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ARTICLE

Brønsted acidic ionic liquid–catalyzed tandem trimerization of indoles: An efficient approach towards the synthesis of indole 3,3′-trimers under solvent-free conditions

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Abstract

We have observed the role of 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]OTs, as an organocatalyst for the tandem type trimerization of indoles to synthesize indole 3,3′-trimers under neat conditions. Using this developed protocol synthesis of indole trimers with various substituted indoles, which are biologically important, has been reported. From the control experiments and literature, a possible mechanism has been proposed via the generation of indolinium cation in the presence of the ionic liquid catalyst. The catalyst has been recycled for several times. The significant advantages of our methodology are clean reaction with very short time, no chromatography for purification, commercially available substrates, neat reaction conditions, and in the absence of metal. Using the protocol, the MDM2-p53 inhibitor has been synthesized in gram scale with high yield.

1 | INTRODUCTION

The application of ionic liquids (ILs) is increasing day by day to carry out many chemical transformations. Ionic liquids has been considered as organocatalyst as well as solvent in both organic and inorganic chemistry for its unique properties.[1] Based on its different structure, ionic liquids can behave as catalyst, and many other purposes in organic reactions.[2] Though ILs have some limitation as solvents,[3] varying the cations and anions a variety of ILs has been developed, which are very useful for different applications.[4] Forbes and Davis synthesized ILs based on phosphonium and imidazolium ion with a suspended acidic sulfonic acid moiety and another Brønsted acidic ionic liquids (BAILs), which are very important in the area of organocatalysis.[5] With normal properties of ionic liquids, BAILs show a strong acidic nature. Accordingly, BAILs have been used for a number of methodologies due to its acidic nature. We are actively engaged to develop various important methodologies in using imidazole-based zwitterions and BAILs as catalysts in organic transformations.[6]

Indole is the core structure of a variety of biologically and pharmaceutically active compounds and well known as *Lord of the Rings* of heterocyclic moiety.[7] Particularly, indole derivatives containing bis(indolyl)alkane or 3,3′-bisindole moiety have wide applications as bioactive natural products and pharmaceuticals drugs.[8] For instance, the bis(indolyl)methane compounds are considered as cytotoxic in opposition to MCF-7 cells and able to exhibit acetylcholinesterase (AChE) inhibitory activity.[9] Some valuable alkaloids like arundine,[10] vidrindole,[11] antibiotic turbomycins[12] or arsindoline B,[13] and streptindole[14] contain bis(indolyl)methane motif (Figure 1). Various biological activities of bis(indolyl)methanes like antimicrobial,[15] anti-fungal,[16] antibacterial and

anti-inflammatory,[17] and anti-hyperlipidemic[18] have been observed. In addition, bis(indolyl)methanes act as potential hypolipidemic and antiobesity agents,[19] and its oxidized form can be used as colorimetric sensors.[20]

Accordingly, a number of methods have been reported to synthesize bis(indolyl)alkanes with the combination of indoles and aldehydes using Lewis or protic acid or other catalytic reagents.[21] Other than using aldehydes, several methods have been reported to achieve bis(indolyl)methane derivatives using different reagents and reaction conditions.[22] On the other hand, it is well established that indole itself gets polymerized to dimer or trimer by self-addition catalyzed by Brønsted or Lewis acids. It is worthy to mention that very few methods are available for the synthesis of indole 3,3′-trimers. After the first report by Keller,[23] few methods have been developed by using different acid catalysts such as HCl/$ZnCl_2$-AcOH, TFA, *p*-toluenesulfonic acid, HCO_2H, and Lewis acid catalysts such as $InCl_3$, $Sc(OTf)_3$, $AlCl_3$, and $SnCl_2$.[24] The main disadvantages of these protocols are low yields, formation of undesired products, and long reaction time. In these reported methods, the indole 3,3′-trimers were formed along with the other polymers of indole, 2,3′-trimers, and dimer in different yields. BAILs are very useful in many organic syntheses, and we are also actively working with this.[6] Here, as an outcome, we report a very selective synthesis of indole 3,3′-trimers in good to excellent yields without any side products in the presence of 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]OTs (BAIL-1) (10 mo%) at 80°C (Scheme 1). This present reaction proceeded under neat conditions, the desired 3,3′-trimers with various *N*-protected indoles obtained in major yield suppressing the formation of other polymers. No column chromatography has been performed to purify the crude compounds.

2 | RESULTS AND DISCUSSION

Initially, for the reaction, we have taken simple indole (**1a**) in the presence of the catalyst 1-butane sulfonic acid-3-methylimidazolium tosylate (10 mol%), [BSMIM]OTs (BAIL-1) at 80°C for 1 hour, under neat conditions (Table 1, entry 1). We are delighted to note that the desired 3,3′-trimer product, namely, 2-(2,2-di[1*H*-indol-3-yl]ethyl)aniline (**2a**) was obtained in 85%. Immediately, we extended the reaction time under the same reaction condition from 1 to 3 hours, but the yield was not improved. Secondly, the role of various ionic liquids such as BAIL-2, BAIL-3, and BAIL-4 have been checked (Table 1, entries 2-4), but BAIL-1 was found to be the best for the formation of indole trimer product. No desired products have been found using other ionic liquids like IL-2 and [BMIM]BF_4 (Table 1, entries 5 & 6). The role of various solvents has been examined to realize the solvent effects. Some protic solvents like water, different alcohols, and polyethylene glycol (PEG) (Table 1, entries 7-11) produced very less product and some aprotic solvents like 1,2-DCE, CH_3CN afforded poor yields (Table 1, entries 12 & 13). We observed 84% yield of the desired product under neat conditions at temperature 80°C in 1 hour (Table 1, entry 1). So, it may be concluded that the solvent has no significant role for this reaction. High temperature was not beneficial for this reaction (Table 1, entry 14), but we observed fewer yields on decreasing temperature (Table 1, entry 15). Finally, we have observed that 10 mol% of BAIL-1 afforded better yield (85%) compared with 5 mol% (67% yield) (Table 1, entry 16). Increasing the catalyst loading to 20 mol%, there is no development of the reaction conversion (Table 1, entry 17). It is worthy to mention that without catalyst, there is no conversion (Table 1, entry 18). So, the

