Synthesis, characterization and antimicrobial activities of fused 1,6-naphthyridines

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An easy two-step synthesis of 1,6-naphthyridines (4a-c, 7a-c, 10a-c, 14a-c) has been arrived from 3-formylquinolin-2(1H)-ones (1a-c) and respective arylamines (2, 5, 8, 12) which underwent condensation and aromatized by dehydration with the help of PPA. All the synthesized compounds have been biologically screened for their antibacterial and antifungal activities.

Keywords: Benzo, pyrido-1, 6-naphthyridines, condensation, dehydration, arylamines, antibacterial activity, antifungal activity.

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In recent years, naphthyridines with fused rings like dibenzo, benzopyrido, diazanaphtho and benzoquinoline have been widely reported. These naphthyridines display characteristic properties in multifarious pharmacological and chemotherapeutic activities1-4. The 3-formylquinolin-2(1H)-ones are the unique starting precursors for further [b] and [c] annelation for various ring systems and for many functional group interconversions5,6. Many derivatives of naphthyridines and quinolines could be prepared out of them and several of them possess diverse biological properties. It is also known that when one biologically active compound is fused with another ring system, there will be enhanced biological activity.

Our interest lies in developing a new route for the synthesis for novel fused naphthyridines from the quinoline systems. Hence, we treated the aldehyde 1a with aromatic amines namely, aniline 2 and naphthylamine 5 to get the titled compounds. As we planned our work on 1a with heteroaromatic amine like 3-aminopyridine 8 with a possibility to get two types of fusion products namely, benzo[b]pyrido[3,2-h][1,6]naphthyridine 10a and benzo[b]pyrido[3,4-h][1,6] naphthyridine 11a ring systems, but ended up with single product only. The above type of results were also obtained in the reaction of 1a with 12. All the hitherto synthesized compounds were screened for their antibacterial and antifungal activities against various pathogens.

Results and Discussion

The reaction of 3-formylquinolin-2(1H)-one7,8 1a with distilled aniline 2 in gl. acetic acid at reflux temperature for 5 hrs afforded an intermediate 3 in 67% yield (m.p. 215°C). Its IR spectrum showed strong absorption peaks at 3448 and 1557 cm\(^{-1}\) for NH and CH=N (at C 3 position) stretching frequencies respectively and at 1670 cm\(^{-1}\) for C=O stretching frequency. The \(^1\)H NMR spectra revealed two fine singlets at \(\delta\) 8.1 and 8.9 accountable for the C 4 and azomethine protons. Rest of the nine aromatic proton resonances showed their signals between \(\delta\) 7.0 and 7.8 as an unresolved complex multiplet and NH gave a broad singlet at \(\delta\) 10.0. The elemental analysis is corroborated with the proposed molecular formula C16H12N2O and the mass spectrum showed the molecular ion peak at m/z 248. All the above spectra supported the compound 3a as 3-(formylanilino)-quinolin-2(1H)-one.

When the reaction was performed on the intermediate 3a with polyphosphoric acid, aromatization was effected by the elimination of a water molecule to yield 4a (Scheme I).

The IR spectra of the product 4a showed the disappearance of NH and carbonyl stretching frequencies which indicates cyclization. The \(^1\)H NMR spectrum gave two singlets at \(\delta\) 8.7 and 8.2 for C1-H and C12-H protons respectively. A multiplet at \(\delta\) 6.9-7.8 appears for rest of eight aromatic protons and also mass spectrum of the product 4a showed its molecular weight to be 230. The molecular formula C16H12N2O was confirmed from its analytical data. From the spectral and analytical data, it was confirmed as dibenzo [b,h][1,6]naphthyridine (yield 72%, m.p. 110°C)(Table I).

