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MICROWAVE ASSISTED SYNTHESIS OF SOME INDOLE BASED (1*H*-INDOL-3-YL)-N-METHYL/PHENYL-PYRAZOLIDIN PYRAZOLE DERIVATIVES AND THEIR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT
In the present investigation, microwave assisted synthesis of Chalcones **(3a-b)** were synthesized by base catalyzed aldol condensation of indole-3-carbaldehyde **(1)** with acetone or acetophenone **(2a-b)** in the presence of piperidine. The mixture of Chalcones **(3a-b)** was carried out with 1*H*-indole-2-carbhydrazide **(7a-e),** prepared by reaction of 1*H*-indole-2-carboxylic acid **(4)** and conc. H_2SO_4 exposed in microwave to get ethyl indole-2-carboxylate ester **(5)** then react with corresponding hydrazines **(6a-e)** in ethanol containing a few drops of glacial acetic acid under microwave irradiation to get target compounds **(8a-j)**. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR and ^{1}H NMR spectral data. The synthesized compounds have been screened for their anti-inflammatory activity.

KEYWORDS: Chalcones, Indole, Pyrazole, Microwave irradiation, Anti-inflammatory activity.

INTRODUCTION
Pyrazole derivatives have to place a major role in pharmaceutical chemistry. The pyrazole ring is a prominent structural moity found in numerous pharmaceutically active compounds. The pyrazole unit is one of the core structures in a number of drugs. El-Moghazy et. al.[1] has reported the synthesis and anti-inflammatory activity of some pyrazole derivatives whereas Sharshira[2] have synthesized some newer pyrazole derivatives and their anti-bacterial activity. Synthesis of some new pyrozaline and pyrazole derivatives and their antibacterial and antifungal activity have been studied by Hassan[3] while Ouyang et. al.[4] has carried out the synthesis and antiviral activity of novel pyrazole derivatives containing oxime esters group.

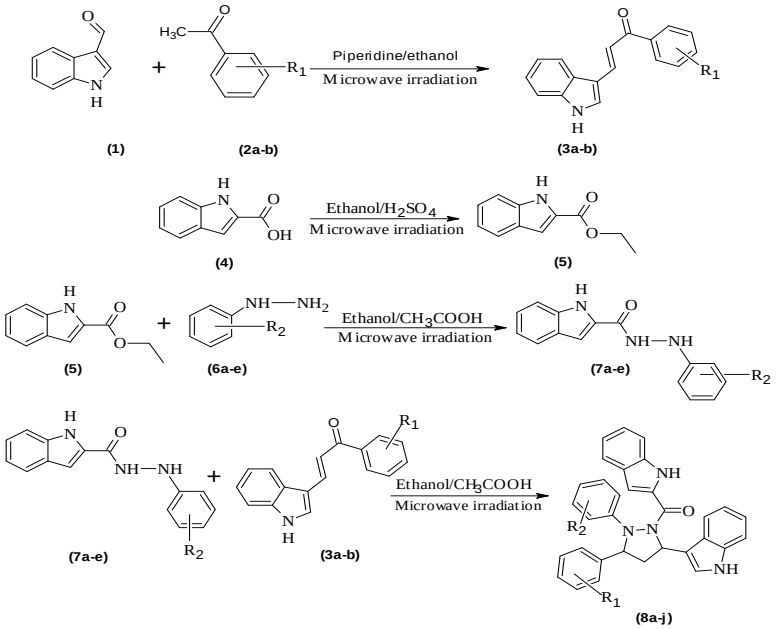
Synthesis and biological evaluation of novel pyrazole derivatives have been synthesized by Balbi et. al.[5] and they have also studied their anticancer activity. Swarts et. al.[6] has studied antioxidant properties of select radiation mitigators, based on semicarbazones and pyrazole derivatives of curcumin. Synthesis of some newer pyrazole derivatives have been synthesized by Bekhit et. al.[7] and studied their anti-malerial activity. Hipparagi et. al.[8] have reported the synthesis and evaluation of anti-tubercular activity of some novel 2-pyrazoline derivatives while Kees et. al.[9] have studied the new potent anti-hyperglycemic agents in db/db mice: synthesis and structure-activity relationship studies of (4-substituted benzyl) (trifluoromethyl) pyrazoles and pyrazolones.

