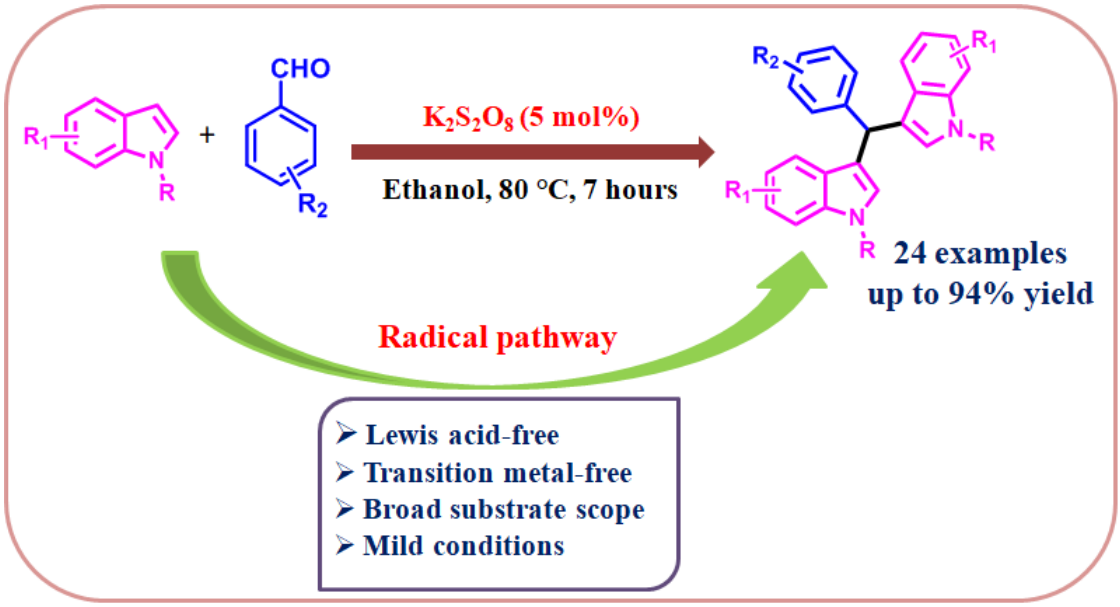
Chapter 2

Potassium Peroxodisulfate Catalyzed Convenient Synthesis of Bis(indolyl)methanes *via* Radical Path



Abstract: This chapter describes the utilization of potassium peroxodisulfate ($K_2S_2O_8$) as an efficient catalyst for the synthesis of pharmaceutically active bis(indolyl)methanes (BIMs) by the reaction of indoles with aldehydes under the ambient conditions. This protocol exhibits a wide range of sterically and electronically diverse substrate scope with good to excellent yield (up to 94%) of the desired product without affecting the bromo, chloro, iodo, nitro, methoxy, and hydroxyl groups. The experimental observation indicates a free radical triggered pathway for this methodology.

2.1 Introduction

Among the different indole-containing molecules, bis(indolyl)methanes (BIMs) are highly attractive because of their wide range of applications in the field of pharmaceutical and agrochemical industries, and material sciences [1]. The derivatives of BIM promote estrogen metabolism, inducing apoptosis in cancer cells of the human, act as an anti-oxidant, anti-bacterial, anti-fungal, anti-inflammatory agent, used in the treatment of chronic fatigue and tuberculosis, etc. (Figure **2.1**) [2-7]. Diverse methodologies are available in the literature for the synthesis of BIM from indole and carbonyl compounds in the presence of different catalysts such as zirconium(IV) chloride [8], zeolite [4], iron(III) chloride along with sodium dodecyl sulfate [9], sulphamic acid [2], molecular bromine [10], oleic acid [11], tungstosilicic acid [12], graphene oxide [13], ammonium niobium oxalate [14], etc. Metal nanoparticles catalyzed methodologies are also available in the literature for the synthesis of BIM. Zolfigol *et al.* first introduced silica-coated iron oxide magnetic nanoparticles stabilized by urea-based ionic liquid for the synthesis of BIM [3]. Carbon nanotubes that were grafted with sulfonated polyacrylamide [15], nickel nanoparticles supported on germanophosphate glass [16] were other examples found in the literature to synthesize BIM. These reported methodologies are mainly based on either Lewis acid catalysts or transition metal catalysts. Lewis acids are usually hygroscopic and hence extra precautions are required [17]. Moreover, in the case of nitrogen-containing substrates, Lewis acids are trapped by substrates resulting in the requirement of a high amount of the catalyst [17]. Alternatively, transition metal catalysts are expensive, generate toxic wastes and in some cases, the reaction requires harsh conditions [18]. In this regard development of a new methodology for the synthesis of BIM using easily available and cheap catalyst under mild reaction conditions is highly desirable. In our work, we have developed an alternative methodology for the synthesis of BIM in ambient conditions using potassium peroxodisulfate ($K_2S_2O_8$) as the catalyst (Scheme **2.1**). $K_2S_2O_8$ is a readily available inexpensive laboratory reagent that generates free radicals easily. This protocol results in a good yield of the desired product with low catalyst loading.

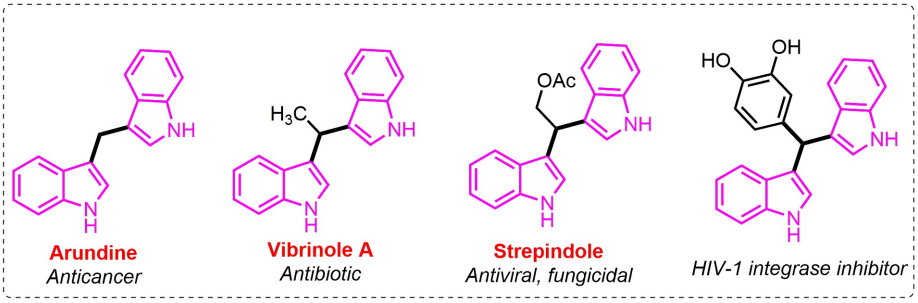
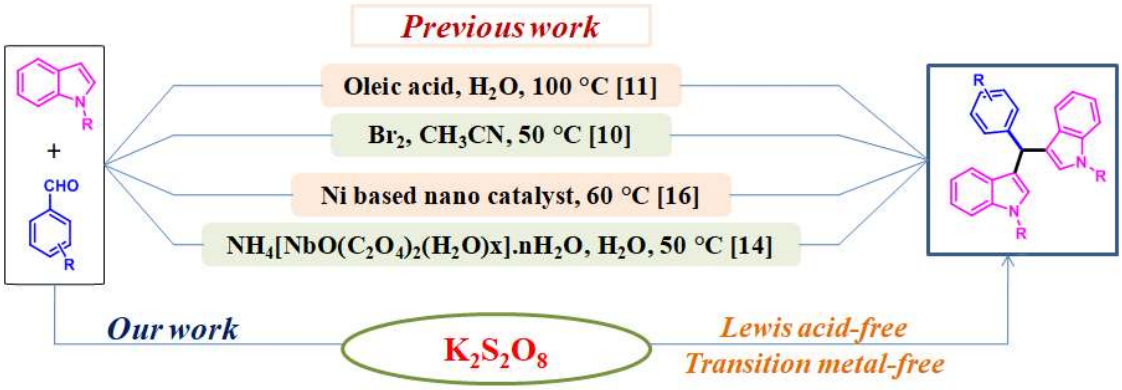


