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Research Article

# MICROWAVE-ASSISTED SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME PYRAZOLE DERIVATIVES

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**ABSTRACT**
Reaction of 3-(1*H*-indol-3-yl)-(1-methyl/phenyl)prop-2-en-1-one (Chalcones) was carried out with hydrazine hydrate, phenyl hydrazine, isoniazide, nicotinic hydrazide and thiosemicarbezide (corresponding hydrazides) in ethanol containing a few drops of glacial acetic acid under microwave irradiation giving *1H*-indol containing pyrazole derivatives. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR and $^1$H NMR. All the synthesized compounds have been screened for their antibacterial and antifungal activities.
**Keywords:** 3-(1*H*-indol-3-yl)-(1-methyl/phenyl) prop-2-en-1-one, Antimicrobial activity, Microwave irradiation.

## INTRODUCTION

Microwave-assisted synthesis is an eco-friendly and efficient method of synthesis of organic compounds as compared to the conventional method of synthesis. In this method, reaction occurs more rapidly, safely and with higher chemical yields and therefore this method becomes superior to the conventional method. The conventional method, requiring a longer reaction time and larger quantities of solvents and reagents, causes environmental pollution and contributes to the health hazards. Pyrazoles are an important class of heterocyclic compounds. They exhibit a wide range of pharmacological activities like antibacterial[1-2], antifungal[3-4], antiviral[5], anti-inflammatory[6], antioxidant[7], anti-tubercular[8], anti-diabetic[9], anti-tumor[10], anesthetic[11], analgesic[12] and insecticidal agents[13]. A microwave- assisted synthesis of chalcones (α, β- unsaturated ketones) was synthesized by base catalyzed aldol condensation of acetone or acetophenone with indol-3-aldehyde. chalcones undergo a cyclization reaction with corresponding hydrazines giving pyrazole derivatives.

## MATERIALS AND METHODS

The melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 spectrometer using KBr pellets. The $^1$H NMR spectra were scanned on a DRX-300 MHz spectrometer (300 MHz) in $CDCl_3$/DMSO-d6 using TMS as internal standard and chemical shifts are expressed in δ ppm. Purity of synthesized compounds was checked by TLC using silica gel-G. Spots were exposed in an iodine chamber.

### General Procedure for Preparation of chalcone (1a-b)

A mixture indol-3-aldehyde (0.005 mol) and different ketones (Acetone and acetophenone) (0.005 mol) in the presence of piperidine, under Microwave irradiation at 5 sec intervals; the specific reaction time was kept 2 minutes and then the reaction mixture was cooled in crushed ice. Progress of the reaction was monitored by TLC method. The solid obtained was filtered, washed with water and re crystallized from ethanol to give (1a) as red dark needle shape crystals.

### Synthesis of 4-(1H-indol-3-yl) but-3-en-2-one (1a)

Yield 92 %, m.p. 154 $^oC$; IR (KBr) $cm^{-1}$: 3394 (-NH); 1630 (C=O); $^1$H NMR (DMSO $d_6$) δ: 9.63 (1H, NH); 2.91 (3H, $CH_3$); Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56 % Found: C, 77.68; H, 5.76; N, 7.30 %.

### Synthesis of 3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one (1b)

Yield 87 %, m.p.173-175 $^oC$; IR (KBr) $cm^{-1}$: 3374 (-NH); 1651 (C=O); $^1$H NMR (DMSO $d_6$) δ: 9.54 (1H, NH); 8.36 (N-CH); 7.05-7.85 (Ar-H); Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66 %. Found: C, 82.36; H, 5.06; N, 5.49 %.

### General Procedure for Preparation of compound 2a-b, 3a-b, 4a-b, 5a-b and 6a-b

A mixture of chalcone (0.004 mol), corresponding hydrazines (hydrazin hydrate, phenyl hydrazine, isoniazide, nicotinic hydrazide and thiosemicarbezide) (0.004 mol) in ethanol (10 mL) and glacial acetic acid (2 drop) was react under microwave irradiation for a specific time of 1 minute. Progress of the reaction was monitored by TLC method. Then the reaction mixture was poured into crushed ice and kept overnight at room temperature. The solid obtained was filtered, washed and re crystallized from ethanol.

### Synthesis of 3-(5-methyl-1H-pyrazol-3-yl)-1H-indole (2a)

Yield 78 %, m.p. 212-215 $^oC$; IR (KBr) $cm^{-1}$: 3387, 3402 (-NH); 1610 (C=N); 1514 (C=C); $^1$H NMR (DMSO $d_6$) δ: 9.92, 9.58 (2H, NH); 7.45 (N-CH); 7.22-7.32 (Ar-H); 6.38 (N=C-CH); 1.78 (3H $CH_3$); Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30 %. Found: C, 73.00; H, 5.48; N, 21.13 %.

