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Research Article

Synthesis and Evaluation of Antimicrobial Activities of Novel N-Substituted Indole Derivatives

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Indole motifs are one of the most significant scaffolds in the discovery of new drugs. We have described a synthesis of new N-substituted indole derivatives (**1**-**3**), and their *in vitro* antimicrobial activities were investigated. The synthesis of titled compounds has been demonstrated by utilizing commercially available starting materials. The antibacterial and antifungal activities were performed using new strains of bacteria *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* using the disc diffusion method. Notably, the compound 4-(1-(2-(1H-indol-1-yl) ethoxy) pentyl)-N,N-dimethyl aniline (**1**) was found to be most potent than the other analogues (**2** and **3**), which has shown higher inhibition than the standard drug chloramphenicol.

1. Introduction

The versatility of heterocycles has been known from the century since their direct involvement in natural products [1–4]. Particularly, the nitrogen-containing heterocycles (N-heterocycles) have proven ubiquitous structural features and pivotal role in medicinal chemistry [5–11]. Amongst the various N-heterocycles, indole motifs have received significant attention due to their presence in proteins, amino acids, bioactive alkaloids, and drugs (Figure 1) [12–23]. In this context, a large number of indole moieties have been investigated in the development of new efficient bioactive molecules with diverse pharmacological properties, such as antimicrobial, antiviral, anticancer, anti-inflammatory, inhibitors, and antioxidant [24–47]. Generally, indoles substituted at 2nd or 3rd position [48–50], are known to exhibit certain bioactivity. On the other hand, the importance of N1-substituted indole derivatives in marketed drug molecules, natural products, and marine organisms are at great extent [51–53]. Despite the structural novelties and valuable biological activities of N1-substituted indoles [54], it remains challenging due to the inertness of the nitrogen atom (-NH-) towards electrophilic reagents [55–61].

A literature survey reveals that the infections caused by bacteria, fungi, or microorganisms in tropical and subtropical regions could be controlled by designing new antimicrobial agents [62, 63]. In an attempt to design and synthesize new antimicrobial agents, herein, we reported the synthesis of N1-alkylated indole derivatives and investigation of their antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *and Candida albicans* (Figure 2).

2. Results and Discussion

As part of our studies to design new bioactive N-substituted indole derivatives, we envisaged that the utilization of commercially available 4-N,N-dimethylamino benzaldehyde might be suitable for the syntheses of target compounds **1**–**3**. The retrosynthetic analyses of N-substituted indoles (**1**-**3**) are outlined in Scheme 1. In order to find suitable synthons, firstly, the cleavage of C-O bond resulted to N-alkylated indole **7** and the corresponding benzylic alcohols **4**-**6**, which could be envisaged to form desired compounds (**1**–**3**) *via* O-alkylation reaction. Furthermore, a common intermediate **7** could be synthesized *via* N-alkylation reaction of commercially available indole (**9**) and 1,2-dibromoethane

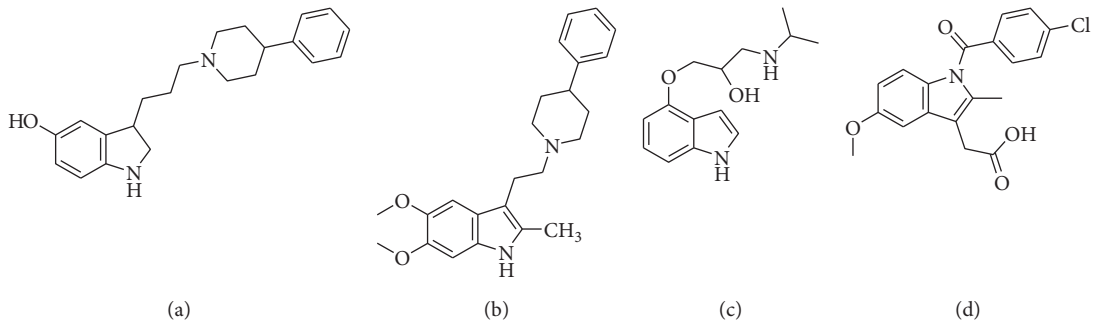


Figure 1: Representative examples of drugs with indole. (a) Roxindole schizophrenia. (b) Oxypertine antipsychotic drug. (c) Pindolol antihypertensive drug. (d) Indometacin anti-inflammatory drug.

