Synthesis and characterization of Pyrazoline derivatives

Naveen Tanwer,1 Rajneesh Kaur,1,2 Devika Rana,1 Raman Singh,2 Kuldeep Singh1,2*

1Jaypee University of Information Technology, Waknaghat, Himachal Pradesh, 173234, India. 2Department of Chemistry, MMU Mullana, Haryana, 133207, India

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ABSTRACT

In the present study the synthesis of pyrazoline derivatives were carried out by cyclization of the chalcone with hydrazine hydrate in the presence of the formic acid. The synthesized pyrazoline derivatives were synthesized on the basis of prediction of activity spectra for substances (PASS). All the synthesized compounds were characterized by spectral analysis (1H NMR).

Keywords: Pyrazole, Chalcone, Anti-Inflammatory, Analgesic, Antipyretic

INTRODUCTION

Among heterocyclic compounds, pyrazole is considered as a unique scaffold possessing nitrogen atom in the five membered ring. Pyrazoline or dihydropyrazole has three possible tautomeric forms: Δ1-pyrazoline (1), Δ2-pyrazoline (2), Δ3-pyrazoline (3).

![Pyrazoline structures](image)

This template attracts attention because of its usefulness in drugs designing. Pyrazole displays various different pharmacological activities such as anti-inflammatory, antipyretic, analgesic, antitussive, antimicrobial, antitumor, antiviral, antihypertensive, antiglaucoma, antioxidant, antidepressant, anxiolytic, neuroprotective and antidiabetic activity. There are some well-established pyrazoline nucleosides containing drugs in market like Aminopyrine (Analgesic and antipyretic), Dipyrone (Analgesic), Antipyrine (antipyretic and anti-rheumatic), Phenylbutazone (NSAIDs), Zeleplon (Hypnotics and sedatives), Celecoxib (Osteoarthritis and rheumatoid arthritis inhibitors), Allopurinol (Treatment of goat), dinitro indazole (Anti-bacterial), 7-amino 5-nitro indazole (Antibacterial), Muzolimine (Diuretics). Therefore there is always demand for new molecules, methodologies and improved protocols for synthesis. The present study deals with the synthesis of pyrazoline derivatives by cyclization of the chalcone with hydrazine hydrate in the presence of the formic acid.

EXPERIMENTAL PROTOCOLS

2.1. Materials and methods

All reagents were purchased from commercial sources and were used without purification. Melting points of compounds were taken on melting apparatus and are uncorrected. The 1H NMR spectra of compounds were recorded in CDCl3 on Bruker AVANCE II 400 MHz spectrometer, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ ppm.

2.1.1. Synthesis of Substituted chalcone (3a-g)

2.1.1.1. General Procedure for synthesis of chalcones: Acetophenone (1, 1.86 g, 10 mmol) was treated with substituted benzaldehyde (2a, 1.08 ml, 10 mmol) using ethanolic alkali (20 ml) as a solvent and stirred for 15 hrs at room temperature. The reaction mixture was kept overnight at 0°C. The reaction mixture then poured into ice water and neutralized with dil HCl to give substituted chalcones 3a in good yields.

![Scheme 1](image)

Scheme 1: Synthesis of Substituted chalcone (3a-g) from acetophenone (1) and substituted benzaldehydes (2a-g).

Similar procedure was adopted for synthesis of other derivatives (3b-g). The products were characterised by 1H NMR. Table-1 lists M.P. and % yields of compounds 3a-g.
Table 1: Physical data of synthesized compounds (3a-g)

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Mp (°C)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>3a</td>
<td>56</td>
<td>82</td>
</tr>
<tr>
<td>4-CH₃</td>
<td>3b</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>4-OCH₃</td>
<td>3c</td>
<td>75</td>
<td>89</td>
</tr>
<tr>
<td>3,4-(OCH₃)₂</td>
<td>3d</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>2-OH</td>
<td>3e</td>
<td>148</td>
<td>57</td>
</tr>
<tr>
<td>4-Cl</td>
<td>3f</td>
<td>110</td>
<td>72</td>
</tr>
<tr>
<td>3-NO₂</td>
<td>3g</td>
<td>140</td>
<td>88</td>
</tr>
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Table 2: Physical data of synthesized compounds (5a-g)

