Synthesis and antimicrobial activity of 1,3,5-triaryl-10-benzyl-1,2,3,4,6,7,8,9-octahydro-8,8-dimethyl-4,6-dioxo-2-thioxo-5H,10H-pyrimido[4,5-b]quinolines

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A convenient one pot synthesis of some pyrimido[4,5-b]quinoline derivatives 2a-g and 3a-g has been reported by the condensation of 5,5-dimethyl-3-benzyl amino-2-cyclohexen-1-one with appropriate arylaldehydes and 1,3-diaryl-2-thiobarbituric acids in methanol and screened for their antimicrobial activity. Some of the compounds show significant activity.

Studies on the synthesis of fused pyrimidines have been extensively carried out in view of their structural diversity and a wide spectrum of biological activities. 6-Aminouracils, barbituric acids and its thioanalogues have been employed as convenient starting materials for the synthesis of various fused pyrimidines e.g. pyrido[2,3-d:6,5-d]dipyrimidines, pyrimido[4,5-b]quinolines, thiazolo[4,5-b]quinolines. Among these, biologically potent pyrimido[4,5-b]quinolines with significant therapeutic importance have drawn much attention to the facile and general route to new derivative of these molecules in synthetically useful yields.

Compounds analogous to the title compounds were prepared earlier by the condensation of arylaldehydes with 6-arylaminoacridines. However, difficulties were encountered in the preparation of pyrimido[4,5-b]quinolines 2 and 3 by this method because attempts to synthesize 6-(N-alkyl/arylaminol)-2-thiourea was not successful under conventional reaction conditions.

Furthermore, other synthetic methods reported earlier have applications limited to only specific derivatives such as 5-deazaflavins, and lack their utility in the synthesis of pyrimido[4,5-b]quinolines substituted at 5,10-positions. We report herein, a novel method which provides a new entry into a variety of pyrimido[4,5-b]quinolines substituted at 5,10-positions.

Antimicrobial activity

For the primary evaluation, agar diffusion method was employed. Antibacterial evaluation was carried out using fluoroquinolone resistant and sensitive gram-positive and gram-negative bacteria S. aureus ATCC 25923, S. aureus 15187, E. coli ATCC 25922, E. coli 24525, Ps. Aeruginosa ATCC 27853, Ps. Aeruginosa 20998. Antimycobacterial testing was done against the rapidly growing M. vaccae ATCC.
**Table 1 – Physical and spectral data of compounds 2a-g and 3a-g**