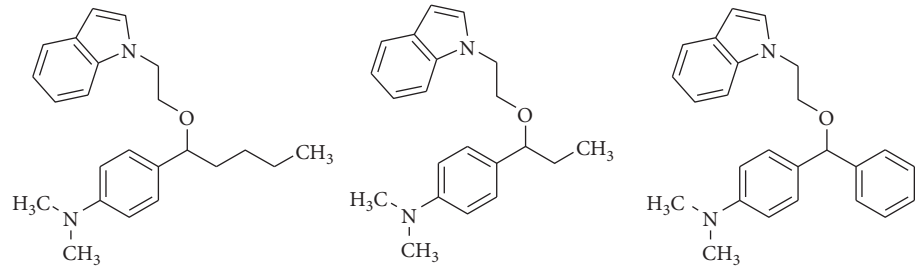
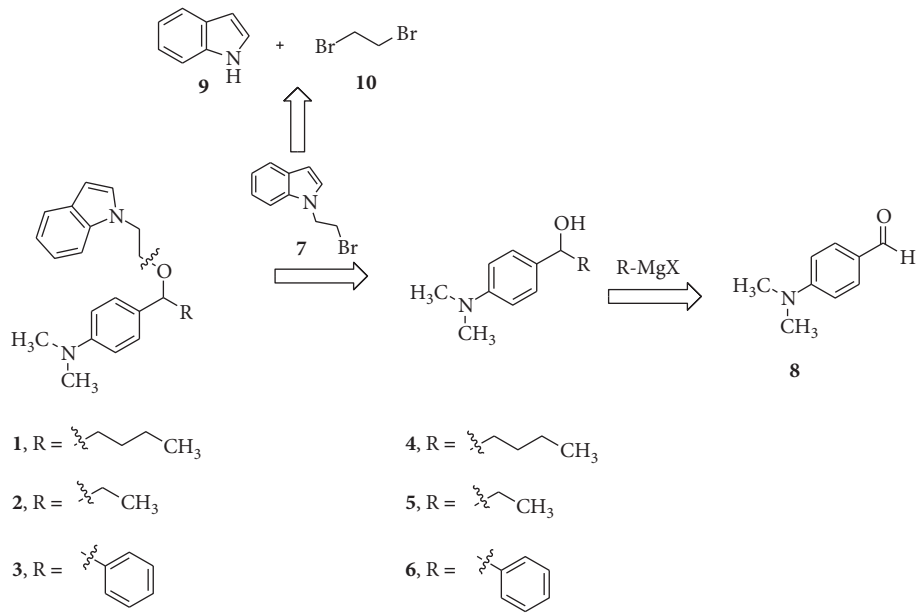


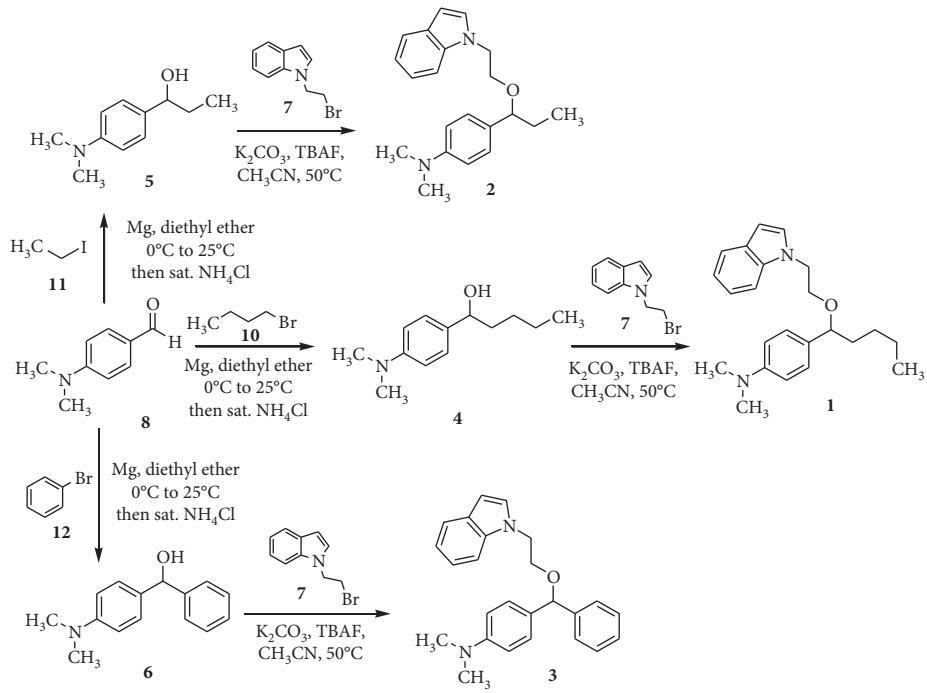
Figure 2: New bioactive indole derivatives.



