Synthesis and antifungal screening of piperidone derivative with pyrazolone substituents

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Abstract

Ethyl 4-piperidone reacts with different amines in presence of toluene as a solvent and water is removed and Schiff base is formed. Then this Schiff base undergoes reduction and reduced product of Schiff base is obtained. Then it is undergoes for benzylation, After benzylation It reacts with two different azides and forms again Schiff base for both azides which further undergoes for Clemensen reduction. The reduction product of both azides reacts with ethyl acetoacetate and undergoes cyclization and formed to get the desired cyclized product. Product for antifungal screening by zone of inhibition study respect to some gram positive and gram negative microbes reference standard antibiotics. The satisfactory result has been found in the antifungal screening.

Key words: 4-piperidone, antifungal activity.

Introduction

The therapeutic problems has achieved increasing importants in hospitalization patient, in immunosuppressed patients with AIDS or undergoing another disease therapy and organ transplants. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotics resistant created in the last decades a substantial medical name for a new classes of antifungal drug is medication used to treat fungal infections such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others. The fungal infections are superficial and
systemic. The causing infections of the hair, mucous membranes, nails or skin include candida and dermatophyte fungi. Drugs are active against fungi like *Candida albicans*, *Aspergillus niger*, etc. [1]

![Figure 1 Fungi](image)

**Synthesized compounds**

\[
\text{Ethyl 4-piperidone}
\]

![Chemistry: Synthetic procedure:](image)

**Ethyl 4-piperidone** reacts with different amines [isobutyl amine (A), ethyl amine (B), methylamine (C)] respectively in presence of toluene as a solvent and water is removed and Schiff base is formed. Then this Schiff base undergoes reduction in presence of Zn-Hg /HCl and reduced product of Schiff base is obtained. Then it is reacted with benzoyl chloride and form benzoylated product. After benzylation it reacts with two different azides: Hydrazide hydrate and semicarbazide .HCl and forms again Schiff base for both azides which further undergoes for
clemensen reduction by reacting with ZnHg/HCl. The reduction product of both azides reacts with ethyl acetoacetate and undergoes cyclization and formed cyclized product. [2-4]

R = -CH\textsubscript{2}CH(CH\textsubscript{3})\textsubscript{2}, -CH\textsubscript{3}, -CH\textsubscript{3}CH\textsubscript{2}
Preparation for Zn-Hg/HCl
A mixture of 200gm of zinc wool, 15gm of mercury(II)chloride, 10ml of concentrated HCl and 250ml of water is stirred or shaken for 5 minutes. The aqueous solution is decanted and amalgamated zinc is covered with with 150ml of water and 200ml of HCl. The material (about 0.3-0.4mol) to be reduced is then added immediately and reaction proceeds.[5]

