Synthesis, characterization and antimicrobial activity of 4-phenyl-3-thiopyrimido[4,5-b]quinolines

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An easy one-step synthesis of substituted pyrimido[4,5-b]quinolines 3a-e has been achieved from 2-chloro-3-formyl quinolines 1 and N-Phenyl thiourea 2. All the synthesized compounds have been biologically screened for their antibacterial and antifungal activities.

From the years of quinolines existence, the growth and utility of pyrimido[4,5-b]quinolines has been phenomenal. These quinolines display characteristics properties in multifarious pharmacological and chemotherapeutic activities. 1,3,7 2-chloro-3-formylquinolines are the unique intermediates for further [b] and [c] annelation for various ring systems and for many functional group interconversions. 8,9 Our interest in developing one-pot synthesis for novel 2,3-heteroannelated 10,11 quinoline systems prompted us to pave a path for the synthesis of the title compounds.

All the hitherto synthesized compounds were screened for their antibacterial and antifungal activities against various pathogens.

Results and Discussions

The reaction of 2-chloro-3-formylquinoline 12,13 with N-phenyl thiourea 2 in glacial acetic acid at reflux temperature for 15 hr afforded the product 3a in 75% yield (Scheme 1). Its IR spectrum showed strong absorption peaks at 1667 and 1610 cm⁻¹ for C=N stretching frequencies and at 1320 cm⁻¹ for C=S group. The ¹H NMR spectrum revealed two fine singlets at δ 7.9 and 8.5 accountable to the C₁-H and C₁₀-H protons. Rest of the nine aromatic proton resonances appeared as multiplets, between δ 7.0 – 7.7. The elemental analysis corroborated with the proposed molecular formula C₁₇H₁₁N₃S and the mass spectrum illustrated the molecular ion peak at m/z 289 and base peak at 93. All the above spectral data supported the compound 3a as 4-phenyl-3-thiopyrimido[4,5-b] quinoline. Here the reaction proceeds through the anil intermediate for the formation of Schiff base and the subsequent aromatization takes places by the elimination of a hydrochloride molecule. A series of similar compounds 3b-e were

![Diagram](image-url)
obtained under identical conditions. The structures of all the compounds were confirmed by their analytical and spectroscopic data (Table 1).

All the synthesized compounds were screened for their antibacterial activities against *Salmonella* typhii, *Escherichia coli* and *Aeromonas hydrophilla* by using the Disc Diffusion Method. Bacteria were cultured in nutrient agar medium and used as inoculum for study. Streptomycin was used as standard. All the compounds exhibited moderate activity against *Salmonella* typhii, *Escherichia coli* and *Aeromonas hydrophilla*. The activity towards *Aeromonas hydrophilla* was found to be very low. According to the observation, the toxicity increases with the increase in concentration of test solution containing new compounds. Although, all the compounds are active, they did not reach the effectiveness of the conventional bacterostatic streptomycin. The higher activity may be due to the additional pyrimido ring and the electron donating nitrogen atoms. The variation in effectiveness of different compounds against different organisms depend either on impermeability of cells of the microbes or diffusion in ribosome's of microbial cells.

The compounds were also screened for their *in vitro* antifungal activities against *Fusarium oxysporum* and *Alternaria macrospora*. The fungi were cultured in Czapek-Dox medium and used as inoculum for study. The inhibitory activities were compared with the commercial fungicide Carben­
dazim tested under similar conditions. The Percentage inhibition after the incubation for five and seven days, were calculated by the following formula,

\[
\% \text{ Inhibition} = (C-T) \times 100/C
\]


