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# APPLICATION OF CHALCONE IN SYNTHESIS OF 1-(1, 5-BENZODIAZEPINO) SUBSTITUTED ANALOGUES OF INDOLE

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**ABSTRACT**

Versatility of chalcone derivative of 3-substituted-1-{(2*E*)-1-phenyl-3-(3,4,5)trimethoxyphenyl)}but-2-en-1-one)indole **(10-13)** and (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-substituted phenyl)-1-phenylprop-2-en-1-one **(15-18)** was explored to provide an easy one pot access to its 1-(1,5-benzodiazepino) substituted analogues **(19-22)** and **(23-26)** respectively.

**Keywords:** Indole, Chalcone, 1, 5-Benzodiazepine, Heterocycles.



## INTRODUCTION

It is well known that the indole nucleus is associated with a large number of pharmacological properties including antibacterial, anticancer, antibiotic, central nervous system modulating, etc.[1-4] By the same token; chalcone is an aromatic ketone that forms the central core for a variety of important biologically active compounds. They show antibacterial, antifungal, antitumor, and anti-inflammatory properties. Some chalcones demonstrated the ability to block voltage-dependent potassium channels.[5-7] This prompted us to explore the possibility of developing some such analogues of indole which contained in its nucleus the vital fragments of 1, 5-benzodiazepine on the premise that their presence in tandem in the same molecular framework could contribute significantly to provide a beneficial effect on the overall biological efficacy in the resulting molecules.[8-11]

In the present study, *N*-alkylation of indole was used. The *N*-metalloid indoles are ambient nucleophiles and can react with electrophiles either at nitrogen or at C-3. The more ionic sodium and potassium salt tend to react preferentially at nitrogen, particularly with hard electrophiles. Substitution at nitrogen is also favored by the use of dipolar aprotic solvents.[12-14]

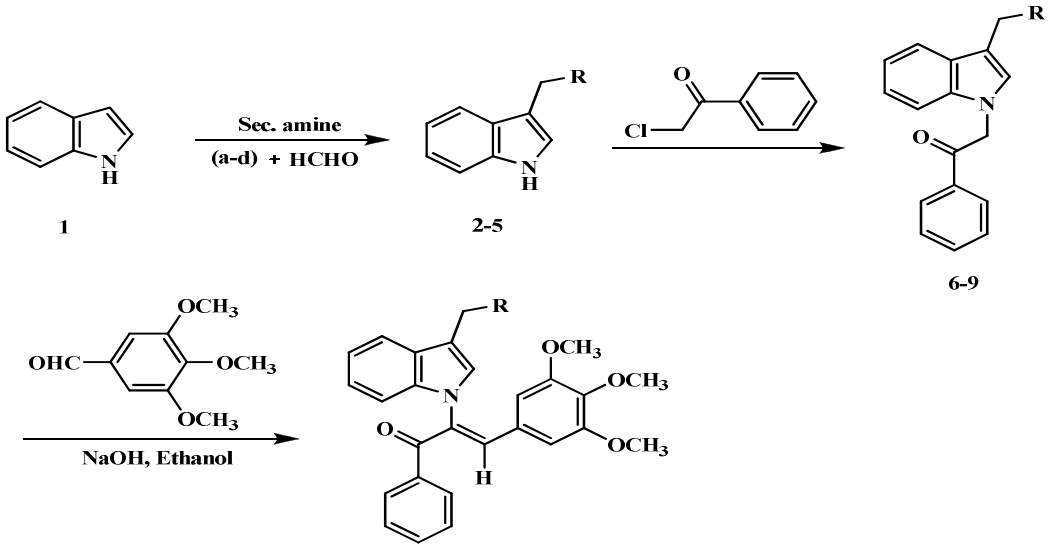
To create the novel heterocyclic scaffolds of biological interest through the simple and straight forward expedient routes, we explored the chalcones **(10-13)** and **(15-18)** based indole cyclization reactions for the incorporation of the 1,5-benzodiazepine based privileged template on the 1-position of indole nucleus **(1)** (Schemes: 1-4).[15-18]

## RESULTS AND DISCUSSION

As a part of our endeavour to create novel heterocyclic scaffolds of anticipated biological activity from easily accessible starting materials, here in this paper we report, the preliminary results of our studies on the synthesis of 1,5-benzodiazepine incorporated indole substituted analogues **(19-22)** and **(23-26)**. Various 3-(substituted)-1*H*-indole **(2-5)** were synthesized by mannich reaction and these products were used as an intermediate for the synthesis of 1-phenyl-2-[-3-(substituted)-1*H*-indole-1-yl]ethanone **(6-9)**, by Friedal-Craft arylation with chloroacetophenone. Finally, this product is used to synthesize chalcone derivatives, 3-substituted-1-{(2*E*)-1-phenyl-3-(3, 4, 5) trimethoxyphenyl)} but-2-en-1-one) indole **(10-13)** (Scheme-1). The *N*-metalloid indoles are ambient nucleophiles and can react with electrophiles either at nitrogen or at C-3. The more ionic sodium and potassium salt tend to react preferentially at nitrogen, particularly with hard electrophiles. Substitution at nitrogen is also favored by the use of dipolar aprotic solvents.[19] Thus; the sodium salt of indole can be *N*-substituted by chloroacetophenone. In this way, 2-

