Synthesis and antibacterial activity of pyrimido[4,5-b]quinolines

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A concise one-pot synthesis of pyrimido[4,5-b]quinolines 3a-e has been achieved from the potential substrates 2-chloro-3-formylquinolines 1 and guanidine nitrate 2. All the synthesized compounds have been biologically screened for their antibacterial activity.

Biologically potent pyrimido[4,5-b]quinolines have significant therapeutic importance. Earlier reported methods have application limited to only specific derivatives such as 5-deazaflavins. In the broad field of quinolines 2-chloro-3-formylquinolines possess a prominent position, as they are the key intermediates for further [b] and [c] annelation for a wide spectrum of rings and for various functional group interconversions.

Our ongoing interest in developing one-pot synthesis for novel 2,3-heteroannelated 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 activities against Salmonella typhi, Escherichia coli and Aeromonas hydrophilla.

Results and Discussion
The reaction of 2-chloro-3-formylquinoline with guanidine nitrate in alcoholic sodium hydroxide at 80°C for 4 hr afforded the product 3a in 85% yield. The IR spectrum of the compound registered absorption peaks at 3325, 1595 and 1586 cm⁻¹ for -NH and C=N stretching vibrations. Its ¹H NMR spectrum exhibited a broad singlet at δ 4.4 for the -NH₂ protons. A doublet at δ 7.8 with J=8.2 Hz was assignable to the C₇-H proton. The aromatic clusters accounting for five protons appeared as an unresolved multiplet between δ 6.7-7.3. The elemental analysis corroborated with the proposed molecular formula C₁₂H₁₂N₄ and the mass spectrum illustrated the molecular ion peak at m/z 196. All the above spectra supported the compound 3a as 3-aminopyrimido[4,5-b]quinoline. The interesting aspect here to be noted is the existence of amino-imino tautomerism in the exclusive product. The IR and NMR spectra of the compounds accounted for it. A series of similar compound 3b-e were obtained under identical conditions (Scheme I). The structures of all the compounds were confirmed by their analytical and spectroscopic data (Table I).

All the synthesized compounds were screened for their antibacterial activities against Salmonella typhi, Escherichia coli and Aeromonas hydrophilla by using the Disc Diffusion Method. Bacteria were cultured in nutrient agar medium and used as inoculum for study. The diameter (mm) of the zone of inhibition around each disc was measured and the results are listed in Table II, for the specified concentration of the samples. Streptomycin was used as standard. All the compounds exhibited moderate activity against Salmonella typhi and Aeromonas hydrophilla. The activity towards Escherichia coli 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 bacteriostatic 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 depends either on impermeability of cells of the microbes or diffusion in ribosome's of microbial cells.

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 Met­
tler-FP5 Melting apparatus and are uncorrected. IR
spectra were recorded in Shimadzu – 8201-FT in­
strument in KBr pellets and only noteworthy absorp­tion levels (reciprocal centimeter) are listed. 'H NMR
spectra were recorded on an AMX-400 MHz spec­trometer in CDCl₃ solution (chemical shifts in δ, 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.

of 2-chloro-3-formylquinoline 1 (0.002 mole) and
guanidine nitrate 2 (0.002 mole) in alcoholic sodium
hydroxide were refluxed for 4 hr. After the comple­tion
of the reaction inferred through TLC studies, the
solvent was completely reduced and poured into
crushed ice. It was then extracted with ethyl acetate
and dried over anhydrous sodium sulfate. The silica
gel column chromatography yielded the product 3a using
pet.ether : ethyl acetate (98:2) as eluent.

Compounds 3b-e were prepared similarly.

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