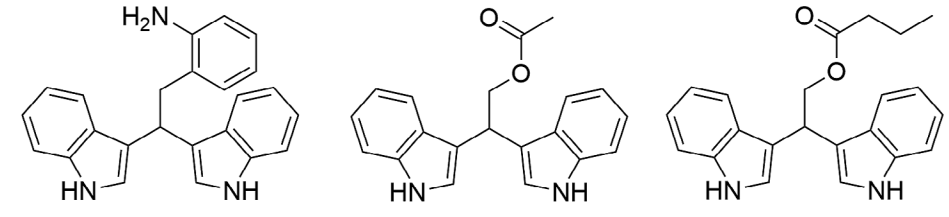
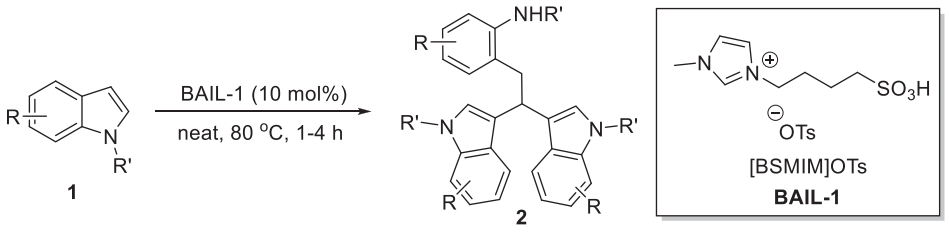
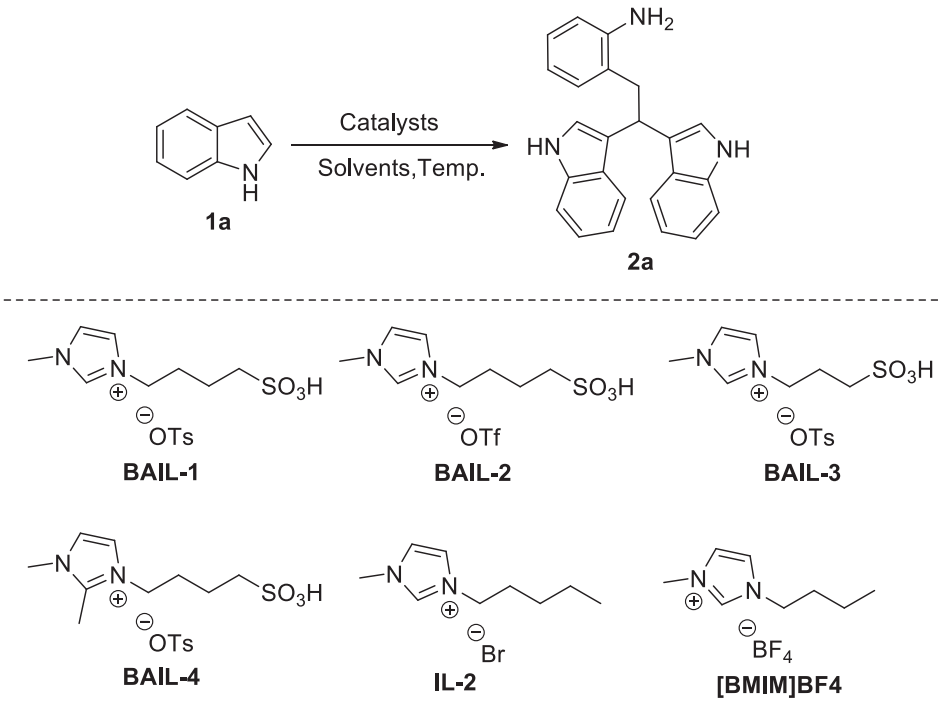


FIGURE 1 Few bioactive bisindolyl derivatives



SCHEME 1 BAIL-catalyzed synthesis of bis(indolyl)alkane

TABLE 1 Optimization of the reaction conditions



Entry	Catalysts (10 mol%)	Solvents	Temp., °C	Yields[a], %
1	BAIL-1	neat	80	85, 82[b]
2	BAIL-2	neat	80	74
3	BAIL-3	neat	80	70
4	BAIL-4	neat	80	75
5	IL-2	neat	80	trace
6	[BMIM]BF_4	neat	80	nr
7	BAIL-1	H_2O	80	61
8	BAIL-1	EtOH	80	40
9	BAIL-1	*n*-PrOH	80	28
10	BAIL-1	*n*-BuOH	80	22
11	BAIL-1	PEG	80	19
12	BAIL-1	1,2-DCE	80	30
13	BAIL-1	CH_3CN	80	33
14	BAIL-1	neat	100	83
15	BAIL-1	neat	60	71
16	BAIL-1	neat	80	67[c]
17	BAIL-1	neat	80	85[d]
18	--	neat	80	ND[e]

Note: Reaction conditions: indole (1.0 mmol), BAIL-1 (10 mol%), stirred for 1 hour.
[a]Isolated yields.
[b]Reaction time 3 hours.
[c]5 mol% BAIL-1 was used.
[d]20 mol% BAIL-1 was used.
[e]Not detected in TLC.