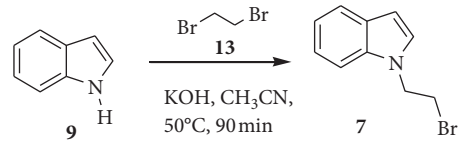
Scheme 1: Retrosynthesis of compounds **1–3**.

(**10**). Finally, the benzylic alcohols **4-6** could be obtained by performing Grignard reaction of 4-N,N-dimethylamino benzaldehyde (**8**) with the corresponding alkyl or aryl halide.

To validate our outlined approach, we have commenced our synthesis by performing Grignard reaction of 4-N,N-dimethylamino benzaldehyde (**8**) with *n*-BuMgBr, which was prepared by in situ reaction of *n*-BuBr (**10**) and Mg in diethyl ether solvent resulting in benzylic alcohol **4** at an excellent yield (Scheme 2). Similarly, the other benzylic alcohols **5** and **6** were successfully obtained by subjecting "Grignard reaction" of 4-N,N-dimethylamino benzaldehyde (**8**) with EtMgBr and PhMgBr, respectively. Next, we investigated the synthesis of N-alkyl indole (**7**) *via* N-alkylation, employing commercially available indole (**9**) with 1,2-dibromoethane (**13**) in the presence of potassium hydroxide as base and DMF as a solvent (Scheme 3) [64]. In



Scheme 2: Synthesis of target compounds **1–3**.



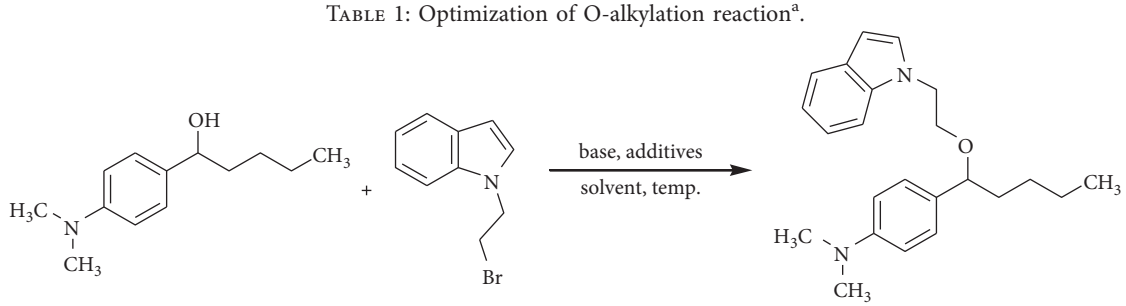
Scheme 3: Synthesis of N-alkylated indole **7**.

order to accomplish the synthesis of desired compounds **1–3**, we decided to facilitate O-alkylation of benzylic alcohol (**4**) with readily synthesized N-alkylated indole (**7**). To our surprise, the O-alkylation reactions reduced the yield and prolonged the reaction time. To overcome this problem, we began to optimize O-alkylation reaction under different conditions, and the results are presented in Table 1.

The O-alkylation between 1-(4-(dimethylamino)phenyl)pentan-1-ol (**4**) and N-alkylated indole (**7**) employing KOH as base under neat conditions resulted traces of O-alkylated product (**1**) along with the domination of unidentified side reactions (Table 1, entry 1). Screening of various solvents such as pyridine, acetonitrile, and dimethyl formamide provided slightly improved yields of O-alkylated product (**1**) (entries 3–6). However, substantial amount of starting material was recovered during the course of reaction. Subsequently, it was found that Chi and Kazemi exploited ionic-liquids and phase transfer catalyst in alkylation reaction [65, 66]. The situation improved dramatically, when we utilized the combination of K_2CO_3/TBAF in acetonitrile to provide the corresponding O-alkylated product (**1**) with 72% yield (entry 7). Thus, the optimized reaction conditions involved benzylic alcohol (**4**) (1.5 mmol), N-alkyl indole (**7**) (1 mmol), K_2CO_3 (1 mmol), TBAF (1 mmol), and acetonitrile (10 mL) heated at 50°C. Under the optimized conditions, we then explored O-alkylation of 1-(4-(dimethylamino)phenyl)propan-1-ol (**5**) and (4-(dimethylamino)phenyl) (phenyl)methanol (**6**) with N-alkyl indole (**7**) to provide the desired compounds **2** and **3** with good yields, respectively.