Figure **2.1**. BIM containing drug molecules



Scheme **2.1**. Methodologies for the synthesis of BIMs

2.2 Experimental section

2.2.1 General procedure for the synthesis of BIM

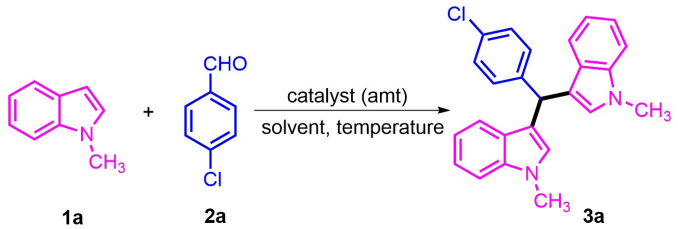
A mixture of indole (0.5 mmol), aldehyde (0.25 mmol), $K_2S_2O_8$ (5 mol%) and ethanol (3ml) were taken in a synthesizer tube. The reaction mixture was refluxed at 80˚C for the appropriate time. After completion of the reaction (monitoring by TLC), the reaction mixture was extracted with ethyl acetate, washed with brine solution and dried over by anhydrous sodium sulfate. The crude was obtained by evaporating the solvent under reduced pressure in a rotary evaporator. To obtain the desired product, purification of the crude was done by column chromatography using silica gel and hexane:ethyl acetate as the solvent system.

2.3 Results and Discussion

2.3.1 Optimization of reaction conditions

The studies of the reaction under various conditions were carried out by taking *N*-methylindole and 4-Chlorobenzaldehyde as model substrates to find out the optimized reaction conditions and the results obtained are summarized in Table **2.1**.

Table **2.1**. Optimization of catalysts, solvents, and temperatures for the synthesis of BIM[a]



Entry	Catalyst (amt)	Solvent (mL)	Temperature (°C)	Yield (%)[b]
1	$K_2S_2O_8$ (0.5 mmol)	Ethanol	100	90
2	$K_2S_2O_8$ (10 mol %)	Ethanol	60	75
3	$K_2S_2O_8$ (10 mol %)	Ethanol	80	87
4	**$K_2S_2O_8$ (5 mol %)**	**Ethanol**	**80**	**94**
5	$K_2S_2O_8$ (5 mol %)	Ethanol	70	88
6	$K_2S_2O_8$ (5 mol %)	Ethanol	60	86
7[c]	$K_2S_2O_8$ (5 mol %)	Ethanol	rt	52
8	$K_2S_2O_8$ (2 mol %)	Ethanol	80	80
9	$K_2S_2O_8$ (5 mol %)	H_2O	80	62
10	$K_2S_2O_8$ (5 mol %)	THF	80	76
11	$K_2S_2O_8$ (5 mol %)	2-MeTHF	80	71
12	$K_2S_2O_8$ (5 mol %)	CH_3CN	80	68
13	$(NH_4)_2S_2O_8$ (5 mol %)	Ethanol	80	65
14[d]	TBHP (0.25 mmol)	Ethanol	80	-
15[e]	-	Ethanol	rt	-
16[f]	-	Ethanol	80	28

[a]Reaction conditions: **1a** (1 equiv.), **2a** (0.5 equiv.), Solvent (3 mL), 7 hours, rt-room temperature. [c, d, e, f]Reactions carried out for 24 hours. [b]Isolated yields.

