Synthesis and biological evaluation of some new aryl pyrazol-3-one derivatives as potential hypoglycemic agents

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Several new aryl substituted pyrazol-3-one derivatives were prepared by the reaction of substituted phenyl hydrazine with diethylethoxymethylene malonate (DEEM). The compounds were synthesized by Michael addition reaction, which is a nucleophilic addition of enolate anions to the carbon–carbon double bond of α,β-unsaturated carboxylic acid derivatives. All the compounds were characterized by UV, IR and NMR spectroscopy and tested for hypoglycemic activity on alloxan induced diabetic rats. Among the tested compounds ethyl-2-para nitrophenyl-2,3-dihydro-1H-pyrazol-3-one-4-carboxylate and ethyl-2-meta nitrophenyl-2,3-dihydro-1H-pyrazol-3-one-4-carboxylate are identified as potent hypoglycemic agents and their activities are comparable with the standard drug metformin.

Keywords: Pyrazol-3-one derivatives, diethylethoxymethylene malonate (DEEM), substituted arylhydrazines, Michael addition reaction, hypoglycemic activity

Pyrazole and pyrazolone ring systems represent an important class of compounds not only for their theoretical interest but also for their anti-inflammatory, postmenopausal osteoporosis, angiotensin antagonists, antibacterial, sedative and anticoagulant activities. Recently some aryl pyrazole are reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activities. Diabetes mellitus is a major growing public health care problem throughout the world. Research on new substances possessing hypoglycemic activity has been going on since long back. The pharmacophoric moiety 3,5 dimethylpyrazole was reported by Gerritsen et al. Based on this pharmacophore numerous compounds were synthesized e.g. 1-(2, 4-dinitrophenyl)-3,5-dimethyl-4-arylacryparyzole and evaluated for antidiabetic activity. Later, a series of 4-arylhydrazono-3,5 dimethylpyrazole was reported by Gerritsen et al.

In the light of above, a new series of aryl substituted pyrazol-3-one derivatives were synthesized and evaluated for their possible hypoglycemic activity. Substituted phenylhydrazines were prepared from anilines by diazotization. Pyrazol-3-one-4-carboxylate derivatives were then generated by reacting diethylethoxymethylene malonate (DEEM) with substituted phenyl hydrazine through base catalyzed cyclisation reaction. The synthesized compounds were tested for hypoglycemic activity. The phenyl ring substituted on both N1 and N2 of pyrazol-3-one as in ethyl-1,2-diphenyl-2,3 dihydro-1H-pyrazol-3-one-4-carboxylate significantly showed increase in the antidiabetic activity but monosubstitution of phenyl ring showed a lower activity profile e.g. ethyl-2-phenyl-2,3 dihydro-1H-pyrazol-3-one-4-carboxylate. The pyrazole substituted by arylhydrazines having electronegative radicals, such as nitro groups carrying at least one substituent at either para or meta position such as ethyl-2-para nitrophenyl-2,3 dihydro-1H-pyrazol-3-one-4-carboxylate and ethyl-2-meta nitrophenyl-2,3 dihydro-1H-pyrazol-3-one-4-carboxylate respectively were significantly active and their activities were comparable with standard drug metformin. The chloro substituted pyrazole derivative, ethyl 2,4 dichlorophenyl-2,3 dihydro-1H-pyrazol-3-one-4-carboxylate was not significantly active and
perhaps the nitro derivatives emerge as active compounds which can be related to their larger size and more powerful electron withdrawing characteristics. The pivotal step for the successful synthesis of the pyrazole derivatives solely depends on the maintenance of temperature at 70°C for exactly 40 min that is optimum condition for cyclisation of substituted phenyl hydrazine with diethyoxymethylene malonate (DEEM) and immediate filtration of compounds. The physicochemical characterization like elemental analysis, melting point and yield were determined for all the synthesized compounds and characterized by UV, IR and NMR spectroscopy. All the synthesized compounds were screened for their hypoglycemic activity Table I, Figure 1.

