Microwave Energized Synthesis of 2-Aroylindole Derivatives: Piperidine/DMF as an Effective Medium

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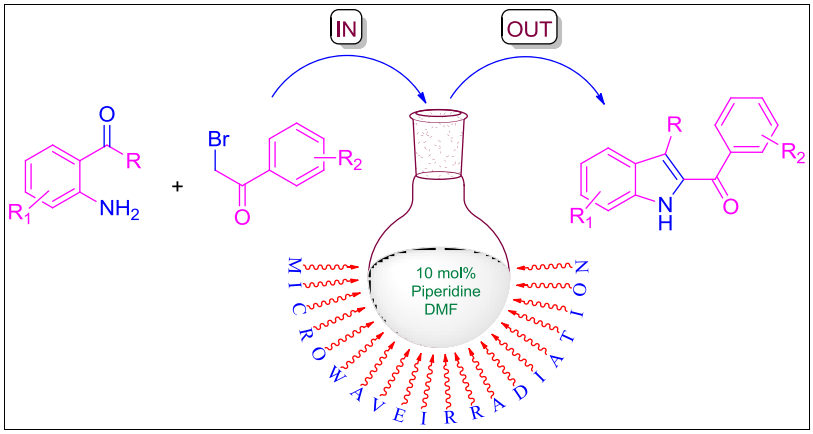

A convenient and efficient protocol has been developed for the synthesis of 2-aroylindoles (**3a–j**) in good yields by the reaction of 2-aminoketones (**1a–c**) with phenacyl bromides (**2a–d**). The reaction success varied with different bases and solvents in both conventional and microwave methods. But finally, it was established that piperidine in DMF was an effective medium to carry out the reaction under microwave irradiation conditions.

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INTRODUCTION

Indole framework is widely found in natural products, pharmaceuticals, and other synthetic compounds [1]. Owing to the great diversity of bioactivity, the indole ring system has become an important structural component in most of the biologically active alkaloids. Considering the significance of the indole pharmacophore, medicinal chemists repeatedly turn to indole-based compounds as they act as targets for the development of potential therapeutic agents [2].

Indole and its synthetic analogs are known to possess promising anticancer, antipyretic, antiHIV, analgesic, antihypertensive, and anticonvulsant [3–6] activity. Some examples in this class, which shows potential biological activity against anticancer, antiHIV, and antihypertensive, are 2-aroylindole (I), Delavirdine (II), and Pindolol (III), shown in Figure 1.

The development of new efficient synthetic methods leading to indole analogs continues to receive much attention in organic synthesis. Substituted indoles have been referred as "privileged structures" because they are capable of binding many receptors with high affinity [7,8]. Several multi component reactions have been reported for the synthesis of substituted indoles [9–11]. Among them, 2, 3-disubstituted indoles are important subclass of indoles, which are the core nucleus of many promising therapeutic agents [12]. Considering the significance of these compounds, a variety of synthetic methods have been developed for the synthesis of indole frameworks over the past hundred years right from fisher indole synthesis [13–17]. Despite these advances, development of new and convenient methods for 2, 3-disubstituted indoles [18–20], from simple and readily available starting materials, still remains to be accomplished.

In recent years, microwave accelerated chemical reactions are growing at a rapid rate. This technique provides an effective alternative energy source for effecting chemical reactions and processes [21]. Thus, application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over the conventional techniques. Microwave reactions are environmentally benign and finds valuable applications in organic [22], peptide synthesis [23], nanotechnology [24], polymer chemistry [25], and biochemical processes [26,27]. Herein, we report piperidine-promoted synthesis of 2, 3-substituted indoles in good to excellent yields by the reaction of phenacyl bromides with 2-aminoketone s in DMF under microwave irradiation conditions.

RESULTS AND DISCUSSION

2-Aroylindoles (**3a–j**) are obtained by the reaction of 2-aminoketone s with phenacyl bromides using piperidine base in DMF solvent under microwave irradiation conditions (Scheme 1).