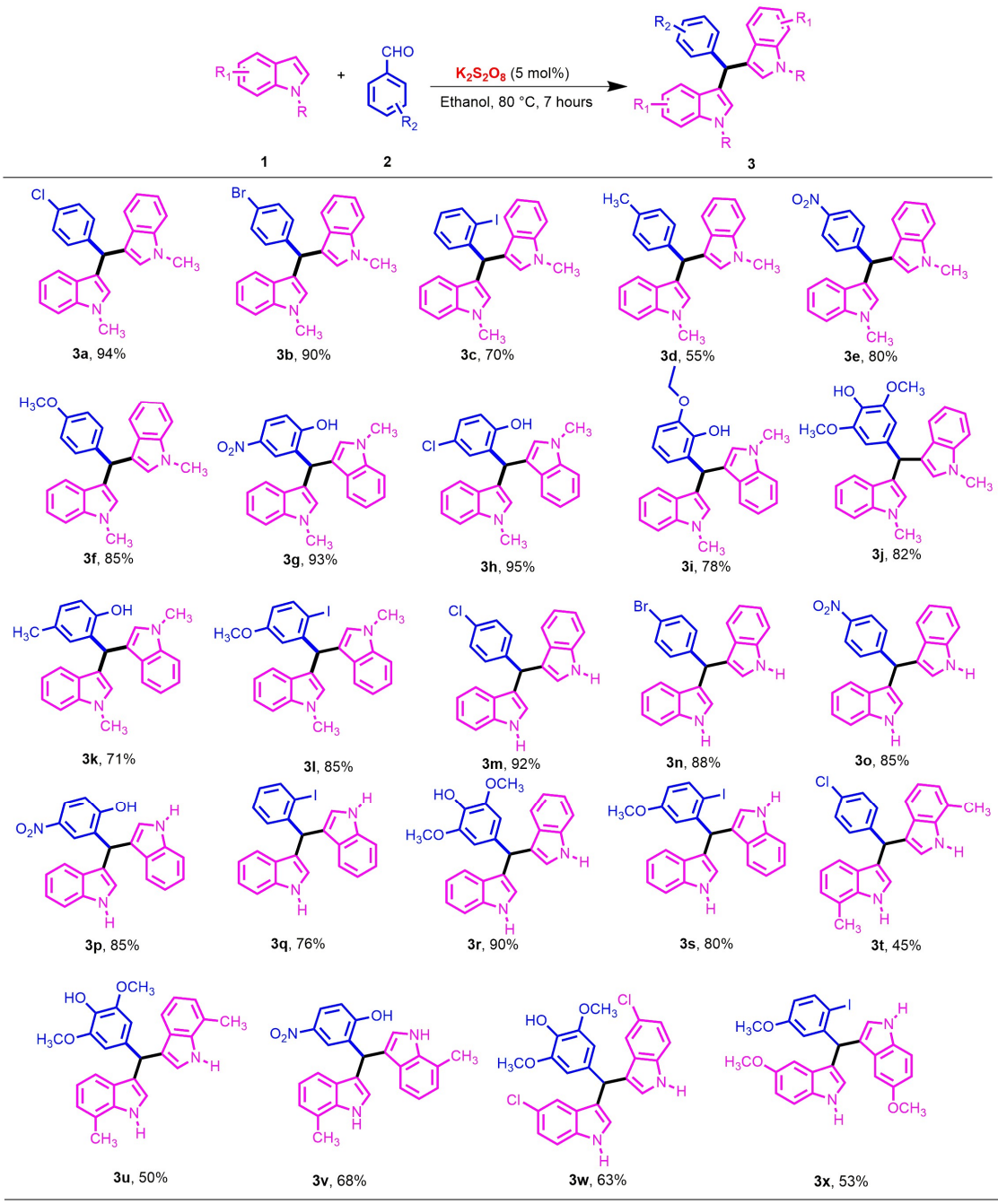
The variation of the amount of $K_2S_2O_8$ with temperature affected the yield of reactions. The maximum yield (94%) of BIM was obtained using 5 mol% of $K_2S_2O_8$ at 80 ˚C in ethanol after 7 hours (entry **4**, Table **2.1**). Reducing the amount of catalyst up to 2 mol% lowered the yield (entry **8**, Table **2.1**). When the reaction was carried out at room temperature using 5 mol% of catalyst, a moderate yield of the product was obtained (entry **7**, Table **2.1**). The use of $(NH_4)_2S_2O_8$, instead of $K_2S_2O_8$ as a catalyst was not so effective and gave only 65% yield (entry **13**, Table **2.1**). On the other hand, no product was formed when TBHP was used as a catalyst. It is well known that TBHP undergoes homolytic fission under thermal conditions to produce *tert*-butoxy and hydroxyl radicals. These two radicals abstract hydrogen radical from aldehyde to form *tert*-butyl alcohol and water. As a result hydrogen radical is not available for further reaction. Additionally, *tert*-butoxy radical further reacts with another molecule of TBHP to generate a *tert*-butylperoxy radical and *tert*-butyl alcohol. Similarly, this *tert*-butylperoxy radical abstracts hydrogen radical from aldehyde to regenerate TBHP and no more hydrogen radical is available for further reaction. Moreover, in the absence of the catalyst, no product was obtained at room temperature. A very low yield of product was obtained at 80 ˚C without the catalyst (entry **16**, Table **2.1**). This indicated that the presence of the catalyst was necessary to get the product in synthetically useful yield. Variation of the protic solvents like H_2O and aprotic solvents such as CH_3CN, 2-MeTHF, and THF also resulted in moderate yields. All these results indicate that the presence of 5 mol% of $K_2S_2O_8$ at 80 ˚C in ethanol is the most effective condition for the current protocol.

2.3.2 Substrate scope study

The scope and limitations of $K_2S_2O_8$ catalyzed synthesis of BIM were studied for various electronically and sterically diverse indoles and aldehydes and the results are summarized in Table **2.2**. Reactions of *N*-methylindole or *N*-H indole with electron-deficient aldehydes were more favourable and gave very good yields as compared to electron-rich aldehydes (entries **3a**, **3b**, **3e**, **3m**, **3n**, **3o**, Table **2.2**). This might be due to the high electrophilic nature of aldehydes containing electron-withdrawing groups. A moderate yield was observed in the case of the reaction with 2-iodobenzaldehyde (entries **3c**, **3q**, Table **2.2**). It might be due to the steric effect of iodine. The reactions of *N*-H indole and *N*-methylindole with electronically diverse salicylaldehyde also showed good yields (entries **3g**, **3h**, **3i**, **3k**, **3p**, Table **2.2**). A lower yield of products was observed in the case of *N*-H indole containing both electron-donating and withdrawing groups. From

these experimentally obtained results, it is seen that electronically diverse aldehydes proceed the reaction in a more favourable way than indoles.

Table **2.2**. BIMs synthesis using indole and aldehyde derivatives[a]



[a]Reaction conditions: **1**(1 equiv.), **2** (0.5 equiv.), EtOH (3 mL)