### Synthesis of 3-(5-phenyl-1H-pyrazol-3-yl)-1H-indole (2b)

Yield 74 %, m.p. 171-172 $^oC$; IR (KBr) $cm^{-1}$: 3379, 3412 (-NH); 1595 (C=N); $^1$H NMR (DMSO $d_6$) δ: 9.89, 9.61 (2H, NH); 7.34 (N-CH); 7.15-7.54 (Ar-H); 6.82 (N=C-CH); Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20 %. Found: C, 78.61; H, 5.00; N, 16.05 %.

**Synthesis of 3-(5-methyl-2-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-1H-indole (3a)**

Yield 81 %, m.p. 223-225 $^{o}$C; IR (KBr) cm$^{-1}$: 3383, 3418 (-NH); $^{1}$H NMR (DMSO $d_6$) δ: 9.73, 9.55 (2H, NH); 7.10-7.21 (Ar-H); 6.89 (N-CH); 4.78 (N=C-CH); 1.74 (3H $CH_3$); Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26 %. Found: C, 78.32; H, 6.04; N, 15.13 %.

**Synthesis of 3-(2,5-diphenyl-2,3-dihydro-1H-pyrazol-3-yl)-1H-indole (3b)**

Yield 76 %, m.p. 235 $^{o}$C; IR (KBr) cm$^{-1}$: 3325, 3372 (-NH); $^{1}$H NMR (DMSO $d_6$) δ: 9.92, 9.65 (2H, NH); 6.95 (N-CH); 7.12-7.38 (Ar-H); 5.42 (N=C-CH); Anal. Calcd. for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45 %. Found: C, 81.70; H, 5.51; N, 12.38 %.

**Synthesis of [5-(1H-indol-3-yl)-3-methyl-2, 5-dihydro-1H-pyrazol-1-yl](pyridin-4yl) methanone (4a)**

Yield 72 %, m.p. 215-218 $^{o}$C; IR (KBr) cm$^{-1}$: 3395, 3422 (-NH); 1656 (–C=N); 1722 (C=O); $^{1}$H NMR (DMSO $d_6$) δ: 9.72, 9.53 (2H, NH); 6.94 (N-CH); 7.15-7.68 (Ar-H); 4.74 (N=C-CH); 1.72 (3H, $CH_3$); Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 74.04; H, 5.30; N, 18.41 %. Found: C, 73.88; H, 5.14; N, 18.28 %.

**Synthesis of [5-(1H-indol-3-yl)-3-phenyl-2, 5-dihydro-1H-pyrazol-1-yl](pyridin-4-yl) methanone (4b)**

Yield 79 %, m.p. 218-219 $^{o}$C; IR (KBr) cm$^{-1}$: 3395, 3423 (-NH); 1695 (C=N); 1655 (C=O); $^{1}$H NMR (DMSO $d_6$) δ: 9.82, 9.53 (2H, NH); 6.94 (N-CH); 7.05-7.68 (Ar-H); 4.74 (N=C-CH); Anal. Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29 %. Found; C, 75.18; H, 4.72; N, 15.06 %.

**Synthesis of [5-(1H-indol-3-yl)-3-methyl-2, 5-dihydro-1H-pyrazol-1-yl](pyridin-3-yl) methanone (5a)**

Yield 72 %, m.p. 212-215 $^{o}$C; IR (KBr) cm$^{-1}$: 3395, 3422 (-NH); 1656 (C=N); 1719 (C=O); $^{1}$H NMR (DMSO $d_6$) δ: 9.72, 9.53 (2H, NH); 6.94 (N-CH); 7.15-7.68 (Ar-H); 4.74 (N=C-CH); 1.72 (3H, $CH_3$); Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 74.04; H, 5.30; N, 18.41 %. Found: C, 73.88; H, 5.14; N, 18.28 %.

**Synthesis of [5-(1H-indol-3-yl)-3-phenyl-2, 5-dihydro-1H-pyrazol-1-yl](pyridin-3-yl) methanone (5b)**

Yield 85 %, m.p. 217-219 $^{o}$C; IR (KBr) cm$^{-1}$: 3384, 3415 (-NH); 1691 (C=N); 1652 (C=O); $^{1}$H NMR (DMSO $d_6$) δ: 9.74, 9.52 (2H, NH); 6.94 (N-CH); 7.05-7.34 (Ar-H); 4.74 (N=C-CH); Anal. Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29 %. Found: C, 75.20; H, 4.75; N, 15.08 %.