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Mp (°C)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>5a</td>
<td>145-146</td>
<td>94</td>
</tr>
<tr>
<td>4-CH₃</td>
<td>5b</td>
<td>110-111</td>
<td>92</td>
</tr>
<tr>
<td>4-OCH₃</td>
<td>5c</td>
<td>121-122</td>
<td>90</td>
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<tr>
<td>3,4-(OCH₃)₂</td>
<td>5d</td>
<td>115-116</td>
<td>88</td>
</tr>
<tr>
<td>2-OH</td>
<td>5e</td>
<td>140-141</td>
<td>63</td>
</tr>
<tr>
<td>4-Cl</td>
<td>5f</td>
<td>105-106</td>
<td>85</td>
</tr>
<tr>
<td>3-NO₂</td>
<td>5g</td>
<td>160-162</td>
<td>87</td>
</tr>
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</table>

RESULT AND DISCUSSION

The condensation of acetophenone 1 with substituted aldehydes 2a-g in ethanolic alkali yielded substituted chalcone 3a-g which were purified by recrystallization in ethanol. All products were characterized by proton NMR spectroscopy. M.P. of these chalcones were recorded (uncorrected) and have been summarized in Table-1. Coupling constant values in ¹H NMR indicate trans geometry of carbon-carbon double bond. Pyrazoline derivatives 5a-g were synthesized by reacting chalcones 3a-g with hydrazine hydrate in formic acid. The products were recrystallized with ethanol. M. P. (Table-2) were recorded and ¹H NMR spectroscopic data satisfies the structure. N-formylation occurred in situ. Formyl group can be replaced by other groups by replacing formic acid with other acids.

2.3: ¹H NMR data of all synthesized compounds

(E)-Chalcone (3a): mp 56-57°C, (82%); ¹H NMR (400 MHz, CDCl₃) δ 8.01-8.04 (m, 2H), 7.82 (d, J = 15.6 Hz, 1H), 7.49-7.66 (m, 6H), 7.40-7.44 (m, 3H),

4-Methylchalcone (3b): mp 89-90 °C (92%); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.00-8.04 (m, 2H), 7.80 (d, J = 15.6 Hz, 1H), 7.48-7.61 (m, 6H), 7.23 (d, J = 7.8 Hz, 2H), 3.08 (s, 3H),

4-Methoxychalcone (3c): mp 75-76 °C, (89%); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.00-8.02 (m, 2H), 7.79 (d, J = 16.0 Hz, 1H), 7.48-7.62 (m, 5H), 7.42 (d, J = 15.6 Hz, 1H), 6.92-6.95 (m, 2H), 3.86 (s, 3H)

2-hydroxychalcone [3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one] (3e): mp 148-149 °C, (57%); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.17 (d, 1H, J = 16.40 Hz), 8.01-8.03 (m, 2H), 7.71 (d, 1H, J = 16.40 Hz), 7.55-7.59 (m, 2H), 7.47-7.51 (m, 2H), 7.28 (d, 1H, J = 8.00 Hz), 6.94 (t, 1H, J = 8.00 Hz), 6.90 (d, 1H, J = 8.00 Hz), 6.58 (bs, 1H, OH),

4-Chlorochalcone (3f): mp 110-111 °C (72%); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.00-8.03 (m, 2H), 7.76 (d, J = 15.6 Hz, 1H), 7.56-7.62 (m, 3H), 7.55 (d, J = 15.6 Hz, 1H), 7.48-7.53 (m, 2H), 7.38-7.40 (m, 2H),

3-Nitrochalcone [3-(nitrophenyl)-1-phenylprop-2-en-1-one] (3g): mp 140-141 °C (88%); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.23-8.51 (m, 2H), 8.02-8.05 (m, 2H), 7.92 (d, 1H, J = 7.60 Hz), 7.84 (d, 1H, J = 16.00 Hz), 7.67 (d, 1H, J = 16.00 Hz), 7.51-7.60 (m, 4H)

