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# Synthesis and Characterization of 3-Substituted Indole Derivatives as Novel Mannich Bases

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In this study, ten 3-substituted indole derivatives at the 3rd position of indole nucleus were synthesized *via* Mannich reaction with microwave assisted synthesis and the conventional reflux heating method. Microwave assisted synthesis is more preferrable than reflux method since the microwave irradiation lead to a higher product yields with better purity and improved energy efficiency with shortened reaction time. The structures of 3-substituted indole derivatives were characterized by FT-IR, elemental analysis, $^{1}$H NMR and $^{13}$C NMR spectroscopy.

**Keywords: Mannich reaction, Indole, 4-Substituted piperazines, Microwave-assisted synthesis.**

## INTRODUCTION

In recent years, design and development of derivatives having indole core structure have become more popular since indole and its derivatives were known to possess a wide range of pharmacological activities [1-5]. Indole derivatives have attracted great attention in the design of various pharmacological probes since nitrogen heterocycles were considered as privileged scaffolds in drug development and discovery [6]. Derivatization of these indole based pharmacophores as novel therapeutic agents is an approach to improve chemical diversity. Sharma *et al.* [7] have reported a wide range of biological properties of indole nucleus such as analgesic, anti-HIV, anti-inflammatory, insecticidal, anticancer, antihyper-tensive, antihistaminic, antiviral, antioxidant, anticonvulsant activities, *etc*.

In medicinal chemistry, Mannich reaction has played a vital role for the construction of methylene bridge between different active pharmacophores [8,9]. It is well known that the Mannich bases have been found to exhibit various pharmacological properties, such as antihelmintic, antimalarial, antibacterial and antifungal activities [10-12]. Piperazine derivatives were known to exhibit various biological properties such as antimicrobial activity and cytotoxicity [13]. A synthesis of novel amino benzylated Mannich bases was reported by Bhat & Chaluvaraju [14]. The compounds were synthesized by reacting aromatic aldehydes, cyclic secondary amines like piperazine and morpholines. Yuksel *et al.* [15] has reported the synthesis of 3-[(4-substitutedpiperazin-1-yl)methyl]-1*H*-indole derivatives and tested for their cytotoxic activity *in vitro* against different cancer cell lines such as MCF-7.

Microwave radiation has been widely preferred in organic chemistry as an energy source and preferred against conventional heating methods since microwave irradiation is a rapid process that produces an efficient internal heating within the reaction mixture [16]. In this study, Mannich bases having 4-substituted piperazine derivatives were synthesized by microwave assisted organic synthesis with higher yields than reflux, a conventional heating method.

## EXPERIMENTAL

All chemicals and solvents were obtained from Sigma Aldrich Chemical Co. Melting point of the compounds was recorded on the Mettler Toledo FP 900 Thermo System. The reactions were monitored *via* thin layer chromatography (TLC). The purity of the compounds was also assessed by TLC on silica gel GF 254 (DC-Alufplien-Kieselgel,Germany). The FT-IR spectra of the compounds were recorded on a Perkin-Elmer Spectrum 100 spectrophotometer with attenuated total reflection (ATR) (in wave numbers) in cm$^{-1}$. The $^{1}$H and $^{13}$C NMR spectra of the compounds were recorded on a Mercury Varian

400 MHz NMR using tetramethylsilane as the internal reference. Deuterated chloroform ($CDCl_3$) was used as NMR solvents. Chemical shifts (δ) values were reported in parts per million (ppm). Elemental analyses (C, H, N) were performed on Leco CHNS 932 analyzer. Microwave irradiation was carried out with a microwave reactor (MicroSYNTH, Milestone, Italy).

**General methods for the synthesis of compounds**

**Method A:** Indole (2 mmol) and appropriate piperazine derivatives (2 mmol) were dissolved in 20 mL of methanol followed by addition of 3 mmol formalin (37% w/v). The reaction mixture was irradiated (100 W, 65 ºC) for 5 min in a microwave reactor. The mixture was poured onto crushed ice and the precipitate was filtered off, dried and purified by recrystallization using an appropriate solvent. The reaction was controlled by TLC in ethylacetate:hexane (2:1).

**Method B:** Indole (2 mmol) and appropriate piperazine derivatives (2 mmol) were dissolved in 20 mL of methanol followed by addition of 3 mmol formalin (37% w/v). The reaction mixture was then refluxed in a water bath for 3 h. The mixture was poured onto crushed ice and the precipitate was filtered off, dried and purified by recrystallization using appropriate solvent.