(1*H*-indol-1-yl)-1-phenylethanone **(14)** was prepared. This compound was used to synthesize desired chalcones, i.e. (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-substituted)-1-phenylprop-2-en-1-ones **(15-18) (scheme-2)**, by the Claisen-Schmidt condensation of 2(1*H*-indol-1-yl)-1-phenylethanone **(14)** and 4-substituted benzaldehydes.[20-21] Indole **(1)** was reacted with 1-phenyl-2-chloroacetophenone in the presence of sodium hydride which is a strong base. Dimethylformamide was used as a solvent, as it provides a better medium for the reaction. The reaction was allowed to proceed on stirring for 10-12 h at room temperature to yield desired indolyl acetophenone **(14)**. This was reacted with 4-substituted benzaldehyde by stirring at room temperature, followed by the Claisen-Schmidt condensations in the presence of sodium hydroxide as a strong base. Finally, we obtained (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-methylphenyl)-1-phenylprop-2-en-1-ones **(15-18)**. The reactants were stirred for 8-10 h (Scheme-2).[22-23]

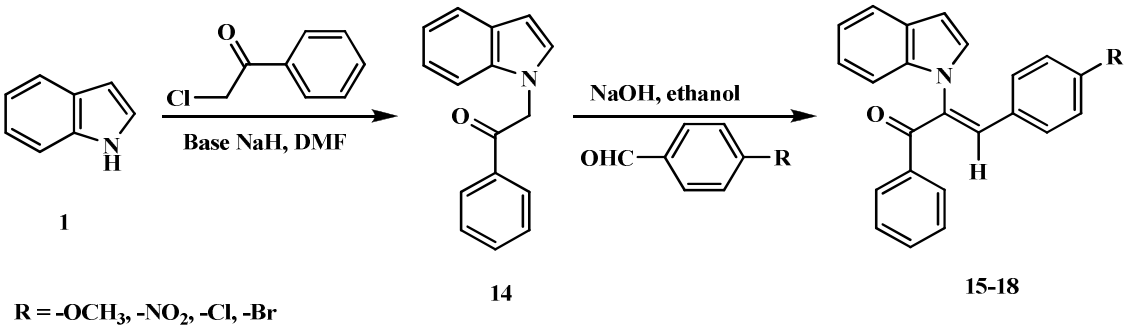
The goal of this study was to combine the two main structures, i.e. indole and 1, 5-benzodiazepine, so as to obtain a hybrid molecules. The versatility of chalcone precursors 3-substituted-1-{(2*E*)-1-phenyl-3-(3,4,5)trimethoxyphenyl)}but-2-en-1-one)indole **(10-13)** and (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-substituted-phenyl)-1-phenylprop-2-en-1-one **(15-18)** in the formation of 1,5-benzodiazepine nucleus was examined by allowing these to react with *o*-phenylenediamine, which resulted in the formation of corresponding 1,5-benzodiazepine incorporated analogues **(19-22)** and **(23-26)** respectively in acceptable yields. All the synthesized compounds gave satisfactory results of their microanalysis, IR, $^{1}$H NMR, $^{13}$C NMR, and MS spectral data which were found to be consistent to the assigned structures.