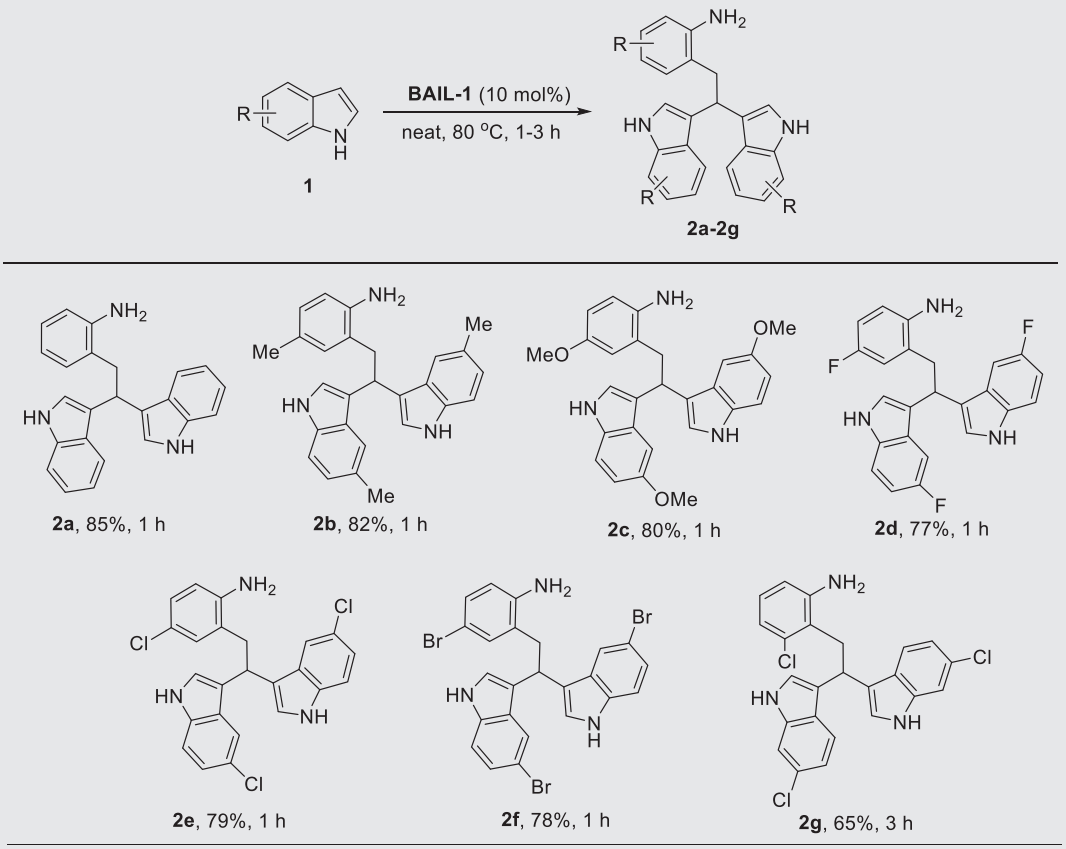
optimized reaction conditions have been considered by employing 10 mol% BAIL-1 at 80°C under solvent-free conditions for 1 h (Table 1, entry 16).

Various indoles (**1**) were examined for trimerization reaction using these reaction conditions, which are summarized in Table 2. During optimization, we have seen that simple indole (**1a**) gave the trimer product in 85% yield, which is an MDM2-p53 inhibitor. The reaction underwent smoothly with indole derivatives substituted with electron-donating substituents (5-Me, 5-OMe) to give the corresponding 3,3′-trimer products (**2b**, **2c**) in excellent yields. Similarly, indoles with different electron-withdrawing groups such as –fluoro, –chloro, and –bromo groups at C-5 position reacted to provide the respective 3,3′-trimer products (**2d-2f**) in good yields; 6-chloro-substituted indole also underwent the reaction to provide desired product **2g** in moderate yield.

Then, the substrate scope with the *N*-protected indoles under the similar reaction conditions has been explored as summarized in Table 3. *N*-methylindole and *N*-ethylindole reacted very smoothly to give the product **2h** in 81% yield and **2i** in 79% yield, respectively. n-Propyl and iso-propylprotected indoles also gave the corresponding 3,3′-trimer products (**2j**, **2k**) in good yields. In addition, *iso*-butyl protected indole derivative provided the respective product (**2l)** with 70% yield. Similarly, long chain alkyl group like *n*-butyl and *n*-pentyl protected indoles nicely underwent the reaction under the optimized conditions and afforded the corresponding products (**2m**, **2n**) in satisfactory yields. Next, *N*-allyl and propargyl substituted indoles were also introduced to react where the corresponding trimers (**2o**, **2p**) were formed in good yields keeping the unsaturated group unaffected. *N*-benzylindole afforded the corresponding product (**2q**) in 74% yield. Other substituted indoles like 5-methyl, 5-methoxy, and 5-chloro substituted *N*-methyl indoles reacted smoothly, and the products **2r**, **2s**, and **2t** were furnished with good yields. In addition, 5-methoxy and 5-chloro substituted *N*-ethyl indoles also gave the corresponding products (**2u** and **2v**) in satisfactory yields. We have subjected pyrrole under the same reaction conditions but could not isolate any considerable product.

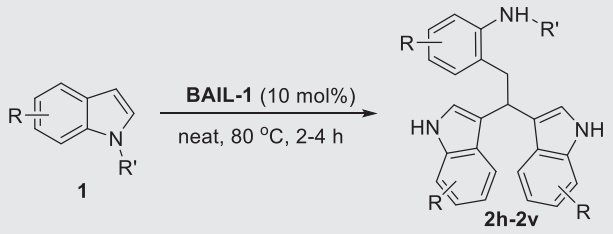
The reactions need no inert medium and were performed under an open atmosphere. No column

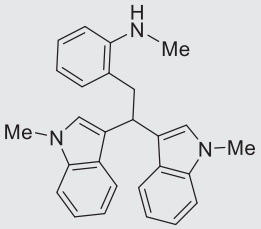
TABLE 2 Synthesis of 3,3′-trimer derivatives of various indoles in presence of BAIL-1



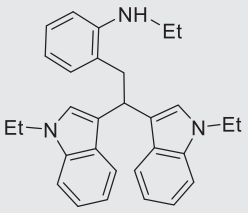
Note: Reaction conditions: 1 mmol of **1**, BAIL-1 (10 mol%) at 80°C. All are isolated yields.