**3-{[4-(2,5-Dimethylphenyl)piperazin-1-yl]methyl}-1*H*-indole (3a):** White solid; m.p.: 176.3 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3403 (N-H), 3068-2772 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (bs, 1H, indole N-H), 7.77 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.27-7.14 (m, 3H, phenyl), 6.92-6.82 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$), 2.3 (s, 3H, $CH_3$), 2.2 (s, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): δ 149.67, 135.45, 130.82, 129.97, 128.32, 127.77, 123.75, 123.85, 122.48, 120.62, 119.86, 119.71, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$), 21.2, 17.4 ($CH_3$). Anal. calcd. (found) % for $C_{21}H_{25}N_3$ (*m.w.* 319.20): C, 78.96 (78.18); H, 7.89 (6.94); N, 13.15 (13.09).

**3-{[4-Methylpiperazin-1-yl]methyl}-1*H*-indole (3b):** White solid; m.p.: 122.6 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3404 (N-H), 3069-2778 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (bs, 1H, indole N-H), 7.78 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 6.94-6.81 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$), 2.42 (s, 3H, $CH_3$).$^{13}$C NMR ($CDCl_3$): δ 123.93, 123.74, 121.28, 120.622, 119.80, 118.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$), 21.50 ($CH_3$). Anal. calcd. (found) % for $C_{14}H_{19}N_3$ (*m.w.* 229.16): C, 73.33 (73.13); H, 8.35 (7.95); N, 18.32 (18.06).

**3-{[4-(1-Napthylmethyl)piperazin-1-yl]methyl}-1*H*-indole (3c):** White solid; m.p.: 143.8 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3406 (N-H), 3065-2771 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (bs, 1H, indole N-H), 7.77 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.27-7.14 (m, 7H, phenyl), 6.92-6.82 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$). $^{13}$C NMR ($CDCl_3$): δ 155.16, 150.82, 142.51, 149.67, 141.1, 136.45, 130.82, 129.97, 128.27, 127.77, 125.93, 123.74, 121.45, 120.62, 119.80, 119.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$). Anal. calcd. (found) % for $C_{24}H_{25}N_3$ (*m.w.* 355.20): C, 81.09 (80.76); H, 7.09 (6.94); N, 11.82 (11.75).

**3-{[4-(2-Furoyl)piperazin-1-yl]methyl}-1*H*-indole (3d):** White solid; m.p.: 191.4 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3403 (N-H), 3068-2772 (C-H), 1705 (C=O). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (bs, 1H, indole N-H), 7.78 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.27-7.14 (m, 3H, furoyl), 6.92-6.82 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$). $^{13}$C NMR ($CDCl_3$): δ 130.82, 128.97, 128.27, 127.77, 123.93, 123.74, 122.28, 120.622, 119.80, 119.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$), 210.23 (furoyl, C=O). Anal. calcd. (found) % for $C_{18}H_{19}N_3O_2$ (*m.w.* 309.15): C, 69.88 (69.58); H, 6.19 (6.10); N, 13.58 (13.42); O, 10.34 (10.25).

**3-{[4-(2-Methylbenzyl)piperazin-1-yl]methyl}-1*H*-indole (3e):** White solid; m.p.: 145.3 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3403 (N-H), 3065-2775 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (bs, 1H, indole N-H), 7.74 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.27-7.14 (m, 4H, phenyl), 6.92-6.82 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.51 (s, 2H, benzyl-$CH_2$), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$), 2.35 (s, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): δ 149.67, 136.45, 130.82, 128.91, 128.27, 126.77, 123.93, 122.74, 122.28, 120.59, 119.80, 119.73, 112.86, 111.21 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (benzyl-$CH_2$), 52.41 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$), 19.12 ($CH_3$). Anal. calcd. (found) % for $C_{21}H_{25}N_3$ (*m.w.* 319.20): C, 78.96 (78.65); H, 7.89 (7.42); N, 13.15 (12.91).