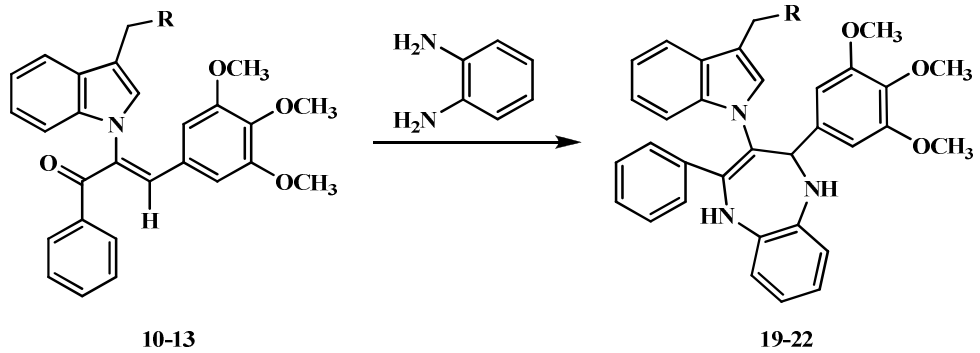

**Scheme-1**

## EXPERIMENTAL

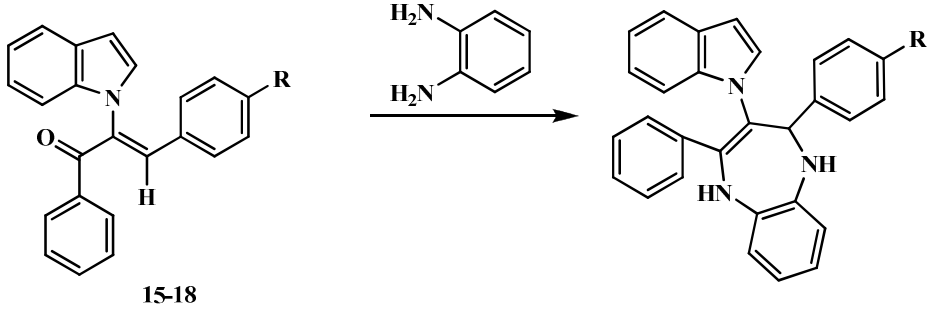
General procedures: All the melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 infrared. $^{1}$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ on Brucker Avance 400 MHz spectrometer with TMS as internal standard (chemical shifts are expressed in δ ppm). The mass spectra were recorded on a Joel SX-102 (FAB) mass spectrometer at 70 eV. The reactions were monitored by the TLC on silica gel G plates in the solvent system benzene-methanol mixture (9:1).




Scheme-2




Scheme-3




Scheme-4

**Preparation of 1-phenyl-2-[3-(pyrolidin-1-yl)-1*H*-indol-1-yl] ethanone (6)**

With starting material 3-(pyrolidin-1-yl)-1*H*-indole **(2)** (1.99 g, 0.01 mol) in DMF (30 ml), chloromethyl phenyl ketone (2.31 g, 0.015 mol) was added and sodium hydride was used as strong base. The mixture was stirred at room temperature for 11 h. DMF was removed from the residue by pouring the reaction mixture into ice cold water for overnight. The mixture was crystallized, filtered off, washed with ice cold water, dried and recrystallized from ethanol to give **6.** Yield, 76%; m.p. 36 °C; IR (KBr) $cm^{-1}$: 1780 (C=O str.), 1220 (C-N str.), 875 (Ar-C); $^1$H NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 5H, *J*=1.8), δ 7.26 (d, 1H, *J*=2.3), 2.50 (s, 1H), 3.50 (s, 2H), 4.52 (m, 2H, *J*=1.125); $^{13}$C NMR: 23.5, 51.4, 53.1, 112.2, 131.9, 120.5, 121.7, 119.6, 140.1, 196.5, 111.0, 65.1, 128.6, 137.4, 132.9; MS (*m*/*z*): 318 ($M^+$+1); Elemental analysis: Calcd./Found C, 79.21/79.44; H, 6.96/6.94; N, 8.80/8.73.

**Preparation of 1-phenyl-2-[3-(piperidinyl/morphonilo/*N*-methypiperazino)-1*H*-indol-1-yl] ethanone (7-9)**

In the same way as stated above for the preparation of 1-phenyl-2-[3-(pyrolidin-1-yl)-1*H*-indol-1-yl]ethanone **(6)**, 1-phenyl-2-[3-(piperidinyl)-1*H*-indole-1-yl]ethanone **(7)**, 1-phenyl-2-[3-(morphonilo)-

1*H*-indole-1-yl]ethanone **(8)** and 1-phenyl-2-[3-(*N*-methypiperazino)-1*H*-indole-1-yl]ethanone **(9)** were synthesized.

**1-phenyl-2-[3-(piperidinyl)-1*H*-indole-1-yl] ethanone (7)**
Yield, 66%; m.p. 38-40 $^{o}$C; IR (KBr) cm$^{-1}$: 1780 (C=O str.), 1220 (C-N str.), 875 (Ar-C); $^{1}$H NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 5H, *J*=1.8), 7.26 (d, 1H, *J*=2.3), 2.7 (s, 1H), 3.50 (s, 2H), 4.52 (m, 2H, *J*=2.8); $^{13}$C NMR: 52.2, 25.5, 26.2, 53.4, 112.4, 131.9, 120.5, 121.7, 119.6, 140.1, 196.5, 111.0, 65.1, 128.6, 137.4, 132.9; MS (*m*/*z*): 332 ($M^{+}$+1); Elemental analysis: Calcd./Found C, 79.48/79.79; H, 7.28/7.31; N, 8.44/8.52.

**1-phenyl-2-[3-(morphonilo)-1*H*-indole-1-yl] ethanone (8)**
Yield, 65%; m.p. 110 $^{o}$C; IR (KBr) cm$^{-1}$: 1780 (C=O str.), 1210 (C-N str.), 875 (Ar-C); $^{1}$H NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 5H, *J*=1.8), 7.26 (d, 1H, *J*=2.3), 3.6 (s, 1H), 2.4 (s, 1H), 3.50 (s, 2H), 4.52 (m, 2H, *J*=1.975); $^{13}$C NMR: 71.8, 56.4, 53.4, 112.4, 131.9, 120.5, 121.7, 119.6, 140.1, 196.5, 111.0, 65.1, 128.6, 137.4, 132.9; MS (*m*/*z*): 334 ($M^{+}$+1); Elemental analysis: Calcd./Found C, 74.42/74.13; H, 6.63/6.60; N, 8.38/8.43.

