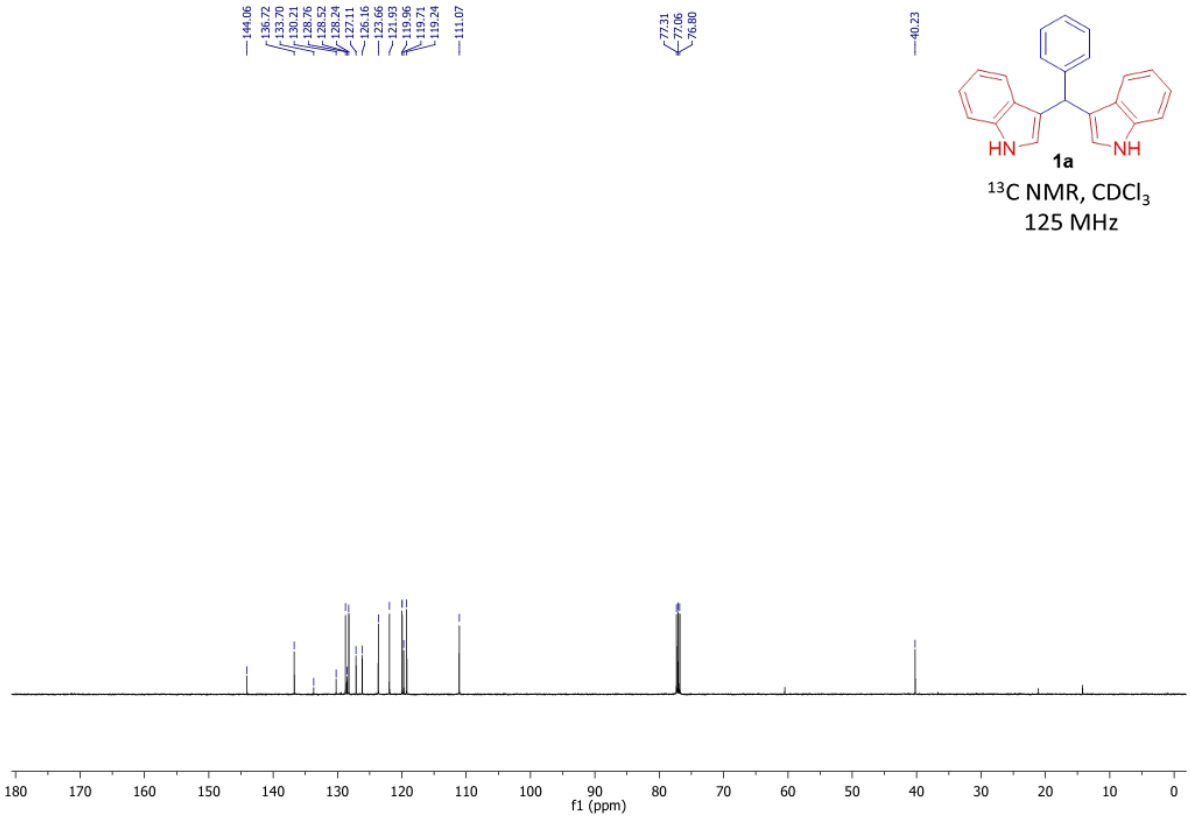


3,3′-((4-Fluorophenyl)methylene)bis(5-bromo-1H-indole) (**2a**). Red semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 7.45 (s, 2H), 7.25–7.21 (m, 6H), 6.97 (t, J = 8.6 Hz, 2H), 6.61 (s, 2H), 5.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J = 244.6 Hz), 138.7 (d, J = 3.0 Hz), 135.3, 129.9 (d, J = 7.9 Hz), 128.5, 125.1, 124.7, 122.2, 118.9, 115.2 (d, J = 21.3 Hz). 112.7, 112.6, 39.1. HRMS (ESI): calculated for $C_{23}H_{16}N_2Br_2F$ [M + H]$^+$ 496.9620, found 496.9664.