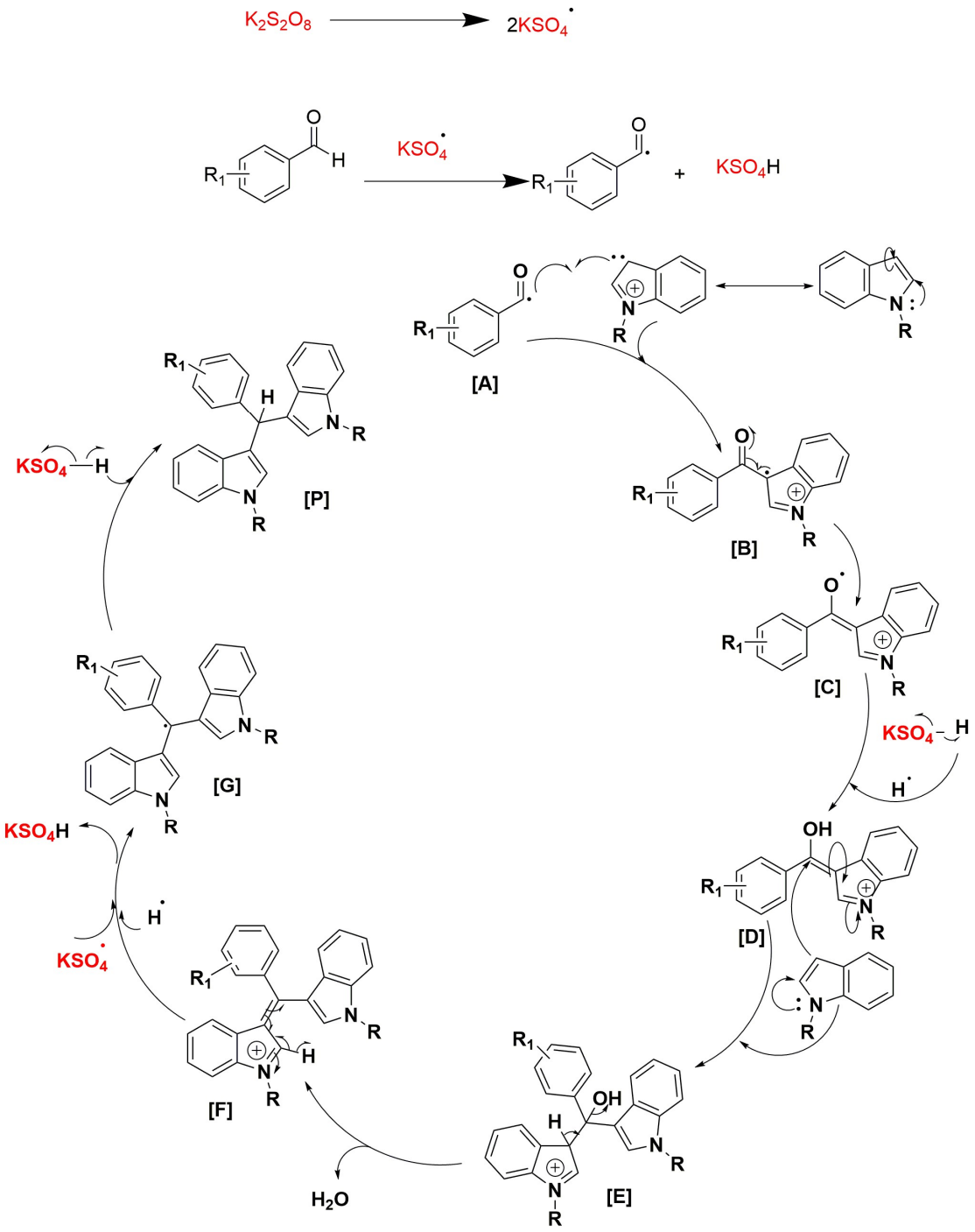
2.3.3 Control experiment

It is believed that the current reaction proceeds through a free radical pathway in presence of $K_2S_2O_8$, which is known as the free radical initiator [19]. To prove the

possible involvement of the free radical path, 2 equivalents (1 mmol) of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was used as a radical-trapping agent under the optimized reaction conditions and we observed that there was a suppression of the formation of our desired product. This indicates that the reaction proceeds through the radical mechanism.

2.3.4 Plausible mechanism

Based on our experimental observations and reported literature we have proposed the plausible mechanism of the reaction shown in Scheme **2.2**. It is believed that $K_2S_2O_8$ first generates KSO_4 radical which reacts with the aldehyde to form carbonyl radical **A**. This radical **A** interacts with indole to form oxygen radical **C** *via* **B**. Then the second molecule of indole attacks intermediate **D** to form **E** which losses a water molecule to form **F**. Now the KSO_4 radical removes a proton from **F** to stabilize the indole molecule and generates a tertiary radical **G** along with KSO_4H. This radical **G** abstracts the proton from KSO_4H to form our desired product and regenerates the KSO_4 radical which re-enters the catalyst cycle.



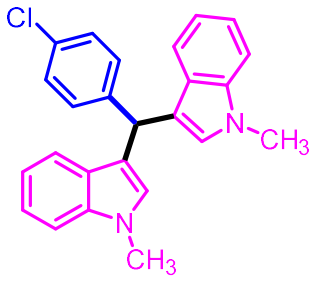
Scheme **2.2**. Possible mechanism proceeds *via* the radical pathway

2.4 Conclusion

In summary, we have reported an efficient methodology for the synthesis of BIMs by the reaction of indoles with aldehydes using only 5 mol% of $K_2S_2O_8$ as the catalyst. The advantages of this synthetic methodology include the cheap and easy availability of the catalyst, Lewis acid-free and transition metal-free mild reaction conditions, compatible

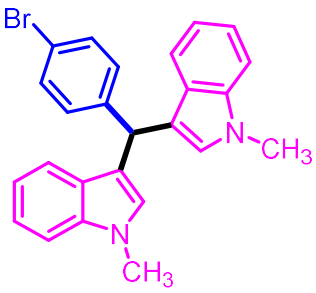
with a wide range of sterically and electronically diverse substrates. Moreover, both unprotected and protected indole derivatives show equal efficiency under the developed reaction conditions.

2.5 ^{1}H and ^{13}C NMR analytical data



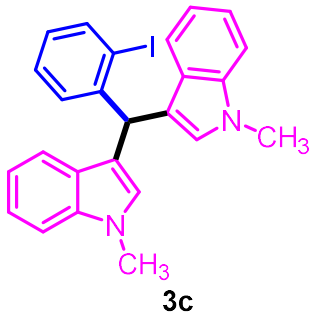
3a

3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1*H*-indole) (3a): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.35–7.23 (m, 8H), 7.07 (m, 2H), 6.87 (m, 2H), 6.77 (s, 2H), 5.80 (s, 1H), 3.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.3, 137.6, 131.8, 130.1, 128.5, 121.6, 120.2, 119.0, 117.8, 109.3, 109.1, 39.6, 32.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{25}H_{22}ClN_2$, calcd 385.1393; found 385.2689.