2.1. In Vitro Antimicrobial Activity. *In vitro* antifungal activities of the synthesized compounds **1–3** were evaluated utilizing *Staphylococcus aureus* and *Escherichia coli* and antifungal activity against *Candida albicans* using disc diffusion method (Table 2). The inhibition zone was measured in diameter. Bavistin and chloramphenicol were used as the standard drug to compare antifungal activity. In order to investigate antifungal activity, the inhibition against the test organisms and ethanol as positive control, and the effectiveness of the target compounds (**1–3**) was measured by calculating inhibition zone against the tested organisms. The zone of inhibition was compared with the standard drug after 72 h. Organisms *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) were subcultured into sterile nutrient broth. Then, aliquots of 50% and 100% of the sample solutions of target compounds, **1–3**, were

Table 1: Optimization of O-alkylation reaction[a].



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Entry	Base (mol%)	Additives (equiv.)	Solvent (mL)	Temperature (°C)	Yield of 1[b,c] (%)
1	KOH	—	Neat	25	Traces
2	Pyridine	—	Pyridine	80	nr
3	K_2CO_3	—	CH_3CN	80	25
4	K_2CO_3	—	DMF	100	20
5	K_2CO_3 (50)	TBAF	DMF	80	35
6	K_2CO_3 (50)	TBAF (1)	CH_3CN	50	50
7	K_2CO_3 (100)	TBAF (1)	CH_3CN	50	72[d]

[a]Reaction conditions: alcohol (1.5 mmol), indole-alkyl bromide (1 mmol), base, and solvent; [b]isolated yield; [c]characterized by IR and NMR; [d]further yield did not improve even when the 1.5 equiv. of base was utilized.

Table 2: Antimicrobial activities of target compound **1–3**.

Sr.No	Compounds	Zone of inhibitions (mm)					
		Escherichia coli		*Staphylococcus aureus*		*Candida albicans*	
		50%	100%	50%	100%	50%	100%
1	**1**	—	—	25	27	—	—
2	**2**	—	—	18	20	—	—
	3			15	20		
3	Chloramphenicol	2	3	18	20	—	—
4	Bavistin	—	—	—	—	20	30
5	Negative control	—	—	—	—	—	—

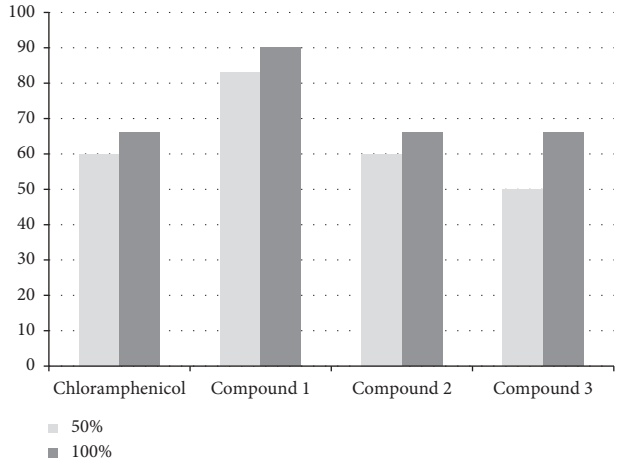

Figure 3: Comparison of % of bioactivity: chloramphenicol drug with compounds **1–3**.

pipetted to the discs in three replications each. The discs were impregnated with the sample solutions and then transferred to nutrient agar (NA) plate seeded with bacteria and incubated at 37°C for 24 h. Subsequently, the plates were examined for microbial growth of inhibition, and the inhibition zone diameter was measured to the nearest mm. All the tests were performed in triplicate. Obtained bioactivity results were compared with commercially available drugs, chloramphenicol and bavistin, and the results are presented in Figure 3.

3. Conclusion

We have reported the synthesis of indole derivatives using commercially available starting materials, and their antimicrobial activity was also investigated. The *in vitro* bioactivity was performed using *Staphylococcus aureus*, *Escherichia coli*, *and Candida albicans* as antibacterial and antifungal, respectively, using the disc diffusion method. The mean inhibition zone of commercially available drug chloramphenicol and bavistin was used as standard, and inhibition zone was calculated in mm. Compounds **1–3** tested for antifungal and antibacterial activity showed poor inhibition against Gram-negative bacteria *Escherichia coli*. On the other hand, compounds **1–3** showed good bioactivity towards pathogen *Staphylococcus aureus*, Gram-positive bacteria. Interestingly, it was observed that compound **1**, which incorporates butyl substitue nts, exhibited enhanced selectivity compared with analogues **2** and **3**. Further

extension of designing new indole derivatives is currently under development.

