MICROWAVE ASSISTED SYNTHESIS OF INDOLE BASED 4-DIMETHYLAMINO-PHENYL-N-METHYL/PHENYL-PYRAZOLIDINE PYRAZOLE DERIVATIVES AND STUDY OF THEIR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

In the present investigation, the microwave assisted synthesis of substituted indole based pyrazole rings has been reported and their anti-inflammatory activity was evaluated. Chalcones (3a-b) were synthesized by base catalyzed aldol condensation of p-dimethylaminobenzaldehyde (1) with acetone or acetophenone (2a-b) in the presence of piperidine. 1H-indole-2-carboxylic acid (4) was prepared by reaction of 1H-indole-2-carboxylic acid (4) and conc. H2SO4 under microwave exposure get ethyl indole-2-carboxylate ester (5). Then this compound (5) was allowed to react with corresponding hydrazines (6a-e) in ethanol containing a few drops of glacial acetic acid under microwave irradiation to obtain compound (7a-e).

Chalcones (3a-b) were treated with 1H-indole-2-carboxylic acid (7a-e) to get target compounds (8a-j). The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR and 1H 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 play a vital role in the medicinal chemistry. The pyrazole ring is a prominent structural moiety found in numerous pharmaceutically active compounds. The pyrazole unit is one of the core structures in a number of drugs. More recently, extensive
studies have been focused on pyrazole derivatives. Mohammed et al. [1] have reported synthesis, molecular docking and biological evaluation of some novel hydrazones and pyrazole derivatives as anti-inflammatory agents whereas Yu et al. [2] have synthesized some pyrazole-fused tricyclic diterpene derivatives and studied their anti-bacterial activity. Synthesis of novel pyrazole carboxamide and isoxazolol, pyrazole, carboxylate derivatives and their anti-fungal activity has been studied by Sun and Zhou [3] while Xiao et al. [4] have carried out the synthesis and anti-Tobacco Mosaic virus (TMV) activity of 5-chloro-N-(4-cyano-1-aryl-1H-pyrazol-5-yl)-1-aryl-3-methyl-1H-pyrazole-4-carboxamide derivatives.

Synthesis of pyrazole derivatives possessing anticancer activity have been reported by Kumari. [5] Abriach et al. [6] have reported the antioxidant activities of N-(3,5-dimethyl-1H-pyrazol-1-yl)methylpyridine-4-amine derivatives whereas Bekhit et al. [7] have synthesized some 1H- pyrazole derivatives acting antimalarial and anti-leishmanial agents. Synthesis of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives and evaluation of their antitubercular and antimicrobial activity has been studied by Pathak et al. [8] while Kees et al. [9] have carried out the synthesis and structure-activity relationship studies of (4-substituted benzyl) (trifluoromethyl) pyrazoles and pyrazolones and evaluated their antihyperglycemic activity.

Soliman [10] synthesized 3-methyl-5-phenylpyrazolesulfonyleurea derivatives and studied their antidiabetic activity while synthesis of some new pyrazoles and triazoles bearing a 6,8-dibromo-2-methylquinazoline moiety and their analgesic activity has been carried out by Saad et al. [11] Bruno et al. [12] have synthesized 3,5-diphenyl-1H-pyrazole derivatives. Like N-substituted 4-amino-1-(2-hydroxy-or 2-alkylaminoethyl)-3,5-diphenyl-1H-pyrazoles with local anesthetic, analgesic and platelet antiaggregating activities. Synthesis of novel N-(2,2,2)-trifluoroethylpyrazole derivatives and their herbicidal activity has been studied by Ning [13] whereas Ma et al. [14] have reported the synthesis and herbicidal activities of novel 4-(1H-pyrazol-1-yl)-6-(alkynyloxy)-pyrimidine derivatives as potential pigment biosynthesis inhibitors. Kang et al. [15] have synthesized novel acetamido derivatives containing N-pyridylpyrazol carboxamides and studied their insecticidal activity.

