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Synthesis Of A Novel Series Of Indole Clubbed Oxazepine Derivatives Using Conventional And Microwave Action

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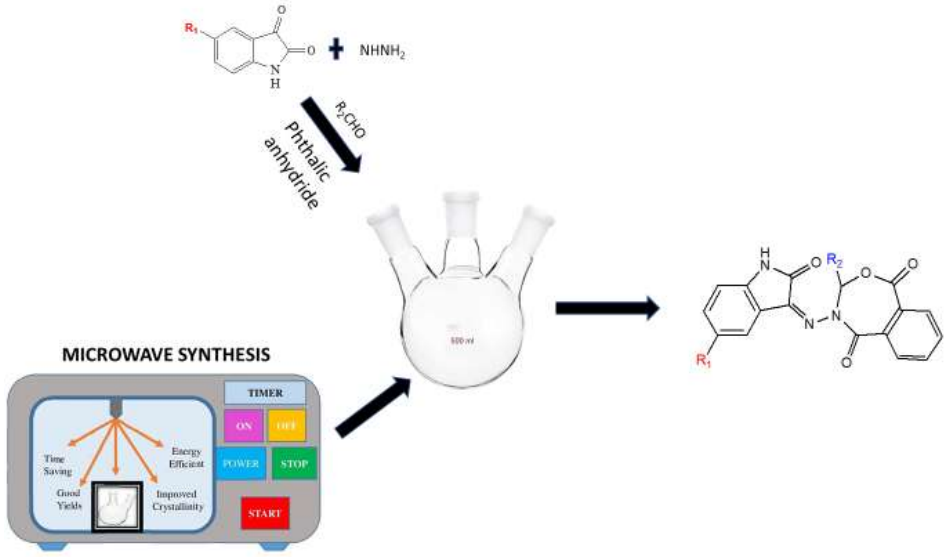
Abstract

A novel series of indole based oxazepine derivatives were synthesized using microwave irradiation and conventional method from commercially available isatin derivatives. Reaction of isain derivatives with hydrazine hydrate and undergo nucleophilic substitution reaction. In the presence of ethanol as a solvent, the compounds (2) will react with different aromatic aldehydes to generate Schiff's bases (3). Further, Schiff's bases **(3)** undergo cyclization in the presence of phthalic anhydride will form the final proposed structure or compounds **(5)**.