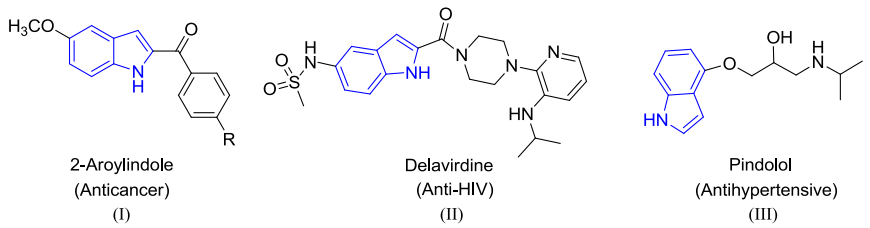
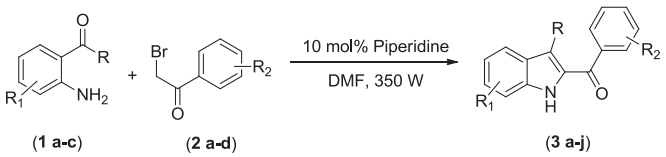


Figure 1. Important indole drugs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 1. 2-Aroylindoles synthesis from 2-aminoketone s and phenacyl bromides (**3a–j**).



To establish the appropriate reaction conditions for the synthesis of 2-aroylindoles, we have chosen the reaction between phenacyl bromide (**2a**) and 2-aminoacetophenone (**1a**) as a model reaction (Table 2). We carried out the model reaction and studied the effect of solvent, base, and reaction time under conventional and microwave conditions. We found significant improvement in the yield of the product with short reaction time by using microwave technique as compared to conventional technique. Overall, the best results were obtained by performing the model reaction in the presence of 10 mol% of piperidine in DMF under microwave conditions to yield the product **3a** in good yield (Table 1, entry 8). Note that increasing the amount of piperidine failed to improve the yield (Table 1, entries 16 and 17) while decreasing these parameters led to reduced yield (Table 1, entry 15). We did not found any improvement of the yield of the product by increasing the reaction time (Table 1, entries 18, 19, and 20). The results are summarized in Table 1.

Further, we repeated the model reaction at various microwave power ranges starting from 140 to 700 W to test its effect on model reaction, and the results are shown in Figure 2. It represents that performance of this reaction with irradiation

Table 1

Scrutinization of solvent and base for the synthesis of **3a**.

			Conventional heating		Microwave condition[c]	
Entry	Solvent	Base (mol%)	Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	Acetonitrile	Et_3N (10)	180	Trace	15	14
2	Ethanol	Et_3N (10)	180	—[b]	15	—[b]
3	THF	Et_3N (10)	180	—[b]	15	Trace
4	DMF	Et_3N (10)	180	28	15	34
5	Acetonitrile	Piperidine (10)	180	44	15	53
6	Ethanol	Piperidine (10)	180	Trace	15	14
7	THF	Piperidine (10)	180	32	15	44
8	DMF	Piperidine (10)	180	55	15	76
9	Acetonitrile	K_2CO_3 (10)	180	33	15	39
10	Ethanol	K_2CO_3 (10)	180	—[b]	15	—[b]
11	THF	K_2CO_3 (10)	180	Trace	15	18
12	DMF	K_2CO_3 (10)	180	43	15	52
13	DMF	No base	180	12	15	26
14	No solvent	No base	180	—[b]	15	—[b]
15	DMF	Piperidine (5)	180	46	15	63
16	DMF	Piperidine (15)	180	55	15	76
17	DMF	Piperidine (20)	180	55	15	76
18	DMF	Piperidine (10)	210	55	30	76
19	DMF	Piperidine (10)	240	55	45	76
20	DMF	Piperidine (10)	300	55	60	76

[a]Isolated yield.
[b]No reaction occurred.
[c]Reactions are carried out at 280 watts of microwave power.