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-d$_6$ using TMS as internal standard and chemical shifts are expressed in $\delta$ 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 (3a-b)**

A convenient route for the synthesis of $\alpha,\beta$-unsaturated ketones (Chalcone) was achieved by the reaction of p-dimethylaminobenzaldehyde (1) (1.49 g, 0.01 mol) with appropriate ketone (2a-b) (0.01 mol) in the presence of piperidine (2 drops), under exposure to microwave at 200 W (95°C) intermittently with 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. 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 1H-indole-2-carboxylic acid (4) (0.161 g, 0.001 mol.) in dichloromethane and ethanol (10 mL) with the appropriate amount of conc. H$_2$SO$_4$ was irradiated under microwave at 200 W (115°C) intermittently with 5 sec intervals. The specified reaction time of 1 min. was kept for synthesis of compound ethyl indole-2-carboxylate ester (5), m.p. 124°C.

**Synthesis of 1H-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) was exposed to microwave at 400 W (230°C) for a specific reaction time of 1 min. with 5 sec intervals. The specified reaction time of 1 min. was kept for synthesis of compounds 1H-indole-2-carbohydrazide derivatives (7a-e).

**General procedure for preparation of (8a-j)**

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

Scheme: 1 Synthesis of indole based 4-dimethylamino-phenyl-n-methyl/phenyl-pyrazolidine (8a-j)

Table 1 Chemical structure of the synthesized compounds (8a-j)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Entry R₁</th>
<th>Entry R₂</th>
<th>Compound</th>
<th>Entry R₁</th>
<th>Entry R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>-H</td>
<td>-H</td>
<td>8f</td>
<td>-CH₃</td>
<td>-H</td>
</tr>
<tr>
<td>8b</td>
<td>-H</td>
<td>-H</td>
<td>8g</td>
<td>-CH₃</td>
<td>-H</td>
</tr>
<tr>
<td>8c</td>
<td>-H</td>
<td>-H</td>
<td>8h</td>
<td>-CH₃</td>
<td>-H</td>
</tr>
<tr>
<td>8d</td>
<td>-H</td>
<td>-H</td>
<td>8i</td>
<td>-CH₃</td>
<td>-H</td>
</tr>
<tr>
<td>8e</td>
<td>-H</td>
<td>-H</td>
<td>8j</td>
<td>-CH₃</td>
<td>-H</td>
</tr>
</tbody>
</table>
(5-[4-(Dimethylamino)phenyl]-3-methyl-4,5-dihydro-1H-pyrazol-1-yl)(1H-indol-2-yl) methanone (8a)
Yield 82 %, m.p. 172-174°C; IR (KBr) cm⁻¹: 3388 (N-H indole); 3044 (--Ar-CH); 2942 (N-CH₃); 1643 (C=O); 1H NMR (DMSO d₆) δ: 9.96 (1H, NH); 4.67 (N-CH); 6.61-7.28 (Ar-H); 2.82 (6H, N-CH₃); 1.81 (3H, C-CH₃); Anal. Calcd. for C₂₁H₂₂N₄O: C, 72.81; H, 6.40; N, 16.17%. Found: C, 72.74; H, 6.32; N, 16.10%.

(5-[4-(Dimethylamino-phenyl)-3-methyl-2-phenyl-pyrazolidin-1-yl-(1H-indol-2-yl) methanone (8b)
Yield 76 %, m.p. 178-180°C; IR (KBr) cm⁻¹: 3381 (N-H indole); 3048 (--Ar-CH); 2940 (N-CH₃); 1645 (C=O); 1H NMR (DMSO d₆) δ: 9.77 (1H, NH); 4.65 (N-CH); 6.51-7.25 (Ar-H); 2.87 (6H, N-CH₃); 1.83 (3H, C-CH₃); Anal. Calcd. for C₂₇H₂₈N₄O: C, 76.39; H, 6.65; N, 13.20%. Found: C, 76.25; H, 6.30; N, 13.12%.

[3-(4-(Dimethylamino-phenyl)-2-(1H-indole-2-carbonyl)-5-methyl-pyrazolidin-1-yl]-pyridin-4-yl-methanone (8c)
Yield 78 %, m.p. 215-217°C; IR (KBr) cm⁻¹: 3385 (N-H indole); 3037 (Ar-CH); 2943 (N-CH₃); 1640, 1645 (C=O); 1595 (C=N); 1H NMR (DMSO d₆) δ: 9.83 (-NH); 4.61 (N-CH); 6.45-7.18 (Ar-H); 2.82 (6H, N-CH₃); 1.85 (3H, C-CH₃); Anal. Calcd. for C₂₇H₂₈N₅O₂: C, 71.50; H, 6.00; N, 15.44%. Found: C, 71.43; H, 6.05; N, 15.38%.