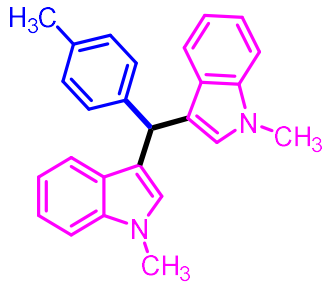
3b

3,3'-((4-bromophenyl)methylene)bis(1-methyl-1*H*-indole) (3b): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.43–7.39 (m, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.3 Hz, 4H), 7.07 (m, 2H), 6.87 (m, 2H), 6.80–6.76(s, 2H), 5.80 (s, 1H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.6, 137.5, 131.3, 130.5, 128.4, 128.3, 127.3, 121.6, 119.8, 118.9, 117.7, 109.2, 40.2, 32.8.



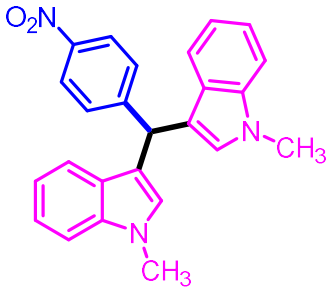
3c

3,3'-((2-iodophenyl)methylene)bis(1-methyl-1*H*-indole) (3c): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.85 (m, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.26–7.15 (m, 4H), 7.09 (m, 2H), 6.97–6.86 (m, 3H), 6.65 (s, 2H), 6.01 (s, 1H), 3.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.6, 139.6, 137.5, 128.7, 128.6, 128.1, 128.0, 127.5, 120.3, 109.2, 101.6, 45.1, 33.2.



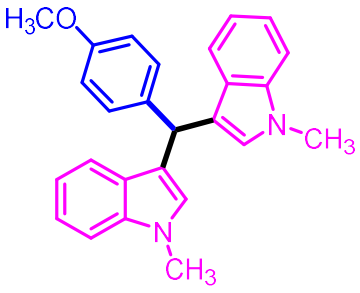
3d

3,3'-((*p*-tolylphenyl)methylene)bis(1-methyl-1*H*-indole) (3d): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.32 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 7.05 (m, 4H), 6.86 (t, J = 7.4 Hz, 2H), 6.75 (s, 2H), 5.75 (s, 1H), 3.64 (s, 6H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 141.5, 137.6, 135.5, 129.1, 128.6, 128.2, 127.6, 121.5, 120.1, 118.7, 118.5, 109.2, 40.2, 33.2, 21.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{26}H_{25}N_2$, calcd 365.2017; found 365.2207.



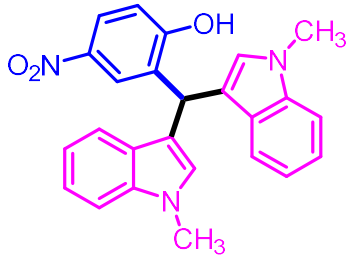
3e

3,3'-(4-nitrolphenyl)methylene)bis(1-methyl-1*H*-indole) (3e): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.14–8.09 (m, 2H), 7.59–7.54 (m, 2H), 7.38–7.33 (m, 2H), 7.30–7.25 (m, 2H), 7.12–7.05 (m, 2H), 6.92–6.84 (m, 4H), 6.01 (s, 1H), 3.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.6, 137.5, 129.6, 129.5, 128.4, 128.3, 123.7, 123.6, 121.9, 119.8, 119.7, 119.1, 40.4, 33.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{25}H_{22}N_3O_2$, calcd 396.1712; found 394.1723.



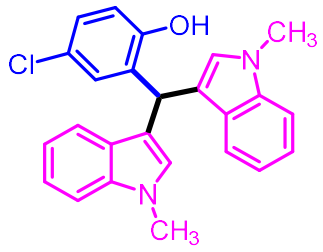
3f

3,3'-(4-methoxylphenyl)methylene)bis(1-methyl-1*H*-indole) (3f): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.32 (d, J = 8.2 Hz, 2H), 7.26–7.18 (m, 4H), 7.06 (t, J = 7.6 Hz, 2H), 6.85 (t, J = 7.5 Hz, 2H), 6.79 (t, J = 5.7 Hz, 2H), 6.74 (s, 2H), 5.72 (s, 1H), 3.66 (s, 3H), 3.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.0, 137.7, 136.8, 129.9, 128.5, 127.6, 121.6, 120.2, 118.7, 113.6, 109.2, 109.1, 55.4, 39.4, 32.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{26}H_{25}N_2O$, calcd 381.1967; found 380.2086.



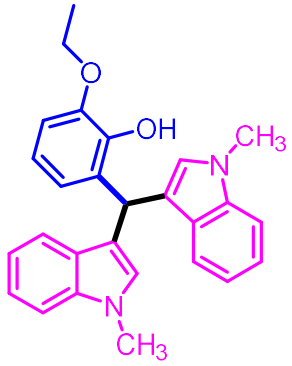
3g

2-(bis(1-methyl-1*H*-indol-3-yl)methyl)-4-nitrophenol (3g): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.17 (s, 1H), 7.97 (m, 1H), 7.86 (d, J = 2.9 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.08 (m, 2H), 7.01 (d, J = 8.9 Hz, 1H), 6.92–6.86 (m, 2H), 6.79 (s, 2H), 6.16 (s, 1H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.5, 141.8, 137.7, 130.4, 128.2, 126.9, 126.1, 124.5, 119.6, 119.4, 117.0, 114.1, 109.7, 36.2, 32.9.



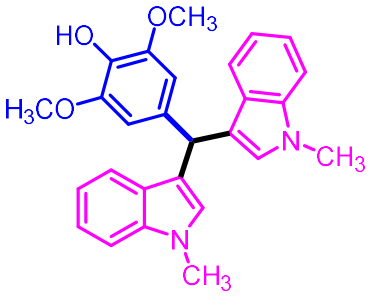
3h

2-(bis(1-methyl-1*H*-indol-3-yl)methyl)-4-chlorophenol (3h): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.74 (s, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.07 (m, 2H), 7.00 (m, 1H), 6.94–6.81 (m, 4H), 6.74 (s, 2H), 6.11 (s, 1H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.3, 137.7, 131.3, 128.3, 127.9, 127.1, 125.5, 122.1, 119.9, 119.3, 118.0, 114.9, 109.5, 36.2, 32.9.