3,5-Diphenyl-4,5-dihydropyrazole-1-carbaldehyde (5a). Yield: 94%; mp: 145-147 C; ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 8.97 (s, 1H), 7.75-7.73 (m, 2H), 7.45-7.42 (m, 3H), 7.36-7.28 (m, 5H), 5.54 (dd, J = 4.5, 12.0 Hz, 1H), 3.82 (dd, J = 12.0, 16.0 Hz, 1H), 3.22 (dd, J = 4.5, 16.0 Hz, 1H),

5-(4-Methylphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5b). Yield: 92%; mp: 110-112 °C; ¹H NMR (CDCl₃, 400MHz) δ (ppm): 8.95 (s, 1H), 7.75-7.72 (m, 2H), 7.46-7.41 (m, 3H), 7.14 (s, 4H), 5.51 (dd, J = 4.92, 11.8 Hz, 1H), 3.79 (dd, J = 11.8, 17.7 Hz, 1H), 3.23 (dd, J = 4.92, 17.76 Hz, 1H), 2.31 (s, 3H)

5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5c). Yield: 90%; mp: 121-123 °C; ¹H NMR (CDCl₃, 400MHz) δ (ppm): 8.94 (s, 1H), 7.75-7.74 (m, 2H), 7.45-7.43 (m, 3H), 7.19 (J = 6.64 Hz, 2H), 6.86 (d, J = 6.64 Hz, 2H), 5.50 (dd, J = 4.8, 11.7 Hz, 1H), 3.78 (dd, J = 11.7, 17.7 Hz, 1H), 3.21 (dd, J = 4.6, 17.76 Hz, 1H)

5-(3,4-Dimethoxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5d). Yield: 88%; mp: 115-117 °C; ¹H NMR (CDCl₃, 400MHz) δ (ppm): 8.97 (s, 1H), 7.76-7.73 (m, 2H), 7.46-7.42 (m, 3H), 6.82-6.81 (d, 2H), 6.76 (s, 1H), 5.50 (dd, J = 4.9, 11.7 Hz, 1H), 3.85 (s, 3H), 3.84(s,3H), 3.80 (dd, J = 11.7, 17.76 Hz, 1H), 3.21 (dd, J = 4.9, 17.7 Hz, 1H)

5-(2-Hydroxyphenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5ε) Yield: 63%; 140–142 °C; 1H NMR (CDCl₃, 400MHz) δ (ppm): 8.82 (s, 1H), 7.99-7.80 (m, 2H), 7.52–7.49 (m, 3H), 7.18-7.14 (m, 1H), 7.01-6.99 (m, 1H), 6.91-6.83 (m, 2H), 5.85 (dd, J=3.7, 11.4 Hz, 1H), 3.77 (dd, J=11.4, 18.04 Hz, 1H), 3.21 (dd, J=3.7, 18.04 Hz, 1H)

5-(4-Chlorophenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5f). Yield: 85%; mp: 105–107 °C; 1H NMR (CDCl₃, 400MHz) δ (ppm): 8.98 (s, 1H), 7.75 (m, 2H), 7.47–7.42 (m, 3H), 7.33–7.30 (m, 2H), 7.21-7.18 (m, 2H), 5.52 (dd, J=4.9, 11.88 Hz, 1H), 3.81 (dd, J=11.8, 17.7 Hz, 1H), 3.20 (dd, J=4.9, 17.7 Hz, 1H)

5-(3-Nitrophenyl)-3-phenyl-4,5-dihydropyrazole-1-carbaldehyde (5g). Yield: 87%; mp: 160–162 °C; 1H NMR (CDCl₃, 400MHz) δ (ppm): 8.98 (s, 1H), 8.17-8.12 (m, 2H), 7.76–7.74 (m, 2H), 7.61 (d, 1H J=6.6), 7.54 (t, 1H J=7.8), 7.48-7.43 (m, 3H), 5.6 (dd, J=5.2, 11.9 Hz, 1H), 3.91 (dd, J=11.9, 17.8 Hz, 1H), 3.21 (dd, J=5.2, 17.8 Hz, 1H)

CONCLUSION

In conclusion, we have synthesized a number of various pyrazoline derivative (5a-5g). The reaction conditions were established and found to be reproducible. These derivatives may exhibit various pharmacological activities as indicated by PASS.13

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