

SYNTHESIS AND ANTIMICROBIAL STUDIES OF PYRIDOQUINOLONE DERIVATIVES

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ABSTRACT

Various 6-hydroxy-4-oxo-pyrido[2,3-h]-3-{N⁴-[N¹-(substituted-aryl) sulfanilamido] carbonyl} quinoline (IV₁₋₁₂) have been synthesized using N¹-substituted arylsulfanilamides at C-3 position of 6-hydroxy-4-oxopyrido [2,3-h] quinoline-3-carboxylic acid. All the derivatives have been screened for antibacterial strain against gram positive and gram negative bacteria by cup plate method. The satisfactory screening results have been obtained.

Key words : Antimicrobial, Pyridoquinolone derivatives

INTRODUCTION

Quinolone (synthetic) antibacterial agents have proved themselves to be one of the most effective therapeutic agents for the treatment of various infectious diseases. Generally, the C-3 carboxylic acid and the C-4 ketone groups of quinolone are considered to be necessary for the binding of quinolone to DNA gyrase and essential for antibacterial activity¹.

Number of quinolones have been synthesized and applied for different diseases with different substitutions. The derivatives are also prepared such as 7-substituted quinolones. Some of the amide derivatives have also been synthesized.

Recently, Lee and Chang^{2,3} synthesized pyridoquinolone derivatives for antibacterial studies. Limited work is available in the literature for pyridoquinolone derivatives with different substituents. In view of this, we have synthesized some pyridoquinolone derivatives and combined with substituted aryl sulfanilamide as amide derivative at C-3 position⁴⁻⁷ and tested for their gram positive and gram negative bacteria^{8,9}. The synthesized compounds have been ascertained by elemental analysis, IR and ¹H-NMR spectra.

RESULTS AND DISCUSSION

Minimum inhibitory concentration (MIC) for all the synthesized compounds have been tested against gram positive bacteria such as *Pseudomonas* sp. and *B. subtilis* and gram negative such as *E. coli* and *Ceretium* by cup plate method^{8,9} using DMSO as a solvent. The

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solution of compounds at 100 µg/mL concentration was taken, and activity was compared with standard drug ampicilline, penicillin-G and amoxicilline.

The activity inhibition observation of antibacterial study leads that the compound **VI₁₁** (R = H) and compounds **VI_{1,3}** (R = H, 4-NO₂) displayed good activity against gram positive bacteria *Pseudomonas* sp. and *B. subtilis*, respectively. The compounds **VI_{3,11, 12}** exhibited moderate activity against *Pseudomonas* sp., while compounds **VI_{4, 9, 10}** exhibited moderate activity against *B. subtilis* and other remaining compounds were mild to least active against both gram positive bacteria.

For gram negative strain, the compounds **VI_{1,2,8, 9}** (R = H, 3-NO₂, 4-OCH₃, 3-Cl) and compounds **VI_{1, 3}** (R = H, 4-NO₂) displayed good activity against *E. coli* and *Ceretium*, respectively. The compounds **VI_{5, 7, 12}** exhibited moderate activity against *E. coli*, while compounds **VI_{4, 9, 10}** exhibited moderate activity against *Ceretium*, and remaining compounds were mild to least active against both gram negative bacteria.

EXPERIMENTAL

The required compound 6-hydroxy-4-oxo-pyrido [2,3-h] quinoline-3-carboxylic acid (**IV**) was obtained by reaction of 5-amino-8-hydroxyquinoline with diethyl ethoxymethylene malonate (EMME) by cyclization and then hydrolysis in acidic condition (Scheme-I).

Preparation of 6-hydroxy-4-oxo-pyrido [2,3-h] quinoline-3-carbonyl chloride (**V₁₁**)^{4,5}

The compound 6-hydroxy-4-oxo-pyridol [2,3-h] quinoline-3-carboxylic acid (**IV**) (1.28 g, 0.005 mole) was dissolved in 25 mL dry benzene. Excess of thionyl chloride (15 mL) was added in about 1.5 h with occasional stirring. After, completion of the addition, reaction mixture was refluxed on a water bath at 80°C for about 4-5 h. The mixture was protected from humidity with calcium chloride guard tube. When evolution of HCl and SO₂ ceased, the excess of thionyl chloride was removed by distillation with benzene. If any trace of thionyl chloride remained, it was removed by further distillation with dry benzene (2 time) and the 6-hydroxy-4-oxopyrido [2,3-h] quinoline-3-carboxylic acid (**IV**) was obtained. It was directly used for the next step without further purification.