3i

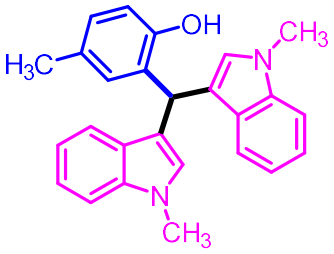
2-(bis(1-methyl-1*H*-indol-3-yl)methyl)-6-ethoxyphenol (3i): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (m, 2H), 7.27 (d, J = 8.2 Hz, 2H), 7.21–7.16 (m, 2H), 7.02–6.97 (m, 2H), 6.79 (m, 1H), 6.74–6.67 (m, 2H), 6.60 (s, 2H), 6.30 (s, 1H), 5.88 (s, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.67 (s, 6H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.1, 142.8, 137.3, 128.2, 121.4, 120.2, 119.1, 118.6, 117.5, 109.4, 109.0, 64.3, 32.7, 21.1, 15.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{27}H_{27}N_2O_2$, calcd 411.2072; found 411.2177.



3j

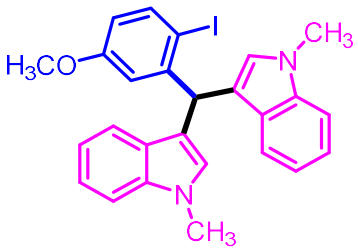
4-(bis(1-methyl-1*H*-indol-3-yl)methyl)-2,6-dimethoxyphenol (3j): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.07 (s, 1H), 7.30 (m, 4H), 7.05 (m, 2H), 6.86 (m, 2H), 6.79 (s, 2H), 6.60 (s, 2H), 5.67 (s, 1H), 3.65 (s, 6H), 3.61 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.9, 137.5, 135.8, 132.9, 128.3, 127.5, 121.5, 120.1, 118.7, 118.4, 109.2, 105.5, 56.5, 40.2, 32.9. HRMS

(ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{27}H_{27}N_2O_3$, calcd 427.2021; found 427.2146.



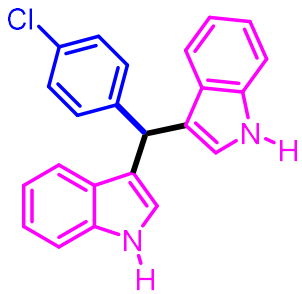
3k

2-(bis(1-methyl-1*H*-indol-3-yl)methyl)-4-methylphenol (3k): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.12 (s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.05 (m, 2H), 6.86 (m, 3H), 6.76–6.69 (m, 4H), 6.12 (s, 1H), 3.64 (s, 6H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.5, 137.9, 130.5, 129.8, 129.3, 128.7, 128.1, 127.3, 122.0, 120.1, 119.2, 116.6, 115.8, 109.3, 36.8, 33.2, 21.0.



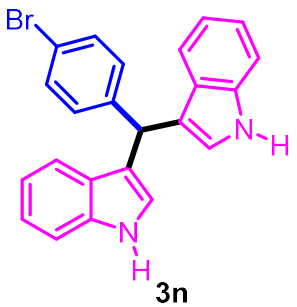
3l

3,3'-((2-iodo-5-methoxyphenyl)methylene)bis(1-methyl-1*H*-indole) (3l): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.80–7.75 (m, 1H), 7.44–7.39 (m, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.23–7.17 (m, 2H), 7.05–6.99 (m, 2H), 6.83 (d, J = 3.1 Hz, 1H), 6.53 (m, 1H), 6.49 (s, 2H), 6.10 (s, 1H), 3.67 (s, 6H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.1, 140.0, 137.3, 128.6, 127.6, 121.6, 120.1, 118.7, 117.2, 117.0, 113.3, 109.0, 90.2, 55.1, 45.5, 32.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{26}H_{24}IN_2O$, calcd 507.0933; found 506.0810.



3m

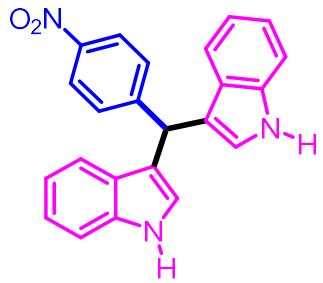
3,3'-((4-chlorophenyl)methylene)bis(1*H*-indole) (3m): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.81 (s, 2H), 7.29 (m, 6H), 7.22 (t, J = 6.3 Hz, 2H), 7.00 (m, 2H), 6.83 (m, 2H), 6.79 (s, 2H), 5.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 142.6, 136.8, 131.9, 130.1, 128.5, 126.9, 123.7, 122.2, 119.9, 119.5, 111.2, 39.7.



3n

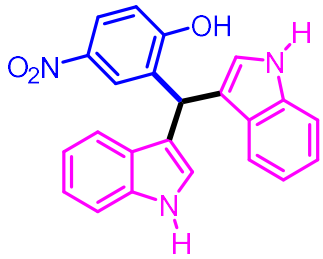
3,3'-((4-bromophenyl)methylene)bis(1*H*-indole) (3n): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.82 (s, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.30 (m, 2H), 7.24 (m, 4H), 7.00 (t, J = 7.6 Hz, 2H), 6.86–6.77 (m, 4H), 5.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.1, 136.7, 131.5, 130.6, 126.9, 123.7, 122.2, 120.0, 119.9, 119.4, 119.1,

111.2, 40.0.



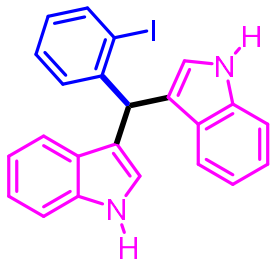
3o

3,3'-((4-nitrophenyl)methylene)bis(1*H*-indole) (3o): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.88 (s, 2H), 8.20–8.05 (m, 2H), 7.66–7.51 (m, 2H), 7.47–7.17 (m, 4H), 7.10–6.93 (m, 2H), 6.92–6.75 (m, 4H), 6.01 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 153.7, 146.3, 137.1, 130.0, 126.8, 124.5, 123.9, 121.6, 119.5, 118.8, 117.1, 112.3.