TABLE 3 Synthesis of 3,3′-trimer derivatives of various *N*-protected indoles

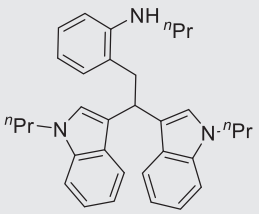




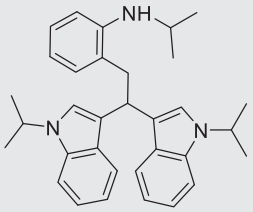
2h, 81%, 2 h



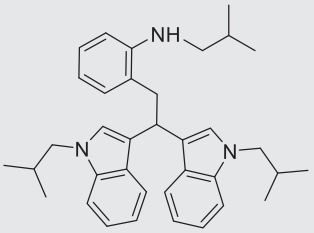
2i, 79%, 2 h



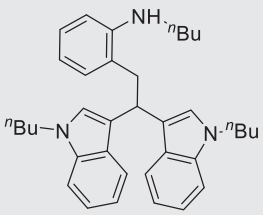
2j, 77%, 2 h



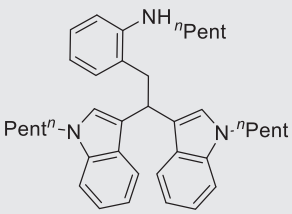
2k, 76%, 3 h



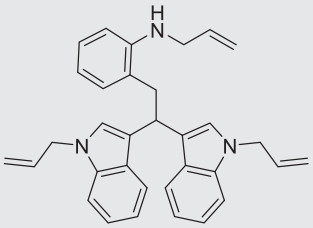
2l, 70%, 3 h



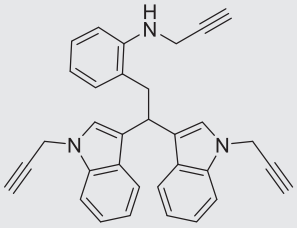
2m, 72%, 3 h



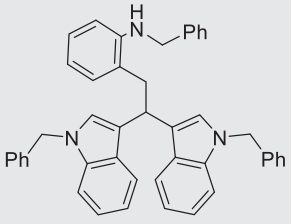
2n, 67%, 4 h



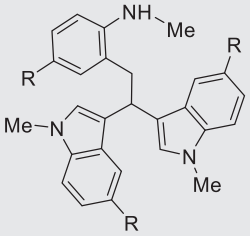
2o, 73%, 3 h



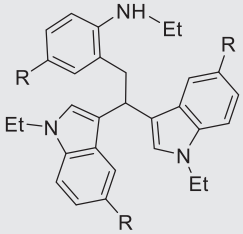
2p, 71%, 3 h



2q, 74%, 3 h



R= Me, **2r**, 78%, 2 h
OMe, **2s,** 76%, 2 h
Cl, **2t,** 77%, 2 h



R= OMe, **2u**, 75%, 3 h
Cl, **2v**, 74%, 3 h

Note: All reactions were carried out on 1 mmol scale using BAIL-1 (10 mol%) at 80°C. All are isolated yields.

chromatography has been performed for purification. Small amount of water was added to the reaction mixture after completion and was then filtered to get the crude product. To get the pure compound, the crude product was washed with ethanol. In our method, no other polymers of indole, 2,3′-trimers, and dimers were observed. All the synthesized compounds, which are reported earlier, have been compared with their spectral data. The

new compounds were characterized by spectral as well as their analytical data. The structure of the compound 2-(2,2-Bis[5-chloro-1-ethyl-1*H*-indol-3-yl]ethyl)-4-chloro-*N*-ethylaniline (**2v**) have been confirmed by X-ray crystallographic analysis as shown in Figure 2.[25]

Our methodology is also valid for gram scale synthesis as shown in Scheme 2. Compound **2a** has been isolated 1.4 g, which acts as an MDM2-p53 inhibitor in 82% yield.

After the successful preparation of bis(indolyl)methane compounds (3,3′-trimer), we checked the recovery and reusability of the catalyst. For this purpose, we have taken 1*H*-indole (**1a**) in presence of BAIL-1 (10 mol%) and the reaction was carried out under the optimized reaction conditions. After completion of the reaction, water was added to the reaction mixture and allowed to cool at room temperature and filtered. Evaporation of water from the solution ionic liquid has been recovered. The catalyst has been tested for five times in this way and found a comparable activity as shown in Table 4 and Figure 3.

A plausible mechanistic pathway for the trimersation of indole has been suggested as shown in Scheme 3. Indole 3,3′-trimers transformation occurs possibly through the generation of indolinium cation **A** by taking a proton from BAIL-1. After that, another indole moiety attacks the indolinium cation from C-3 position to form intermediate **B**. The intermediate **B** gets broken and converted to **C**, which then involves the addition of third indole to produce the indole trimer **2a** through the formation of **D**.

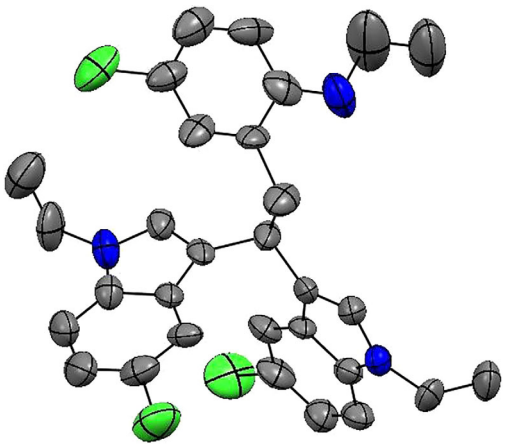
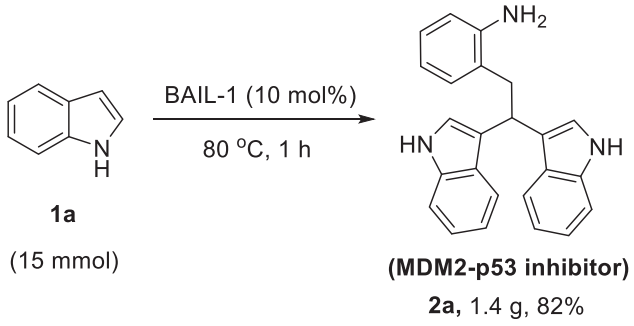


FIGURE 2 X-ray crystallographic structure of compound **2v**



SCHEME 2 Gram-scale reaction

3 | CONCLUSION

In conclusion, an efficient methodology has been reported to synthesize indole 3,3′-trimer derivatives by the self-coupling of indoles using Brønsted acidic ionic liquid (BAIL-1) as catalyst. No other polymers of indole, 2,3′-trimers, and dimers were observed during the reaction. Possibly, the reaction goes through the formation of indolinium cation in tandem fashion in the presence of BAIL-1. A library of indole 3,3′-trimer derivatives has been synthesized using the present reaction conditions. We have found that there is no considerable role of external solvent for this reaction. The reusability of the catalyst BAIL-1 has been tested, and it is effective for five times without comparable catalytic activities. The reported methodology shows a very clean reaction, reaction time is very short, the product can be easily isolated, chromatography is not needed, and all the reactants are easily available. Above all, the reaction is under neat condition and

TABLE 4 Synthesis of **2a**[a] and recycling of BAIL

No. of cycle	Yields, %[b]	Catalyst Recovery, %
1	85	95
2	84	92
3	80	88
4	80	85
5	77	82

[a]**1a** (1 mmol), 10 mol% of catalyst (BAIL-1) under neat condition at 80°C for 1 hour.
[b]Isolated yields.