4. Experimental

4.1. General Experimental Procedure. FTIR spectra of the synthesized compounds were recorded on a Shimadzu 4000 instrument using KBr pellet within the range of 400 ± 10 to $4000 \pm 10\ cm^{-1}$. ^{1}H-NMR, ^{13}C-NMR, and DEPT-135 spectra of compounds were recorded on Bruker Avance II-400 MHz NMR spectrometer in deuterated $CDCl_3$, MeOD and DMSO solvents using TMS as internal standard. Chemical shift values are expressed in δ (ppm).

4.1.1. Pharmacological Reagents. Reagents for biochemical assays such as potato dextrose agar (PDA, Micro master laboratories, India), nutrient agar (NA, Aldrich chemical company, Germany), bavistin (Domina Pharmaceuticals, India), chloramphenicol (Addis Pharmaceuticals S.C., Adigrat, Ethiopia) were used for the antimicrobial studies.

4.2. Synthesis of 1-(4-(dimethylamino)phenyl)pentan-1-ol (4). To an oven-dried three necked round bottom flask, Mg turnings (1.25 g, 5.14 mmol) was charged followed by the addition of iodine crystals (3 piece) and covered the flask with a $CaCl_2$ dry tube. To this, anhydrous diethyl ether (100 mL) was added using addition funnel. The whole reaction mixture was allowed to stir for 10 minutes. Then, bromobutane (**10**) (4.4 mL, 4.0 mmol) was introduced dropwise with the help of syringe. In order to initiate the reaction, the flask was warmed using hot water, and the addition of bromobutane was continued. It was observed that vigorous reaction between magnesium and bromobutane leads to the formation of Grignard reagent. The Grignard reagent in the flask appears grey in color. To the formed Grignard reagent (BuMgBr), 4-dimethylamino benzaldehyde (**8**) (5 g, 3.35 mmol) dissolved in 50 mL anhydrous DEE was introduced with the help of an addition funnel (dropwise). After the completion of the reaction (1 h), which was monitored by TLC, the mixture was quenched with saturated solutions of NH_4Cl (20 mL). The resulting mixture was transferred to a separatory funnel followed by the addition of ethyl acetate (50 mL), and the aqueous layer was removed, and the organic layer was dried with sodium sulphate. The solvent was removed using rotary evaporator, and compound **4** was obtained as the crude product. Then, further purification of the residue was performed using column chromatography using 20% ethyl acetate in petroleum ether as an eluent to give the pure 1-(4-(dimethylamino)phenyl)pentan-1-ol (**4**).

4.2.1. Appearance. Pale yellow oil yield = 72% (4.9 g); FT-IR (KBr, cm^{-1}). 3311(O-H str), 3072(C-H str, ring/cyclic), 2927(C-H str, acyclic), 1615(C=C str), 1464(C-C str); ^{1}H-NMR ($CDCl_3$/TMS) δ 0.92 (*t*, 3H, -CH_2CH_3), 1.21-1.29 (*m*, 2H,-$CH_2CH_2CH_3$), 1.40 (*q*, 2H, -CH_2-CH-OH), 3.06 (*s*, 6H, N-CH_3), 4.0 (*t*, 1H, OH), 4.58 (*t*, 1H, Ar-CH-OH), 6.76 (*d*, 1H,Ar-H), 6.76 (*d*, 1H,Ar-H), 7.25 (*d*, 1H,Ar-H); ^{13}C-NMR ($CDCl_3$/TMS) δ 76-78 ($CdCl_3$), δ 14.09, 22.69, 28.19, 38.47, 40.78, 74.47, 112.45, 126.97, 132.99, 150.19.

4.3. Synthesis of 1-(4-(dimethylamino)phenyl)propan-1-ol (5) via Grignard Reaction. The synthesis 1-(4-(dimethylamino) phenyl)propan-1-ol (**5**) was also achieved by Grignard reaction. This reaction was carried out similar to the aforementioned process. A 500 mL oven-dried round bottom flask was charged with Mg (1.25 g, 51.42 mmol) and iodine crystal (0.2 g) followed by the addition of anhydrous diethyl ether (100 mL) and stirred for 5 min. To this solution, ethyl iodide (**6**) (3.23 mL, 40.17 mmol) was added slowly with the help of a syringe. Upon addition of ethyl iodide, the reaction mixture color was changed from brown to grey color, which indicates the formation of Grignard reagent. To this Grignard reagent, 4-N,N-dimethylamino benzaldehyde (**8**) (5 g, 33.51 mmol) dissolved in anhydrous DEE was added with the help of the addition funnel. The resulting reaction mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC 20% of ethyl acetate in petroleum ether. After completion of the reaction, saturated NH_4Cl (15 mL) was added to the reaction mixture. The combined organic layers was separated, washed, and dried over anhydrous Na_2SO_4. The crude product was obtained by removing organic solvent evaporated using the rotatory evaporator. Furthermore, the purification of crude product was performed using column chromatography: silica gel (100–200 mesh) and 30% ethyl acetate in petroleum ether as eluents to obtain pure 1-(4-(dimethylamino)phenyl)propan-1-ol (**5**).

