Synthesis and antimicrobial screening of cyanopyridines

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2-Amino-3-cyano-4-(2'-chloro-7'-methylquinolin-3'-yl)-6-arylpyridines (3a-n) have been synthesized by the condensation of chalcones (2a-n) with malononitrile and ammonium acetate. All the compounds have been screened for their antimicrobial activity.

Cyanopyridines¹ and quinolines² are associated with various pharmacological activities. This led us to synthesise cyanopyridine derivatives bearing quinoline nucleus.

The starting compound 2-chloro-7-methylquinoline-3-carboxaldehyde³ (1) was prepared by the action of *m*-methylacetanilide with dimethylformamide and phosphorus oxychloride. The reaction of 1 with different arylketones yielded the corresponding 1-aryl-3-(2'-chloro-7'-methylquinolin-3'-yl)-2-propen-1-ones (2a-n). Compounds 2a-n were then reacted with malononitrile and ammonium acetate to afford 2-amino-3-cyano-4-(2'-chloro-7'-methylquinolin-3'-yl)-6-arylpyridines.

Antimicrobial activity *in vitro* were determined by using cup-plate diffusion method⁴. Antibacterial activity was evaluated against *B. megaterium*, *S. aureus*, *P. vulgaris* and *E. coli* using ampicillin and amoxicillin as standard, and

antifungal activity against *A. niger* using greseofulvin as standard. Compounds 2a, e, f, i, j, l and 3a, b, d, e, f, h, i, j showed similar antibacterial activity as that of the standard drugs, and compounds 2a, e, f and 3b, e similar antifungal activity as that of the standard.

Experimental

All m.ps. were determined in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on Perkin-Elmer FT-IR and Shimadzu-435 spectrophotometer and ¹H NMR spectra (CDCl₃ + TFA) on Bruker (300 MHz) and Hitachi 1200 (60 MHz) spectrometers using TMS as internal reference.

2-Chloro-7-methylquinolin-3-carboxaldehyde (1) : Dimethylformamide (0.125 mol) was cooled to 0° and phosphorus oxychloride (0.35 mol) was added dropwise with stirring followed by 3-methylacetanilide (0.05 mol), and after 10–15 min, the solution was refluxed for 6 h at 75°. The reaction mixture was then poured into ice-water (300 ml) and stirred for 30 min at 10°. The resulting solid crystallized from ethyl acetate, (66%), m.p. 145° (Found : C, 64.40; H, 3.86; N, 6.78. Calcd. for C₁₁H₈ONCl : C, 64.23; H, 3.89; N, 6.81%); ν_{max} 1690 cm⁻¹ (C=O); δ 2.7 (3H, s, CH₃), 7.49 (1H, dd, C-H₆), 7.79 (1H, s, C-H₈), 7.95 (1H, d, C-H₅), 8.75 (1H, s, C-H₄), 10.47 (1H, s, CHO); *m/z* 50, 51, 63, 75, 89, 100, 115, 141, 150, 169, 176, 178, 200, 205 (B), 207 (M⁺).

1-(*p*-Methylphenyl)-3-(2'-chloro-7'-methylquinolin-3'-yl)-2-propen-1-ones (2a-n) : To a well stirred solution of 1 (0.01 mol) and *p*-methylacetophenone (0.01 mol) in ethanol (25 ml), 40% NaOH (2 ml) was added. The reaction mixture was stirred for 24 h, then poured in ice-water, acidified, filtered and the resulting solid was crystallized from ethanol to give 2k, (65%), m.p. 173° (Found : C, 74.61; H, 4.93; N, 4.23. Calcd. for C₂₀H₁₆ONCl : C, 74.65; H,

4.97; N, 4.35%); $\nu_{\max}$ 1655 (C=O), 1600 (C=N), 1600 (C=C), 755 cm^{-1} (C-Cl); δ 2.4 (3H, s, Ar-CH₃), 2.5 (3H, s, quinoline-CH₃), 7.31–7.34 (1H, d, -CH=CH_B vinyl), 7.41–7.44 (2H, d, Ar-H_{a,b}), 7.75–7.61 (1H, dd, C-H₆ quinoline), 7.75–7.76 (1H, d, -CH_A=CH vinyl), 7.80 (1H, s, C-H₈ quinoline), 7.95–7.96 (1H, d, C-H₅ quinoline), 8.15–8.20 (2H, d, Ar-H_{c,d}), 8.43 (1H, s, C-H₄ quinoline); m/z 41, 51, 61, 79, 91, 115, 119, 140, 156, 202, 215, 230, 242, 258, 270, 286 (B), 321(M⁺). Other compounds were similarly derived from **1** : **2a**, m.p. 118°; **b**, 121°; **c**, 169°; **d**, 181°; **e**, 189°; **f**, 176°; **g**, 187°; **h**, 138°; **i**, 166°; **j**, 192°; **l**, 169°; **m**, 219°; **n**, 224°. All compounds gave satisfactory N analysis.

2-Amino-3-cyano-4-(2'-chloro-7'-methylquinolin-3'-yl)-6-(p-methoxyphenyl)pyridines (3a-n) : A mixture of 1-(p-methoxyphenyl)-3-(2'-chloro-7'-methylquinolin-3'-yl)-2-propen-1-one (0.01 mol), malononitrile (0.01 mol) and ammonium acetate (0.08 mol) dissolved in ethanol (25 ml) was refluxed for 6 h. The resulting solid was crystallized from ethanol to yield **3l**, (68%), m.p. 186° (Found : C, 68.86; H, 4.21; N, 13.90. Calcd. for C₂₃H₁₇ON₄Cl : C, 68.91; H,

4.24; N, 13.98%); $\nu_{\max}$ 3158 (N-H), 2197 (C≡N), 1620–1580, 1232 (C–O–C), 761 cm^{-1} (C-Cl); δ 2.5 (3H, s, Ar-CH₃), 4.1 (3H, s, Ar-O-CH₃), 7.17–7.58 (5H, m, ArH), 7.49 (1H, dd, C-H₆ quinoline), 7.61 (1H, dd, C-H₈ quinoline), 7.78 (1H, d, C-H₅ quinoline), 8.2 (1H, s, C-H₄ quinoline); m/z 42, 50, 63, 76, 90, 115, 140, 154, 165, 176, 178, 187, 202, 221, 224, 240, 253, 282, 320, 336, 363, 370, 395, 400 (B), 401(M⁺). Similarly, other compounds were prepared from **2** : **3a**, m.p. 243°; **b**, 244°; **c**, 194°; **d**, 179°; **e**, 235°; **f**, 217°; **g**, 261°; **h**, 221°; **i**, 249°; **j**, 203°; **k**, 189°; **l**, 186°; **m**, 216°; **n**, 257°. All compounds gave satisfactory N analysis.

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