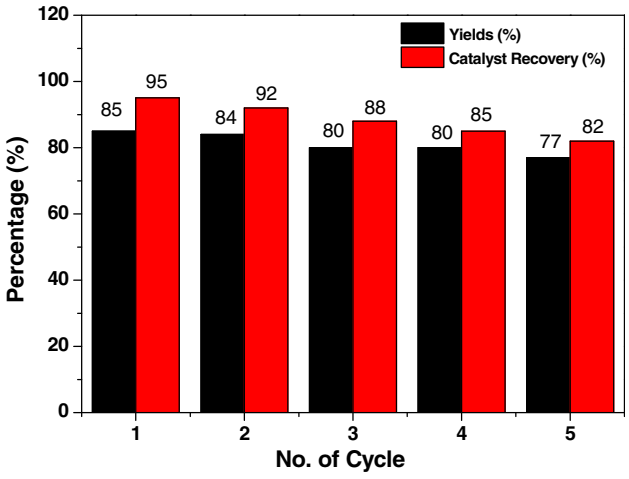
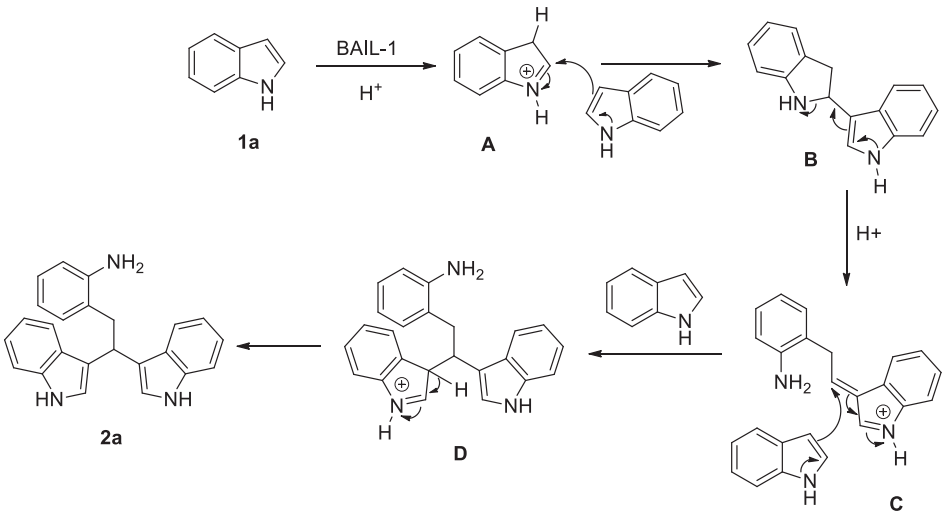


FIGURE 3 Representation of catalyst recycling and recovery



SCHEME 3 Proposed mechanistic pathway for synthesis of indole 3,3′-trimer

in the absence of any solvent. The MDM2-p53 inhibitor can be synthesized in gram scale under the present condition in high yield. Our present methodology thus may be a meaningful effort to synthesize biologically active indole 3,3′-trimer with different substituents.

4 | EXPERIMENTAL SECTION

4.1 | General information

A glass disk with an electric hot plate has been used for determination of melting points and is uncorrected. DMSO-d_6 and $CDCl_3$ solutions have been used to record ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra. Before the reaction, all the purchased substrates have been distilled. Different reagents and solvents were bought from Aldrich, Merck, Fluka, SRL, Process Chemicals, and Spectrochem. Oven-dried glass wares were used for all the reactions. We have prepared the Brønsted acidic ionic liquids following the literature.[26]

4.2 | General procedure for the synthesis of 2-(2,2-di[1*H*-indol-3-yl]ethyl)aniline (2a)

In the reaction vessel, BAIL-1 (10 mol%) was added with indole (**1a**, 1 mmol), and then the mixture was stirred continuously for 1 hour at 80°C. Water was added to the reaction mixture after its completion (TLC). By filtration, the crude product was separated, and by evaporation of the water, the ionic liquid was recovered. Again, after reactivation of the recovered ionic liquid, it was reused for another new reaction. Ethanol has been used to wash the crude product to afford the desired pure product (**2a**) as brown solid.

4.2.1 | 2-(2,2-Di[1*H*-indol-3-yl]ethyl) aniline (2a)

Yield: 85%, 99 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (s, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 7.16-7.12 (m, 2H), 7.01-6.96 (m, 4H), 6.92 (d, J = 2.4 Hz, 2H), 6.66-6.62 (m, 1H), 6.56-6.54 (m, 1H), 4.86 (t, J = 14.8 Hz, 1H), 3.41 (d, J = 7.2 Hz, 2H), 3.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.8, 136.6, 130.4, 127.0 (2C), 126.1, 122.0, 121.9, 119.7, 119.6, 119.2, 118.8, 115.8, 111.2, 37.2, 34.5.[24e]

4.2.2 | 2-(2,2-Bis[5-methyl-1*H*-indol-3-yl] ethyl)-4-methylaniline (2b)

Yield: 82%, 107 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (s, 2H), 7.28 (s, 2H), 7.19 (d, J = 8 Hz, 2H), 7.02-6.99 (m, 2H), 6.93-6.83 (m, 4H), 6.48 (d, J = 8 Hz, 2H), 4.83 (t, J = 14.4 Hz, 1H), 3.38 (d, J = 7.2 Hz, 2H), 3.09 (s, 2H), 2.40 (s, 6H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.3, 134.9, 130.9, 128.2, 128.0, 127.3, 127.2, 126.5, 123.4, 122.2, 119.4, 119.3, 116.0, 110.7, 37.3, 34.6, 21.5, 20.6.[24e]