Keyword: Indole, oxazepine, conventional method, microwave synthesis

Graphical Abstract

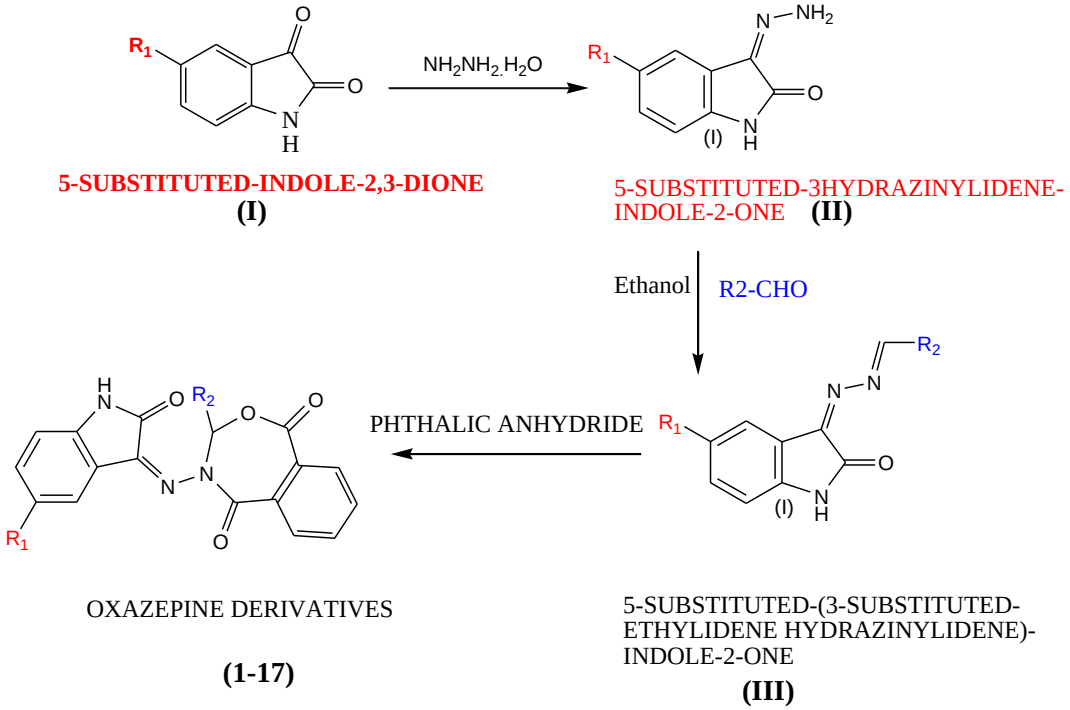


Introduction

Heterocyclic molecules have led to an increase in their significance in recent times due to its pharmacological actions [1-2]. In the field of medicinal chemistry [3], natural products, and drug discovery [4-6], the indole nucleus is a crucial synthetic approach. [7]. Indole is an exceptional heterocyclic molecule with a broad spectrum of pharmacological activity owing to various modes of action. It is also a versatile pharmacophore and a favoured scaffold. Its only characteristic, which makes it an excellent moiety in drug development, is that it resembles several protein structures. In recent years, a great deal of study has been conducted to summarize and investigate the numerous medicinal prospects of this moiety [8-10]. Indole produces different activities such as, antidiabetic activity [11-15], anti-inflammatory [16-19], anticancer [20-23].

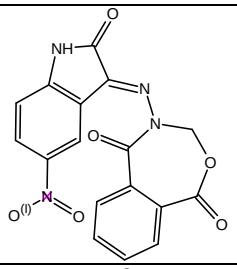
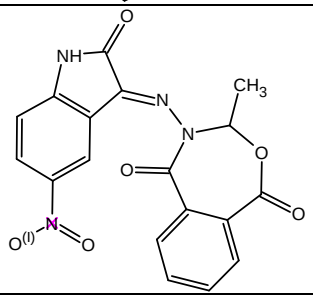
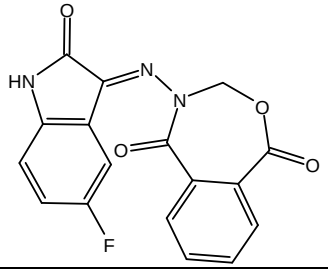
2. METHODS

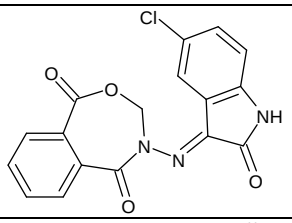
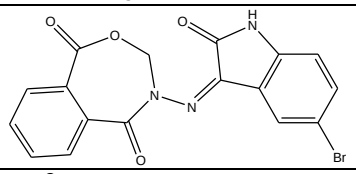
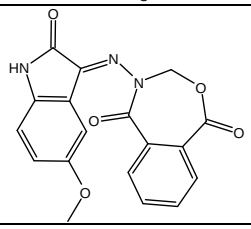
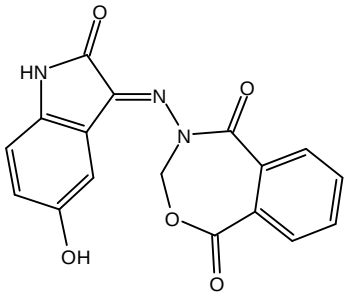
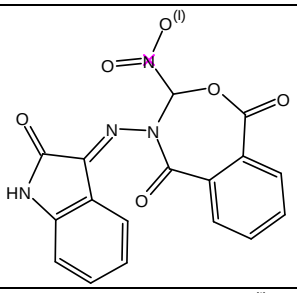
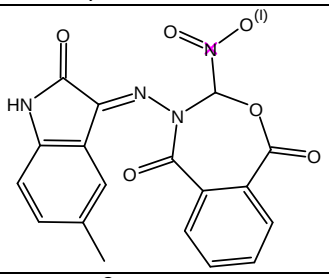
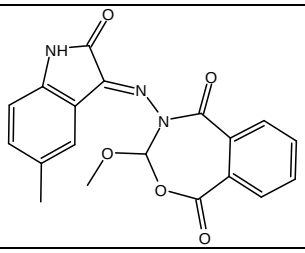
2.1 SYNTHESIS OF OXAZEPINE DERIVATIVES