**Synthesis of 5-(1H-indol-3-yl)-3-methyl-2, 5-dihydro-1H-pyrazole-1-carbothioamide (6a)**

Yield 89 %, m.p. 235-237 $^{o}$C; IR (KBr) cm$^{-1}$: 3309 ($NH_2$), 3342, 3379 (-NH); 1249 (C=S); $^{1}$H NMR (DMSO $d_6$) δ: 9.79, 9.51 (2H, NH); 7.37 (2H, $NH_2$); 6.92 (N-CH); 7.11-7.18 (Ar-H); 4.71 (N=C-CH); 1.77 (3H, $CH_3$); Anal. Calcd. for $C_{13}H_{14}N_4S$: C, 60.44; H, 5.46; N, 21.69 %. Found: C, 60.29; H, 5.24; N, 21.48 %.

**Synthesis of 5-(1H-indol-3-yl)-3-phenyl-2, 5-dihydro-1H-pyrazole-1-carbothioamide (6b)**

Yield 87 %, m.p. 247-249 $^{o}$C; IR (KBr) cm$^{-1}$: 3315 ($NH_2$), 3384, 3405 (-NH); 1252 (C=S); $^{1}$H NMR (DMSO $d_6$) δ: 7.39 (2H, $NH_2$); 9.98, 9.51 (2H, NH); 6.92 (N-CH); 7.12-7.42 (Ar-H); 4.96 (N=C-CH); Anal. Calcd. for $C_{18}H_{16}N_4S$: C, 67.47; H, 5.03; N, 17.49 %. Found: C, 67.20; H, 5.00; N, 17.18 %.

## RESULTS AND DISCUSSION

The starting compounds 3-(1*H*-indol-3-yl)-(1-methyl/phenyl) prop-2-en-1-one (chalcone) (1a-b) react with corresponding hydrazides in ethanol containing a few drops of glacial acetic acid under microwave irradiation to give (2a-b)-(6a-b), respectively. The structure was established though IR and $^{1}$H NMR spectral data. The IR spectra of (2a-b), exhibited absorption bands for primary amine (-NH) at 3387-3432 cm$^{-1}$ and (–C=N) at 1595-1610 cm$^{-1}$. The $^{1}$H NMR spectra of these compound revealed signals at δ = 9.58-9.92 ppm for (-NH) pyrazole ring proton, a singlet at δ = 6.82-6.38 ppm for (-N=C-CH) at pyrazole ring, a multiplet at δ = 7.07-7.54 ppm for the aromatic protons. The IR of (3a-b), exhibited absorption bands for primary amine (-NH) at 3381-3387 cm$^{-1}$. The $^{1}$H NMR spectra of these compound revealed signals at δ = 9.55-9.92 ppm for (-NH) proton, a singlet at δ = 6.89-6.95 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 6.64-7.38 ppm for the aromatic proton. The IR of (4a-b), exhibited absorption bands for primary amine (-NH) at 3381-3395 cm$^{-1}$ and (–C=N) at 1632-1656 cm$^{-1}$. The $^{1}$H NMR spectra of these compound revealed signals at δ = 9.52-9.74 ppm for (-NH) proton, a singlet at δ = 6.94 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 7.05-7.47 ppm for the aromatic proton. The IR of (5a-b), exhibited absorption bands for primary amine (-NH) at 3389-3395 cm$^{-1}$ and (–C=N) at 1610-1630 cm$^{-1}$. The $^{1}$H NMR spectra of these compound revealed signals at δ = 9.52-9.74 ppm for (-NH) proton, a singlet at δ = 6.94 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 7.05-7.24 ppm for the aromatic proton. The IR of (6a-b), exhibited absorption bands for primary amine (-NH) at 3385-3398 cm$^{-1}$, 3228 cm$^{-1}$ for (-$NH_2$), 1265-1270 cm$^{-1}$ for (–C=S). The $^{1}$H NMR spectra of these compound revealed signals at δ = 9.98-9.51 ppm for (-NH) proton, a singlet at δ = 6.92 ppm for (-N-CH) at pyrazole ring and a multiplet at δ = 7.12-7.29 ppm for the aromatic proton.