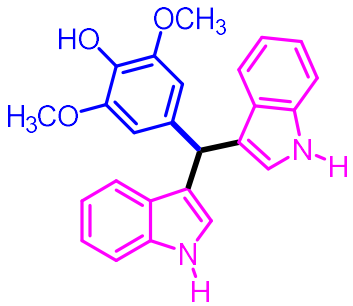
3p

2-(di(1*H*-indol-3-yl)methyl)-4-nitrophenol (3p): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.17 (s, 1H), 10.82 (d, J = 1.8 Hz, 2H), 7.97 (m, 1H), 7.86 (d, J = 2.9 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.06–6.98 (m, 3H), 6.89–6.81 (m, 2H), 6.77 (s, 2H), 6.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 161.8, 140.0, 137.3, 133.0, 127.3, 125.5, 124.2, 122.1, 121.5, 119.4, 118.7, 117.2, 112.1, 112.0, 32.8.



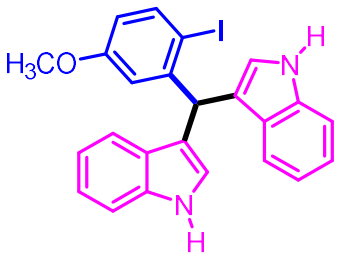
3q

3,3'-((2-iodophenyl)methylene)bis(1*H*-indole) (3q): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.91 (d, J = 7.7 Hz, 1H), 7.84 (s, 2H), 7.40 (d, J = 7.9 Hz, 3H), 7.34 (d, J = 8.2 Hz, 2H), 7.21–7.15 (m, 4H), 7.05–7.00 (m, 2H), 6.54 (s, 2H), 6.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.4, 139.7, 136.7, 128.2, 124.1, 124.0, 122.1, 120.1, 119.4, 118.7, 111.2, 101.8, 45.1.



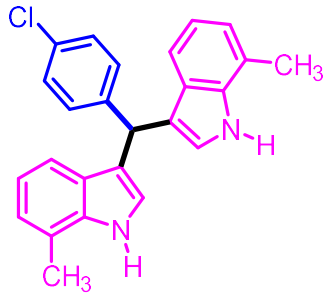
3r

4-(di(1*H*-indol-3-yl)methyl)-2,6-dimethoxyphenol (3r): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (s, 2H), 7.42–7.37 (m, 2H), 7.33 (m, 2H), 7.19–7.12 (m, 2H), 7.03–6.97 (m, 2H), 6.64 (m, 2H), 6.57 (s, 2H), 5.80 (s, 1H), 5.42 (s, 1H), 3.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.9, 136.8, 135.4, 132.9, 127.1, 123.6, 122.1, 119.9, 119.3, 111.4, 105.7, 105.6, 56.4, 56.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ for $C_{25}H_{23}N_2O_3$, calcd 399.1708; found 398.1677.



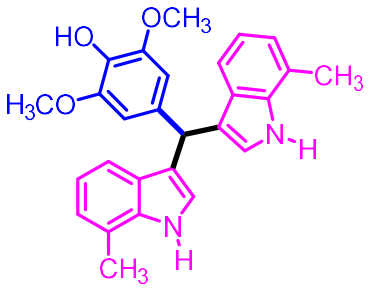
3s

3,3'-((2-iodo-5-methoxyphenyl)methylene)bis(1*H*-indole) (3s): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 (s, 2H), 7.77 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.20–7.13 (m, 2H), 7.05–6.98 (m, 2H), 6.80 (t, J = 5.1 Hz, 1H), 6.58–6.51 (m, 3H), 6.09 (s, 1H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.1, 147.4, 140.4, 136.9, 127.3, 123.8, 122.2, 120.0, 119.4, 118.6, 116.7, 111.1, 90.4, 45.1, 44.9.



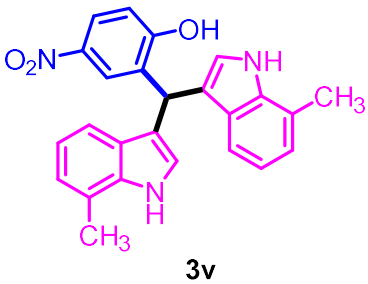
3t

3,3'-((4-chlorophenyl)methylene)bis(7-methyl-1*H*-indole) (3t): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.79 (s, 2H), 7.30–7.24 (m, 4H), 7.04 (d, J = 7.7 Hz, 2H), 6.82–6.71 (m, 6H), 5.75 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 142.8, 136.3, 131.8, 130.1, 128.4, 126.5, 123.4, 122.6, 120.4, 119.7, 119.6, 117.6, 40.2, 17.1.



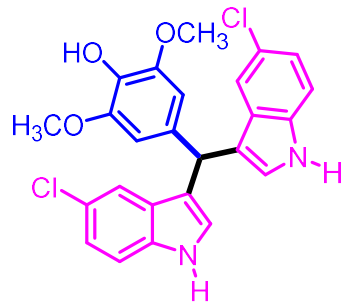
3u

4-(bis(7-methyl-1*H*-indol-3-yl)methyl)-2,6-dimethoxyphenol (3u): ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.69 (s, 2H), 8.05 (s, 1H), 7.09 (d, J = 7.7 Hz, 2H), 6.81–6.70 (m, 6H), 6.59 (s, 2H), 5.64 (s, 1H), 3.59 (s, 6H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.9, 136.4, 135.6, 133.1, 126.6, 123.3, 120.4, 120.2, 119.5, 117.7, 105.4, 56.4, 56.3, 17.1.



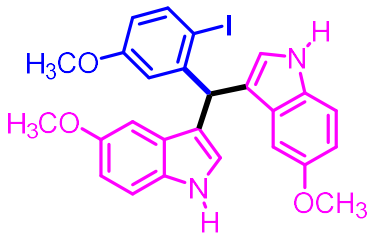
3v

2-(bis(7-methyl-1*H*-indol-3-yl)methyl)-4-nitrophenol (3v): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (s, 1H), 8.06 (m, 1H), 7.90 (s, 2H), 7.21 (d, J = 7.7 Hz, 2H), 7.04–6.95 (m, 4H), 6.89 (d, J = 8.8 Hz, 1H), 6.65 (s, 2H), 6.04 (s, 1H), 2.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.3, 141.7, 136.5, 130.3, 126.2, 126.2, 124.4, 123.4, 123.2, 120.9, 120.1, 117.2, 116.9, 116.6, 35.9, 16.7.