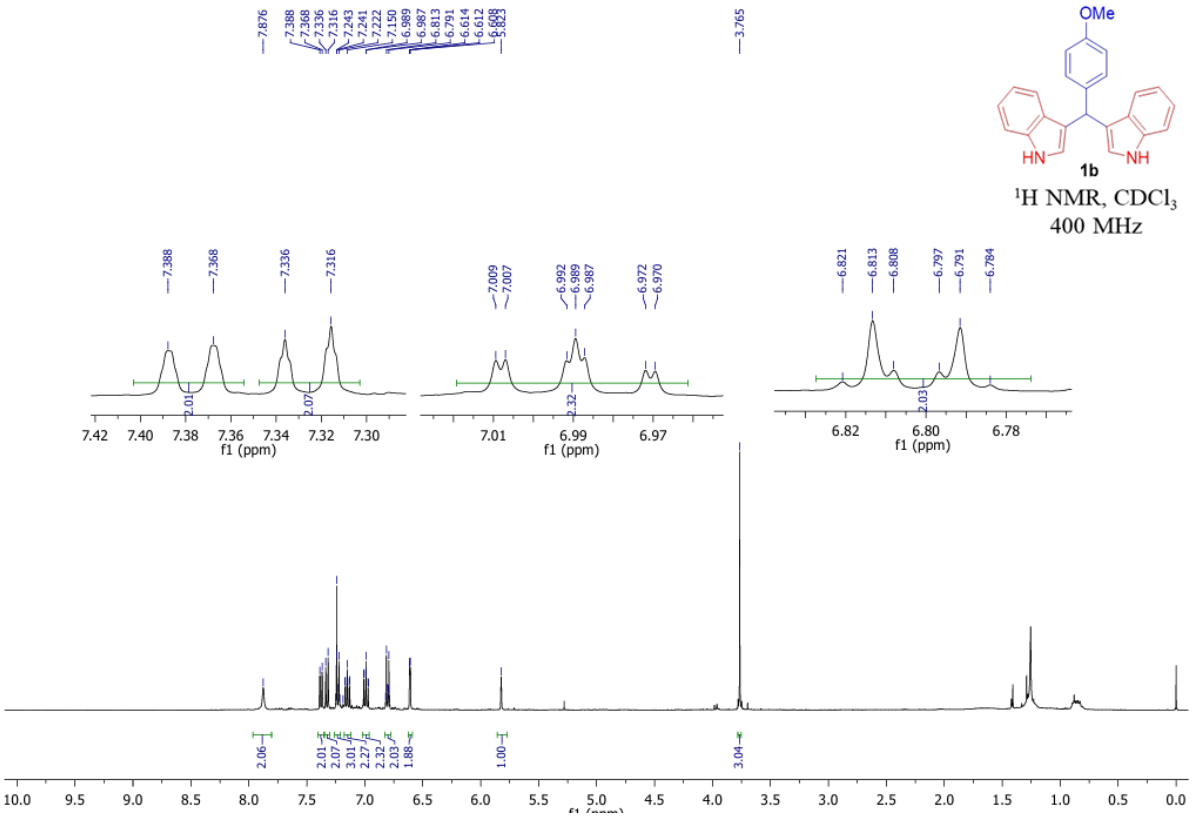
3.6. Spectral Data of Synthesized Products



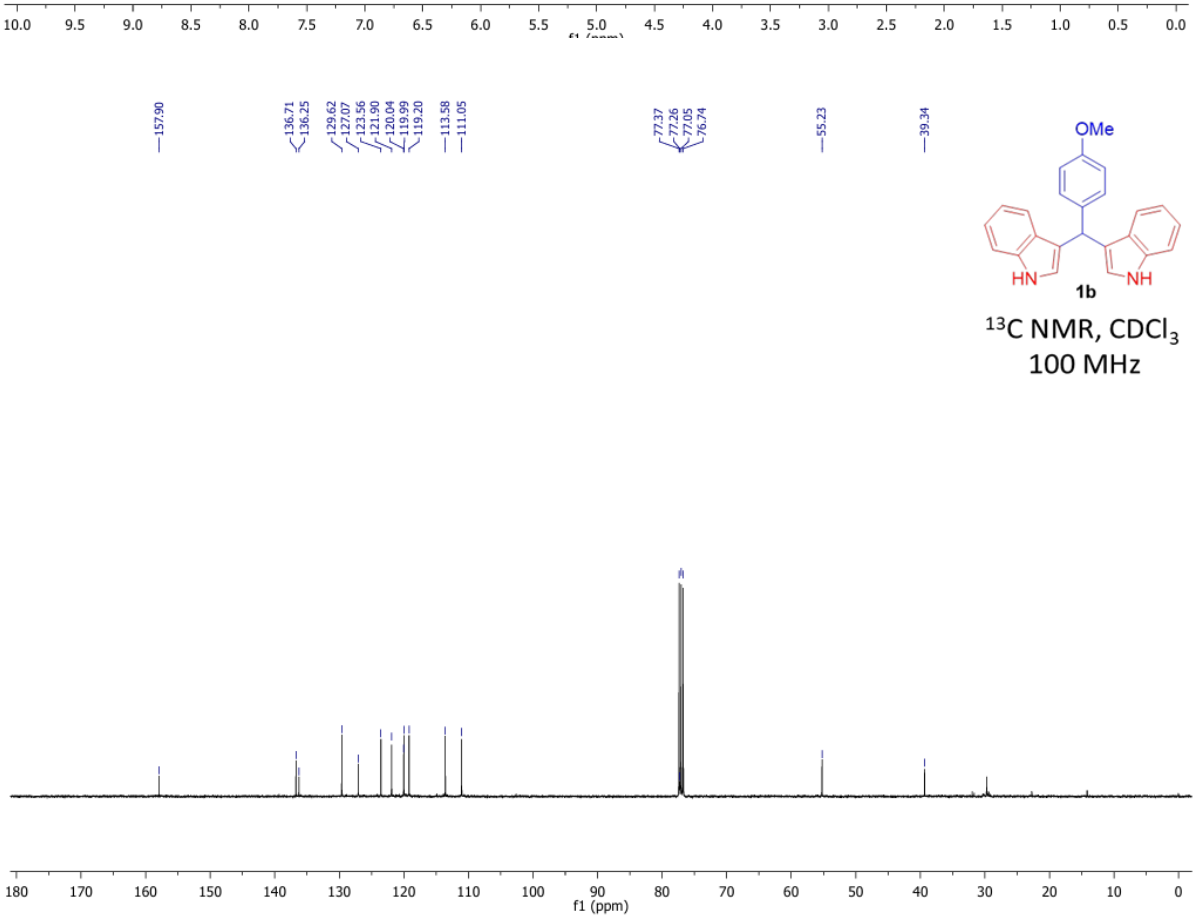
^{1}H NMR, $CDCl_3$
500 MHz



^{13}C NMR, $CDCl_3$
125 MHz



^{1}H NMR, $CDCl_3$
400 MHz



^{13}C NMR, $CDCl_3$
100 MHz

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