Soliman et. al.[10] have synthesized some sulfonylurea derivatives of 3,4,5-trisubstituted pyrazoles and their anti-diabetic activity whereas synthesis and analgesic activity of some new pyrazoles and triazoles bearing a 6,8-dibromo-2-methylquinazoine moiety have been studied by Saad[11]. Zelaru et. al.[12] has carried out synthesis of some novel 2-(1H-pyrazole-1-yl)-acetamides as lidocaine analogue and studied their anesthetic activity. Ha et. al.[13] have carried out the synthesis and herbicidal activity of novel N-(2,2,2)-trifluoroethylpyrazole derivatives whereas Wu et. al.[14] has studied the synthesis and herbicidal activity of substituted pyrazole isothiocyanates. Song et. al.[15] have carried out the synthesis and insecticidal evaluation of new pyrazole derivatives containing imine, oxime ether, oxime ester and dihydroisooxazoline groups based on the inhiditor binding pocket of respiratory complex.

MATERIALS AND METHODS
Raga's microwave synthesis system (Model- RG311R, with reflux condensers and temperature controller up to 600C) was used to perform reactions. 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

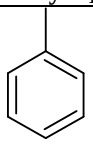
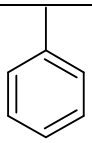
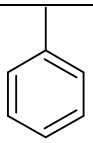
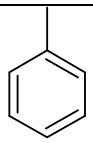
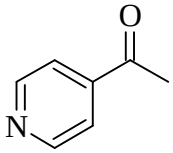
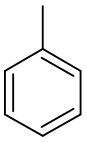
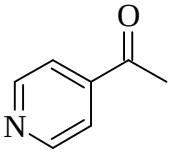
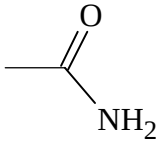
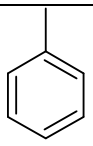
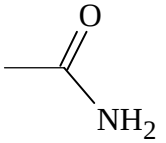
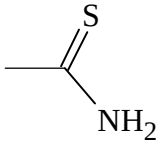
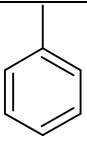
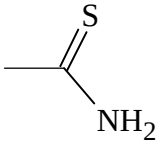
(300 MHz) in $CDCl_3$/DMSO-d6 using TMS as internal standard and chemical shifts are expressed in δ ppm. Purity of synthesized compounds was checked by TLC using silica gel-G. Spots were exposed in an iodine chamber.

Scheme 1



Scheme 1 Synthesis of some indole based (1*h*-indol-3-yl)-n-methyl/phenyl-pyrazolidin derivatives (8a-j).

Table I Chemical structure of the synthesized compounds (8a-j).

Compound	Entry R_1	Entry R_2	Compound	Entry R_1	Entry R_2
8a	$-CH_3$	-H	8f		-H
8b	$-CH_3$		8g		
8c	$-CH_3$		8h		
8d	$-CH_3$		8i		
8e	$-CH_3$		8j		

General procedure for preparation of chalcone (3a-b)

A convenient route for the synthesis of *α,β*-unsaturated ketones (Chalcone) was achieved by the reaction of indole-3-carbaldehyde **(1)** (0.725 g, 0.005 mol) with appropriate ketone **(2a-b)** (0.005 mol) in the presence of piperidine, were exposed to microwave at 200 W (95°C) intermittently at 5 sec intervals. The specific reaction time was kept 2 min and then the reaction mixture was cooled in crushed ice. Progress of the reaction was monitored by TLC method. The solid thus obtained was

filtered, washed with water, dried and purified by recrystallization from ethanol.

Synthesis of ethyl indole-2-carboxylate ester (5)
A solution of 1*H*-indole-2-carboxylic acid **(4)** (0.161 g, 0.001 mol.) in Dichloromethane and ethanol (10 mL) with the appropriate amount of Conc. H_2SO_4 were irradiated to microwave at 200 W (115°C) intermittently at 5 sec intervals. The specified reaction time of 1 min. was observed of compound ethyl indole-2-carboxylate ester **(5)**, m.p. 124°C.

Synthesis of 1*H*-indole-2-carbohydrazide (7a-e)
A solution of ethyl indole-2-carboxylate ester **(5)** (0.001 mol.) in ethanol (10 mL) with the appropriate amount of corresponding hydrazides (hydrazine hydrate, phenyl hydrazine, nicotinic hydrazide, semicarbezide and thiosemicarbezide) were exposed to microwave at 400 W (230°C) intermittently at 5 sec intervals. The specified reaction time of 1 min. was observed of compound 1*H*-indole-2-carbohydrazide **(7a-e)** derivatives.