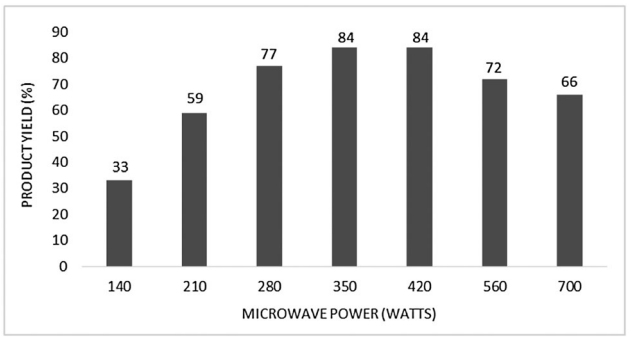


Figure 2. Effect of microwave power on model reaction.

power of 140, 210, 280, 350, and 420 W afforded the corresponding products with yields of 33%, 59%, 77%, 84%, and 84%, respectively. Further increase of the microwave oven power (560 and 700 W) showed decrease in the product yield with 72% and 66%, respectively. Perhaps this may be due to the formation of complex reaction mixtures at high MW power. Hence, 350 W of MW power is suitable to carry out this reaction for better results (Fig. 2).

After optimizing the experimental conditions for this reaction, we investigated its scope by reacting different phenacyl bromides and 2-aminoketones. The results are summarized in Table 2. Various phenacyl bromides worked well under the standardized reaction conditions. Particularly, trimethoxy phenacyl bromide (**2c**) reacted well and gave good product yields (Table 2, entries **3c**, **3g**, and **3j**). The effect of the electronic properties of the substituents on the phenyl ring of the 2-aminoketone s was also investigated. 4, 5-dimethoxy 2-aminoacetophenone (**1b**) shows good reactivity and provides comparatively good yields than 2-aminoacetophenone (**1a**); this might be due to the presence of electron donating groups. 2-Aminobenzophenone (**1c**) exhibited moderate reactivity than 2-aminoacetophenones (**1a**). This might be due to steric interference of the phenyl group during cyclization. Consequently, this produced low product yields. All the results are summarized in Table 2.

Further, we extended the scope of the reaction with aliphatic acyl bromide (**2e**) for the synthesis of 2-methyl-1-(3-methyl-1H-indol-2-yl) propan-1-one (**3k**). Accordingly, we treated 2-amino acetophenone (**1a**) with 1-bromo-3-methylbutan-2-one (**2e**) in the presence of 10 mol% piperidine in DMF under microwave conditions (350 MW). In contrast, aliphatic acyl bromide gave lower product yield compared to aromatic phenacyl bromides (Scheme 2).

A plausible mechanism for the synthesis of 2-aroylindoles is described in Scheme 3. Probably, the mechanism proceeds *via* the initial attack of piperidine to the acidic proton of phenacyl bromide to produce carbanion (**I**), which is in equilibrium with oxonium ion (**II**). The oxonium ion attacks at carbonyl carbon of 2-amino acetophenone, and subsequent protonation, dehydrobromination reproduces the cyclic intermediate 2-acyl-3-hydroxy-dihydro indole (**III**) and regenerates piperidine. The cyclized intermediate (**III**) undergoes dehydration and ultimately forms 2-aroylindole. The regenerated piperidine is again involved in reaction cycle (Scheme 3).

CONCLUSION

We described a simple and an efficient pathway for the synthesis of 2-aroylindoles (**3a–k**) using piperidine in DMF medium under MWI conditions within 25–45 min from readily available substrates. From the synthetic point of view, the present protocol is very simple, the conversion proceeds smoothly, and has no effect of air and moisture resulting 2-aroylindoles in moderate to good yields. We believe that the present approach will be better and more practical alternative to the existing methodologies for the synthesis of 2-aroylindoles.