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The same reaction procedures were extended to its derivatives 1b-c with 2, and products were confirmed by their spectral and analytical data (Table I). The same synthetic route on aldehyde 1a with naphthylamine 5 gave the desired compounds 6a and 7a.
The compound $1a$ was treated with 3-amino-pyridine $8$ in gl. acetic acid and refluxed for 5 hrs. After usual work-up, the compound $9a$ was obtained (yield 61%, m.p. 235°C) and its IR spectra showed absorption peaks for the two C=N groups at 1585 and 1560 cm$^{-1}$. The carbonyl and NH stretching frequencies gave signals at 1614 and 3445 cm$^{-1}$. Its $^1$H NMR spectrum represented five quinoline aromatic protons multiplet at $\delta$ 6.9 - 7.8 along with a singlet at $\delta$ 7.7 for azomethine proton. The broad singlet at $\delta$ 10.5 was attributed to the NH proton. Rest of pyridine protons were assigned as $\delta$ 8.7 (s, 1H, $-C_2\'-$H), 7.9(d, 1H, $-C_4\'-$H, $J=6.8$Hz), 8.1-8.2(m,1H, $C_5\'-$H), 8.5(d, 1H, $C_6\'-$H, $J=8.0$Hz) and disappearance of singlet at $\delta$ 8.7 confirmed the cyclized product through removal of $C_2$ proton. Therefore, another possible product $11a$ was ruled out. Hence, based on the above spectral data, it was confirmed that $10a$ was formed by $[b]$ annelated fusion of the pyridine ring. Its mass spectrum showed the molecular ion peak at m/z 231. The analytical data corresponding with the molecular formula $C_{15}H_9N_3$, revealed the compound to be benzo$[b]$pyrido[3,2-$h$][1,6]naphthyridines $10a$ (yield 52%, m.p. 197°C).

The same reaction conditions were performed on $1a$-$c$ with $12$ and got the expected products $13a$-$c$ and $14a$-$c$ (Scheme II, Table I).

**Antimicrobial activity**

All the synthesized compounds were screened for their antibacterial activities against *Salmonella typhii*, *Escherichia coli* and *Aeromonas hydrophilla* by using the disc diffusion method$^{9,10}$. 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
Table I — Characterization data of newly synthesized compounds

<table>
<thead>
<tr>
<th>Compd</th>
<th>Mol. formula</th>
<th>Calcd (Found) (%)</th>
<th>MS M⁺ (m/z)</th>
<th>¹H NMR (CDCl₃) (δ, ppm)</th>
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<tbody>
<tr>
<td>3a</td>
<td>C₁₄H₁₂N₂O</td>
<td>77.40 11.28</td>
<td>248</td>
<td>7.0-7.8 (m, 9H, Ar-H), 8.1 (s, 1H, C₂-H), 8.9 (s, 1H, C₁⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻ bidi</td>
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Salmonella typii and Escherichia coli. 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. All the compounds were less active than streptomycin. 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 carbendazim tested under similar conditions. The percentage inhibition after the incubation for five and seven days, were calculated by using Abbott formula:

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

From the results obtained, compounds were found toxic to both the test fungi at various concentrations. Their activity decreases with dilution and their toxicity towards both the species was as effective as standard carbendazim.

### 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 a AMX-400 MHz spectrometer in CDCl\(_3\) solution (chemical shifts in \(\delta\), ppm relative to TMS). Satisfactory microanalysis 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

3-Formylquinolin-2(1H)-ones 1a-c (0.002 mole) and respective amines 2, 5, 8, 12 (0.002 mole) were dissolved in 20 mL of gl. acetic acid and refluxed for 5-7 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. Na₂SO₄. Further, the organic extract was filtered, concentrated and subjected to silica gel column chromatography to yield the products 3a-c, 6a-c, 9a-c and 11a-c using pet.ether - ethyl acetate (80:20) as eluant.

Cyclization of intermediates 3a-c, 6a-c, 9a-c and 11a-c. 3-(Formylarylamino)quinolin-2(1H)-ones (3a-c, 6a-c, 9a-c, 11a-c) and freshly prepared polyphosphoric acid (P₂O₅; 2.34 g, H₃PO₄; 0.65 mL) were mixed together and heated in an oil-bath for 8 hr maintaining temperature at 140°C. After the completion of the reaction inferred through TLC, it was poured into 300 g of crushed ice. The mixture was then extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate. Further, the extract was filtered, concentrated and subjected to silica gel column chromatography to yield the product (pet.ether-ethyl acetate, 65:35) and it was recrystallized from methanol. All the synthesized compounds were confirmed through their spectral and analytical data.

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References