**1-phenyl-2-[3-(*N*-methypiperazino)-1*H*-indole-1-yl] ethanone (9)**
Yield, 63%; m.p. 90-93 $^{o}$C; IR (KBr) cm$^{-1}$: 1780 (C=O str.), 1220 (C-N str.), 875 (Ar-C); $^{1}$H NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 5H, *J*=1.8), 7.26 (d, 1H, *J*=2.3), 2.50, 2.27 (2s, 3H piperazine), 3.50 (s, 2H), 4.52 (m, 2H, *J*=2.8); $^{13}$C NMR: 38.7, 58.0, 55.1, 112.2, 131.9, 120.5, 121.7, 119.6, 140.1, 196.5, 111.0, 65.1, 128.6, 137.4, 132.9; MS (*m*/*z*): 347 ($M^{+}$+1); Elemental analysis: Calcd./Found C, 75.90/75.61; H, 7.27/7.31; N, 12.12/12.19.

**Preparation of 3-pyrolidin-1-yl-1-(2*E*)-1-phenyl-3-(3, 4, 5-trimethoxyphenyl) but-2-en-1-one) indole (10)**
With product 1-phenyl-2-[3-(pyrolidin-1-yl)-1*H*-indol-1-yl] ethanone **(6)** (3.18 g, 0.01 mol) in ethanol (30 ml), 3, 4, 5-trimethoxybenzaldehyde (1.96 g, 0.001 mol) was added and sodium hydroxide was used as strong base. The mixture was stirred at room temperature for 8 h. The product mixture was obtained by pouring the reaction mixture into ice cold water for overnight. The mixture was crystallized, filtered off, washed with ice cold water, dried and recrystallized from ethanol. Yield, 74%; m.p. 190 $^{o}$C; IR (KBr) cm$^{-1}$:1720 (C=O str.), 1165 (C-N str.), 1090, 1050 (ether str.), 1600 (C=C str.), 875 (Ar-C), 1444 ($CH_3$ bend.); $^{1}$H NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 6H, *J*=1.8), 7.26 (d, 1H, *J*=2.3), 2.50 (s, 1H), 3.50 (s, 2H), 1.70 (s, 1H), 3.3 (s, 3H); $^{13}$C NMR: 56.3, 51.4, 53.1, 112.2, 132.0, 121, 122, 120, 137, 129, 111.0, 129.7, 129, 134, 187, 120.5, 136.7, 125.7, 105.1, 129.2, 148.5, 132.0; MS (*m*/*z*): 497 ($M^{+}$+1); Elemental analysis: Calcd./Found C, 77.50/77.91; H, 6.70/6.67; N, 5.63/5.65.

**Preparation of 3-piperidinyl/morphonilo/*N*-methypiperazino-1-(2*E*)-1-phenyl-3-(3, 4, 5-trimethoxyphenyl) but-2-en-1-one) indole (11-13)**
In the same way as stated above for the preparation of compound 3-pyrolidin-1-yl-1-{(2*E*)-1-phenyl-3-(3,4,5-trimethoxyphenyl)but-2-en-1-one)indole} **(10),** 3-piperidinyl-1-{(2*E*)-1-phenyl-3-(3,4,5-trimethoxyphenyl)but-2-en-1-one)indole} **(11)**, 3-morphonilo-1-{(2*E*)-1-phenyl-3-(3,4,5-trimethoxyphenyl)but-2-en-1-one)}indole **(12)** and 3-*N*-methypiperazino-1-{(2*E*)-1-phenyl-3-(3,4,5-trimethoxyphenyl)but-2-en-1-one)}indole **(13)** were synthesized.

**3-piperidinyl-1-(2*E*)-1-phenyl-3-(3, 4, 5-trimethoxyphenyl) but-2-en-1-one) indole (11)**
Yield, 65%; m.p. 86-88 $^{o}$C; IR (KBr) cm$^{-1}$: 1720 (C=O str.), 1165 (C-N str.), 1090, 1050 (ether str.), 1600 (C=C str.), 875 (Ar-C), 1444 ($CH_3$ bend.); $^{1}$H NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 5H, *J*=1.8), 7.26 (d, 1H, *J*=2.3), 2.7 (s, 1H), 3.50 (s, 2H), 1.70 (s, 1H), 3.3 (s, 3H); $^{13}$C NMR: 25.6, 26.2, 52.2, 53.3, 148.5, 132, 121, 122, 120, 137, 129, 111.0, 129.7, 134, 187, 120.5, 136.7, 125.7, 105.1, 129.2, 148.5, 132.0; MS (*m*/*z*): 511 ($M^{+}$+1); Elemental analysis: Calcd./Found C, 75.01/75.31; H, 6.55/6.52; N, 5.46/5.48.