EXPERIMENTAL

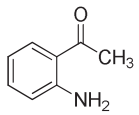
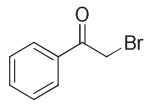
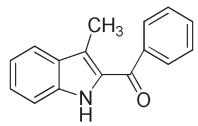
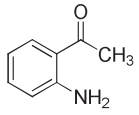
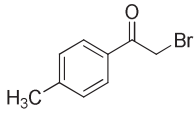
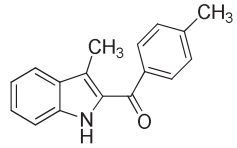
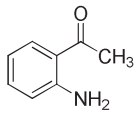
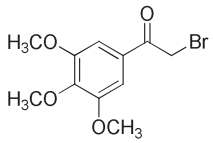
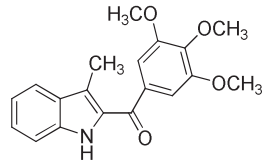
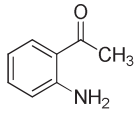
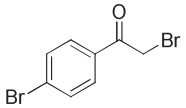
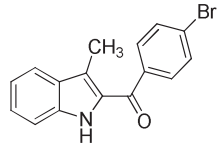
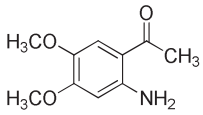
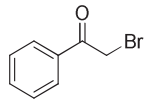
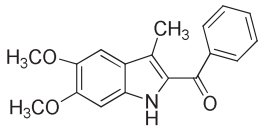
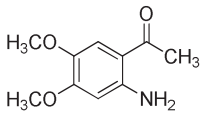
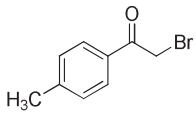
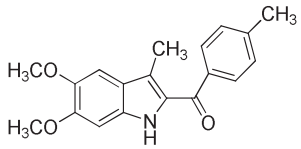
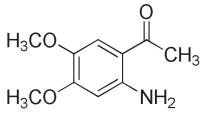
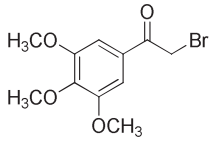
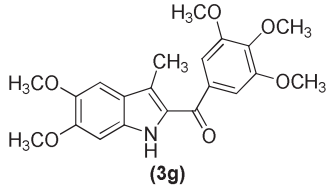
General. Solvents and reagents were procured from Sigma-Aldrich (Hyderabad, India) and Merck (Mumbai, India) and were used as such without further purification. The reactions were carried out on Microwave Oven, CATALYST-4R, Research Model, Made in India. Melting points were determined using a calibrated thermometer by Guna Digital Melting Point apparatus (Chennai, India). IR spectra of samples were recorded as potassium bromide pellet on a Bruker Vector 21 FT-IR spectrophotometer (France). ^{1}H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ on a Bruker AMX 500 MHz spectrometer operating at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C. For ^{1}H and ^{13}C chemical shifts, tetramethylsilane was used as an internal standard. ESI mass spectra were recorded on a Micromass Quattro LC instrument at Indian Institute of Technology (IICT), Hyderabad, India (Sparta, NJ). Elemental analysis was performed on Thermo Finnigan Instrument at the University of Hyderabad, India (San Jose, CA).

General procedure for the synthesis of 2-aroylindoles (3a–k). In a Pyrex tube 2-Aminoacetophenone (**1a**, 1 mmol), Phenacyl bromide (**2a**, 1 mmol) and piperidine (10 mol%) were taken and were exposed to microwaves until completion of the reaction (Table 2). After completion of the reaction as indicated by TLC analysis, the reaction mixture was cooled to room temperature and added 20 ml of water and extracted with ethyl acetate and concentrated by rotary evaporator. The residue was purified by silica gel column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the product **3a**. The same procedure was used for the synthesis of (**3b–k**).

Spectral data of the titled compounds (3a–k). ***(3-Methyl-1H-indol-2-yl)(phenyl)methanone (3a).*** mp 112–114°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.25 (s, 3H), 7.05–7.15 (m, 1H), 7.27–7.38 (m, 2H), 7.45–7.66 (m, 4H), 7.63–7.81 (m, 2H), 8.90 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 11.2, 111.8, 120.1, 121.2 126.4, 127.9 128.4, 128.7, 129.6, 131.5, 131.9, 136.5, 139.3, 189.3; IR (KBr, cm^{-1}) 3315, 2920, 1622, 1447, 1336; MS (ESI): *m/z* 236 $[M+H]^+$. *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: 81.57; H, 5.49; N, 5.88.