Yield (80%), FR-IR (KBr) stretch(str) cm^{-1}: 1522.83, 1615.41 (str, C=C-Ar), 2873.98 (str, -CH_3), 2930.89 (str, -CH_2), 2959.82 (str, N(CH_3)$_2$), 3075.55(str, C-H), 3096.77, 3141.13 (str C-H-Ar), 3357.16 (str, O-H)^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 1.01 (t, 3H, CH_3), 1.62–1.96 (m, 2H, CH_2), 2.2 (brs, 1H, OH), 2.84 (s, 6H, N(CH_3)$_2$), 4.63 (t, 1H, -CH), 6.52 (d, 2H, Ar-H), 6.97 (d, 2H, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 07.87 (1C, -CH_3), 31.18 (1C,-CH_2), 40.67 (2C, N(CH_3)$_2$), 79.32 (1C, -C-OH), 114.87 (2C, Ar-C), 128.11 (2C, Ar-C), 129.17 (1C,Ar-C), 146.12 (1C, Ar-C).

4.4. Synthesis of (4-(dimethyl Amino) Phenyl) (Phenyl) Methanol (6). To a three-necked round bottom flask, oven-dried Mg 1.17 g (4.87 mmol) and few crystals of iodine were taken and maintained inert atmosphere. To this flask, anhydrous diethyl ether (100 mL) was added with continuous stirring. The solution turned into brown color, and the flask was warmed using hot water. Then, bromobenzene (**12**) (6.5 mL, 6.2 mmol) was added dropwise maintaining the flask in ice cold water while the addition of bromobenzene was continued. The color of the reaction mixture turned to grey due to the formation of Grignard reagent phenyl magnesium bromide (PhMgBr). To this reaction mixture, 4-dimethylamino benzaldehyde (**8**) (5 g, 3.35 mmol) dissolved in 40 mL of anhydrous DEE was added drop wise. After completion of reaction, which was monitored by TLC, the

reaction mixture was quenched with saturated solution of ammonium chloride (20 mL). The resulting organic layer was then transferred to the separatory funnel, and the collected organic layer was dried over sodium sulphate. The solvent was removed using rotary evaporator, and the crude residue was further purified by column chromatography. The column chromatography was performed using 20% ethyl acetate in petroleum ether as the eluent to give pure (4-(dimethyl amino) phenyl) (phenyl) methanol in 67% yield (5.15 g) as a pale yellow solid.

FT-IR (KBr, cm^{-1}): 3454(O-H str), 2923–2955(C-H str), 1615(C=C str); ^{1}H-NMR ($CDCl_3$/TMS): δ 2.90 (*s*, 6H, N-CH_3), 5.72 (*s*, 1H, $(Ar)_2$-CH-OH), 6.67 (*d*, 1H, OH), 7.16–7.38 (*d*, Ar-H); ^{13}C-NMR ($CDCl_3$/TMS): δ 40.12, 79.67, 114.22, 125.87, 129.12, 129.82, 130.11, 130.80, 131.13, 140.06, 146.67.

4.5. Synthesis of 1-(2-bromoethyl)-1H-indole (7). A 100 mL round bottom flask was charged with potassium hydroxide (3.83 g, 68.3 mmol) and tetrabutylammonium fluoride (0.14 g, 0.54 mmol). Then, indole (**9**) (2 g, 17.1 mmol), which was dissolved in anhydrous DMF (25 mL), was added slowly to the above mixture with stirring. Then, the reaction mixture was heated at 50 C for 1.5 h and then cooled to 0 C. To this cooled reaction mixture 1,2-dibromoethane (**10**) (1.5 mL, 17.1 mmol) was added slowly with the help of syringe. Furthermore, the reaction mixture was allowed to stir for 30 min at 0 C and again heated at 50 C for 2 h. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured in 70 mL water and extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine, and collected organic layers were dried over sodium sulphate. The solvent was removed using rotary evaporator, and the crude residue was subjected to column chromatography. The column chromatography was performed using silica gel and eluent combinations of petroleum ether/ethyl acetate (9 : 1) to obtain pure 1-(2-bromoethyl)-1H-indole in 54% yield (2.3 g) as pale yellow oil.