**3-morphonilo-1-(2*E*)-1-phenyl-3-(3, 4, 5-trimethoxyphenyl) but-2-en-1-one) indole (12)**
Yield, 61%; m.p. 120 °C; IR (KBr) $cm^{-1}$: 1720 (C=O str.), 1165 (C-N str.), 1090, 1050 (ether str.), 1600 (C=C str.), 875 (Ar-C), 1444 ($CH_3$ bend.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 5H, *J*=1.8), 7.26 (d, 1H, *J*=2.3), 3.6 (s, 1H), 2.4 (s, 1H), 3.50 (s, 2H), 1.70 (s, 1H), 3.3 (s, 3H); $^{13}C$ NMR: 71.8, 56.4, 53.4, 132, 112, 121, 122, 120, 177, 111.0, 123, 56.6, 56.3, 48.5, 187, 136.3, 134.3, 132, 129, 123, 105.1, 53.5; MS (*m*/*z*): 120 ($M^+$+1); Elemental analysis: Calcd./Found C, 75.25/7.96; H, 6.70/6.73; N, 5.50/5.48.

**3-*N*-methypiperazino-1-(2*E*)-1-phenyl-3-(3, 4, 5-trimethoxyphenyl) but-2-en-1-one) indole (13)**
Yield, 63%; m.p. 65-68 °C; IR (KBr) $cm^{-1}$: 1720 (C=O str.), 1165 (C-N str.), 1090, 1050 (ether str.), 1600 (C=C str.), 875 (Ar-C), 1444 ($CH_3$ bend.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 7.35 (m, 5H, *J*=1.8), 7.26 (d, 1H, *J*=2.3), 2.50, 2.27 (s, 1H), 3.50 (s, 2H), 1.70 (s, 1H), 3.3 (s, 3H); $^{13}C$ NMR: 122, 120, 111, 137, 132, 121, 123, 112, 53.2, 129.6, 187, 136.7, 129.7, 129, 134.3, 120.5, 105.1, 148.4, 132.4, 55.1, 58, 56.6, 56.3, 38.7; MS (*m*/*z*): 526 ($M^+$+1); Elemental analysis: Calcd./Found C, 72.64/72.92; H, 6.29/6.26; N, 7.99/7.96.

**Preparation of 2-(1*H*-Indol-1-yl)-1-phenylethanone (14)**
To a solution of indole **(1)** (1.0 g, 0.01 mol) in DMF (30 ml) were added chloromethylphenyl ketone (2.31 g, 0.015 mol) and sodium hydride as a strong base. The mixture was stirred at room temperature for 12 h. The target compound was crystallized by pouring the reaction mixture into ice-cold water and standing for 24 h. Crystals were separated by filtration and recrystallized from suitable solvent. Yield, 70%; m.p. 213 °C; IR (KBr) $cm^{-1}$: 1700 (C=O str.), 1240 (C-N str.), 780-670 (=C–C str.), 1575 (C=C str.), 1460 ($CH_3$ bend.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 7.17 (m, 6H, *J*=0.125), 6.97-7.86 (m, 1H, *J*=0.050 & 0.450), 5.11 (s, 1H); $^{13}C$ NMR: 121.7, 119, 111, 139.1, 127.9, 120.5, 127.4, 102.5, 64.8, 196.5, 137, 128.5, 128.3, 132.9, 129.7; MS (*m*/*z*): 235 ($M^+$+1); Elemental analysis: Calcd./Found C, 81.68/81.45; H, 5.57/5.54; N, 5.95/5.97.

**Preparation of (2*Z*)-2-(1*H*-Indol-1-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (15)**
To a solution of 2-(1*H*-indol-1-yl)-1-phenylethanone **(14)** (3.55 g, 0.01 mol) in ethanol (30 ml) was added *p*-methoxybenzaldehyde (1.36 g, 0.01 mol) and sodium hydroxide as a base and the mixture was stirred for about 8 h. The target compound was crystallized by pouring the reaction mixture into ice-cold water and standing for 24 h. Crystals were separated by filtration and recrystallized from suitable solvent. Yield, 70%; m.p. 213 °C; IR (KBr) $cm^{-1}$: 1680 (C=O str.), 1600 (C=C str.), 1360 (C-N str.), 1240 (O-$CH_3$ str.), 1444 ($CH_3$ bend.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 7.3 (m, 6H, *J*=0.525), 7.45-7.81 (m, 4H, *J*=0.550), 7.9 (s, 1H), 3.73 (s, 3H); $^{13}C$ NMR: 122, 120, 111, 136, 128, 121, 124, 102, 129, 187, 136.7, 129.7, 129, 134.3, 120.5, 127.2, 114, 162, 56; MS (*m*/*z*): 353 ($M^+$+1); Elemental analysis: Calcd./Found C, 81.23/80.94; H, 5.43/5.45; N, 3.96/3.97.

**Preparation of (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-nitro/chloro/bromophenyl)-1-phenylprop-2-en-1-one (16-18)**
In the same way as stated above for the preparation of compound (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **(15),** (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one **(16)**, (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one **(17)** and (2*Z*)-2-(1*H*-indol-1-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one **(18)** were synthesized.