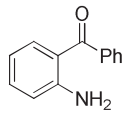
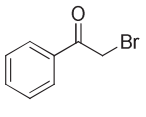
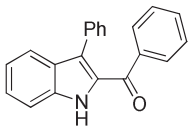
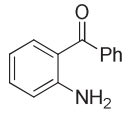
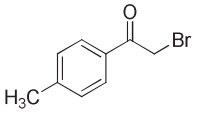
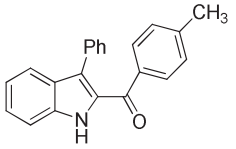
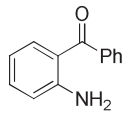
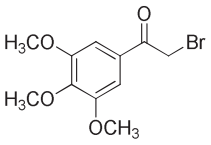
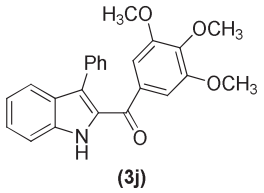
Table 2

Synthesis of 2-aroylindoles (**3a–j**).

Entry	2-Aminoketone (**4a–c**)	Bromo ketone (**5a–d**)	Product (**6a–j**)	Time (min)	Yield (%)[a]
1	 **(1a)**	 **(2a)**	 **(3a)**	30	84
2	 **(1a)**	 **(2b)**	 **(3b)**	30	86
3	 **(1a)**	 **(2c)**	 **(3c)**	25	89
4	 **(1a)**	 **(2d)**	 **(3d)**	30	76
5	 **(1b)**	 **(2a)**	 **(3e)**	30	78
6	 **(1b)**	 **(2b)**	 **(3f)**	30	81
7	 **(1b)**	 **(2c)**	 **(3g)**	25	87

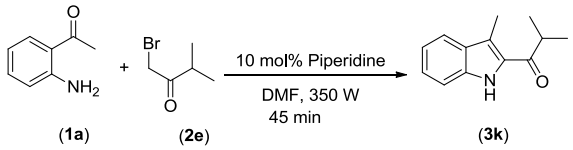
(*Continued*)

Table 2
(*Continued*)

Entry	2-Aminoketone (**4a–c**)	Bromo ketone (**5a–d**)	Product (**6a–j**)	Time (min)	Yield (%)[a]
8	 (**1c**)	 (**2a**)	 (**3h**)	45	68
9	 (**1c**)	 (**2b**)	 (**3i**)	45	72
10	 (**1c**)	 (**2c**)	 (**3j**)	30	76

[a]Isolated yield.

Scheme 2. Synthesis of 2-methyl-1-(3-methyl-1H-indol-2-yl) propan-1-one (**3k**).