Physicochemical parameters of synthesis compound

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mol.formula</th>
<th>Mol.wt (g/mol)</th>
<th>M.P. (°C)</th>
<th>Yield (%w/w)</th>
<th>Composition Calculated C, H, N (%)</th>
<th>Composition Found C, H, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl -4 -Piperidone</td>
<td>C₇H₁₂NO</td>
<td>127.18</td>
<td>45-47</td>
<td>58.60</td>
<td>C₆.₆₆₅:H₉.₅₅₀; N₁₁.₅₀; O₁₂.₄₀</td>
<td>C₆.₆₆₃:H₁₀.₃₅₀; N₁₁.₀₁; O₁₂.₅₈</td>
</tr>
<tr>
<td>A4b</td>
<td>C₁₀H₁₃N₂O₂</td>
<td>280.41</td>
<td>110-112</td>
<td>41.58</td>
<td>C₆.₄₄₂:H₁₀.₀₂; N₁₉.₉₀; O₅.₄₅</td>
<td>C₆.₄₄₂:H₁₀.₄₀; N₁₉.₉₈; O₅.₇₁</td>
</tr>
<tr>
<td>A5b</td>
<td>C₁₀H₁₅N₂O₂</td>
<td>329.43</td>
<td>102-104</td>
<td>46.37</td>
<td>C₆.₅₄₇; H₉.₉₅₀; N₁₂.₄₅</td>
<td>C₆.₅₄₇; H₉.₉₅₀; N₁₂.₉₅</td>
</tr>
<tr>
<td>B4b</td>
<td>C₁₀H₁₆N₄O₂</td>
<td>252.25</td>
<td>114-116</td>
<td>38.46</td>
<td>C₆.₄₇₅; H₉.₉₅₀; N₁₂.₃₅</td>
<td>C₆.₄₇₅; H₉.₉₅₀; N₁₂.₃₅</td>
</tr>
<tr>
<td>B5b</td>
<td>C₁₀H₁₇N₄O₂</td>
<td>295.38</td>
<td>138-140</td>
<td>43.67</td>
<td>C₆.₅₉₃; H₉.₉₅₀; N₁₂.₅₆</td>
<td>C₆.₅₉₃; H₉.₉₅₀; N₁₂.₅₆</td>
</tr>
<tr>
<td>C4b</td>
<td>C₁₀H₁₈N₄O₂</td>
<td>238.33</td>
<td>146-148</td>
<td>46.33</td>
<td>C₆.₄₂₇; H₉.₉₅₀; N₁₂.₃₅</td>
<td>C₆.₄₂₇; H₉.₉₅₀; N₁₂.₃₅</td>
</tr>
<tr>
<td>C5b</td>
<td>C₁₀H₁₉N₄O₂</td>
<td>281.95</td>
<td>152-154</td>
<td>51.57</td>
<td>C₆.₅₉₃; H₉.₉₅₀; N₁₂.₅₆</td>
<td>C₆.₅₉₃; H₉.₉₅₀; N₁₂.₅₆</td>
</tr>
</tbody>
</table>

Antifungal screening method
All the Petri dishes were sterilized in oven at 160°C for 1 hour. Agar media, Filter paper discs and test solutions were sterilized in autoclave at 121°C 16 lbs/square inches. Pouring the molten sterile agar in sterile Petri dishes aseptically. Allow to cool the agar at RT and pouring the bacterial suspension on the petri dishes aseptically.

Histogram of antifungal activity
Placing the sterile filter paper discs in appropriate four quadrants of petridishes aseptically after soaking in the sterile test solutions. Incubate the Petridishes at 27°C for antifungal and observed the zone of inhibition.[6]

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>CONC. (µg/ml)</th>
<th>Zone of inhibition (mm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(A4b)</td>
<td></td>
<td>C.albicans</td>
<td>A.niger</td>
</tr>
<tr>
<td>100</td>
<td>8 ±0.6</td>
<td>5 ±0.6</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>10 ±0.4</td>
<td>6 ±0.2</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>11 ±0.1</td>
<td>7 ±0.8</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>12 ±0.8</td>
<td>9 ±0.4</td>
<td></td>
</tr>
<tr>
<td>(A5b)</td>
<td></td>
<td>C.albicans</td>
<td>A.niger</td>
</tr>
<tr>
<td>100</td>
<td>6 ±0.3</td>
<td>7 ±0.3</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>8 ±0.5</td>
<td>8 ±0.4</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>10 ±0.2</td>
<td>9 ±0.1</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>11 ±0.7</td>
<td>11 ±0.5</td>
<td></td>
</tr>
<tr>
<td>(B4b)</td>
<td></td>
<td>C.albicans</td>
<td>A.niger</td>
</tr>
<tr>
<td>100</td>
<td>5 ±0.5</td>
<td>8 ±0.3</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>7 ±0.3</td>
<td>9 ±0.2</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>9 ±0.6</td>
<td>10 ±0.7</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>10 ±0.8</td>
<td>12 ±0.2</td>
<td></td>
</tr>
<tr>
<td>(B5b)</td>
<td></td>
<td>C.albicans</td>
<td>A.niger</td>
</tr>
<tr>
<td>100</td>
<td>6 ±0.2</td>
<td>5 ±0.4</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>7 ±0.45</td>
<td>7 ±0.5</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>8 ±0.3</td>
<td>8 ±0.6</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>10 ±0.6</td>
<td>10 ±0.3</td>
<td></td>
</tr>
<tr>
<td>(C4b)</td>
<td></td>
<td>C.albicans</td>
<td>A.niger</td>
</tr>
<tr>
<td>100</td>
<td>7 ±0.4</td>
<td>6 ±0.1</td>
<td></td>
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<tr>
<td>250</td>
<td>9 ±0.6</td>
<td>7 ±0.4</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>10 ±0.4</td>
<td>8 ±0.2</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>11 ±0.3</td>
<td>10 ±0.6</td>
<td></td>
</tr>
<tr>
<td>(C5b)</td>
<td></td>
<td>C.albicans</td>
<td>A.niger</td>
</tr>
<tr>
<td>100</td>
<td>7 ±0.2</td>
<td>5 ±0.6</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>8 ±0.6</td>
<td>7 ±0.4</td>
<td></td>
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<tr>
<td>500</td>
<td>9 ±0.4</td>
<td>8 ±0.5</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>10 ±0.7</td>
<td>9 ±0.1</td>
<td></td>
</tr>
<tr>
<td>Greseofulvin</td>
<td></td>
<td>C.albicans</td>
<td>A.niger</td>
</tr>
<tr>
<td>100</td>
<td>10 ±0.1</td>
<td>9 ±0.5</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>12 ±0.5</td>
<td>10 ±0.2</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>14 ±0.6</td>
<td>12 ±0.4</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>16 ±0.3</td>
<td>12 ±0.7</td>
<td></td>
</tr>
</tbody>
</table>