**Antimicrobial activity**

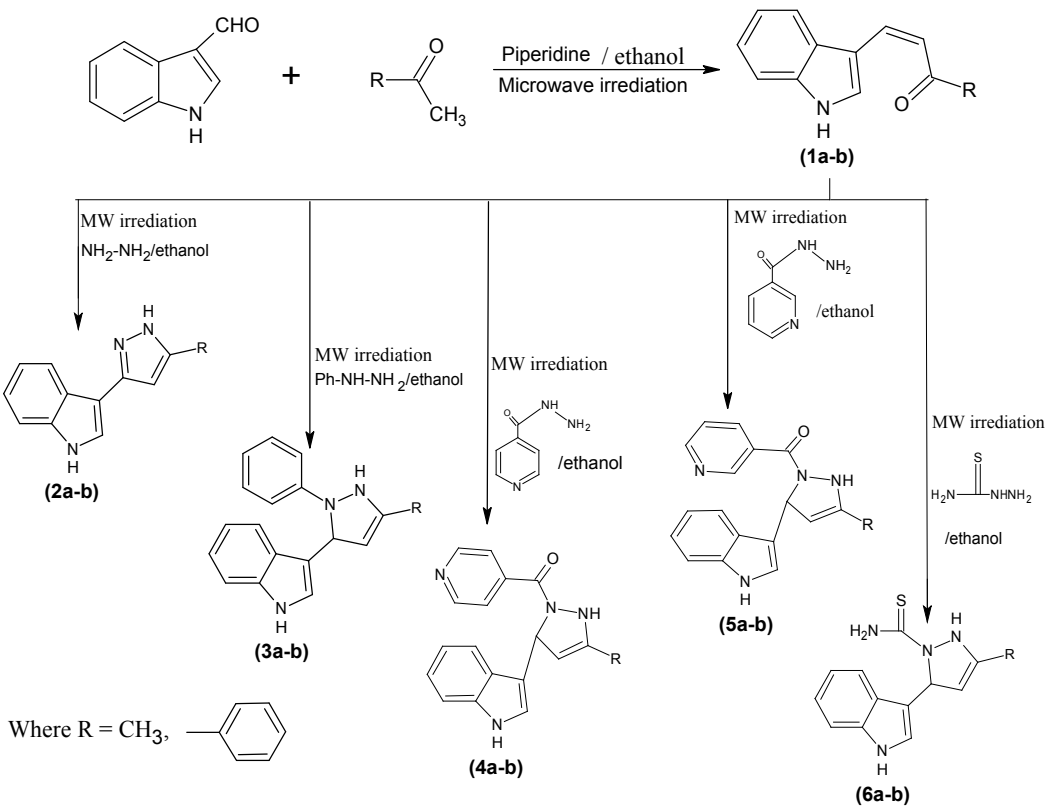
All the compounds ie., (2a-b), (3a-b), (4a-b), (5a-b) and (6a-b) were tested for antibacterial activity against *Escherichia coli* (Gram -ve), *Staphylococcus aureus* (Gram +ve), *Pseudomonas aeruginosa* (Gram +ve) bacteria and antifungal activity against three fungal strains *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. Ampicillin and griseofulvin were used as standard drugs for antibacterial and antifungal activity, respectively. Minimal Bactericidal Concentrations (MBC) and Minimal Fungicidal Concentration (MFC) were determined using Broth dilution method. Serial dilution for primary and secondary screening, material and method was followed as per NCCLS-1992 manual.[14] A stock solution was prepared of each drug (2000 µg/mL concentration). In primary screening, 1000, 500, 250 and 125 µg/mL concentrations of the synthesized drugs were taken. The synthesized drugs found active in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 µg/mL concentrations. The standard drug used in the present study is ampicilin for evaluating antibacterial activity which showed (50, 50 and 100 µg/mL MBC against *S. aureus*, *E. coli* and *P. aeruginosa,* respectively. Griseofulvin is used as the standard drug for antifungal activity, which showed 100 µg/mL MFC

against all the species, used for the antifungal activity. The results of antimicrobial and antifungal activities of our synthesized compounds are shown in Table 1.

**Table 1: Antimicrobial activity of all the synthesized compounds**

| S. No. | Minimal Bactericidal Concentration (MBC) (µg/mL) | | | Minimal Fungicidal Concentrations (FBC) (µg/mL) | | |
|---|---|---|---|---|---|---|
| | Gram negative | | Gram positive | *C. albicans* | *A. niger* | *A. clavatus* |
| | *E. coli* | *P. aeruginosa* | *S. aureus* | | | |
| **2a** | 250 | 500 | 250 | 500 | 500 | 500 |
| **2b** | 500 | 500 | 500 | 250 | 500 | 500 |
| **3a** | 100 | 250 | 250 | 250 | 250 | 500 |
| **3b** | 100 | 250 | 100 | 100 | 250 | 250 |
| **4a** | 250 | 500 | 250 | 500 | 500 | 500 |
| **4b** | 250 | 500 | 500 | 250 | 250 | 500 |
| **5a** | 100 | 250 | 250 | 100 | 250 | 250 |
| **5b** | 100 | 250 | 100 | 100 | 100 | 100 |
| **6a** | 100 | 250 | 250 | 250 | 250 | 500 |
| **6b** | 100 | 250 | 100 | 100 | 250 | 250 |
| **S.D.** | 50 | 100 | 50 | 100 | 100 | 100 |

**Scheme 1: Synthesis of compound (1a-b), (2a-b), (3a-b), (4a-b), (5a-b) and (6a-b)**




## CONCLUSION

Microwave assisted organic synthesis is rapid, efficient, safe and eco-friendly method for synthesis of some pyrazole derivatives. All the compounds show good antimicrobial activity against all micro-organisms.

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