**(2*Z*)-2-(1*H*-Indol-1-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (16)**
Yield, 70%; m.p. 213 °C; IR (KBr) $cm^{-1}$: 1760 (C=O str.), 1600 (C=C str.), 1340 (C-N str.), 1350 (sym nitro str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 7.3 (m, 6H, *J*=0.525), 7.45-7.81 (m, 4H, *J*=0.550), 7.9 (s, 1H); $^{13}C$ NMR: 122, 120, 111, 136, 128, 121, 124, 102, 129, 187, 136.7, 134.3, 129, 129.7, 120.5, 127.2, 114, 162, 56; MS (*m*/*z*): 357 ($M^+$+1); Elemental analysis: Calcd./Found C, 75.00/75.27; H, 4.50/4.52; N, 7.60/7.63.

**(2*Z*)-2-(1*H*-Indol-1-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (17)**
Yield, 70%; m.p. 213 °C; IR (KBr) $cm^{-1}$: 1750 (C=O str.), 1600 (C=C str.), 3220 (N-H str.), 785 (C-Cl str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 7.3 (m, 6H, *J*=0.525), 7.45-7.81 (m, 6H, *J*=0.550), 7.9 (s, 1H); $^{13}C$ NMR: 122, 120, 111, 136, 128, 121, 124, 102, 129, 187, 136.7, 129.7, 134.3, 120.5, 127.2, 114, 162, 56; MS (*m*/*z*): 355 ($M^+$+1); Elemental analysis: Calcd./Found C, 77.00/76.76; H, 4.54/4.56; N, 3.91/3.92.

**(2*Z*)-2-(1*H*-Indol-1-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (18)**
Yield, 70%; m.p. 213 °C; IR (KBr) $cm^{-1}$: 1760 (C=O str.), 1600 (C=C str.), 3225 (N-H str.), 580 (C-Br str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 7.3 (m, 6H, *J*=0.525), 7.45-7.81 (s, 4H), 7.9 (s, 1H); $^{13}C$ NMR: 122, 120, 111, 136, 128, 121, 124, 102, 129, 187, 136.7, 129.7, 129, 134.3, 120.5, 127.2, 114, 162, 56; MS (*m*/*z*): 481 ($M^+$+1); Elemental analysis: Calcd./Found C, 69.01/69.25; H, 4.32/4.34; N, 3.48/3.50, Br, 19.77/19.85.

**Preparation of (*E*)-2, 5-dihydro-2-(3', 4', 5'-trimethoxyl)-4-phenyl-3-(3'-pyrrolidin-1-yl) methyl)-1*H*-indol-1-yl)-1*H*-benzo[b] [1, 4] diazepine (19)**
A mixture of *o*-phenylenediamine (1.08 g, 0.01 mol), 3-pyrolidinyl-1-(2*E*)-1-phenyl-3-(3, 4, 5-trimethoxyphenyl) but-2-en-1-one) indole **(10)** (0.482 g, 1.0 mmol) and ethanol (25 ml) was refluxed for 4 h. The solvent was distilled under reduced pressure and the reaction was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulfate to give **19**. Yield, 74%; m.p. 260-62 °C; IR (KBr) $cm^{-1}$: 1250-1040 (C-O-C, O-$CH_3$ str.), 1390 (C-N str.), 1444 ($CH_3$ bend.), 1510-80 (C=C str.), 2950 (C-H str.), 3240 (NH str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 2.8, 1.6 (m, 8H, *J*=0.612), 3.8 (s, 3H), 4.0 (s, 2H), 6.18-6.40 (d, 4H, *J*=2.3), 7.0-7.6 (d, 6H, *J*=1.93), 7.30 (m, 5H, *J*=0.745); $^{13}C$ NMR: 57, 23, 125.4, 135.7, 107.8, 130.4, 155.6, 115.5, 120.3, 134.2, 137.3, 114, 123, 125, 120, 115, 124, 119, 123, 117, 127, 55; MS (*m*/*z*): 573 ($M^+$+1); Elemental analysis: Calcd./Found C, 75.75/76.04; H, 6.53/6.57; N, 9.30/9.34.

**Preparation of (*E*)-2, 5-dihydro-2-(3', 4', 5'-trimethoxyl)-4-phenyl-3-(3'-piperidin/morphon/*N*-methylpiperazin-1-yl) methyl)-1*H*-indol-1-yl)-1*H*-benzo[b] [1, 4] diazepine (20-22)**
In the same way as stated above for the preparation of compound (*E*)-2,5-dihydro-2-(3',4',5'-trimethoxyl)-4-phenyl-3-(3'-pyrrolidin-1-yl)methyl)-1*H*-indol-1-yl)-1*H*-benzo[b][1,4]diazepine **(19),** (*E*)-2,5-dihydro-2-(3',4',5'-trimethoxyl)-4-phenyl-3-(3'-piperidin-1-yl)methyl)-1*H*-indol-1-yl)-1*H*-benzo[b][1,4]diazepine **(20)**, (*E*)-2,5-dihydro-2-(3',4',5'-trimethoxyl)-4-phenyl-3-(3'-morphon-1-yl)methyl)-1*H*-indol-1-yl)-1*H*-benzo[b][1,4]diazepine **(21)** and (*E*)-2,5-dihydro-2-(3',4',5'-trimethoxyl)-4-phenyl-3-(3'-(*N*-methyl-piperaz)-1-yl)methyl)-1*H*-indol-1-yl)-1*H*- benzo[b][1,4]diazepine **(22)** were synthesized.

