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 antibacterial 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' organisms – *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.

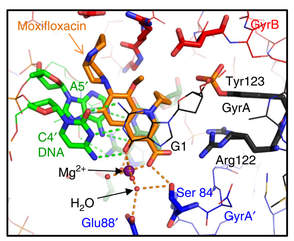
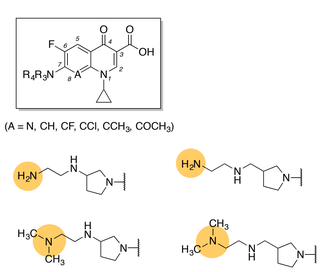
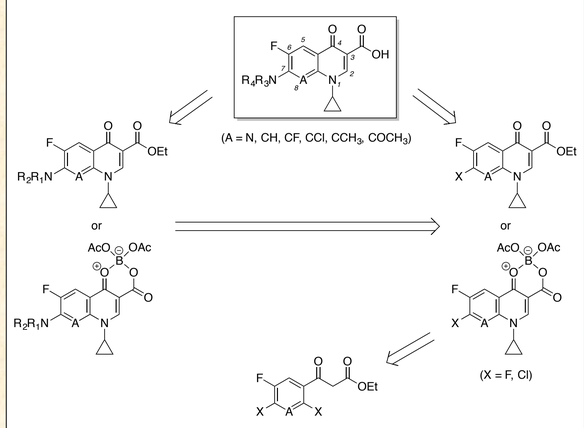


Figure 1. Binding site for moxifloxacin in *S. aureus* DNA gyrase complex.[4]

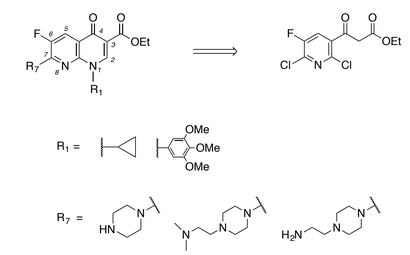
One way to potentiate the activity of antibiotics against Gram-negative bacteria is to incorporate additional basic amino groups. At physiologic pH, such groups are generally protonated. The resulting quaternary ammonium salts enhance penetration of the Gram–negative outer membrane. Polymyxin B is an 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



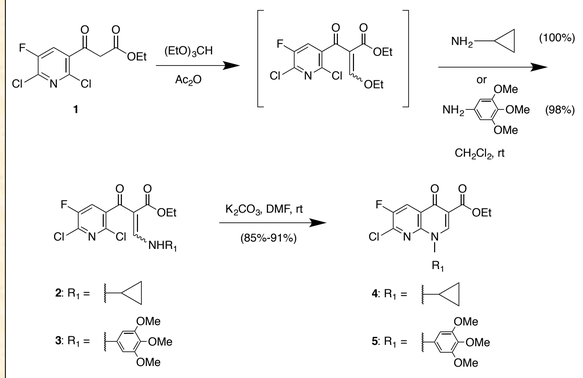
General Objectives

- Generate adequate supplies of key 7-chloro-1-cyclopropyl-6-fluoro-1,8-naphthyridone ester intermediate to explore the subsequent nucleophilic aromatic substitution reaction with a variety of amine nucleophiles
- Identify the best method(s) for introducing the desired amino substituents to the C-7 position
  - Direct amination with a triamine fragment
  - Aminoalkylation of a diamine-substituted quinolone
- Begin exploring compounds bearing a 3,4,5-trimethoxyphenyl moiety at N-1
- Purify and characterize compounds for testing at Walter Reed Army Institute of Research

Results: Synthesis of 1,8-Naphthyridone intermediates

Ethyl-3-(2,6-dicholoro-5-fluoro-3-pyridyl)-3-oxopropionate **(1)** was used as the starting material. Converting it to the ethoxymethylene derivative by using triethylorthoformate 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 (Scheme1). Base-induced cyclization then provided the key 7-chloro-6-fluoro-1,8-naphthyridone intermediates **4** and **5**.

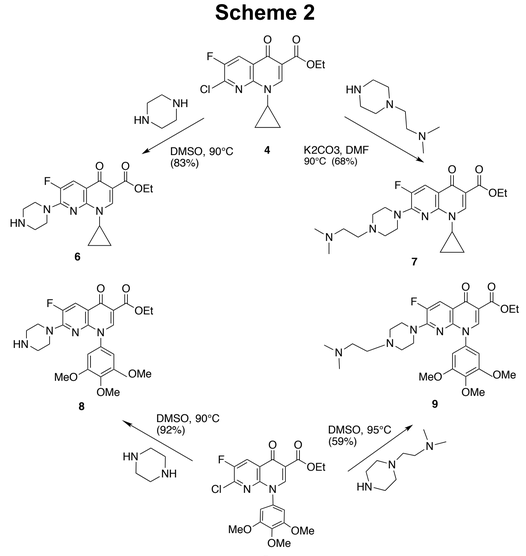
Scheme 1



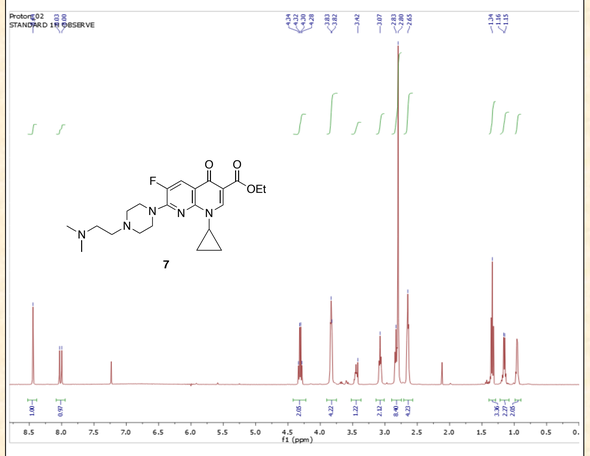
Results: C-7 Nucleophilic Aromatic Substitution

With intermediates **4** and **5** available, we then explored the nucleophilic aromatic substitutuion 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).

Scheme 2



NMR Spectrum of 1,8-Naphthyridone Ester Intermediate



Conclusions

- The synthesis of penultimate fluoronaphthyridone 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

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