3-(4-Dimethylamino-phenyl)-2-(1H-indole-2-carbonyl)-5-methyl-pyrazolidin-1-carboxylic acid amide (8d)
Yield 74 %, m.p. 165-167°C; IR (KBr) cm⁻¹: 3308 (NH₂); 3391 (N-H, indole); 3045 (Ar-CH); 2948 (N-CH₃); 1635, 1648 (C=O); 1H NMR (DMSO d₆) δ: 7.38 (2H, NH₂); 9.78 (-NH); 5.43 (N-CH); 6.58-7.36 (Ar-H); 2.88 (6H, N-CH₃); 1.77 (3H, C-CH₃); Anal. Calcd. for C₂₂H₂₅N₅O₂: C, 67.50; H, 6.44; N, 17.89%. Found: C, 67.47; H, 6.34; N, 17.81%.

3-(4-Dimethylamino-phenyl)-2-(1H-indole-2-carbonyl)-5-methyl-pyrazolidin-1-carbothioic acid amide (8e)
Yield 82 %, m.p. 162-164°C; IR (KBr) cm⁻¹: 3312 (NH₂); 3389 (N-H, indole); 3047 (Ar-CH); 2952 (N-CH₃); 1637 (C=O); 1247 (C=S); 1H NMR (DMSO d₆) δ: 7.42 (2H, NH₂); 9.82 (-NH); 5.47 (N-CH); 6.54-7.36 (Ar-H); 2.91 (6H, N-CH₃); 1.75 (3H, C-CH₃); Anal. Calcd. for C₂₂H₂₅N₅OS: C, 64.84; H, 6.18; N, 17.18%. Found: C, 64.77; H, 6.74; N, 17.11%. 
[5-(4-Dimethylamino-phenyl)-3-phenyl-4,5-dihydro-pyrazol-1-yl]-(1H-indol-2-yI) methanone (8f)
Yield 72%, m.p. 180-182°C; IR (KBr) cm\(^{-1}\): 3388 (N-H indole); 3044 (–Ar-CH); 2942 (N-CH\(_3\)); 1643 (C=O); \(^1\)H NMR (DMSO \(_d_6\)) \(\delta\): 9.96 (1H, NH); 4.67 (N-CH); 6.61-7.28 (Ar-H); 2.82 (6H, N-CH\(_3\)); 1.81 (3H, C-CH\(_3\)); Anal. Calcd. for C\(_{26}\)H\(_{33}\)N\(_4\)O: C, 76.45; H, 5.92; N, 13.72%. Found: C, 76.39; H, 5.88; N, 13.70%.

[5-(4-(Dimethylamino-phenyl)-2,3-diphenyl-pyrazolidin-1-yl]-(1H-indol-2-yI)- methanone (8g)
Yield 80%, m.p. 186-188°C; IR (KBr) cm\(^{-1}\): 3389 (N-H indole); 3053 (–Ar-CH); 2945 (N-CH\(_3\)); 1650 (C=O); \(^1\)H NMR (DMSO \(_d_6\)) \(\delta\): 9.81 (1H, NH); 4.70 (N-CH); 6.57-7.31 (Ar-H); 2.92 (6H, N-CH\(_3\)); Anal. Calcd. for C\(_{32}\)H\(_{39}\)N\(_4\)O: C, 78.98; H, 6.21; N, 11.51%. Found: C, 78.92; H, 6.15; N, 11.43%.

[5-(4-(Dimethylamino-phenyl)-3-phenyl-2-(pyridine-4-carbonyl)-pyrazolidin-1-yl]-(1H- indole-2-yI)-methanone (8h)
Yield 77%, m.p. 223-225°C; IR (KBr) cm\(^{-1}\): 3387 (N-H indole); 3043 (Ar-CH); 2948 (N-CH\(_3\)); 1642, 1648 (C=O); 1597 (C=N); \(^1\)H NMR (DMSO \(_d_6\)) \(\delta\): 9.86 (-NH); 4.64 (N-CH); 6.49-7.21 (Ar-H); 2.85 (6H, N-CH\(_3\)); Anal. Calcd. for C\(_{33}\)H\(_{36}\)N\(_4\)O\(_2\): C, 77.02; H, 5.88; N, 10.89%. Found: C, 77.08; H, 5.81; N, 10.82%.