<table>
<thead>
<tr>
<th>Compd</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Mol. formula</th>
<th>Found (Caled) (%)</th>
<th>$^1$H NMR[Solvent] $^b$ (δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>60</td>
<td>194</td>
<td>C$<em>{18}$H$</em>{20}$NO$_{6}$S (669.7)</td>
<td>73.32 5.79 6.29</td>
<td>7.55-6.8 (m, 17H, Ar-H), 5.7 (s, 1H, C$_5$-H), 4.6 (s, 2H, N-CH$_2$), 3.9 (s, 6H, 2 × OCH$_2$), 2.4 (brs, 4H, 2 × CH$_2$), 2.25 (s, 3H, CH$_3$), 1.12 (s, 6H, 2 × CH$_3$)</td>
</tr>
<tr>
<td>2b</td>
<td>62</td>
<td>189</td>
<td>C$<em>{18}$H$</em>{20}$NO$_{6}$S (669.7)</td>
<td>73.61 5.78 6.25</td>
<td>7.4-6.8 (m, 17H, Ar-H), 5.65 (s, 1H, C$_5$-H), 4.55 (s, 2H, N-CH$_2$), 3.9 (s, 6H, 2 × OCH$_2$), 2.4 (brs, 4H, 2 × CH$_2$), 2.2 (s, 3H, CH$_3$), 1.05 (s, 6H, 2 × CH$_3$)</td>
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<tr>
<td>2c</td>
<td>66</td>
<td>162</td>
<td>C$<em>{18}$H$</em>{20}$NO$_{6}$S (609.6)</td>
<td>76.74 5.68 6.89</td>
<td>7.5-7.0 (m, 19H, Ar-H), 5.65 (s, 1H, C$_5$-H), 4.5 (s, 2H, N-CH$_2$), 2.3 (brs, 7H, 2 × CH$_2$ and CH$_3$), 1.2 (s, 3H, CH$_3$), 1.1 (s, 3H, CH$_3$)</td>
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<tr>
<td>2d</td>
<td>64</td>
<td>142</td>
<td>C$<em>{18}$H$</em>{20}$NO$_{6}$S (637.7)</td>
<td>77.27 6.08 6.61</td>
<td>7.55-7.02 (m, 17H, Ar-H), 5.7 (s, 1H, C$_5$-H), 4.6 (s, 2H, N-CH$_2$), 2.3 (brs, 13H, 2 × CH$_2$ and 3 × CH$_3$), 1.05 (s, 6H, 2 × CH$_3$)</td>
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<tr>
<td>2e</td>
<td>69</td>
<td>138</td>
<td>C$<em>{18}$H$</em>{20}$NO$_{6}$S (637.7)</td>
<td>77.26 4.84 6.41</td>
<td>7.55-7.0 (m, 17H, Ar-H), 5.6 (s, 1H, C$_5$-H), 4.5 (s, 2H, N-CH$_2$), 2.35 (brs, 4H, 2 × CH$_2$ and 3 × CH$_3$), 1.05 (s, 6H, 2 × CH$_3$)</td>
</tr>
<tr>
<td>2f</td>
<td>65</td>
<td>196</td>
<td>C$<em>{18}$H$</em>{20}$NO$_{6}$S (637.7)</td>
<td>77.19 6.14 6.65</td>
<td>7.4-6.85 (m, 17H, Ar-H), 5.65 (s, 1H, C$_5$-H), 4.55 (s, 2H, N-CH$_2$), 2.5 (brs, 13H, 2 × CH$_2$ and 3 × CH$_3$), 1.0 (s, 6H, 2 × CH$_3$)</td>
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<td>2g</td>
<td>67</td>
<td>199</td>
<td>C$<em>{8}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (678.4)</td>
<td>69.06 4.73 6.21</td>
<td>7.5-6.95 (m, 17H, Ar-H), 5.7 (s, 1H, C$_5$-H), 4.6 (s, 2H, N-CH$_2$), 2.5 (s, 2H, CH$_2$), 2.4 (s, 2H, CH$_2$), 2.2 (s, 3H, CH$_3$), 1.05 (s, 6H, 2 × CH$_3$)</td>
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<tr>
<td>3a</td>
<td>62</td>
<td>201</td>
<td>C$<em>{10}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (700.7)</td>
<td>68.48 5.10 8.08</td>
<td>7.7-7.05 (m, 17H, Ar-H), 6.3 (s, 1H, C$_5$-H), 4.65 (s, 2H, N-CH$_2$), 3.9 (s, 6H, 2 × OCH$_3$), 2.32 (s, 2H, CH$_2$), 2.25 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 0.9 (s, 3H, CH$_3$)</td>
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<tr>
<td>3b</td>
<td>64</td>
<td>192</td>
<td>C$<em>{10}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (700.7)</td>
<td>68.51 4.19 8.04</td>
<td>7.75-6.9 (m, 17H, Ar-H), 6.25 (s, 1H, C$_5$-H), 4.5 (s, 2H, N-CH$_2$), 3.85 (s, 6H, 2 × OCH$_3$), 2.4 (s, 2H, CH$_2$), 1.05 (s, 3H, CH$_3$), 0.9 (s, 3H, CH$_3$)</td>
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<tr>
<td>3c</td>
<td>60</td>
<td>218</td>
<td>C$<em>{6}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (640.6)</td>
<td>71.20 5.05 8.71</td>
<td>7.7-7.11 (m, 19H, Ar-H), 6.35 (s, 1H, C$_5$-H), 4.7 (s, 2H, N-CH$_2$), 2.5 (s, 2H, CH$_2$), 2.39 (s, 2H, CH$_2$), 1.1 (s, 6H, 2 × CH$_3$)</td>
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<tr>
<td>3d</td>
<td>63</td>
<td>178</td>
<td>C$<em>{6}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (668.7)</td>
<td>71.47 4.46 8.42</td>
<td>7.5-7.1 (m, 17H, Ar-H), 6.2 (s, 1H, C$_5$-H), 4.68 (s, 2H, N-CH$_2$), 2.5 (s, 2H, CH$_2$), 2.4 (s, 2H, CH$_2$), 2.25 (s, 6H, 2 × CH$_3$), 1.2 (s, 2H, CH$_2$), 1.0 (s, 3H, CH$_3$)</td>
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<tr>
<td>3e</td>
<td>59</td>
<td>159</td>
<td>C$<em>{6}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (668.7)</td>
<td>70.91 5.31 7.41</td>
<td>7.5-7.05 (m, 17H, Ar-H), 6.25 (s, 1H, C$_5$-H), 4.5 (s, 2H, N-CH$_2$), 2.3 (s, 10H, 2 × CH$_2$ and 3 × CH$_3$), 1.05 (s, 3H, CH$_3$), 0.9 (s, 3H, CH$_3$)</td>
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<tr>
<td>3f</td>
<td>67</td>
<td>191</td>
<td>C$<em>{6}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (668.7)</td>
<td>72.76 5.41 8.31</td>
<td>7.6-7.0 (m, 17H, Ar-H), 6.2 (s, 1H, C$_5$-H), 4.6 (s, 2H, N-CH$_2$), 2.3 (s, 10H, 2 × CH$_2$ and 2 × CH$_3$), 1.05 (s, 3H, CH$_3$), 0.9 (s, 3H, CH$_3$)</td>
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<tr>
<td>3g</td>
<td>63</td>
<td>200</td>
<td>C$<em>{6}$H$</em>{12}$N$<em>{2}$O$</em>{2}$S$_{2}$ (709.5)</td>
<td>64.26 4.28 7.74</td>
<td>7.6-7.1 (m, 17H, Ar-H), 6.3 (s, 1H, C$_5$-H), 4.6 (s, 2H, N-CH$_2$), 2.5 (s, 2H, CH$_2$), 2.3 (s, 2H, CH$_2$), 1.1 (s, 6H, 2 × CH$_3$)</td>
</tr>
</tbody>
</table>