**Antifungal zone of inhibition**
Spectral data of synthesized compounds

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>U.V. λ max(nm)</th>
<th>IR (cm⁻¹)</th>
<th>Mass (m/e)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4b</td>
<td>235.87</td>
<td>~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino), ~1243(C-N), ~3005,3041(Ar C-H)</td>
<td>282.9</td>
<td>7.59(8H)d, 2.5(2H)q, 3.4(2H)s, 3.7(1H)s</td>
</tr>
<tr>
<td>A5b</td>
<td>266.67</td>
<td>~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino), ~1243(C-N), ~3005,3041(Ar C-H)</td>
<td>325</td>
<td>2.1(3H)s, 2.4(2H)q, 3.8(1H)s, 8.1(2H)d</td>
</tr>
<tr>
<td>B4b</td>
<td>270.34</td>
<td>~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino), ~1243(C-N), ~3005,3041(Ar C-H)</td>
<td>250.1</td>
<td>1.4(2H)q, 1.3(3H)t, 7.1(8H)d, 2.2(1H)m</td>
</tr>
<tr>
<td>B5b</td>
<td>258.43</td>
<td>~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino), ~1243(C-N), ~3005,3041(Ar C-H)</td>
<td>294.1</td>
<td>-</td>
</tr>
<tr>
<td>C4b</td>
<td>265.64</td>
<td>~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino), ~1243(C-N), ~3005,3041(Ar C-H)</td>
<td>237.2</td>
<td>-</td>
</tr>
<tr>
<td>C5b</td>
<td>266.67</td>
<td>~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino), ~1243(C-N), ~3005,3041(Ar C-H)</td>
<td>279</td>
<td>1.2(2H)m, 7.5(1H)t, 2.1(3H)s, 1.4(3H)t</td>
</tr>
</tbody>
</table>

Result

Antifungal activity was performed using turbidometric method using sabourad dextrose both against *C. Albicans* and *A. niger*. Greseofulvin as standard. All synthesized compounds were tested for antifungal activity against *C. Albicans*. Compounds A4b, A5b, B4b, B5b, C4b, C5b were shown antifungal activity at higher concentrations. Standard drug greseofulvin showed inhibition at all concentration (100, 250, 500, 750 µg/ml). All six compounds were found to be less potent compared to greseofulvin.

Conclusion

From IR, Mass and NMR spectra data synthesized compounds are confirm. Among all synthesized compounds, compound A4b gives a better antimicrobial activity against gram positive (*S. citrus* and *B. subtilis*) and gram negative (*E. coli*) bacteria than other synthesized
compounds. And compound A4b gives a better antifungal activity against fungi (C. albicans) than other synthesise compounds.

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References