3-(4-Dimethylamino-phenyl)-2-(1H-indole-2-carbonyl)-5-phenyl-pyrazolidine-1- carboxylic acid amide (8i)
Yield 81%, m.p. 173-175°C; IR (KBr) cm\(^{-1}\): 3310 (NH\(_2\)); 3394 (N-H, indole); 3048 (Ar-CH); 2951 (N-CH\(_3\)); 1637, 1651 (C=O); \(^1\)H NMR (DMSO \(_d_6\)) \(\delta\): 7.41 (2H, NH\(_2\)); 9.81 (-NH); 5.45 (N-CH); 6.60-7.38 (Ar-H); 2.89 (6H, N-CH\(_3\)); Anal. Calcd. For C\(_{27}\)H\(_{27}\)N\(_3\)O\(_2\): C, 71.50; H, 6.00; N, 15.44%. Found: C, 71.47; H, 6.04; N, 15.41%.

3-(4-Dimethylamino-phenyl)-2-(1H-indole-2-carbonyl)-5-phenyl-pyrazolidine-1- carbothioic acid amide (8j)
Yield 76%, m.p. 170-172°C; IR (KBr) cm\(^{-1}\): 3313 (NH\(_2\)); 3390 (N-H, indole); 3049 (Ar-CH); 2955 (N-CH\(_3\)); 1639 (C=O); 1249 (C=S); \(^1\)H NMR (DMSO \(_d_6\)) \(\delta\): 7.45 (2H, NH\(_2\)); 9.84 (-NH); 5.49 (N-CH); 6.56-7.38 (Ar-H); 2.93 (6H, N-CH\(_3\)); Anal. Calcd. For C\(_{27}\)H\(_{27}\)N\(_3\)OS: C, 69.06; H, 5.80; N, 14.91%. Found: C, 69.01; H, 5.74; N, 14.87%.
RESULTS AND DISCUSSION

In the present work, some indole based pyrazole derivatives (8a-j) was prepared by the reaction of starting compounds 1H-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 of the compounds 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 by compounds (8h) and (8i) is greater then standard at the 240 min after drug administration. The percentage inhibition of edema shown by compounds (8a) and (8f) at 240 min after drug administration was also good. Compounds (8b), (8c), (8e), (8g) and (8j) was moderately active while compound (8d) was found less active than standard at the 240 min after drug administration.

Anti-inflammatory activity

Anti-inflammatory activity was carried out using carrageenan-induced rat paw oedema method. Albino rats (150-200 g) 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 and Porto$^{16}$. Diclofenac sodium (10 mg/kg) was administered orally as a reference drug. The test compounds were dissolved in DMSO at dose (20 mg/kg) 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.
Table 2 Anti-inflammatory activity of the synthesized compounds

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Paw volume (mean ± SEM)</th>
<th>Percentage of Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 min</td>
<td>60 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 min (%)</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>0.671±0.035</td>
<td>0.693±0.031</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>10</td>
<td>0.663±0.017</td>
<td>0.551±0.022</td>
</tr>
<tr>
<td>8a</td>
<td>20</td>
<td>0.653±0.035</td>
<td>0.561±0.023</td>
</tr>
<tr>
<td>8b</td>
<td>20</td>
<td>0.659±0.025</td>
<td>0.543±0.021</td>
</tr>
<tr>
<td>8c</td>
<td>20</td>
<td>0.659±0.025</td>
<td>0.553±0.015</td>
</tr>
<tr>
<td>8d</td>
<td>20</td>
<td>0.658±0.036</td>
<td>0.535±0.021</td>
</tr>
<tr>
<td>8e</td>
<td>20</td>
<td>0.655±0.013</td>
<td>0.562±0.034</td>
</tr>
<tr>
<td>8f</td>
<td>20</td>
<td>0.658±0.036</td>
<td>0.553±0.015</td>
</tr>
<tr>
<td>8g</td>
<td>20</td>
<td>0.655±0.025</td>
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<td>0.648±0.036</td>
<td>0.523±0.018</td>
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<tr>
<td>8i</td>
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<td>20</td>
<td>0.669±0.032</td>
<td>0.543±0.018</td>
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</table>
CONCLUSION
Some indole based pyrazole derivatives have been synthesized with better yields under microwave irradiation. These compounds showed good anti-inflammatory activity in comparison with the standard drug diclofenac sodium.

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REFERENCES