**3-{[4-(1-Piperonyl)piperazin-1-yl]methyl}-1*H*-indole (3f):** White solid; m.p.: 164.3 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3402 (N-H), 3068-2771 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (bs, 1H, indole N-H), 7.77 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.27-7.14 (m, 3H, piperonyl), 6.92-6.82 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.51 (s, 2H, piperonyl-$CH_2$), 3.46 (s, 2H, piperonyl-O-$CH_2$-O), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$).$^{13}$C NMR ($CDCl_3$): δ 149.67, 136.45, 130.82, 128.97, 128.27, 127.77, 123.93, 123.74, 122.28, 120.622, 119.80, 119.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperonyl-$CH_2$), 52.18 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$), 46.23 (piperonyl-O-C-O). Anal. calcd. (found) % for $C_{21}H_{23}N_3O_2$ (*m.w.* 349.18): C, 72.18 (71.68); H, 6.63 (6.24); N, 12.03 (11.93); O, 9.16 (8.97).

**3-{[4-(4-Acetylphenyl)piperazin-1-yl]methyl}-1*H*-indole (3g):** White solid; m.p.: 128.6 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3407 (N-H), 3063-2779 (C-H), 1706 (C=O). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (bs, 1H, indole N-H), 7.77 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.25-7.12 (m, 4H, phenyl), 6.94-6.81 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.78 (s, 2H, C-**$CH_2$** -N), 3.24 (t, 4H, piperazine $H^3$, $H^5$), 2.67 (t, 4H, piperazine $H^2$, $H^6$), 2.42 (s, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): δ 149.67, 136.45, 130.82, 128.97, 128.27, 127.77, 123.93, 123.74, 122.28, 120.62, 119.80, 119.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$), 24.35

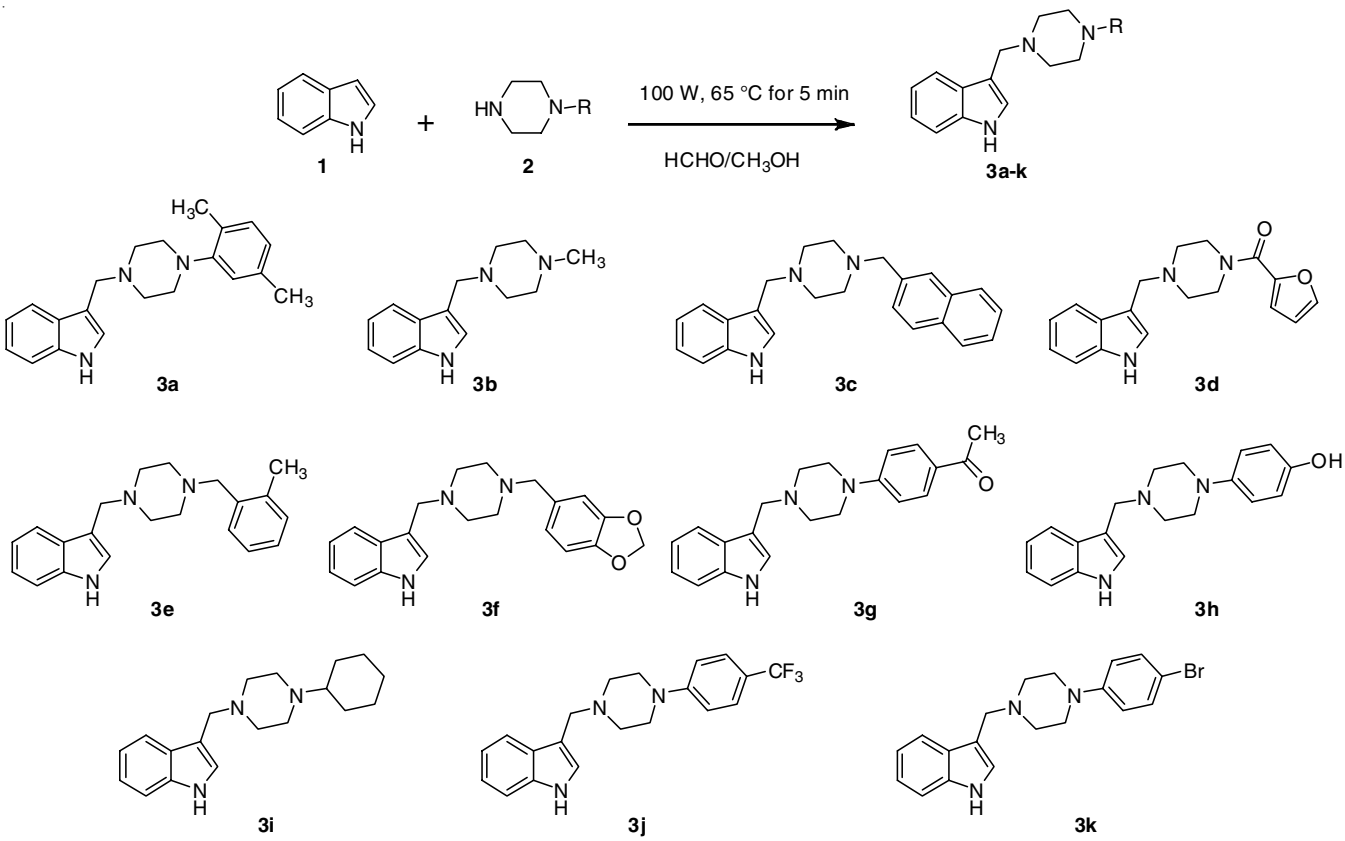
($CH_3$), 210.36 (C=O). Anal. calcd. (found) % for $C_{21}H_{23}N_3O$ (*m.w.* 333.18): C, 75.65 (75.15); H, 6.95 (6.42); N, 12.60 (12.30); O, 4.80 (4.75).

