Synthesis and antibacterial activity of 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles

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Condensation of 2-hydrazino-3-(3-chlorophenyl)-1,8-naphthyridine 2 with different acetophenones in methanol containing a catalytic amount of glacial acetic acid affords the corresponding acetophenone 3-(3-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 3 in excellent yields. The hydrazones 3 when subjected to the Vilsmeier-Haack reaction with POCl₃-DMF gives 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles 4 in good yields. The structural assignments to compounds 3 and 4 are based on their elemental analyses and spectral data. Compounds 4 have been tested for their antibacterial activity.

Keywords: 2-Hydrazino-3-(3-chlorophenyl)-1,8-naphthyridine, acetophenones, 1,8-naphthyridin-2-ylhydrazones, Vilsmeier-Haack reagent, 1,8-naphthyridinyl-pyrazoles.

1,8-Naphthyridones are an important class of heterocyclic compounds, several derivatives of which have been found to possess diverse types of biological activities including antibacterial, antihypertensive, antitumor and anti-inflammatory. Pyrazoles represent one of the most active classes of compounds possessing wide spectrum of biological activities. In continuation of the earlier work on synthesis of new 1,8-naphthyridine derivatives with potential biological activity, the present work involves the synthesis and antibacterial activity of 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles.

The starting compound, 2-hydrazino-3-(3-chlorophenyl)-1,8-naphthyridine 2 (ref. 13) required for the preparation of the target compounds, was obtained by the hydrazinolysis of 2-chloro-3-(3-chlorophenyl)-1,8-naphthyridine 1. Compound 2 on condensation with different acetophenones in methanol in the presence of a catalytic amount of glacial acetic acid afforded the corresponding acetophenone 3-(3-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 3 in excellent yields. The hydrazones 3 on treatment with Vilsmeier-Haack reagent (POCl₃-DMF) furnished 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles 4 in good yields (Scheme I, Table I).

The structures of the compounds 3 and 4 have been confirmed on the basis of analytical and spectral (IR and ¹H NMR) data.

Antibacterial activity
All the title compounds 4 were screened in vitro for their antibacterial activity against the Gram-negative Escherichia coli and Gram-positive Bacillus subtilis using filter paper disc method of Vincent and Vincent on treatment with Gentamycin was used as standard for comparison. The results are given in Table II.

Experimental Section
Melting points were recorded using Cintex melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC on silica gel G plates. IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer and ¹H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard.

General procedure for the synthesis of acetophenone 3-(3-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 3. A mixture of 2 (0.01 mole) and appropriate acetophenone (0.01 mole) in methanol (30 mL) containing a drop of glacial acetic acid was refluxed for 0.5 hr. The solid that separated out on cooling was filtered and recrystallized from methanol to afford 3 (Table I).