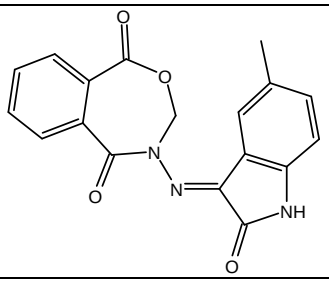
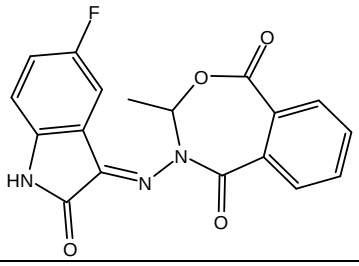
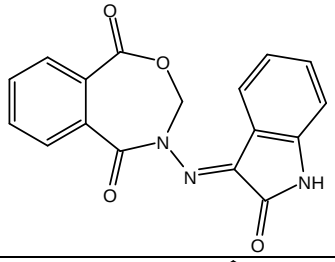
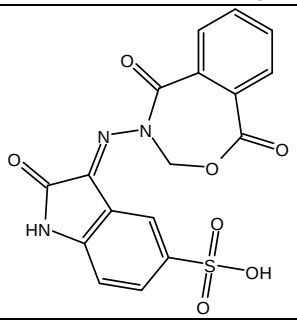
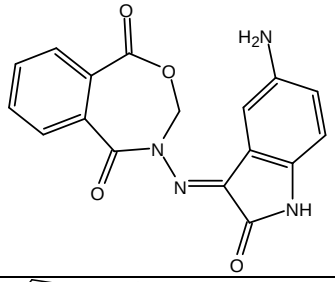
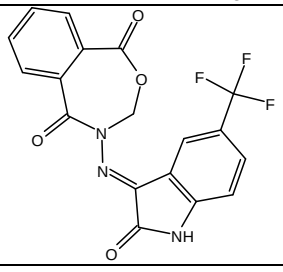


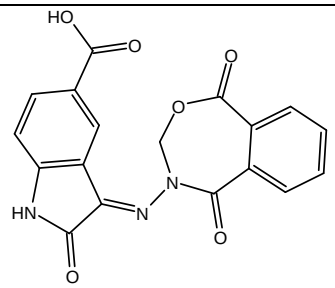
Scheme 1: Synthetic route for the title compounds (1-17)

Table 1: Represents a list of the different lead compounds' substituents.