General procedure for preparation of (8a-j)
A solution of 1*H*-indole-2-carbohydrazide **(7a-e)** derivatives and chalcones **(3a-b)** in ethanol was exposed (400 W, 220°C), in the presence of glacial acetic acid (2 drops) in microwave. The specific reaction time was kept 1 min. Then the reaction mixture was cool in ice cold water and extracted with diethyl ether. Then the extract was washed with water, dried and dried and purified by recrystallization from ethanol.

1*H*-indol-2-yl[5-(1*H*-indol-3-yl)-3-methylpyrazolidin-1-yl]methanone (8a)
Yield 82%, m.p. 172-174°C; IR (KBr) cm^{-1}: 3388, 3412 (N-H indole); 3044 (–Ar-CH); 2845 (Ar-CH_3); 1725 (C=O str.); 1588 (C=N str.) ^{1}H NMR (DMSO d_6) δ: 9.74, 9.95 (1H, NH); 4.67 (N-CH); 6.61-7.28 (Ar-H); 1.81 (3H, C-CH_3); MS: *m/z:* 342; Anal. Calcd for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27%. Found: C, 73.35; H, 5.82; N, 16.32%.

(1*H*-indol-2-yl)-[5-(1*H*-indol-3-yl)-3-methyl-2-phenyl-pyrazolidin-1-yl]methanone (8b)
Yield 76%, m.p. 178-180°C; IR (KBr) cm^{-1}: 3381, 3418 (N-H indole); 3048 (–Ar-CH); 2847 (Ar-CH_3); 1645 (C=O); ^{1}H NMR (DMSO d_6) δ: 9.77, 9.95 (1H, NH); 4.65 (N-CH); 6.51-7.25 (Ar-H); 1.83 (3H, C-CH_3); MS: *m/z:* 420; Anal. Calcd. for $C_{27}H_{24}N_4O$: C, 77.12; H, 5.75; N, 13.32%. Found: C, 77.05; H, 5.70; N, 13.30%.

(1*H*-Indol-2-yl)-[5-(1*H*-indol-3-yl)-3-methyl-2-(pyridine-4-carbonyl)-pyrazolidin-1-yl] methanone (8c)
Yield 78%, m.p. 215-217°C; IR (KBr) cm^{-1}: 3385, 3410 (N-H indole); 3037 (Ar-CH); 2849 (Ar-CH_3); 1710, 1718 (C=O); 1656 (C=N); ^{1}H NMR (DMSO d_6) δ: 9.83, 9.92 (-NH indole); 4.61 (N-CH); 6.45-7.18 (Ar-H); 1.85 (3H, C-CH_3); MS: *m/z:* 449; Anal. Calcd. for $C_{27}H_{23}N_5O_2$: C, 72.14; H, 5.16; N, 15.58%. Found: C, 72.11; H, 5.15; N, 15.52%.

3-(1*H*-indol-3-yl)-2-(1*H*-indol-2-ylcarbonyl)-5-methylpyrazolidine-1-carboxamide (8d)
Yield 74%, m.p. 165-167°C; IR (KBr) cm^{-1}: 3308 (NH_2); 3391, 3418 (N-H, indole); 3045 (Ar-CH); 2948 (Ar-CH_3); 1711, 1722 (C=O); ^{1}H NMR (DMSO d_6) δ: 7.38 (2H, NH_2); 9.78, 9.95 (-NH indole); 5.43 (N-CH); 6.58-7.36 (Ar-H); 1.77 (3H, C-CH_3); MS: *m/z:*387; Anal. Calcd. For $C_{22}H_{21}N_5O_2$: C, 68.20; H, 5.46; N, 18.08%. Found: C, 68.17; H, 5.44; N, 18.01%.

3-(1*H*-indol-3-yl)-2-(1*H*-indol-2-ylcarbonyl)-5-methylpyrazolidine-1-carbothioamide (8e)
Yield 82%, m.p. 162-164°C; IR (KBr) cm^{-1}: 3312 (NH_2); 3389, 3415 (N-H, indole); 3047 (Ar-CH); 2945 (Ar-CH_3); 1719 (C=O); 1249 (C=S); ^{1}H NMR (DMSO d_6) δ: 7.42 (2H, NH_2); 9.82, 9.99 (-NH indole); 5.47 (N-CH); 6.54-7.36 (Ar-H); 1.75 (3H, C-CH_3); MS: *m/z:*403; Anal. Calcd. For $C_{22}H_{21}N_5OS$: C, 65.49; H, 5.25; N, 17.36%. Found: C, 65.47; H, 5.14; N, 17.21%.