**(*E*)-2,5-dihydro-2-(3',4',5'-trimethoxyl)-4-phenyl-3-(3'-piperidin-1-yl)methyl)-1*H*-indol-1-yl)-1*H*-benzo[b][1,4]diazepine (20)**
Yield, 74%; m.p. 72-74 °C; IR (KBr) $cm^{-1}$: 1250-1040 (C-O-C, O-$CH_3$ str.), 1360-1310 (C-N str.), 1450 ($CH_3$ bend.), 1590 (C=C str.), 2923 (C-H str.), 3260 (NH str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 2.8, 1.6 (m, 8H, *J*=0.723), 3.8 (3H, s), 4.0 (s, 2H), 6.18-6.40 (4H, d, *J*=2.1), 7.0-7.6 (m, 6H, *J*=0.832), 7.30 (m, 5H, *J*=0.931); $^{13}C$ NMR: 54, 25, 24, 125.4, 135.7, 107.8, 130.4, 155.6, 115.5, 120.3, 134.2, 137.3, 114, 123, 125, 114, 120, 115, 124, 119, 117, 127, 55; MS (*m*/*z*): 587 ($M^+$+1); Elemental analysis: Calcd./Found C, 76.09/76.34; H, 6.76/6.78; N, 9.96/10.02.

**(*E*)-2,5-dihydro-2-(3',4',5'-trimethoxyl)-4-phenyl-3-(3'-morphon-1-yl)methyl)-1*H*-indol-1-yl)-1*H* benzo[b][1,4]diazepine (21)**
Yield, 70%; m.p. 183-85 °C; IR (KBr) $cm^{-1}$: 1250-1040 (C-O-C, O-$CH_3$ str.), 1360-1310 (C-N str.), 1450 ($CH_3$, bend.), 1590 (C=C str.), 2955 (C-H str.), 3265 (NH str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 2.8, 3.7 (m, 8H, *J*=0.698), 3.8 (s, 3H), 4.0 (s, 2H), 6.18-6.40 (m, 4H, *J*=0.968), 7.0-7.6 (m, 6H, *J*=0.845), 7.30 (m, 5H, *J*=0.812); $^{13}C$ NMR: 54, 48, 46, 125.4, 135.7, 107.8, 130.4, 155.6, 115.5, 120.3, 134.2, 137.3, 114,

123, 125, 114, 120, 115, 124, 119, 125, 123, 117, 123, 127, 55, 25, 24, 135.7; MS (*m*/*z*): 589 ($M^+$+1); Elemental analysis: Calcd./Found C, 74.08/74.35; H, 6.35/6.37; N, 9.90/9.93.

**(*E*)-2,5-dihydro-2-(3',4',5'-trimethoxyl)-4-phenyl-3-(3'-(*N*-methyl-piperaz)-1-yl)methyl)-1*H*-indol-1-yl)-1*H*-benzo[b][1,4]diazepine (22)**
Yield, 78%; m.p. 73-75 $^oC$; IR (KBr) $cm^{-1}$: 1118 (C-O-C, O-$CH_3$ str.), 1360-1310 (C-N str.), 1475 ($CH_3$ bend.), 1535 (C=C str.), 2923 (C-H str.), 3278 (NH str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 2.5 (m, 8H, *J*=0.623), 2.3 (s, 3H), 3.8 (s, 3H), 4.0 (s, 2H), 6.18-6.40 (m, 4H, *J*=0.913), 7.0-7.6 (m, 6H, *J*=0.724), 7.30 (5H, d, *J*=0.810); $^{13}C$ NMR: 52, 55, 45, 125.4, 135.7, 107.8, 130.4, 155.6, 115.5, 120.3, 134.2, 137.3, 114, 123, 125, 120, 115, 124, 119, 117, 127, 55; MS (*m*/*z*): 589 ($M^+$+1); Elemental analysis: Calcd./Found C, 74.23/73.98; H, 6.74/6.76; N, 11.37/11.42.

**Preparation of (*E*)-2, 5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-methoxyphenyl)-4-phenyl-1*H*-benzo[b] [1, 4] diazepine (23)**
A mixture of *o*-phenylenediamine (1.08 g, 0.01 mol), (2*Z*)-2-(1*H*-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **(15)** (0.353 g, 1.0 mmol) and ethanol (25 ml) were refluxed for 4 h. The solvent was distilled under reduced pressure and the reaction was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulfate to give **23**. Yield, 77%; m.p. 148-50 $^oC$; IR (KBr) $cm^{-1}$: 1250-1040 (C-O-C, O-$CH_3$ str.), 1440 ($CH_3$ bend.), 1530 (C=C str.), 2990 (C-H str.), 3240 (NH str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 3.8 (s, 3H), 4.0 (s, 2H), 6.18-6.40 (m, 4H, *J*=0.736), 6.4-7.6 (m, 6H, *J*=0.687); $^{13}C$ NMR: 125.4, 135.7, 107.8, 130.4, 155.6, 115.5, 120.3, 134.2, 137.3, 114, 123, 125, 120, 115, 124, 119, 117, 119, 127, 55; MS (*m*/*z*): 458 ($M^+$+1); Elemental analysis: Calcd./Found C, 81.24/81.57; H, 5.68/5.70; N, 9.16/9.18.