**3-{[4-(4-Hydroxyphenyl)piperazin-1-yl]methyl}-1*H*-indole (3h):** White solid; m.p.: 177.2 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3403 (N-H), 3068-2772 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (bs, 1H, indole N-H), 7.79 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.28-7.12 (m, 4H, phenyl), 6.94-6.81 (m, 3H, indole $H^2$, $H^5$, $H^6$), 6.21 (bs, 1H, OH), 3.79 (s, 2H, C-**$CH_2$** -N), 3.24 (t, 4H, piperazine $H^3$, $H^5$), 2.65 (t, 4H, piperazine $H^2$, $H^6$).$^{13}$C NMR ($CDCl_3$): δ 149.67, 136.45, 130.82, 128.97, 128.27, 127.77, 123.93, 123.74, 122.28, 120.622, 119.80, 119.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$). Anal. calcd. (found) % for $C_{19}H_{21}N_3O$ (*m.w.* 307.17): C, 74.24 (73.84); H, 6.89 (6.53); N, 13.67 (13.21); O, 5.20 (5.15).

**3-{[4-Cyclohexylpiperazin-1-yl]methyl}-1*H*-indole (3i):** White solid; m.p.: 182.7 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3404 (N-H), 3066-2775 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (bs, 1H, indole N-H), 7.77 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 6.92-6.82 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$), 2.25 (m, 1H, cyclohexyl- CH $H^1$), 1.82 (m, 4H, cyclohexyl-$CH_2$ $H^2$,$H^6$), 1.24 (m, 4H, cyclohexyl-$CH_2$ $H^3$,$H^5$) 1.18 (m, 1H, cyclohexyl-CH $H^4$). $^{13}$C NMR ($CDCl_3$): δ 123.93, 123.74, 122.28, 120.622, 119.80, 119.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 52.37 (cyclohexyl-CH), 51.58 (piperazine $C^3$, $C^5$), 50.47 (piperazine $C^2$, $C^6$), 28.9, 26.2, 25.8 (cyclohexyl- $CH_2$). Anal. calcd. (found) % for $C_{19}H_{27}N_3$ (*m.w.* 297.22): C, 76.72 (76.22); H, 9.15 (8.93); N, 14.13 (14.05).

**3-{[4-(4-Trifluoromethylphenyl)piperazin-1-yl]-methyl}-1*H*-indole (3j):** White solid; m.p.: 119.3 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3404 (N-H), 3061-2778 (C-H). $^1$H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.11 (bs, 1H, indole N-H), 7.77 (d, 1H, indole $H^4$), 7.36 (d, 1H, indole $H^7$), 7.27-7.14 (m, 4H, phenyl), 6.92-6.82 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.79 (s, 2H, C-**$CH_2$** -N), 3.20 (t, 4H, piperazine $H^3$, $H^5$), 2.68 (t, 4H, piperazine $H^2$, $H^6$). $^{13}$C NMR ($CDCl_3$): δ 149.67, 136.45, 130.82, 128.97, 128.27, 127.77, 123.93, 123.74, 122.28, 120.622, 119.80, 119.77, 112.86, 111.27 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 52.53 (piperazine $C^2$, $C^6$), 45.61 ($CF_3$). Anal. calcd. (found) % for $C_{20}H_{20}F_3N_3$ (*m.w.* 359.16): C, 66.84 (66.51); H, 5.61 (5.57); F, 15.86 (15.64); N, 11.69 (11.48).