Note
Table I — Characterization data of compounds 3 and 4

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. Formula</th>
<th>Found (%) (Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>p-CH₂OC₆H₄</td>
<td>140</td>
<td>92</td>
<td>C₂₂H₁₉N₄OCl</td>
<td>68.76 (68.57)</td>
</tr>
<tr>
<td>3b</td>
<td>p-CH₃C₆H₄</td>
<td>160</td>
<td>95</td>
<td>C₂₃H₁₉N₄Cl</td>
<td>71.59 (71.41)</td>
</tr>
<tr>
<td>3c</td>
<td>p-ClC₆H₄</td>
<td>190</td>
<td>94</td>
<td>C₂₂H₁₈N₄Cl₂</td>
<td>64.97 (64.86)</td>
</tr>
<tr>
<td>3d</td>
<td>p-BrC₆H₄</td>
<td>212</td>
<td>92</td>
<td>C₂₂H₁₈N₄ClBr</td>
<td>58.79 (58.60)</td>
</tr>
<tr>
<td>3e</td>
<td>o-HOC₆H₄</td>
<td>155</td>
<td>89</td>
<td>C₂₂H₁₇N₄OCl</td>
<td>67.78 (67.95)</td>
</tr>
<tr>
<td>3f</td>
<td>p-HOC₆H₄</td>
<td>258</td>
<td>90</td>
<td>C₂₂H₁₇N₄OCl</td>
<td>67.77 (67.95)</td>
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<tr>
<td>3g</td>
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<td>88</td>
<td>C₂₂H₁₈N₄O₂Cl</td>
<td>63.41 (63.23)</td>
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<td>3h</td>
<td>p-NO₂C₆H₄</td>
<td>255</td>
<td>92</td>
<td>C₂₂H₁₈N₄O₂Cl</td>
<td>63.40 (63.23)</td>
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<tr>
<td>3i</td>
<td>C₆H₅</td>
<td>110</td>
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<td>C₂₃H₁₇N₄Cl</td>
<td>71.04 (70.87)</td>
</tr>
<tr>
<td>3j</td>
<td>β-Napthyl</td>
<td>88</td>
<td>90</td>
<td>C₂₉H₁₉N₄Cl</td>
<td>74.05 (73.85)</td>
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<tr>
<td>4a</td>
<td>p-CH₂OC₆H₄</td>
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<td>72</td>
<td>C₂₃H₁₉N₄O₂Cl</td>
<td>68.24 (68.10)</td>
</tr>
<tr>
<td>4b</td>
<td>p-CH₃C₆H₄</td>
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<td>80</td>
<td>C₂₃H₁₉N₄OCl</td>
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<td>4c</td>
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<td>&gt;300</td>
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<td>C₂₃H₁₉N₄OCl₂</td>
<td>64.90 (64.72)</td>
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— Contd
NMR (CDCl₃) prepared from DMF (10 mL) and POCl₃ [12].

**Table I — Characterization data of compounds 3 and 4 — Contd**

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. Formula</th>
<th>Found (%)</th>
<th>(Calcd)</th>
</tr>
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<tr>
<td>4d</td>
<td>p-BrC₆H₄</td>
<td>&gt;300</td>
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<td>C₁₂H₁₄N₂OClBr</td>
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<td>C₁₂H₁₂N₂O₂Cl</td>
<td>67.73</td>
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<td>p-HOC₆H₄</td>
<td>&gt;300</td>
<td>70</td>
<td>C₁₂H₁₂N₂O₂Cl</td>
<td>67.71</td>
<td>3.57</td>
</tr>
<tr>
<td>4g</td>
<td>m-NO₂C₆H₄</td>
<td>&gt;300</td>
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<td>C₁₂H₁₂N₂O₂Cl</td>
<td>63.41</td>
<td>3.12</td>
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<tr>
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<td>3.11</td>
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<tr>
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<td>C₁₂H₁₇N₂Cl</td>
<td>75.77</td>
<td>3.87</td>
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**Table II — Antibacterial activity data of compounds 4**

<table>
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<tr>
<th>Compd</th>
<th>Inhibition zone in mm</th>
<th>E. coli at</th>
<th>B. subtilis at</th>
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<tr>
<td></td>
<td></td>
<td>250 µg/disc</td>
<td>500 µg/disc</td>
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<tr>
<td>4a</td>
<td></td>
<td>5.5</td>
<td>8.0</td>
</tr>
<tr>
<td>4b</td>
<td></td>
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<td>12.5</td>
</tr>
<tr>
<td>4c</td>
<td></td>
<td>9.5</td>
<td>15.0</td>
</tr>
<tr>
<td>4d</td>
<td></td>
<td>7.5</td>
<td>9.0</td>
</tr>
<tr>
<td>4e</td>
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<td>5.0</td>
<td>7.0</td>
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<tr>
<td>4f</td>
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<td>6.5</td>
<td>10.0</td>
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<tr>
<td>4g</td>
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<td>4.5</td>
<td>7.5</td>
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<tr>
<td>4h</td>
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<td>5.5</td>
<td>8.0</td>
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<tr>
<td>4i</td>
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<td>6.0</td>
<td>9.5</td>
</tr>
<tr>
<td>4j</td>
<td></td>
<td>6.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Gentamycin</td>
<td></td>
<td>12</td>
<td>22</td>
</tr>
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C₆H, C₅H, C₆-H, 8.30 (m, 1H, C₇-H), 6.95 – 7.65 (m, 8H, Ar-H), 10.05 (s, 1H, NH).