S.NO	R1	R2	OXAZEPINE DERIVATIVES
1	NO_2	H	
2	NO_2	CH_3	
3	F	H	

4	Cl	H	
5	Br	H	
6	OCH_3	H	
7	OH	H	
8	H	NO_2	
9	CH_3	NO_2	
10	CH_3	OCH_3	

11	CH_3	H	
12	F	CH_3	
13	H	H	
14	SO_3H	H	
15	NH_2	H	
16	CF_3	H	

17	COOH	H	

3. MATERIAL AND METHODS

Modified described methods for conventional synthesis were used to carry out the synthesis [24] and procedures with reactions had been modified to enhance product yield and purity. In contrast, synthesis using microwave assistance was also done [25]. For the synthesis, general reagent grade solvents and reagents were utilized in equal amounts. A Shimadzu, Japan-based FTIR-DRS 8000A spectrophotometer was used to obtain infrared spectra (KBr). Bruker Avance Neo 500 MHz spectrometer NMR findings were obtained. Each and every chemical shift measurement (ppm) was recorded using it. A thin layer chromatography method (Merck, silica gel, HF254e361, type 60, 0.25 mm, Darmstadt, Germany) was employed to ascertain the purity of the substances. At the SAIF, Punjab University, Chandigarh, mass spectra (ESI-MS) were taken utilizing a Waters Q-TOF-MS apparatus (Waters, Micromass MS, USA). Elements were analyzed using Thermo Finnigan's FLASH EA 112 CHN analyzer in Italy, and the results were found to be within range. At 180 and 300 W, MW-assisted reactions were conducted in a catalyst microwave synthesizer which range from 85 W to 850 W (CATA R/2R) as shown in figure1.

Figure 1: Microwave synthesizer

3.1 SYNTHESIS OF 5-SUBSTITUTED 3-HYDRAZINYLIDINE INDOLE-2-ONE (II) (SCHIFF BASE) [26]
Conventional synthesis: 0.753 gm of substituted isatin, 0.27 ml hydrazine hydrate and 12.5 ml Methanol refluxed for 1hr.

Microwave synthesis: 0.753 gm of substituted isatin, 0.27 ml hydrazinwe hydrate and 12.5 ml Methanol refluxed for 3minute by microwave irradiation (180W) using microwave oven for microwave-assisted synthesis. Product was obtained as a dark brown crystalline powder

3.2 SYNTHESIS OF 5-SUBSTITUTED-(3-SUBSTITUTED ETHYLIDINE HYDRAZINYLIDENE INDOLE-2-ONE) (III)
[26]
Conventional Synthesis: 0.8 gm product II dissolved in 30 ml ethanol and 0.5 ml substituted aldehyde with few drops of glacial acetic acid. Refluxed for 7 hrs, cooled it poured onto crushed ice then filter it and recrystallised.

Microwave synthesis: 0.8 gm product II dissolved in 30 ml ethanol and 0.5 ml substituted aldehyde with few drops of glacial acetic acid. Refluxed for 4 minutes by microwave irradiation (180W) using microwave oven for microwave-assisted synthesis, cooled it poured onto crushed ice then filter it and recrystallised.

3.3 SYNTHESIS OF OXAZEPINE DERIVATIVES (1-17) (CYCLOADDITION REACTION) [27]
Conventional Synthesis: 0.14 mmol Schiff base dissolved in 0.14mmol phthalic anhydride in 10 ml dioxane refluxed for 24 hours. Recrystallised from ethanol.

Microwave synthesis: 0.14 mmol Schiff base dissolved in 0.14mmol phthalic anhydride in 10 ml dioxane refluxed for 10 minutes by microwave irradiation (300W) using microwave oven for microwave-assisted synthesis. Product was obtained as a dark brown crystalline powder**.** Recrystallised from ethanol.

4.RESULTS AND DISCUSSION

4.1 Chemistry

Compound (I) will combine with hydrazine hydrate to create compounds (1–17), which will then go through a nucleophilic substitution process. The compounds (II) will combine with various aromatic aldehydes in the presence of ethanol as a solvent to produce Schiff's bases (III). Additionally, Schiff's bases (III) cyclize in the presence of phthalic anhydride to create the compounds (1–17) that make up the final structure that is suggested in Scheme 1.

Table 1: Comparative data of conventional and microwave (MW) methods for the synthesis of compounds (**1–17)**