^{1}H-NMR ($CDCl_3$ + MeOD)/TMS): δ 3.33 (*t*, 2H, -CH_2-Br), 4.31 (*t*, 2H, N-CH_2-), 6.61 (*d*, 1H, pyrrole - H), 7.12 (*d*, 1H, benzene - H), 7.23 (*d*, 1H, pyrrole - H), 7.45 (*t*, 1H, benzene - H), 7.60 (*d*, 1H, benzene - H); ^{13}C-NMR ($CDCl_3$ + MeOD)/TMS): δ 80.9 ($CDCl_3$), 52.6 (MeOD), 25.4, 100.2, 108.7, 113.4, 124.5, 126.5, 127.2, 133.5, 139.4, 139.6.

4.6. Synthesis of 4-(1-(2-(1H-indol-1-yl) Ethoxy) pentyl)-N,N-dimethyl Aniline (1). A compound 1 was synthesized using *O*-alkylation reaction by combining intermediate **4** with **7**. To a round bottom flask Grignard product, secondary alcohol (**4**) (0.31 g, 1.5 mmol) was charged followed by the addition of phase transfer catalyst TBAF (0.31, 1.0 mmol) and acetonitrile (10 mL). This reaction mixture was stirred at room temperature, and then K_2CO_3 (0.14 g, 1 mmol) was added slowly and allowed whole reaction mixture to heat at 50 C. To this hot reaction mixture, N-alkylated product 1-(2-bromoethyl)-1H-indole (**7**) (0.224 g, 1 mmol) was added slowly. The reaction mixture was stirred further, and the progress of the reaction was monitored by TLC. After cooling the reaction mixture at room temperature, the reaction mixture was poured in 30 mL water and then extracted with 50 mL ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed using rotary evaporator.

The residue was purified by column chromatography and air pressure using a 1 : 12 (v/v) mixture of ethyl acetate and petroleum ether as eluting solution to afford 4-(1-(2-(1H-indol-1-yl) ethoxy) pentyl)-N, N-dimethyl aniline (**1**) in 72% yield (0.28 g) as yellow color oil.

^{1}H-NMR (DMSO/TMS): δ 1.30 (*t*, 3H, -CH_2CH_3), 1.65–1.81 (*m*, 4H, -$CH_3CH_2CH_2$-), 2.50 (*t*, 2H, O-CH-CH_2-), 3.14 (*s*, 6H, -N-$(CH_3)_2$), 4.76 (*t*, 2H, O-CH_2-), 4.94 (*t*, 2H, N-CH_2-), 5.36 (*t*, 1H, -O-CH-Ar), 6.37 (d, 1H,,pyrrole), 6.62 (*d*, 1, 1H, Ph.-H), 6.62 (*d*, 1H, Ar-H), 6.95, (t, 1H, Ar-H), 7.39 (d, 1H, Ph - H), 7.46 (*d*, 1H, pyrrole), 7.54 (*t*, 1H, Ar-H), 7.62 (*d*, Ar-H, 1H), 7.89 (*d*, 1H, Ar-H); ^{13}C-NMR (DMSO/TMS): δ 14.19, 23.27, 28.59, 35.62, 39.03, 40.80, 74.53, 77.68, 96.38, 105.29, 109.80, 113.01, 121.08, 121.43, 122.99, 127.15, 129.86, 130.22, 133.61, 149.93.

4.7. Synthesis of 4-((2-(1H-indol-1-yl) Ethoxy) (Phenyl) methyl)-N,N-dimethyl Aniline (2). The synthesis of target compound **2** was carried out by using the same procedure and conditions, which was described for the synthesis of compound **1**. To a round bottom flask Grignard product, secondary alcohol **6** (0.34 g, 1.5 mmol) was charged followed by the addition of phase transfer catalyst TBAF (0.316, 1.0 mmol) and acetonitrile (10 mL). The reaction mixture was stirred at room temperature, and then K_2CO_3 (0.14 g, 1 mmol) was added slowly and allowed whole reaction mixture to heat at 50°C. To this hot reaction mixture, N-alkylated product 1-(2-bromoethyl)-1H-indole (**7**) (0.224 g, 1.0 mmol) was added slowly. The reaction mixture was stirred further, and the progress of the reaction was monitored by TLC. After cooling the reaction mixture at room temperature, the reaction mixture was poured in 30 mL water and then extracted with 50 mL ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed using rotary evaporator. The residue was purified by column chromatography with air pressure using a 1 : 12 (v/v) mixture of ethyl acetate and petroleum ether as eluent to afford 4-((2-(1H-indol-1-yl) ethoxy) (phenyl) methyl)-N, N-dimethyl aniline (**2**) in 64% yield (0.25 g).