**3-{[4-(4-Bromophenyl)piperazin-1-yl]methyl}-1*H*-indole (3k):** White solid; m.p.: 139.7 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3406 (N-H), 3065-2775 (C-H). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (bs, 1H, indole N-H), 7.75 (d, 1H, indole $H^4$), 7.38 (d, 1H, indole $H^7$), 7.28-7.13 (m, 4H, phenyl), 6.90-6.81 (m, 3H, indole $H^2$, $H^5$, $H^6$), 3.77 (s, 2H, C-**$CH_2$** -N), 3.22 (t, 4H, piperazine $H^3$, $H^5$), 2.66 (t, 4H, piperazine $H^2$, $H^6$). $^{13}$C NMR ($CDCl_3$): δ 149.67, 136.45, 131.82, 125.97, 124.29, 123.77, 122.98, 121.75, 120.18, 119.52, 118.70, 117.74, 111.84, 110.25 (arom.), 53.75 (C-**$CH_2$** -N), 53.48 (piperazine $C^3$, $C^5$), 51.55 (piperazine $C^2$, $C^6$). Anal. calcd. (found) % for $C_{19}H_{20}N_3Br$ (*m.w.* 369.08): C, 61.63 (61.37); H, 5.44 (5.28); Br, 21.58 (21.46); N, 11.35 (11.17).




**Scheme-I:** Synthesis of derivatives **3a-k** with microwave irradiation

## RESULTS AND DISCUSSION

**Synthesis:** Synthesis was carried out according to Method A, microwave irradiation was used to assist organic synthesis. The derivatives **(3a-k)** were synthesized by Mannich reaction between indole (**1**) and appropriate 4-substituted piperazines (**2**). Synthesis was also carried out according to Method B, under reflux conditions. The derivatives **(3a-k)** were synthesized by Mannich reaction between indole (**1**) and appropriate 4-substituted piperazines (**2**) (**Scheme-I**).

In general, the yields of compounds were higher in microwave assisted synthesis method than reflux method as shown in Table-1. In both methods, compounds **3g** and **3j** were obtained with the highest percentage of yields.

TABLE-1
YIELDS OF COMPOUNDS SYNTHESIZED WITH MICROWAVE IRRADIATION AND REFLUX METHOD

| Compd. | R | Yield (%) | |
|---|---|---|---|
| | | Microwave irradiation | Reflux method |
| **3a** | 2,5-Dimethylphenyl | 61 | 31 |
| **3b** | Methyl | 58 | 43 |
| **3c** | 1-Napthylmethyl | 67 | 36 |
| **3d** | 2-Furoyl | 42 | 42 |
| **3e** | 2-Methylbenzyl | 56 | 26 |
| **3f** | 1-Piperonyl | 64 | 21 |
| **3g** | 4-Acetylphenyl | 75 | 56 |
| **3h** | 4-Hydroxyphenyl | 53 | 32 |
| **3i** | Cyclohexyl | 46 | 28 |
| **3j** | 4-Trifluoromethylphenyl | 71 | 54 |
| **3k** | 4-Bromophenyl | 62 | 49 |

**Characterization:** The target derivatives showed N-H bands at 3400-3100 $cm^{-1}$ indicated that the condensation occured at third position of indole ring. Absorption bands were occured at 3060-2800 $cm^{-1}$ due to aliphatic C-H and 1700-1650 $cm^{-1}$ shows the presence the C=O in compounds **3d** and **3g**. In the $^1H$ NMR spectrum, characteristic peaks at about 8.1 ppm (bs, 1H, indole N-**H**) and 3.7 ppm (s, 2H, C-C**H**$_2$-N) hydrogen atoms of methylene bridge, which is the evidence of formation of Mannich reaction.

### Conclusion

In conclusion, indole-based 4-substituted piperazine derivatives were synthesized *via* microwave assisted organic synthesis showed a higher percentage of yields than reflux method as expected. It is clearly indicated that the formation of methylene bridge in Mannich reaction of indoles and appropriate piperazine derivatives happens at position 3 of indole ring as the N-H bands appeared in IR spectrum.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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