3h: IR (KBr): 3360 (NH), 1620 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 3.84 (s, 3H, OCH₃), 8.10 (m, 1H, C₆-H), 8.22 (s, 1H, C₅-H), 8.40 (m, 1H, C₇-H), 8.75 (m, 1H, C₈-H), 6.80 – 7.95 (m, 9H, CH of pyrazole, 8Ar-H), 9.70 (s, 1H, CHO).

4a: IR (KBr): 1671 (C=O), 1620 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 3.84 (s, 3H, OCH₃), 8.10 (m, 1H, C₆-H), 8.22 (s, 1H, C₅-H), 8.40 (m, 1H, C₇-H), 8.75 (m, 1H, C₈-H), 6.80 – 7.95 (m, 9H, CH of pyrazole, 8Ar-H), 9.70 (s, 1H, CHO).

4c: IR (KBr): 1678 (C=O), 1612 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 8.02 (m, 1H, C₆-H), 8.15 (s, 1H, C₄-H), 8.30 (m, 1H, C₅-H), 8.72 (m, 1H, C₇-H), 7.15 – 7.80 (m, 9H, CH of pyrazole, 8Ar-H), 9.66 (s, 1H, CHO).

4d: IR (KBr): 1684 (C=O), 1612 cm⁻¹ (C=N); ¹H NMR (CDCl₃ + DMSO-d₆): δ 8.15 (m, 1H, C₆-H), 8.40 (m, 2H, C₄-H, C₅-H), 8.70 (m, 1H, C₇-H), 7.15 – 7.90 (m, 9H, CH of pyrazole, 8Ar-H), 9.62 (s, 1H, CHO).

4j: IR (KBr): 1674 (C=O), 1615 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 8.00 (m, 1H, C₆-H), 8.20 (m, 2H, C₄-H, C₅-H), 8.60 (m, 1H, C₇-H), 7.22 – 7.88 (m, 9H, CH of pyrazole, 8Ar-H), 9.70 (s, 1H, CHO).

General procedure for the synthesis of 3-aryl-4-formyl-1-[3-(3-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles 4. To the Vilsmeier-Haack reagent prepared from DMF (10 mL) and POCl₃ (1.1 mL, 0.012 mole), hydrazone 3 (0.01 mole) was added and the reaction mixture stirred at 60-65°C for 3 hr and then poured into ice-cold water. The solid that separated on neutralization with NaHCO₃ was filtered, washed with water and recrystallized from methanol to give 4 (Table I).

4d: IR (KBr): 1684 (C=O), 1612 cm⁻¹ (C=N); ¹H NMR (CDCl₃ + DMSO-d₆): δ 8.15 (m, 1H, C₆-H), 8.40 (m, 2H, C₄-H, C₅-H), 8.70 (m, 1H, C₇-H), 7.15 – 7.90 (m, 9H, CH of pyrazole, 8Ar-H), 9.62 (s, 1H, CHO).

4h: IR (KBr): 1674 (C=O), 1615 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 8.00 (m, 1H, C₆-H), 8.20 (m, 2H, C₄-H, C₅-H), 8.60 (m, 1H, C₇-H), 7.22 – 7.88 (m, 9H, CH of pyrazole, 8Ar-H), 9.70 (s, 1H, CHO).

4j: IR (KBr): 1678 (C=O), 1610 cm⁻¹ (C=N); ¹H NMR (CDCl₃ + DMSO-d₆): δ 8.15 (m, 1H, C₆-H), 8.40 (m, 2H, C₄-H, C₅-H), 8.70 (m, 1H, C₇-H), 7.20 – 7.98 (m, 12H, CH of pyrazole, 11Ar-H), 9.63 (s, 1H, CHO).
Acknowledgement
The authors are thankful to the Director, IICT, Hyderabad for providing $^1$H NMR spectra.

References