S. N.	Der No.	Conventional Method (Time h)			% Yield			MW Method (Min)			% Yield		
		Step I	Step II	Step III	Step I	Step II	Step III	Step I	Step II	Step III	Step I	Step II	Step III
1.	1.	1	7	24	87	88	98	3	4	10	91	93	94
2.	2.	1	7	24	85	78	98	3	4	11	90	81	91
3.	3.	1	7	24	80	72	98	5	4	9	81	82	98
4.	4.	1	7	24	72	77	88	3	4	11	79	77	89
5.	5.	1	7	24	71	67	91	3	4	9	80	87	95
6.	6.	1	7	24	82	90	92	3	4	9	88	91	94
7.	7.	1	7	24	80	80	82	3	4	10	90	90	91
8.	8.	1	7	24	75	78	93	3	4	11	85	88	94
9.	9.	1	7	24	90	89	92	3	4	11	90	89	92
10.	10.	1	7	24	74	91	98	3	4	9	79	90	90
11.	11.	1	7	24	81	88	89	5	4	11	85	89	91
12.	12	1	7	24	78	89	98	3	4	11	76	82	97
13.	13.	1	7	24	69	89	89	3	4	10	67	90	90
14.	14.	1	7	24	71	91	91	5	4	11	70	89	92
15.	15.	1	7	24	87	89	91	3	4	9	89	90	92
16.	16.	1	7	24	94	94	94	5	4	11	84	86	91
17.	17.	1	7	24	87	97	97	5	4	10	80	92	91

Note: For all synthesis180 W MW was used except for step III for which 300 W MW was used

5. CHARECTERISATION:

Derivative 1. Molecular Formula: $C_{17}H_{10}N_4O_6$, Mol wt.: 366.89, Yield 98%, mp: 241-244^{0}C, Rf: 0.38 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3402.05(N-H), 1738.22 (C=O), 1612.42(C=N), 2879.38(C-H), 1498.41(N=O), 1 H NMR (DMSO, ppm): ϭ 7.48-8.80 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$367.06. Ana. Calcd for: C, 55.74; H,2.75; N, 15.30 O, 26.21. Found: C, 58.81; H, 3.45; N, 16.25; O, 27.21.

Derivative 2. Molecular Formula: $C_{18}H_{12}N_4O_6$, Mol wt.: 380.16, Yield 98%, mp: 241-244 ^{0}C, Rf: 0.38 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3206.18(N-H), 1738.22 (C=O), 1712.29(C=N), 2789.39(C-H), 1510.22 (N=O), 1 H NMR (DMSO, ppm): ϭ 6.90-8.73 (m, 8H, Ar-H, 10.77 (s, 2H, N-H), 6.92 (d, J= 7.4Hz, 1H, CO-CH), 7.27 (d, J= 6.7 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 381.08 Ana. Calcd for: C, 56.85; H, 3.18; N, 14.73, O, 25.24; Found: C, 58.90; H,4.18; N, 14.75; O, 25.24.

Derivative 3. Molecular Formula: $C_{17}H_{10}N_3O_4$, Mol wt.: 339.28, Yield 98%, mp: 241-244 ^{0}C, Rf: 0.38 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3368.08(N-H), 1895.97 (C=O), 1653.00(C=N), 2804.50(C-H),1247.94(C-F), 1 H NMR (DMSO, ppm): σ 7.08-8.81 (m, 8H, Ar-H, 9.87 (s, 1H, N-H), 6.60 (d, J= 8.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 340.07 Ana. Calcd for: C, 60.18 ; H,2.97 ; F, 5.60; N, 12.39; O, 18.86;.Found: C, 61.18 ; H,2.97 ; F, 5.59; N, 13.29; O, 19.86.

Derivative 4. Molecular Formula: $C_{17}H_{10}ClN_3O_4$, Mol wt.: 355.73, Yield 88%, mp: 241-244 ^{0}C, Rf: 0.38 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3196.05(N-H), 1828.52 (C=O), 1616.36 (C=N), 2887.44(C-H),771.58(C-Cl), 1 H NMR (DMSO, ppm): σ 6.48-9.02 (m, 7H, Ar-H, 10.47 (s, 2H, N-H), 6.49 (d, J=8.4Hz, 1H, CO-CH), 6.47 (d, J= 8.2 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 356.04. Ana. Calcd for: C, 57.40; H,2.83; Cl, 9.97; N, 11.81; O, 17.99. Found, C, 58.30; H,2.81; Cl, 10.97; N, 12.80; O, 18.89

Derivative 5. Molecular Formula: $C_{17}H_{10}BrN_3O_4$, Mol wt.: 400.18, Yield 98%, mp: 251-254 ^{0}C, Rf: 0.37 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3401.04(N-H), 1716.65 (C=O), 1595.13(C=N), 2889.37(C-H), 659.11(C-Br), 1 H NMR (DMSO, ppm): σ 6.88-8.20 (m, 8H, Ar-H, 10.77 (s, 2H, N-H), 6.47 (d, J= 7.7Hz, 1H, CO-CH), 7.67 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 399.99. Ana. Calcd for: C, 51.02; H,2.52; Br, 19.97; N, 10.51; O, 15.99. Found, C, 52.12; H, 3.52; Br, 20.87; N, 11.50; O, 16.80.