Preparation of 6-hydroxy-4-oxo-pyrido [2,3-h]-3-{N⁴[substituted-aryl sulfanilamide] carbonyl} quinoline (**VI₁₁**)^{6,7}

N¹-substituted aryl sulfanilamide (0.005 mole) in dry pyridine was taken and placed in an ice bath and the solution of 6-hydroxy-4-oxo-pyridol [2,3-h] quinoline-3-carbonyl]

SCHEME - I

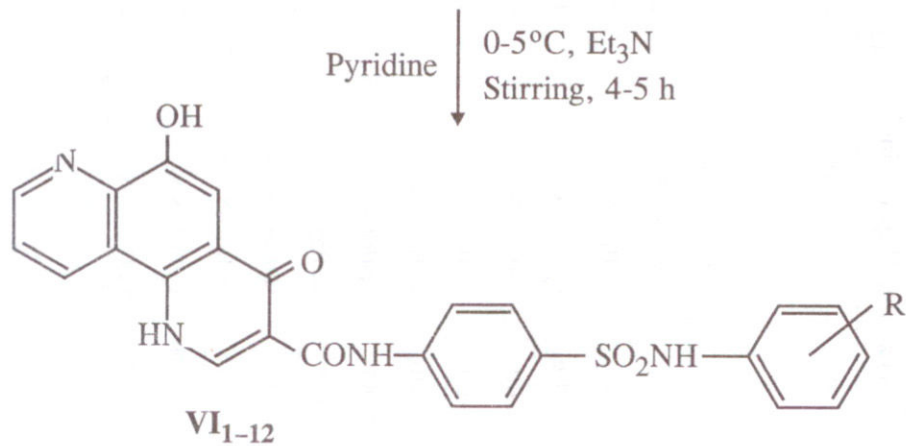
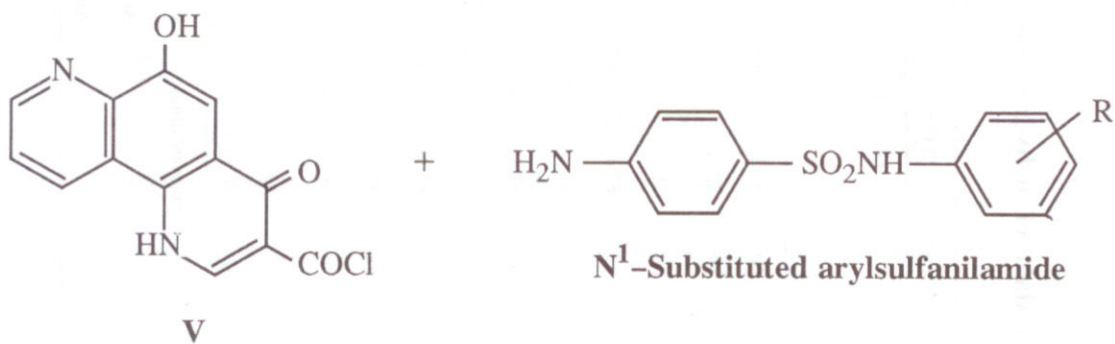
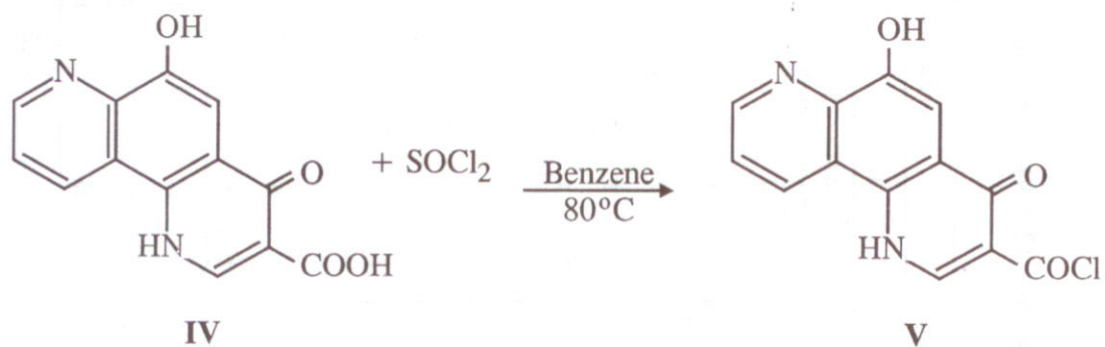


Table 1 Characterization and antimicrobial data of 6-hydroxy-4-oxo-pyrido [2,3-h]-3-[N⁴(substituted aryl) sulfanilamide] carbonyl} quinoline (VI₁₋₁₂)