<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Calcd % (Found)</th>
<th>( ^1 )H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>108</td>
<td>75</td>
<td>C(<em>{12})H(</em>{15})N(_3)S (299.361)</td>
<td>70.57 (70.51) 03.83 (03.75) 14.52 (14.42)</td>
<td>( \delta ) 7.0-7.72 (m, 9H, Ar-H), 7.90 (s, 1H, C(<em>1)-H), 8.50 (s, 1H, C(</em>{16})-H)</td>
</tr>
<tr>
<td>3b</td>
<td>147</td>
<td>82</td>
<td>C(<em>{12})H(</em>{15})N(_3)S (303.388)</td>
<td>71.26 (71.11) 04.32 (04.38) 13.85 (13.80)</td>
<td>( \delta ) 2.70 (s, 3H, CH(_3)), 6.85-7.68 (m, 8H, Ar-( \delta )), 7.85 (s, 1H, C(<em>1)-H), 8.50 (s, 1H, C(</em>{16})-H)</td>
</tr>
<tr>
<td>3c</td>
<td>192</td>
<td>67</td>
<td>C(<em>{12})H(</em>{15})N(_3)S (303.388)</td>
<td>71.26 (71.34) 04.32 (04.41) 13.85 (13.93)</td>
<td>( \delta ) 2.65 (s, 3H, CH(_3)), 7.0-7.70 (m, 8H, Ar-H), 7.95 (s, 1H, C(<em>1)-H), 8.68 (s, 1H, C(</em>{16})-H)</td>
</tr>
<tr>
<td>3d</td>
<td>157</td>
<td>58</td>
<td>C(<em>{12})H(</em>{15})N(_3)OS (319.387)</td>
<td>67.69 (67.61) 04.10 (04.01) 13.16 (13.08)</td>
<td>( \delta ) 3.73 (s, 3H, OCH(_3)), 6.94-7.68 (m, 8H, Ar-H), 7.98 (s, 1H, C(<em>1)-H), 8.40 (s, 1H, C(</em>{16})-H)</td>
</tr>
<tr>
<td>3e</td>
<td>212</td>
<td>68</td>
<td>C(<em>{12})H(</em>{15})N(_3)OS (319.387)</td>
<td>67.69 (67.75) 04.10 (04.16) 13.16 (13.12)</td>
<td>( \delta ) 3.81 (s, 3H, OCH(_3)), 6.90-7.70 (m, 8H, Ar-H), 7.85 (s, 1H, C(<em>1)-H), 8.59 (s, 1H, C(</em>{16})-H)</td>
</tr>
</tbody>
</table>

Where C is the diameter of the mycelial colony (in mm) on the control plate and T is the diameter of the mycelial colony (in mm) on the treated plate. From the results observed, compounds were found toxic to both the test fungi at various concentrations. Their activity decreases with dilution. Among the synthesized compounds, 3b and 3d were found to be more toxic to both the test fungi. Its toxicity towards both the species was very effective as equal to that of the conventional fungicide Carben­
dazim.

**Experimental Section**

Thin layer chromatography was used to access the reactions and purity of products. Melting Points were determined on a Boetius Microheating Table and Mettler-FP5 Melting apparatus and are uncorrected. IR spectra were recorded in Shimadzu – 8201-FT instrument in KBr pellets and only noteworthy absorption levels (reciprocal centimeter) are listed. \(^1 \)H NMR spectra were recorded on the AMX-400 MHz spectrometer in CDCl\(_3\) solution (chemical shifts in \( \delta \), ppm relative TMS). Satisfactory microanalyses were obtained on Carlo Erba 1106 and Perkin Elmer models 240 CHN analyzer. Mass spectra were recorded on a Jeol – 300 mass spectrometer.

**Preparation of 3: General procedure.** 2-Chloro-3-formylquinoline 1 (0.002 mole) and N-phenyl thiourea 2 (0.002 mole) were dissolved in 20 mL of glacial acetic acid and refluxed for 15 hr. After the completion of the reaction inferred through TLC studies, it was poured onto crushed ice and neutralized with 1 % NaOH. It was then extracted with ethyl acetate and dried over anhyd. Na\(_2\)SO\(_4\). The silica gel column chromatography yielded the product 3a using pet.ether: ethyl acetate (80:20) as eluent. Compounds 3b-e were prepared similarly.
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References
8 Meth-Cohn O, Heterocycles, 35, 1993, 539 and references cited there in.