(1*H*-indol-2-yl)-[5-(1*H*-indol-3-yl)-3-phenyl-pyrazolidin-1-yl]-methanone (8f)
Yield 72%, m.p. 180-182°C; IR (KBr) cm^{-1}: 3388, 3414 (N-H indole); 3046 (–Ar-CH); 1714 (C=O str.);1610 (C=N str.); ^{1}H NMR (DMSO d_6) δ: 9.78, 9.98 (1H, NH); 4.69 (N-CH); 6.63-7.26 (Ar-H); MS: *m/z:* 404; Anal. Calcd. for $C_{26}H_{22}N_4O$: C, 76.83; H, 5.46; N, 13.78%. Found: C, 76.79; H, 5.44; N, 13.72%.

(1*H*-indol-2-yl)-[5-(1*H*-indol-3-yl)-2,3-diphenyl-pyrazolidin-1-yl]-methanone (8g)
Yield 80%, m.p. 186-188°C; IR (KBr) cm^{-1}: 3389, 3415 (N-H indole); 3053 (–Ar-CH); 1712 (C=O str.); ^{1}H NMR (DMSO d_6) δ: 9.81, 9.98 (2H, NH indole); 4.70 (N-CH); 6.57-7.31 (Ar-H); MS: *m/z:* 482; Anal. Calcd. for $C_{32}H_{26}N_4O$: C, 79.64; H, 5.43; N, 11.61%. Found: C, 79.62; H, 5.35; N, 11.58%.

(1*H*-indol-2-yl)-[5-(1*H*-indol-3-yl)-3-phenyl-2-(pyridine-4-carbonyl)-pyrazolidin-1-yl] methanone (8h)
Yield 77%, m.p. 223-225°C; IR (KBr) cm^{-1}: 3387, 3417 (N-H str. indole); 3043 (Ar-CH); 1712, 1722 (C=O str.); 1658 (C=N str.); ^{1}H NMR (DMSO d_6) δ: 9.86, 9.97 (-NH); 4.64 (N-CH); 6.49-7.21 (Ar-H); MS: *m/z:* 511; Anal. Calcd. for $C_{32}H_{25}N_5O_2$: C, 75.13; H, 4.93; N, 13.69%. Found: C, 75.15; H, 4.91; N, 13.62%.

2-(1*H*-indol-2-carbonyl)-3-(1*H*-indol-3-yl)-5-phenyl-pyrazolidin-1-carboxylic acid amide (8i)
Yield 81%, m.p. 173-175°C; IR (KBr) cm^{-1}: 3310 (NH_2); 3394, 3419 (N-H, indole); 3048 (Ar-CH); 1711, 1722 (C=O str.); ^{1}H NMR (DMSO d_6) δ: 7.41 (2H, NH_2); 9.81, 9.96 (-NH indole); 5.45 (N-CH); 6.60-7.38 (Ar-H); MS: *m/z:*449; Anal. Calcd. For $C_{27}H_{23}N_5O_2$: C, 72.14; H, 5.16; N, 15.58%. Found: C, 72.11; H, 5.14; N, 15.51%.

2-(1*H*-indol-2-carbonyl)-3-(1*H*-indol-3-yl)-5-phenyl-pyrazolidin-1-carbothioic acid amide (8j)
Yield 76%, m.p. 170-172^{o}C; IR (KBr) cm^{-1}: 3313 (NH_2); 3390, 3418 (N-H, indole); 3049 (Ar-CH); 1721 (C=O str.); 1251 (C=S str.); ^{1}H NMR (DMSO d_6) δ: 7.45 (2H, NH_2); 9.84, 9.98 (-NH indole); 5.49 (N-CH); 6.56-7.38 (Ar-H); MS: *m/z:*465; Anal. Calcd. For $C_{27}H_{23}N_5OS$: C, 69.65; H, 4.98; N, 15.04%. Found: C, 69.61; H, 4.94; N, 15.00%.