4.2.3 | 2-(2,2-Bis[5-methoxy-1*H*-indol-3-yl]ethyl)-4-methoxyaniline (2c)

Yield: 80%, 117 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (s, 2H), 7.21 (s, 1H), 7.18 (s, 1H), 6.99 (d, J = 2.4 Hz, 2H), 6.85 (d, J = 2.4 Hz, 2H), 6.79 (d, J = 2.4 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.58-6.54 (m, 2H), 6.47 (d, J = 8.4 Hz, 1H), 4.71 (t, J = 14.8 Hz, 1H), 3.69 (s, 6H), 3.55 (s, 3H), 3.38 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 152.9, 138.7, 131.9, 128.0, 127.5, 122.7, 119.5, 117.1, 116.3, 112.7, 112.1, 111.8, 101.8, 55.9, 55.7, 37.7, 35.0.[24e]

4.2.4 | 2-(2,2-Bis[5-fluoro-1*H*-indol-3-yl] ethyl)-4-fluoroaniline (2d)

Yield: 77%, 103 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 2H), 7.25-7.22 (m, 2H), 7.09 (d, J = 2.4 Hz, 2H), 7.00-6.97 (m, 2H), 6.89-6.84 (m, 2H), 6.69-6.66 (m, 1H), 6.60-6.57 (m, 1H), 6.52-6.48 (m, 1H), 4.66 (t, J = 16 Hz, 1H), 3.34 (d, J = 7.6 Hz, 2H), 3.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.6 (d, $J_{C\text{-}F}$ = 233 Hz), 140.8, 133.2, 127.2 (d, $J_{C\text{-}F}$ = 15 Hz), 123.5, 119.0 (d, $J_{C\text{-}F}$ = 7 Hz), 116.9, 116.7 (d, $J_{C\text{-}F}$ = 7 Hz), 113.7, 113.4, 111.9, 111.8, 110.7, 110.5, 104.5 (d, $J_{C\text{-}F}$ = 23 Hz), 36.9, 34.5.[24e]

4.2.5 | 2-(2,2-Bis[5-chloro-1*H*-indol-3-yl] ethyl)-4-chloroaniline (2e)

Yield: 79%, 119 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 2H), 7.30 (d, J = 2 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.08-7.06 (m, 2H), 7.00 (d, J = 2.4 Hz, 2H), 6.95-6.92 (m, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 4.66 (t, J = 14.8 Hz, 1H), 3.28 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4, 135.0, 133.7, 130.1, 127.8, 127.1, 125.1, 123.4, 123.2, 122.5, 119.0, 118.6, 117.0, 112.4, 36.9, 34.3.[24e]

4.2.6 | 2-(2,2-Bis[5-bromo-1*H*-indol-3-yl] ethyl)-4-bromoaniline (2f)

Yield: 78%, 151 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 2H), 7.43 (d, J = 8 Hz, 2H), 7.22-7.16 (m, 4H), 7.09-7.06 (m, 1H), 6.98 (d, J = 2.4 Hz, 2H), 6.94 (d, J = 2.4 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.65 (t, J = 14.8 Hz, 1H), 3.27 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 135.3, 133.0, 130.1, 128.5, 127.5, 125.1, 123.0, 122.1, 118.5, 117.5, 112.8, 112.7, 110.6, 37.0, 34.3.[24e]

4.2.7 | 2-(2,2-Bis[6-chloro-1*H*-indol-3-yl] ethyl)-3-chloroaniline (2g)

Yield: 65%, 98 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (s, 2H), 7.29 (d, J = 1.6 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 1.6 Hz, 2H), 6.92-6.89 (m, 2H), 6.75-6.72 (m, 1H), 6.56-6.53 (m, 2H), 4.68 (t, J = 16 Hz, 1H), 3.35 (s, 2H), 3.30 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 136.9, 132.3, 131.5, 128.0, 125.3, 123.7, 122.3, 120.3, 120.0, 119.1, 118.5, 115.3, 111.1, 36.5, 34.3.[24e]

4.2.8 | 2-(2,2-Bis[1-methyl-1*H*-indol-3-yl] ethyl)-*N*-methylaniline (2h)

Yield: 81%, 106 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J = 8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.21-7.17 (m, 2H), 7.13-7.08 (m, 1H), 7.02-6.98 (m, 3H), 6.86 (s, 2H), 6.63-6.59 (m, 1H), 6.48 (d, J = 7.6 Hz, 1H), 4.82 (t, J = 14.8 Hz, 1H), 3.71 (s, 6H), 3.36 (d, J = 7.2 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.8, 137.4, 129.9, 127.4, 127.2, 126.6, 125.8, 121.5, 119.8, 118.7, 118.4, 117.1, 109.7, 109.2, 37.7, 34.5, 32.8, 30.7.[24e]

4.2.9 | 2-(2,2-Bis[1-ethyl-1*H*-indol-3-yl] ethyl)-*N*-ethylaniline (2i)

Yield: 79%, 114 mg; brown solid; mp 148-150°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.19-7.15 (m, 2H), 7.10-7.05 (m, 2H), 7.00-6.96 (m, 2H), 6.93 (s, 2H), 6.65-6.61 (m, 1H), 6.48 (d, J = 7.6 Hz, 1H), 4.77 (t, J = 14.4 Hz, 1H), 4.13-4.07 (m, 4H), 3.40 (d, J = 7.2 Hz, 2H), 2.72-2.67 (m, 2H), 1.40 (t, J = 14.8 Hz, 6H), 0.77 (t, J = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.0, 136.4, 130.3, 127.5, 127.1, 126.2, 125.1, 121.3, 120.1, 118.6, 118.3, 117.0, 110.4, 109.3, 40.9, 38.4, 37.5, 35.6, 15.7, 14.2.