Derivative 6. Molecular Formula: $C_{18}H_{13}N_3O_5$, Mol wt.: 351.31, Yield 92%, mp: 249-252 ^{0}C, Rf: 0.42 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3400.50(N-H), 1728.22 (C=O), 1612.49(C=N), 2833.25(C-H), 1 H NMR (DMSO, ppm): σ 6.48-8.210 (m, 9H, Ar-H, 10.67 (s, 2H, N-H), 6.49 (d, J= 7.8Hz, 1H, CO-CH), 7.65 (d, J= 6.9 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 352.09. Ana. Calcd for: C, 61.54; H,3.73; N, 11.96; O, 22.77. Found, C, 63.64; H, 3.9; N, 12.16; O, 23.72.

Derivative 7. Molecular Formula: $C_{17}H_{11}N_3O_5$, Mol wt.: 337.29, Yield 82%, mp: 261-264 ^{0}C, Rf: 0.42 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3292.78(N-H), 1722.43 (C=O), 1612.49(C=N), 2889.39(C-H), 3622.18(O-H), 1 H NMR (DMSO, ppm): σ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 338.07. Ana. Calcd for: C, 60.54; H, 3.29; N, 12.46; O, 23.72. Found, C, 61.44; H, 3.83; N, 12.96; O, 22.92.

Derivative 8. Molecular Formula: $C_{17}H_{10}N_4O_6$, Mol wt.: 366.28, Yield 93%, mp: 231-234 ^{0}C, Rf: 0.39 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1612.49(C=N), 2809.22(C-H), 1577.27(N=O), 1 H NMR (DMSO, ppm): σ 7.18-8.23 (m, 9H, Ar-H, 10.77 (s, 2H, N-H), 6.80 (d, J= 6.6Hz, 1H, CO-CH), 9.07 (d, J= 6.2 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 367.06, Ana. Calcd for: C, 55.74; H,2.75; N,15.30; O, 26.21; Found: C, 55.74; H,2.75; N,15.30; O, 26.21;

Derivative 9. Molecular Formula: $C_{18}H_{12}N_4O_6$, Mol wt.: 380.31, Yield 92%, mp: 242-245 ^{0}C, Rf: 0.31 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3356.14(N-H), 1735.93 (C=O), 1685.79(C=N), 2804.50(C-H), 1519.91(N=O), 1 H NMR (DMSO, ppm): σ 7.12-8.23 (m, 9H, Ar-H, 10.82 (s, 2H, N-H), 6.90 (d, J= 7.8Hz, 1H, CO-CH), 7.13 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 381.08. Ana. Calcd for: C, 56.85; H, 3.18; N,14.73; O, 25.24; Found: C, 57.85; H, 3.20; N,14.83; O, 28.24.

Derivative 10. Molecular Formula:$C_{19}H_{15}N_3O_5$, Mol wt.: 365.34, Yield 98%, mp: 241-244 ^{0}C, Rf: 0.38 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1612.49(C=N), 2889.39(C-H), 1 H NMR (DMSO, ppm): σ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 366.10. Ana. Calcd for: C, 62.46; H, 4.14; N, 11.50; O, 21.90. Found: C, 67.80; H, 4.88; N, 15.23; O, 25.34.

Derivative 11. Molecular Formula: $C_{18}H_{13}N_3O_4$, Mol wt.: 335.31, Yield 89%, mp: 241-244 ^{0}C, Rf: 0.38 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1612.49(C=N), 2889.39(C-H), 1 H NMR (DMSO, ppm): σ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 336.09 Ana. Calcd for: C, 64.48; H, 3.91; N, 12.53; O, 19.09. Found: C, 68.80; H, 4.28; N, 15.23; O, 21.34.