Experimental Section
Preparation of substituted phenyl hydrazine from substituted aniline
Substituted phenylhydrazines were prepared by reducing diazonium salts of commercially available anilines with excess warm sodium sulphite solution, followed by acidification with hydrochloric acid.

Preparation of aryl substituted pyrazole derivatives
Substituted phenyl hydrazine (0.02 mole) was dissolved in minimum amount of cold water then ethanolic KOH was added. The solution was then refluxed for 40 min at 70°C in presence of diethylethoxymethylene malonate (0.02 mole) (DEEM). The precipitate obtained was filtered, washed with water and dried. The product (Scheme I) so obtained was recrystallized from ethanol and was dried for 24 hr at room temperature and kept in a vacuum desiccator.

Ethyl 2-phenyl-1H-pyrazol-3-one-4-carboxylate 3a
Yield: 56.65%; m.p.158°C; UV-Vis: 269 nm; IR (KBr): 1624 (-C=O), 1114 cm\(^{-1}\) (-C=O str. of ester); \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 1.3 (s, 3H, -CH\(_3\)), 4.3 (s, 2H, -CH\(_2\)), 7.8 (s, 1H heterocyclic ring proton), 2.4 (s, 1H, NH D\(_2\)O exchangeable), 7.2-7.8 (m, 5H, Ar-H); Anal. Found: C, 62.32; H, 5.90; N, 11.12. C\(_{12}\)H\(_{12}\)N\(_2\)O\(_3\) requires C, 63.15; H, 6.11; N, 11.33%.

Table I — Biological evaluation of compounds on wistar rats

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<thead>
<tr>
<th>Compd</th>
<th>Dose</th>
<th>Average±SD</th>
<th>40mg/kg</th>
<th>%Decrease (Mean±SD)</th>
<th>P Value</th>
<th>Average±SD</th>
<th>20mg/kg</th>
<th>%Decrease (Mean±SD)</th>
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<tr>
<td>Standard</td>
<td>151.2±11.37</td>
<td>73.78±1.50</td>
<td>&gt;0.05</td>
<td>171±22.7</td>
<td>61.81±10.244</td>
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<tr>
<td>3a</td>
<td>191.4±14.66</td>
<td>70.54±1.693</td>
<td>&lt;0.01</td>
<td>244.6±21.08</td>
<td>47.28±2.986</td>
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<tr>
<td>3b</td>
<td>207.4±11.52</td>
<td>65.80±1.378</td>
<td>&lt;0.01</td>
<td>258±8.17</td>
<td>56.20±1.608</td>
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<tr>
<td>3c</td>
<td>198.8±8.07</td>
<td>68.42±1.678</td>
<td>&lt;0.01</td>
<td>257±7.71</td>
<td>58.00±2.854</td>
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<tr>
<td>3d</td>
<td>282.8±21.83</td>
<td>53.42±2.934</td>
<td>&lt;0.01</td>
<td>221.8±19.15</td>
<td>70.16±5.35</td>
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<tr>
<td>3e</td>
<td>168.4±20.86</td>
<td>71.62±1.787</td>
<td>&gt;0.05</td>
<td>311.4±25.76</td>
<td>59.94±5.238</td>
<td>&gt;0.05</td>
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Ethyl 1,2-diphenyl-2,3-dihydro-1H-pyrazol-3-one-4-carboxylate 3b
Yield: 70.32%, m.p. 207°C; UV-Vis: 225, 317 nm; IR (KBr): 1624 (-C=O), 1070 (-C-O str. of ester), 2987 (Ar -CH), 775 cm\(^{-1}\) (Ar out of plane bending); \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 1.5 (s, 3H, -CH\(_3\)), 4.3 (s, 2H, -CH\(_2\)), 8.0 (s, 1H heterocyclic ring proton), 6.1-7.0 (m, 5H, CH-Ar), 6.8-7.4 (m, 5H, Ar-H); Anal. Found: C, 70.24; H, 5.10; N, 8.15. C\(_{18}\)H\(_{16}\)N\(_2\)O\(_3\) requires C, 70.57; H, 5.92; N, 8.66%.