| Comp. No. | R | M.F. | M.P.°C | Yield % | % Carbon | | % Nitrogen | | Zone of inhibition in mm | | | | | | | |
|------------------|------------------------|---|------------------|---------|----------|-------|------------|-------|--------------------------|--------------------|---------------------|----------------|----|----|----|----|
| | | | | | Found | Calcd | Found | Calcd | Gram +ve | | Gram -ve | | | | | |
| | | | | | | | | | | <i>Pseudomonas</i> | <i>B. Cereitium</i> | <i>E. coli</i> | | | | |
| VI ₁ | H | C ₂₅ H ₁₈ O ₅ N ₄ S | 240 | 60 | 61.80 | 61.85 | 11.49 | 11.54 | 7 | 7 | 6 | 6 | 8 | 8 | | |
| VI ₂ | 3-NO ₂ | C ₂₅ H ₁₇ O ₇ N ₅ S | 256 ^d | 68 | 56.56 | 56.60 | 13.18 | 13.20 | 4 | 4 | 4 | 4 | 8 | 8 | | |
| VI ₃ | 4-NO ₂ | C ₂₅ H ₁₇ O ₇ N ₅ S | 189 | 64 | 56.55 | 56.60 | 13.16 | 13.20 | 5 | 7 | 6 | 6 | 4 | 4 | | |
| VI ₄ | 2-CH ₃ | C ₂₆ H ₂₀ O ₅ N ₄ S | 268 ^d | 55 | 62.49 | 62.52 | 11.20 | 11.22 | 4 | 5 | 5 | 5 | 5 | 5 | | |
| VI ₅ | 3-CH ₃ | C ₂₆ H ₂₀ O ₅ N ₄ S | 252 | 63 | 62.46 | 62.52 | 11.18 | 11.22 | 4 | 4 | 3 | 3 | 5 | 5 | | |
| VI ₆ | 4-CH ₃ | C ₂₆ H ₂₀ O ₅ N ₄ S | 166 | 68 | 62.46 | 62.52 | 11.20 | 11.22 | 3 | 0 | 4 | 4 | 0 | 0 | | |
| VI ₇ | 2-OCH ₃ | C ₂₆ H ₂₀ O ₆ N ₄ S | 260 | 65 | 60.52 | 60.58 | 10.86 | 10.87 | 0 | 3 | 4 | 4 | 5 | 5 | | |
| VI ₈ | 4-OCH ₃ | C ₂₆ H ₂₀ O ₆ N ₄ S | 224 | 69 | 60.55 | 60.58 | 10.83 | 10.87 | 3 | 4 | 4 | 4 | 6 | 6 | | |
| VI ₉ | 3-Cl | C ₂₅ H ₁₇ O ₅ N ₄ SCI | 245 | 58 | 57.69 | 57.74 | 10.73 | 10.78 | 4 | 5 | 5 | 5 | 6 | 6 | | |
| VI ₁₀ | 4-Cl | C ₂₅ H ₁₇ O ₅ N ₄ SCI | 195 | 60 | 57.70 | 57.74 | 10.75 | 10.78 | 3 | 5 | 5 | 5 | 4 | 4 | | |
| VI ₁₁ | 2,5-di-CH ₃ | C ₂₇ H ₂₂ O ₅ N ₄ S | 220 | 61 | 63.11 | 63.15 | 10.87 | 10.92 | 5 | 0 | 4 | 4 | 4 | 4 | | |
| VI ₁₂ | 2-CN,4-NO ₂ | C ₂₆ H ₁₆ O ₇ N ₆ S | 288 ^d | 56 | 56.17 | 56.21 | 15.10 | 15.14 | 5 | 3 | 4 | 4 | 5 | 5 | | |
| | | | | | | | | | | Standard drugs | | Penicillin-G | 12 | 14 | 13 | 14 |
| | | | | | | | | | | | | Ampicilline | 15 | 17 | 18 | 18 |
| | | | | | | | | | | | | Amoxicilline | 13 | 16 | 15 | 16 |

chloride (**V₁₁**) (1.37 g, 0.005 mole) in pyridine was added drop wise in about 1.5 h with constant stirring at 0–5°C. The reaction mixture was stirred further for 2 h at room temperature. The whole content was poured into crushed ice (acidic) with gentle shaking. The resultant solid was filtered and washed thoroughly with aqueous NaHCO₃ (10%) solution. The purity of the compounds were checked by TLC on silica gel plate using benzene : ethyl acetate (1:1). All the compounds were purified from HAC : DMSO (1:2).

Similarly all the compounds were prepared by same method using various N¹ substituted aryl sulfanilamide.

The characterization data and antibacterial data of compounds (**VI₁₋₁₂**) are described in Table I.

IR (KBr) : ν (cm⁻¹)

1670–1640 (amide-I); 1560–1540 (amide-II); 1260–1245 (amide-III); 1350–1320 (S=O); 1180–1160 (S=O); 1040–1020 (S–N); 1695–1665 (C=O); 3440–3300 (–NH); 3400–3200 (–OH); 1240–1220 (–OH).

¹H-NMR(δ ppm)**VI₁₁**

2.17 (6 H, m, 2 CH₃); 6.90–7.83 (7 H, m, Ar–H); 7.9 (1H, q, C–5H); 8.6 (1H, s, C–2H); 8.6–10.1 (3H, m, pyrido); 10.02 (1H, s, –CONH–); 10.32 (1H, s, –SO₂NH–); 12.8 (1H, b, >NH).

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