3w

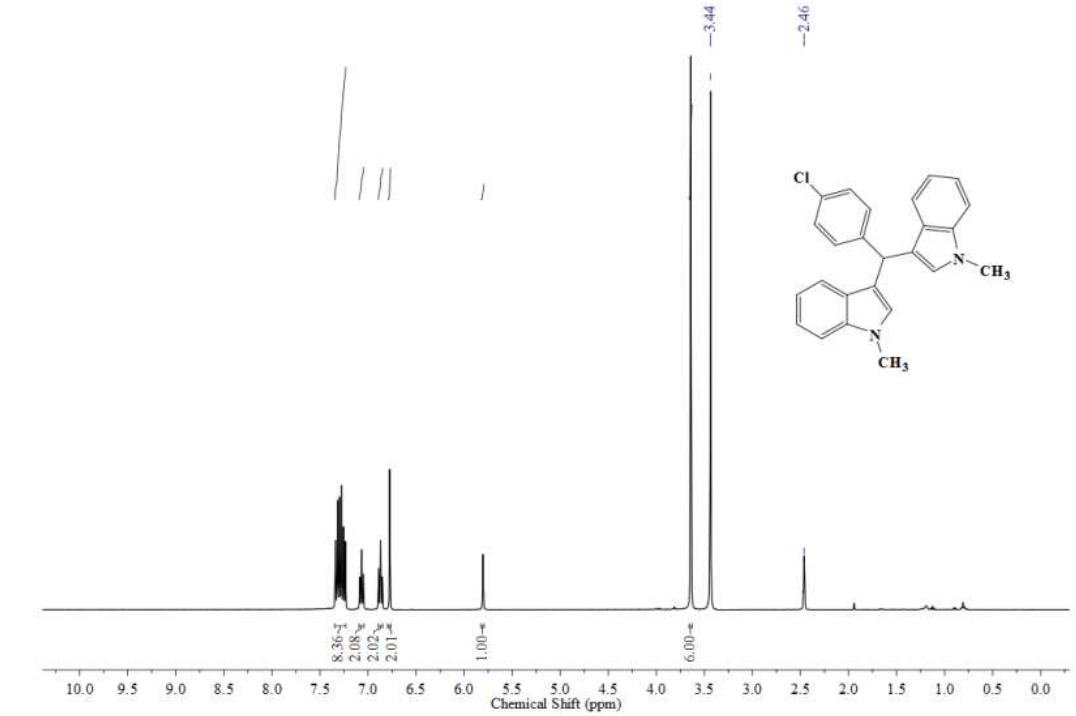
4-(bis(5-chloro-1*H*-indol-3-yl)methyl)-2,6-dimethoxyphenol (3w): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 (s, 2H), 7.32 (d, J = 0.9 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.10 (m, 2H), 6.66 (d, J = 1.9 Hz, 2H), 6.52 (s, 2H), 5.66 (s, 1H), 5.45 (s, 1H), 3.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 147.4, 135.1, 134.5, 133.3, 128.1, 125.1, 124.9, 119.3, 112.4, 112.2, 105.5, 56.5, 39.8.

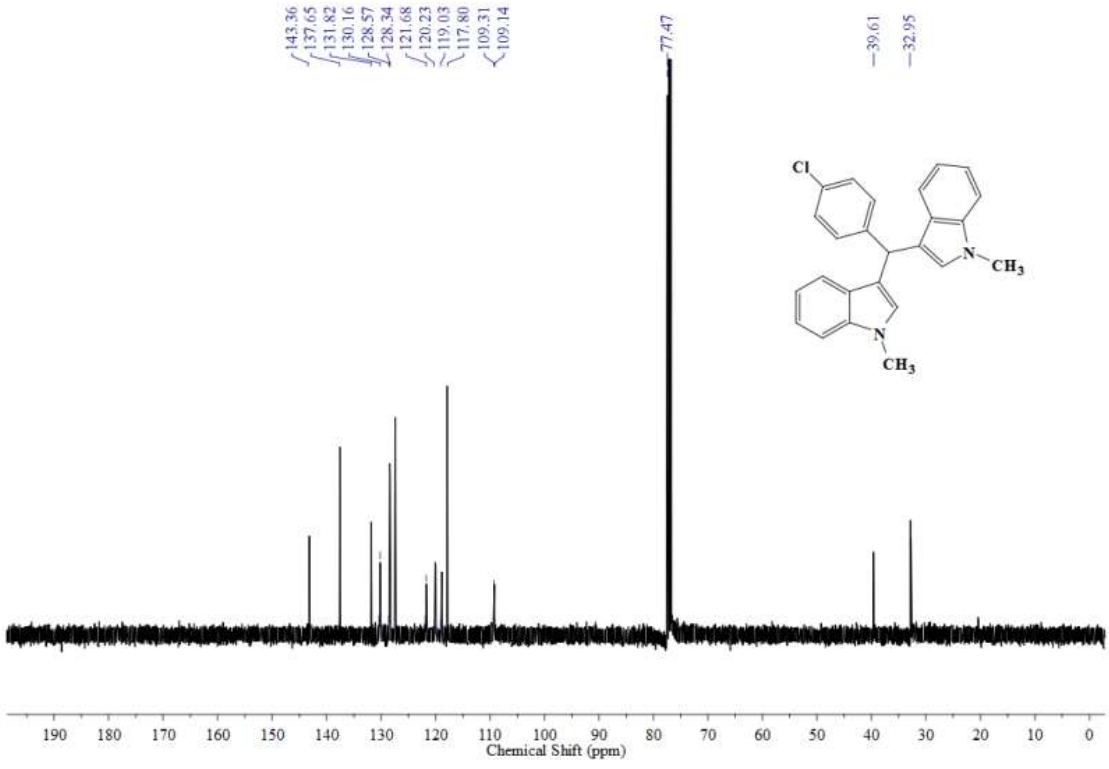


3x

3,3'-((2-iodo-5-methoxyphenyl)methylene)bis(5-methoxy-1*H*-indole) (3x): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.80 (s, 2H), 7.76 (d, J = 8.6 Hz, 1H), 7.21 (m, 2H), 6.82 (m, 5H), 6.58 (s, 2H), 6.53 (s, 1H), 5.98 (s, 1H), 3.72 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.9, 153.9, 147.4, 139.9, 131.9, 127.6, 124.7, 124.6, 118.2, 116.8, 112.0, 111.6, 102.2, 102.1, 90.4, 56.1, 55.0.

^{1}H and ^{13}C NMR spectra of 3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1*H*-indole)





2.6 Bibliography

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