Derivative 12. Molecular Formula: $C_{18}H_{12}FN_3O_4$, Mol wt.: 353.30,Yield 98%, mp: 241-244 ^{0}C, Rf: 0.38 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1612.49(C=N), 2889.39(C-H), 1 H NMR (DMSO, ppm): σ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 354.08. Ana. Calcd for: C, 61.19; H, 3.42; F, 5.38; N, 11.89; O, 18.11. Found: C, 62.72; H, 3.47; F, 5.58; N, 12.79; O, 19.21.

Derivative 13. Molecular Formula: $C_{17}H_{11}N_3O_4$, Mol wt.: 321.29,Yield 89%, mp: 246-249 ^{0}C, Rf: 0.41 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1612.49(C=N), 2889.39(C-H), 1 H NMR (DMSO, ppm): ϭ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 322.08. Ana. Calcd for: C, 63.55; H, 3.45; N, 13.08; O, 19.92. Found: : C, 63.55; H, 4.55; N, 13.12; O, 20.12.

Derivative 14. Molecular Formula: $C_{17}H_{11}N_3O_7S$, Mol wt.: 401.35, Yield 91%, mp: 241-244 ^{0}C, Rf: 0.39 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1622.13(C=N), 2839.22(C-H), 1 H NMR (DMSO, ppm): ϭ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 402.03. Ana. Calcd for: C, 50.88; H, 2.76; N, 10.47; O, 27.90; S, 7.99. Found: , 51.75; H, 2.91 N, 11.27; O, 27.93; S, 8.12.

Derivative 15. Molecular Formula: $C_{17}H_{12}N_4O_4$, Mol wt.: 336.30, Yield 91%, mp: 251-254 ^{0}C, Rf: 0.42 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1612.49(C=N), 2889.39(C-H), 1 H NMR (DMSO, ppm): ϭ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 337.09. Ana. Calcd for: C, 60.71; H, 3.60; N, 16.66; O, 19.03. Found: C, 61.61; H, 4.20; N, 17.56; O, 19.82.

Derivative 16. Molecular Formula:$C_{18}H_{10}F_3N_3O_4$, Mol wt.: 389.88, Yield 94%, mp: 257-260 ^{0}C, Rf: 0.41 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3408.22(N-H), 1728.22 (C=O), 1612.49(C=N), 2889.39(C-H), 1 H NMR (DMSO, ppm): ϭ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 390.06. Ana. Calcd for : C, 55.54 ; H, 2.59 ; F, 14.64; N, 10.79; O, 16.44;.Found: C, ; H, ;N, ; C, 55.54 ; H, 2.89 ; F, 15.60; N, 10.19; O, 17.44;.

Derivative 17. Molecular Formula: $C_{18}H_{11}N_3O_6$, Mol wt.: 365.30, Yield 97%, mp: 231-234 ^{0}C, Rf: 0.48 (Methanol: Toluene 1:4) IR (KBr, cm-1): 3412.08(N-H), 1728.22 (C=O), 1612.49(C=N), 2889.39(C-H), 1 H NMR (DMSO, ppm): ϭ 7.48.60 (m, 9H, Ar-H, 10.87 (s, 2H, N-H), 6.90 (d, J= 7.6Hz, 1H, CO-CH), 7.07 (d, J= 6.8 Hz, 1H, CH-Ar), EI-MS: m/z $[M+H]^+$ 366.06. Ana. Calcd for: C, 59.18; H, 3.04; N, 11.50; O, 26.28. Found: C, 61.10; H, 3.24; N, 11.50; O, 26.48.

6. CONCLUSION:

Ultimately in conclusion, we explore the potential of MWI in heterocyclization to create a range of indole clubbed oxazepine derivatives. The MW method yielded very good yields, a significant short reaction time, and high pure products, which motivates us to continue exploring this synthetic approach.

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