4.2.10 | 2-(2,2-Bis[1-propyl-1*H*-indol-3-yl] ethyl)-*N*-propylaniline (2j)

Yield: 77%, 122 mg; white solid; mp 128-130°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, J = 8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.23-7.19 (m, 2H), 7.15-7.08 (m, 2H), 7.05-7.01 (m, 2H), 6.97 (s, 2H), 6.65 (t, J = 14.8 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 4.85 (t, J = 14 Hz, 1H), 4.05 (t, J = 14.4 Hz, 4H), 3.45 (d, J = 6.8 Hz, 2H), 3.29 (s, 1H), 2.74 (t, J = 14.4 Hz, 2H), 1.90-1.81 (m, 4H), 1.23-1.16 (m, 2H), 0.94 (t, J = 14.8 Hz, 6H), 0.88 (t, J = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.9, 136.7, 130.2, 127.4, 126.9, 126.4, 125.8, 121.2, 120.0, 118.4, 117.9, 116.7, 110.2, 109.3, 47.9, 45.8, 37.2, 35.3, 23.5, 22.3, 11.7, 11.5.

4.2.11 | 2-(2,2-Bis[1-isopropyl-1*H*-indol-3-yl]ethyl)-*N*-isopropylaniline (2k)

Yield: 76%, 120 mg; brown solid; mp 112-114°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.05-7.01 (m, 2H), 6.95-6.91 (m, 4H), 6.88-6.84 (m, 2H), 6.49-6.46 (m, 1H), 6.36 (d, J = 8 Hz, 1H), 4.62 (t, J = 14 Hz, 1H), 4.52-4.45 (m, 2H), 3.30 (d,

J = 6.8 Hz, 2H), 3.30-3.22 (m, 1H), 2.98 (s, 1H), 1.36 (d, J = 6.4 Hz, 6H), 1.31 (d, J = 6.8 Hz, 6H), 0.63 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 136.4, 130.7, 127.5, 126.9, 126.4, 121.7, 121.1, 120.1, 118.6, 118.2, 116.5, 110.9, 109.5, 46.9, 43.4, 37.4, 36.4, 22.9, 22.8.

4.2.12 | 2-(2,2-Bis[1-isobutyl-1*H*-indol-3-yl]ethyl)-*N*-isobutylaniline (2l)

Yield: 70%, 121 mg; white solid; mp 106-108°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, J = 8 Hz, 2H), 7.27-7.25 (m, 2H), 7.14-7.10 (m, 2H), 7.05-7.01 (m, 1H), 6.97-6.92 (m, 3H), 6.89 (s, 2H), 6.54-6.48 (m, 2H), 4.78 (t, J = 14.8 Hz, 1H), 3.83-3.80 (m, 4H), 3.40 (d, J = 7.2 Hz, 2H), 3.38 (s, 1H), 2.59 (d, J = 6.8 Hz, 2H), 2.18-2.09 (m, 2H), 0.88 (d, J = 6.4 Hz, 12H), 0.81 (d, J = 6.4 Hz, H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.8, 137.0, 130.3, 127.4, 127.0, 126.4, 125.6, 121.2, 120.0, 118.5, 117.8, 116.6, 110.2, 109.6, 54.0, 52.0, 37.2, 35.1, 31.7, 29.6, 20.7, 20.4.

4.2.13 | 2-(2,2-Bis[1-butyl-1*H*-indol-3-yl]ethyl)-*N*-butylaniline (2m)

Yield 72%, 124 mg; brown gummy mass; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 7.15-7.11 (m, 2H), 7.07-7.00 (m, 2H), 6.97-93 (m, 2H), 6.89 (s, 2H), 6.60-6.56 (m, 1H), 6.46 (d, J = 8 Hz, 1H), 4.74 (t, J = 14 Hz, 1H), 4.05-4.00 (m, 4H), 3.38 (d, J = 7.2 Hz, 2H), 3.16 (s, 1H), 2.67 (t, J = 14.4 Hz, 2H), 1.78-1.70 (m, 4H), 1.30-1.21 (m, 6H), 1.08-1.02 (m, 2H), 0.91 (t, J = 14.8 Hz, 3H), 0.84 (t, J = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.2, 136.8, 131.1, 130.4, 129.0, 127.5, 127.1, 125.9, 121.3, 120.1, 118.5, 117.9, 110.4, 109.4, 46.0, 37.3, 35.6, 32.5, 31.2, 20.5, 20.3, 19.3, 14.0, 13.9.

4.2.14 | 2-(2,2-Bis[1-pentyl-1*H*-indol-3-yl]ethyl)-*N*-pentylaniline (2n)

Yield: 67%, 125 mg; brown gummy mass; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 7.07-7.03 (m, 2H), 6.97-6.92 (m, 2H), 6.88-6.85 (m, 2H), 6.81 (s, 2H), 6.52-6.48 (m, 1H), 6.39 (d, J = 7.6 Hz, 1H), 4.66 (t, J = 8 Hz, 1H), 3.96-3.92 (m, 4H), 3.31 (t, J = 7.2 Hz, 2H), 3.09 (s, 1H), 2.58 (t, J = 15.2 Hz, 2H), 1.75-1.61 (m, 6H), 1.24-1.15 (m, 12H), 0.81-0.78 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.8, 136.6, 130.2, 127.3, 126.9, 125.9, 125.7, 121.1, 119.9, 118.4, 117.8, 116.7, 110.1, 109.2, 53.4, 46.1, 37.1, 35.4, 29.9, 29.4, 29.0, 29.7, 22.4, 22.3, 14.0, 13.9.

4.2.15 | *N*-Allyl-2-(2,2-bis[1-allyl-1*H*-indol-3-yl]ethyl)aniline (2o)

Yield: 73%, 114 mg; brown solid; mp 84-86°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, J = 8 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.15-7.11 (m, 2H), 7.06-6.91 (m, 6H), 6.61-6.57 (m, 1H), 6.46 (d, J = 8 Hz, 1H), 5.98-5.89 (m, 2H), 5.60-5.52 (m, 1H), 5.16-5.13 (m, 2H), 5.06-4.98 (m, 4H), 4.80 (t, J = 14.4 Hz, 1H), 4.65-4.63 (m, 4H), 3.40 (d, J = 7.2 Hz, 2H), 3.36-3.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4, 136.9, 135.5, 133.8, 130.3, 127.6, 127.1, 126.0, 125.8, 121.5, 120.0, 118.8, 118.7, 117.3, 117.0, 115.9, 110.7, 109.6, 48.8, 46.6, 37.5, 35.1.