^{1}H-NMR (DMSO/TMS): δ 2.95 (d, 6H, -N-$(CH_3)_2$), 4.63 (*t*, 2H, -O-CH_2-), 5.07 (*t*, 2H, -N-CH_2), 5.66 (*s*, 1H, -O-CH-), 6.54 (*d*, 1H, Ar-H), 7.13 (*t*, 1H, Ar-H), 7.28 (*d*, 1H, Ar-H), 7.32 (*d*, 1H, pyrrole), 7.60 (*t*, 1H, Ar-H),7.68 (*d*, 1H, Ar-H); ^{13}C-NMR (DMSO/TMS): δ 40.59, 58.21, 96.48, 109.54, 110.52, 112.41, 120.71, 121.05, 123.42, 126.54, 127.73, 128.04, 129.30, 131.20, 132.66, 135.38, 139.23, 145.71, 149.73, 153.36.

4.8. Synthesis of 4-((2-(1H-indol-1-yl) Ethoxy) (Phenyl) methyl)-N,N-dimethyl Aniline (3). The synthesis of target compound **3** was carried out by using same procedure and

conditions, which was described for the synthesis of compound **1**.

The synthesis of target compound **2** was carried out by using same procedure and conditions, which was described for the synthesis of compound **1**. To a round bottom flask Grignard product, secondary alcohol **5** (0.34 g, 1.5 mmol) was charged followed by the addition of phase transfer catalyst TBAF (0.316, 1.0 mmol) and acetonitrile (10 mL). The reaction mixture was stirred at room temperature, and then K_2CO_3 (0.14 g, 1 mmol) was added slowly and allowed whole reaction mixture to heat at 50°C. To this hot reaction mixture, N-alkylated product 1-(2-bromoethyl)-1H-indole (**3**) (0.224 g, 1.0 mmol) was added slowly. The reaction mixture was stirred further, and the progress of the reaction was monitored by TLC. After cooling the reaction mixture at room temperature, the reaction mixture was poured in 30 mL water and then extracted with 50 mL ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed using rotary evaporator. The residue was purified by column chromatography with air pressure using a 1 : 12 (v/v) mixture of ethyl acetate and petroleum ether as eluent to afford 4-((2-(1H-indol-1-yl) ethoxy) (phenyl) methyl)-N, N-dimethyl aniline (**2**) in 64% yield (0.25 g).

^{1}H-NMR (DMSO/TMS): δ 2.95 (d, 6H, -N-$(CH_3)_2$), 4.63 (*t*, 2H, -O-CH_2-), 5.07 (*t*, 2H, -N-CH_2), 5.66 (*s*, 1H, -O-CH-), 6.54 (*d*, 1H, Ar-H), 7.13 (*t*, 1H, Ar-H), 7.28 (*d*, 1H, Ar-H), 7.32 (*d*, 1H, pyrrole), 7.60 (*t*, 1H, Ar-H),7.68 (*d*, 1H, Ar-H); ^{13}C-NMR (DMSO/TMS): δ 40.59, 58.21, 96.48, 109.54, 110.52, 112.41, 120.71, 121.05, 123.42, 126.54, 127.73, 128.04, 129.30, 131.20, 132.66, 135.38, 139.23, 145.71, 149.73, 153.36.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

This section includes FT-IR spectrum, 1H-NMR spectrum, 13C-NMR spectrum, and DEPT-135 spectrum of 1-(4-(dimethylamino)phenyl)pentan-1-ol (4); FT-IR spectrum and 1H-NMR spectrum of (4-(dimethyl amino)phenyl)(-phenyl) methanol (6); 1H-NMR spectrum of and 13C-NMR spectrum of 1-(2-bromoethyl)-1H-indole (6); 1H-NMR spectrum, 13C-NMR spectrum, and DEPT-135 spectrum of 4-(1-(2-(1H-indol-1-yl)ethoxy) pentyl)-N,N-dimethyl aniline (1); 1H-NMR spectrum and 13C-NMR spectrum of 4-((2-(1H-indol-1-yl)ethoxy) (phenyl) methyl)-N,N-dimethyl aniline (3). (*Supplementary Materials*)

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