RESULTS AND DISCUSSION

In the present work the synthesis of some indole based pyrazole derivatives **(8a-j)** was prepared the starting compounds 1*H*-indole-2-carbohydrazide **(7a-e)** derivatives and chalcones **(3a-b)** in ethanol containing a few drops of glacial acetic acid under microwave irradiation. The structure was established though IR and ^{1}H NMR spectral data. The IR spectra of (**8a-j)** exhibited absorption bands for amine (-NH indole) at 3381-3394 cm^{-1}, (NH_2) 3308-3313 cm^{-1}, (-N-N) at 1241-1246 cm^{-1}, (-C-N) at 1083-1087 cm^{-1}, (C=O) at 1635-1651 cm^{-1} and (C=S) at 1247-1249 cm^{-1}. The ^{1}H NMR spectra of these compounds revealed signals at δ = 9.77-9.96 ppm for (-NH) ring proton, δ = 7.38-7.45 ppm for (-NH_2) ring proton, a singlet at δ = 4.61-5.49 ppm for (-N-CH) at pyrazole ring.

The results of anti-inflammatory activity reveal that percentage inhibition of edema of compound **8f** and **8i** is grater then standard at the 240 min after drug administration. The percentage inhibition of edema shown by **8a, 8b** and **8j** at 240 min after drug administration is also good. Compounds **8c, 8e, 8g,** and **8h** is moderately active and compound **8d** is less active then standard at the 240 min after drug administration.

Anti-inflammatory activity

Anti-inflammatory activity was carried out using carrageenan-induced rat paw oedema method in albino rats (150-200 gm) were devided into different groups with six animals in each group. Rats were selected by random sampling technique. Edema was induced in the right hind paw of rat by the sub planter injection of 0.1 ml of 1% carrageenan in distilled water according to the method described by Winter et al (1962).[16] Diclofenac sodium orally (10mg/kg) was administered as a reference drug. The test compounds were dissolved in DMSO at dose (20 mg/kg) orally orally 30 min. after carrageenan injection. The paw volume was measured by plethysmographically at various intervals (30, 60, 120, 180 min.). Mean increase in paw volume was measured and % inhibition was calculated in Table II.

Table II Anti-inflammatory activity of all the synthesized compounds.

Group	Dose (mg/kg)	Paw volume (mean ± SEM)					Percentage of Inhibition			
		0 min	60 min	120 min	180 min	240 min	60 min (%)	120 min (%)	180 min (%)	240 min (%)
Control	-	0.671± 0.035	0.683± 0.031	0.688± 0.028	0.693± 0.031	0.697± 0.015	00	00	00	00
Diclofenac sodium	**10mg/kg**	0.663± 0.017	0.623± 0.035	0.551± 0.024	0.432± 0.010	0.371± 0.028	8.78	19.91	36.21	46.77
8a	**20mg/kg**	0.668± 0.012	0·639± 0·022	0·585± 0·035	0·521± 0·025	0·375± 0·032	4.97	16.42	26.26	44.76
8b	**20mg/kg**	0·659± 0·032	0·643± 0·038	0·551± 0·025	0·452± 0·033	0·383± 0·027	7.32	18.45	33.33	43.61
8c	**20mg/kg**	0·657± 0·022	0·626± 0·024	0·553± 0·023	0·475± 0·026	0·399± 0·024	6.88	21.07	32.90	43.32
8d	**20mg/kg**	0·669± 0·017	0·652± 0·026	0·541± 0·037	0·445± 0·015	0·401± 0·011	6.00	19.91	34.34	41.03
8e	**20mg/kg**	0·669± 0·015	0·616± 0·025	0·563± 0·017	0·472± 0·035	0·385± 0·014	9.07	19.62	33.33	43.32
8f	**20mg/kg**	0·655± 0·032	0·637± 0·042	0·525± 0·025	0·428± 0·026	0·369± 0·018	8.19	22.23	36.79	48.49
8g	**20mg/kg**	0·658± 0·029	0·622± 0·032	0·552± 0·025	0·479± 0·016	0·395± 0·032	7.46	18.31	32.32	44.04
8h	**20mg/kg**	0·649± 0·032	0·633± 0·026	0·523± 0·019	0·428± 0·044	0·392± 0·024	8.78	23.98	36.79	45.19
8i	**20mg/kg**	0·656± 0·044	0·622± 0·024	0·553± 0·024	0·442± 0·033	0·346± 0·027	7.46	21.07	37.66	48.92
8j	**20mg/kg**	0·662± 0·035	0·648± 0·041	0·533± 0·016	0·445± 0·045	0·380± 0·035	6.58	21.07	34.34	44.04

CONCLUSIONS

In conclusion, we have synthesized indole based pyrazole derivatives in better yields in microwave irradiation. These compounds showed good anti-inflammatory activity in comparison with the standard drug diclofenac sodium.

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