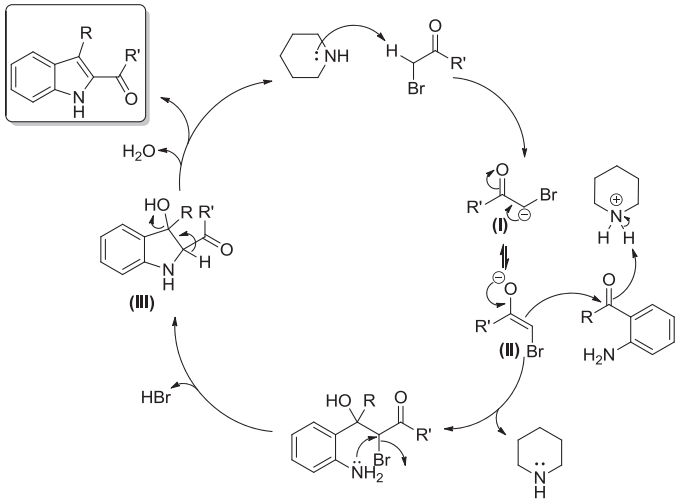


(**1a**) (**2e**) (**3k**)
Yield: 32%

(3-Methyl-1H-indol-2-yl)(p-tolyl)methanone (3b). mp 123–125°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.28 (s, 3H), 2.47 (s, 3H), 7.07–7.14 (m, 1H), 7.30–7.39 (m, 4H), 7.51–7.65 (m, 3H), 8.85 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 11.1, 21.2, 111.8, 120.0, 121.1, 126.0, 126.3 128.2, 128.4, 128.9, 129.3, 130.0, 132.7, 138.2, 139.3, 194.0; IR (KBr, cm^{-1}) 3313, 2924, 2863, 1618, 1448, 1324; MS (ESI): *m/z* 250 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.84; H, 5.94; N, 5.54.

(3-Methyl-1H-indol-2-yl)(3,4,5-trimethoxyphenyl)methanone (3c). mp 129–131°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.38 (s, 3H), 3.85 (s, 6H), 3.90 (s, 3H), 7.02 (s, 2H), 7.10–7.17 (m, 1H), 7.27–7.40 (m, 2H), 7.60–7.63 (m, 1H), 8.84 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 11.4, 56.2, 60.9, 106.5, 111.8, 119.9, 120.2, 121.1, 126.3, 128.8, 134.2, 136.5, 141.5, 153.0, 188.3; IR (KBr, cm^{-1}) 3324, 2926, 2853, 1618, 1433, 1337, 1132; MS

Scheme 3. Plausible mechanistic pathway for the reaction.



(ESI): *m/z* 326 $[M+H]^+$. *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.11; H, 5.78; N, 4.24.

(4-Bromophenyl)(3-methyl-1H-indol-2-yl)methanone (3d). mp 174–176°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.32 (s, 3H), 7.12–7.14 (m, 1H), 7.34–7.37 (m, 1H), 7.39–7.41 (m, 1H), 7.62–7.68 (m, 5H), 8.91 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 11.4, 112.7, 119.9, 120.7, 121.6, 127.3, 127.5, 130.0, 131.1, 132.2, 137.4, 138.9, 187.6; IR (KBr, cm^{-1}) 3338, 2932, 1623, 1435, 1342, 588; MS (ESI): *m/z* 314 $[M+H]^+$. *Anal.* Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.09; H, 3.78; N, 4.38.

(5,6-Dimethoxy-3-methyl-1H-indol-2-yl)(phenyl)methanone (3e). mp 163–165°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.19 (s, 3H), 3.91 (s, 6H), 6.78 (s, 1H), 6.90 (s, 1H), 7.44–7.58 (m, 3H), 7.68–7.70 (m, 2H), 8.79 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 11.4, 56.0, 56.2, 93.6, 101.0, 121.1, 122.0, 128.3, 128.6, 128.8, 129.4, 131.5, 132.3, 139.8, 145.9, 146.4, 188.1; IR (KBr, cm^{-1}) 3319, 2936, 2863, 1621, 1438, 1321, 1160; MS (ESI): *m/z* 296 $[M+H]^+$. *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.12; H, 5.74; N, 4.63.

(5,6-Dimethoxy-3-methyl-1H-indol-2-yl)(p-tolyl)methanone (3f). mp 141–143°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.12 (s, 3H), 2.43 (s, 3H), 3.92 (s, 6H), 6.75 (s, 1H), 6.91 (s,1H), 7.30–7.39 (m, 2H), 7.49–7.60 (m, 2H), 8.68 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 11.3, 21.3, 56.1, 56.2, 93.6, 101.2, 125.8, 128.2, 129.1, 132.2, 138.2, 139.8, 144.6, 146.0, 166.5, 176.4; IR (KBr, cm^{-1}) 3316, 2924, 2862, 1621, 1442, 1321, 1146; MS (ESI): *m/z* 310 $[M+H]^+$. *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.67; H, 6.08; N, 4.43.