**Preparation of (*E*)-2, 5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-nitro/chloro/bromophenyl)-4-phenyl-1*H*-benzo[b] [1, 4] diazepine (24-26)**
In the same way as stated above for the preparation of compound (*E*)-2,5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-methoxyphenyl)-4-phenyl-1*H*-benzo[b][1,4]diazepine **(23),** (*E*)-2,5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-nitrophenyl)-4-phenyl-1*H*-benzo[b][1,4]diazepine **(24)**, (*E*)-2,5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-chlorophenyl)-4-phenyl-1*H*-benzo[b][1,4]diazepine **(25)** and (*E*)-2,5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-bromophenyl)-4-phenyl-1*H*-benzo[b][1,4]diazepine **(26)** were synthesized.

**(*E*)-2,5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-nitrophenyl)-4-phenyl-1*H*-benzo[b][1,4]diazepine (24)**
Yield, 71%; m.p. 140-42 $^oC$; IR (KBr) $cm^{-1}$: 870, 610 (str, C-N, C-N-O, $NO_2$ bend.), 1520 (C=C str, Ar-H), 3020 (C-H str. Ar-H), 3260 (NH); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 4.0 (s, 2H), 6.18-6.40 (m, 4H, *J*=0.767), 6.4-7.6 (m, 6H, *J*=0.694), 7.14-7.30 (m, 5H, *J*=0.713); $^{13}C$ NMR: 129, 107, 130, 120, 119, 124, 135, 115, 134, 128, 127, 117, 55, 99, 121, 142, 129, 131, 121, 125; MS (*m*/*z*): 473 ($M^+$+1); Elemental analysis: Calcd./Found C, 75.65/75.93; H, 4.87/4.88; N, 11.88/11.96.

**(*E*)-2,5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-chlorophenyl)-4-phenyl-1*H*-benzo[b][1,4]diazepine (25)**
Yield, 69%; m.p. 140-42 $^oC$; IR (KBr) $cm^{-1}$: 750-700 (C-Cl str.), 1510 (C=C str.), 2980 (C-H str.), 3271 (NH str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 4.0 (s, 2H), 6.18-6.40 (m, 4H, *J*=0.747), 6.4-7.6 (m, 6H, *J*=0.647), 7.14-7.30 (m, 5H, *J*=0.784); $^{13}C$ NMR: 125.4, 135.7, 107.8, 130.4, 155.6, 115.5, 120.3, 134.2, 137.3, 114, 123, 125, 120, 115, 124, 119, 117, 119, 123, 127; MS (*m*/*z*): 462 ($M^+$+1); Elemental analysis: Calcd./Found C, 77.76/78.04; H, 4.76/4.78; N, 9.10/9.15.

**(*E*)-2,5-dihydro-3-(1*H*-indol-1-yl)-2-(4'-bromophenyl)-4-phenyl-1*H*-benzo[b][1,4]diazepine (26)**
Yield, 68%; m.p. 83-85 $^oC$; IR (KBr) $cm^{-1}$: 1750 (C=O str.), 3100-3040 (C-H str.), 3260 (NH str.); $^1H$ NMR ($CDCl_3$/TMS) δ ppm: 4.0 (s, 2H), 6.18-6.40 (m, 4H, *J*=0.789), 6.4-7.6 (m, 6H, *J*=0.691), 7.14-7.30 (m, 5H, *J*=0.723); $^{13}C$ NMR: 129, 107, 130, 120, 119, 124, 135, 115, 134, 128, 127, 117, 55, 99, 121,142,

129, 131, 125; MS (*m/z*): 507 ($M^+$+1); Elemental analysis: Calcd./Found C, 70.74/71.04; H, 5.50/5.52; N, 8.46/8.51, Br, 16.54/16.63.

## CONCLUSION

We have developed a novel, convenient and simple method for the preparation of indole-1, 5-benzodiazepine hybrid compounds. In conclusion, two elegant protocols have been developed to provide an easy access of the novel 1, 5-benzodiazepine incorporated analogues of indole derivatives, utilizing the potential of chalcone intermediates in high yield and purity. Chalcone-indolo derivatives are very prone to undergo Michael addition reactions with various bi-nucleofiles such as *o*-phenylediamine. Chalcone-indolo derivatives which were synthesized by the sequences of the reactions were found to react smoothly with *o*-phenylediamine to afford the corresponding benzodiazepine.

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