Ethyl 2-para nitrophenyl-2,3-dihydro-1H-pyrazol-3-one-4-carboxylate, 3c
Yield: 65.43%, m.p. 163°C; UV-Vis: 224, 369 nm; IR (KBr): 3362  (NH str.), 1629 (-C=O), 1444 (-NO), 1587 (Ar -C-C str.), 754 (Ar -CH), 1114 cm\(^{-1}\) (-C-O str. of ester); \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 1.5 (s, 3H, CH\(_3\)), 4.3 (s, 2H, -CH\(_2\)), 7.3-8.0 (m, 5H, Ar-H), 7.5 (s, 1H heterocyclic ring proton), 2.5 (s, 1H, NH D\(_2\)O exchangeable); Anal. Found: C, 50.21; H, 3.86; N, 14.54. C\(_{12}\)H\(_{11}\)N\(_2\)O\(_5\) requires C, 51.99; H, 4.00; N, 15.16%.

Ethyl 2-meta nitrophenyl-2,3-dihydro-1H-pyrazol-3-one-4-carboxylate 3d
Yield: 59.96%, m.p. 151°C; UV-Vis: 209,316 nm; IR (KBr): 3362 (NH str.), 1629 (-C=O), 1444 (-NO), 1587 (Ar -C-C str.), 754 (Ar-C-H), 1114 cm\(^{-1}\) (-C-O str. of ester); \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 1.3 (s, 3H, -CH\(_3\)), 4.3 (s, 2H, -CH\(_2\)), 7.5-7.8 (m, 4H, Ar-H), 7.5 (s, 1H heterocyclic ring proton), 2.5 (s, 1H, NH D\(_2\)O exchangeable); Anal. Found: C, 51.99; H, 4.00; N, 15.16%.
(s,1H heterocyclic ring proton), 2.2 (1H, NH D_{2}O exchangeable); Anal. Found: C, 50.10; H, 3.59; N, 14.63. C_{12}H_{11}N_{3}O_{5} requires C, 51.99; H, 4.00; N, 15.16%.

**Ethyl-2,4 dichlorophenyl-2,3-dihydro-1H pyrazol-3-one-4-carboxylate 3e**

Yield: 74.23%, m.p. 147°C; UV-Vis: 254.5 nm; IR (KBr): 3358 (NH str.), 1697 (-C=O), 3043 (Ar), 1545 (Ar-C-C-str.), 1114 (-C-O str. of ester) 721 cm^{-1} (Ar - \text{CH}); \text{^1H NMR (CDCl}_3\text{)}: \delta 1.3 (s, 3H, -\text{CH}_3), 3.5 (s, 2H, -\text{CH}_2), 2.4 (1H, NH D_{2}O exchangeable), 6.1 (s,1H,Ar-H) 6.6 (s ,1H, Ar-H), 7.8 (s,1H, Ar-H), 8.5 (s,1H, heterocyclic ring proton); Anal. Found: C,
47.23; H, 3.43; N, 22.92. C_{12}H_{10}N_{3}Cl_{2}O_{3} requires C, 47.86; H, 3.35; Cl, 23.55; N, 9.30%.

**Biological evaluation**

The synthesized compounds were subjected for assessment of hypoglycemic activity. The rats of both sexes of Wistar strain weighing between 150-200 g were taken for *in vivo* activity. The compounds that were synthesized for their possible antidiabetic activity based on the model generated by Bertrand Cottineau *et al.* 3-methoxy-1H-pyrazole-4-carboxylic acid were found to have potency. Ten animals were used for screening the activity of each compound, the animals were divided into 2 groups as above 40 mg/kg, and 20 mg/kg dose were given for three consecutive days using metformin as standard drug and alloxan was used to induce glycemia.

**Conclusion**

The nature of the substituent at the phenyl ring of the 2nd position of pyrazole-4-carboxylate could be correlated to an important electronic variation. In conclusion it is found that pyrazole compounds may emerge as potential and promising antidiabetic agents by preparing more derivatives and analogs and screening their toxicity. Further derivatives may be prepared so as to establish a SAR (Structure Activity Relationship) based on rational studies.

**References**