(5,6-dimethoxy-3-methyl-1H-indol-2-yl)(3,4,5-trimethoxyphenyl) methanone (3g). mp 190–192°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.29 (s, 3H), 3.87 (s, 6H), 3.89 (s, 3H), 3.91 (s, 6H), 6.79 (s, 1H), 6.91 (s, 1H), 6.99 (s, 2H), 8.83 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 11.6, 56.0, 56.1, 56.2, 60.9, 93.5, 100.9, 106.3, 120.5, 121.9, 130.6, 132.2, 134.7, 141.1, 145.9, 151.1, 153.0, 187.2; IR (KBr, cm^{-1}) 3352, 2931, 1619, 1452, 1318, 1128; MS (ESI): *m/z* 386 $[M+H]^+$. *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.38; H, 5.88; N, 3.52.

Phenyl(3-phenyl-1H-indol-2-yl)methanone (3h). mp 192–194°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 7.01–7.07 (m,2H), 7.08–7.21 (m, 4H), 7.21–7.25 (m, 1H), 7.32–7.38 (m,1H), 7.41–7.53 (m, 4H), 7.62–7.70 (m, 2H), 9.29 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 111.9, 121.1, 122.0, 126.5, 126.7, 127.4, 127.9, 127.9, 128.8, 129.4, 130.1, 130.6, 130.8, 131.6, 132.1, 133.6, 134.2, 134.5, 143.1, 189.5; IR (KBr, cm^{-1}) 3321, 2926, 1619, 1338; MS (ESI): *m/z* 298 $[M+H]^+$. *Anal.* Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.69; H, 4.87; N, 4.63.

(3-Phenyl-1H-indol-2-yl)(p-tolyl)methanone (3i). mp 188–190°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 2.25 (s, 3H), 7.05–7.15 (m, 1H), 7.27–7.38 (m, 2H), 7.45–7.66 (m, 4H), 7.63–7.81 (m, 2H), 8.90 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 21.7, 111.8, 120.9, 122.3, 127.1, 127.6, 128.2, 129.1, 129.6, 130.2, 130.8, 131.7, 132.3, 133.9, 134.7, 143.3, 187.1; IR (KBr, cm^{-1}) 3311, 2923, 2892, 1698, 1426, 1332; MS (ESI): *m/z* 312 $[M+H]^+$. *Anal.* Calcd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.73; H, 5.42; N, 4.37.

(3-Phenyl-1H-indol-2-yl)(3,4,5-trimethoxyphenyl)methanone (3j). mp 139–141°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 3.58 (s, 6H), 3.75 (s, 3H), 6.73 (s, 2H), 7.10–7.17 (m, 4H), 7.19 (s, 1H), 7.23–7.65 (m, 4H), 9.22 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 155.9, 60.7, 107.2, 113.1, 121.3, 123.8, 126.9, 127.3, 128.2, 128.4, 129.8, 130.5, 131.6, 132.2, 133.4, 134.6, 141.7, 152.5, 188.2; IR (KBr, cm^{-1}) 3315, 2920, 1622, 1447, 1336; MS (ESI): *m/z* 388 $[M+H]^+$. *Anal.* Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.31; H, 5.36; N, 3.48.

2-Methyl-1-(3-methyl-1H-indol-2-yl) propan-1-one (3k). mp 119–121°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 1.28 (d, J = 6.7 Hz, 6H), 3.39–3.51 (m, 1H), 7.06–7.11 (m, 1H), 7.27–7.36 (m, 2H), 7.63 (d, J = 8.3 Hz, 1H), 9.13 (brs, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 10.9, 18.8, 37.1, 111.7, 120.0, 121.1, 126.3, 129.1, 131.4, 136.0, 197.6; IR (KBr, cm^{-1}) 3323, 2958, 1632, 1423, 1329; MS (ESI): *m/z* 202 $[M+H]^+$. *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 76.91; H, 7.36; N, 6.45.

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