$^a$MS: m/z 669(M$^+$)

$^b$CDCl$_3$ for 2a, 3a, 3b & CDCl$_3$+TFA for 2b, 2d-g, 3b-e and 3e-f

Ciprofloxacin was used as a standard compound for antibacterial and antimycobacterial testing while antifungal activity was evaluated using Amphotericin B and Fluconazole. The compounds were tested at 5-10 times higher concentrations compared to standard antimicrobial agents employed.
Results of antimicrobial evaluation

All the fourteen compound 2a-g and 3a-g were tested for their antifungal, antibacterial and antitycobacterial activities. The following results were obtained.

(i) Compound 3g showed significant activity against the mycobacterial strains M. phlei and M. xenopi at relatively high concentrations.

(ii) Compounds 2g, 3g and 3f showed antibacterial activity against gram-positive organisms with low potency and narrow spectrum of activity.

(iii) Compound 3c showed weak antifungal activity only against C. kefry at high concentration.

(iv) Rest of compounds did not show any activity.

Experimental Section

General. Melting points are uncorrected. 1H NMR spectra were recorded on a Perkin-Elmer (90-MHz) instrument with TMS as internal standard, IR spectra on a Shimadzu Spectrophotometer model 435, and mass spectra were recorded on Jeol JMS-D 300 instrument.

1,2,3,5-Triaryl-10-benzyl-1,2,3,4,6,7,8,9-octahydro-8,8-dimethyl-4, 6-dioxo-2-thioxo-5H, 10H-pyrimido-[4,5-b]quinolines 2 and 3: General procedure. A mixture of 1,3-diaryl-2-thiobarbituric acid 1 (1 mmole), the appropriate arylaldehyde (1 mmole) and 5,5-dimethyl-3-benzylamino-2-cyclohexen-1-one (0.22 g, 1 mmole) was refluxed in anhydrous methanol for 4.5-5 hr. The solid thus separated was filtered and crystallised from chloroform-methanol(1:3).

The physical and spectral data of compounds are given in Table I.

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References