4.2.16 | 2-(2,2-Bis(1-[prop-2-yn-1-yl]-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl) aniline (2p)

Yield: 71%, 110 mg; brown solid; mp 108-110°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, J = 8 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.12-7.09 (m, 2H), 7.03-6.96 (m, 2H), 6.92-6.88 (m, 4H), 6.62-6.58 (m, 1H), 6.45 (d, J = 8 Hz, 1H), 4.70-4.67 (m, 5H), 3.37 (s, 1H), 3.31-3.27 (m, 4H), 2.27 (t, J = 4.8 Hz, 2H), 2.03 (t, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.7, 136.5, 130.4, 127.9, 127.2, 126.6, 125.1, 122.0, 120.1, 119.4, 119.3, 118.5, 111.1, 109.4, 81.4, 78.2, 73.5, 71.0, 37.8, 35.9, 35.0, 31.7.

4.2.17 | *N*-Benzyl-2-(2,2-bis[1-benzyl-1*H*-indol-3-yl]ethyl)aniline (2q)

Yield: 74%, 153 mg; white solid; mp 135-137°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, J = 8 Hz, 2H), 7.33-7.24 (m, 11H), 7.19-7.05 (m, 12H), 6.66 (t, J = 14.8 Hz, 1H), 6.54 (d, J = 8 Hz, 1H), 5.27 (s, 4H), 4.94 (t, J = 14.8 Hz, 1H), 3.97 (s, 2H), 3.86 (s, 1H), 3.52 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.5, 139.7, 138.0, 137.0, 130.4, 128.8, 128.6, 127.6, 127.5, 127.4, 127.1, 127.0, 126.6, 126.2, 125.7, 121.7, 120.0, 119.0, 118.7, 117.3, 110.8, 109.8, 49.9, 48.2, 37.3, 35.0.

4.2.18 | 2-(2,2-Bis[1,5-dimethyl-1*H*-indol-3-yl]ethyl)-*N*,4-dimethylaniline (2r)

Yield: 76%, 122 mg; white solid; mp 154-156°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.28 (m, 2H), 7.21 (d,

J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.98-6.94 (m, 2H), 6.84 (s, 2H), 6.42 (d, J = 8 Hz, 1H) 4.79 (t, J = 13.2 Hz, 1H), 3.71 (s, 6H), 3.33 (d, J = 5.6 Hz, 2H), 2.42 (s, 6H), 2.39 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 135.9, 130.8, 127.7, 127.6, 126.8, 126.3, 126.1, 123.1, 119.7, 118.2, 110.0, 108.8, 38.0, 34.7, 32.8, 31.0, 21.6, 20.6.

4.2.19 | 2-(2,2-Bis[5-methoxy-1-methyl-1*H*-indol-3-yl]ethyl)-4-methoxy-*N*-methylaniline (2s)

Yield: 76%, 122 mg; brown solid; mp 79-81°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16-7.13 (m, 2H), 6.83-6.81 (m, 6H), 6.68-6.66 (m, 2H), 6.40-6.37 (m, 1H), 4.66 (t, J = 14.4 Hz, 1H), 3.71 (s, 6H), 3.68 (s, 6H), 3.59 (s, 3H), 3.31 (d, J = 7.2 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.5, 151.9, 142.5, 132.9, 127.9, 127.7, 127.2, 118.0, 116.9, 112.2, 111.7, 111.0, 109.9, 101.9, 56.0, 38.2, 34.8, 33.0, 31.5.

4.2.20 | 2-(2,2-Bis[5-chloro-1-methyl-1*H*-indol-3-yl]ethyl)-4-chloro-*N*-methylaniline (2t)

Yield: 76%, 122 mg; white solid; mp 188-190°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.28 (m, 2H), 7.19-7.17 (m, 2H), 7.12-7.04 (m, 3H), 6.86-6.82 (m, 3H), 6.40 (d, J = 8.8 Hz, 1H), 4.62 (t, J = 14.8 Hz, 1H), 3.71 (s, 6H), 3.27 (s, 1H), 3.22 (d, J = 6.4 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.3, 135.9, 129.7, 128.1, 127.8, 127.2, 126.8, 124.7, 122.1, 121.8, 119.1, 117.3, 111.0, 110.4, 37.3, 34.2, 33.1, 30.8.

4.2.21 | 2-(2,2-Bis[1-ethyl-5-methoxy-1*H*-indol-3-yl]ethyl)-*N*-ethyl-4-methoxyaniline (2u)

Yield: 75%, 131 mg; white solid; mp 70-72°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19-7.17 (m, 2H), 6.92 (s, 2H), 6.82-6.80 (m, 4H), 6.72 (d, J = 2.8 Hz, 1H), 6.67-6.64 (m, 1H), 6.38 (d, J = 8.8 Hz, 1H), 4.63 (t, J = 14.8 Hz, 1H), 4.09-4.04 (m, 4H), 3.69 (s, 6H), 3.64 (s, 3H), 3.37 (d, J = 7.2 Hz, 2H), 2.58-2.52 (m, 2H), 1.38 (t, J = 14.4 Hz, 6H), 0.73 (t, J = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 151.8, 141.8, 131.8, 128.4, 127.8, 125.5, 117.7, 116.8, 112.1, 111.7 (2C), 109.9, 101.9, 55.9, 55.8, 41.1, 39.1, 37.8, 36.0, 15.7, 14.3.

4.2.22 | 2-(2,2-Bis[5-chloro-1-ethyl-1*H*-indol-3-yl]ethyl)-4-chloro-*N*-ethylaniline (2v)

Yield: 74%, 132 mg; brown solid; mp 145-47°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.27 (m, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.01-7.07 (m, 2H), 7.03-7.01 (m, 1H), 6.93 (s, 2H), 6.85 (d, J = 2.4 Hz, 1H), 6.37 (d, J = 8.8 Hz, 1H), 4.57 (t, J = 14.4 Hz, 1H), 4.13-4.06 (m, 4H), 3.26 (d, J = 7.6 Hz, 2H), 2.98 (s, 1H), 2.70-2.65 (m, 2H), 1.40 (t, J = 14.4 Hz, 6H), 0.80 (t, J = 14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.6, 134.9, 130.1, 128.3, 127.2, 127.1, 126.2, 124.6, 121.9, 121.6, 119.3, 117.0, 111.5, 110.5, 41.2, 38.6, 36.9, 35.4, 15.7, 14.3.

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