Efforts Aimed at Potentiating the Gram-negative Activity of Fluoroquinolone Antibacterial Agents: 1,8-Naphthyridones

Sherrice Zhang* and Dr. Michael Barbachyn
Calvin College, Department of Chemistry and Biochemistry, 1726 Knollcrest Circle SE, Grand Rapids, MI 49546

Introduction

Bacterial resistance to currently available antimicrobial agents continues to be a growing threat to public health. The CDC recently reported that each year in the United States at least 2 million people acquire serious infections caused by bacteria resistant to one or more antimicrobial agents, with 23,000 of them dying as a direct result.1 Many more die from underlying medical conditions that are exacerbated by these difficult-to-treat infections. Multidrug-resistant (MDR) strains of the so-called “ESKAPE” pathogens are of particular concern because of their association with considerable morbidity and mortality in the hospital setting.2 The Gram-negative “KAPE”-organism – Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp. – are especially problematic because of the dearth of new and effective agents found in the existing clinical development pipeline. The recent emergence of infections caused by Gram-negative pathogens such as carbapenem-resistant Enterobacteriaceae (CRE) has further increased the magnitude of the problem.1

The fluoroquinolones (FQs), exemplified by moxifloxacin (vide infra), are generally broad-spectrum antibacterial agents that have been on the market for many years and have been useful, at least in part, in treating Gram-negative infections.3 The FQs target bacterial DNA gyrase (A subunit)4 and topoisomerase IV (C subunit), tetrameric enzymes that can now be considered as clinically validated.

One way to potentiate the activity of antibiotics against Gram-negative bacteria is to incorporate additional basic amino groups. At physiologic pH, such groups are generally protonated. The resulting quaternary ammonium salts enhance penetration of the Gram-negative outer membrane. Polymyxin B is an exemplar in this area. We hypothesized that the Gram-negative activity of fluoroquinolones would be further enhanced by appending an additional basic amino group, highlighted below, to the usual C-7 diamine substituent.

General Retrosynthetic Analysis

Retrosynthetic analysis of 1,8-Naphthyridone System

Results: Synthesis of 1,8-Naphthyridone intermediates

Ethyl-3-(2,6-dichloro-5-fluoro-3-pyridyl)-3-oxopropionate (1) was used as the starting material. Converting it to the ethoxymethylene derivative by using triethyl orthoformate and acetic anhydride. Next, the addition of cyclopropyl amine or 3,4,5-trimethoxyaniline provided the corresponding enamine products 2 and 3, respectively, in good yields (Scheme 1). Base-induced cyclization then provided the key 7-chloro-6-fluoro-1,8-naphthyridone intermediates 4 and 5.

Results: C-7 Nucleophilic Aromatic Substitution

With intermediates 4 and 5 available, we then explored the nucleophilic aromatic substitution reaction at C-7 by adding several amine groups. By initially examining piperazine, 1-[2-(dimethylamino)ethyl] piperazine and Boc-pyrrolidine (not shown) as nucleophilic partners in this reaction, the C-7 substituted 1,8-naphthyridine products 6-9 were obtained in good isolated yields (Scheme 2).

Conclusions

• The synthesis of penultimate fluoronaphthyridine esters 6-9 incorporating C-7 triamino substituents was achieved.
• Hydrolysis of esters 6-9 to give the final antibacterial carboxylic acids is under active investigation.
• N-1 cyclopropyl and 3,4,5-trimethoxyphenyl variants were explored.
• Initial microbiological assessment of the final products will be done at the Walter Reed Army Institute of Research (WRAIR).
• Structure-activity relationships (SAR) in this series will be evaluated once minimum inhibitory concentration (MIC) data is available.

References


Acknowledgments

• Rich Huisman
• Scott Prentice
• Barbachyn lab
• Brummel Chair
• Walter Reed Army Institute of Research