Design and Synthesis of Novel Antibacterial Agents Targeting Bacterial DNA Gyrase

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This summer we began a new project aimed at finding undiscovered anti-bacterial drugs that are effective against Gram-negative bacteria in response to an executive order issued by the White House that called for the development of "next-generation antibiotics." This is a challenging task, since Gram-negative bacteria are more difficult to target than Gram-positive bacteria due to a double membrane that tends to filter out or deactivate certain drugs. For our research, we are primarily concerned with the fluoroquinolone class of antibiotics (**Figure 1**), which work by targeting bacterial DNA gyrase and topoisomerase IV, both of which are necessary for DNA replication in bacteria. Our project has two goals in mind: increasing the penetration of existing antibiotics by examining the effects of adding an extra amine functional group, and decreasing the rate at which bacteria can develop resistance to antibiotics by increasing the number of sites that the drug targets during DNA replication.

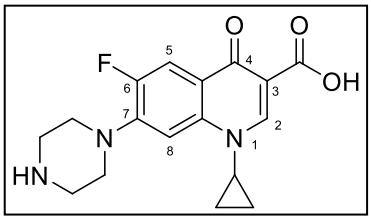

Figure 1: Ciprofloxacin, an example of a fluoroquinolone antibiotic

The project's first goal of increasing drug penetration against Gram-negative bacteria was inspired by the structure of Polymixin B (**Figure 2**). Through the addition of a free amine (R_1, R_2 = H), or a tertiary amine (R_1, R_2 = CH_3) on the distal alkyl side chain of the C_7 piperazine ring (**Figure 3**), or other bioisosteres of piperazine, hopefully the fluoroquinolone will be able to mimic Polymixin B and exhibit enhanced penetration.

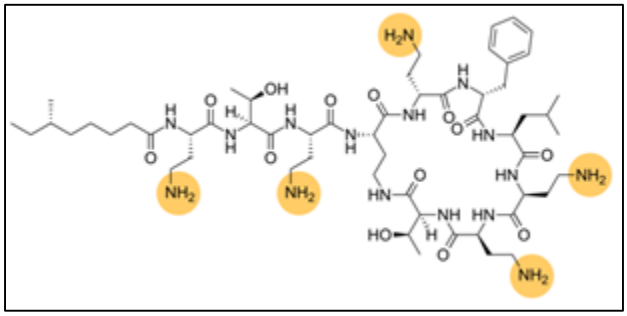

Figure 2: Polymixin B, with its amine functional groups highlighted

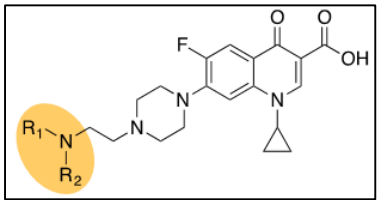

Figure 3: Proposed modification to Ciprofloxacin

The project's second goal is to decrease drug susceptibility to antibiotic resistance by increasing the amount of sites targeted by the drug. The binding structure of moxifloxacin, another fluoroquinolone antibiotic, was observed and compared to that of QPT-1 and etoposide, which also target bacterial DNA gyrase. What was found was that QPT-1 and etoposide disrupted DNA gyrase by binding to different residues than moxifloxacin. By taking the active substituents from QPT-1 and etoposide (barbituric acid and dimethoxy phenol moiety, respectively) and adding it in place of the cyclopropyl group off of the N_1 position, it is theoretically possible to create a drug that effectively disrupts both sites, making the development of antibiotic resistance more difficult.

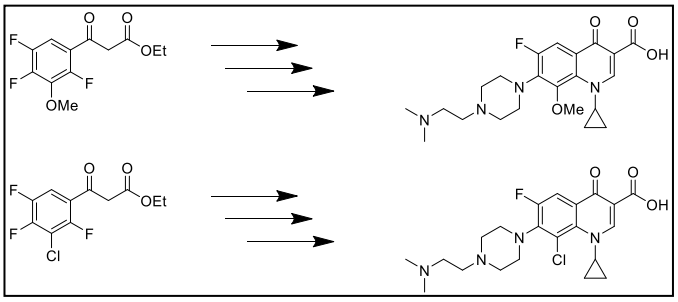

Figure 4: My assigned starting materials, with the final products that I was able to synthesize this summer

Each of us in the Barbachyn lab were given slightly different compounds to work with (**Figure 4**), but we soon discovered how small changes in a molecule can drastically affect its chemistry. This summer gave me an enormous opportunity to learn about the application of organic synthesis in a laboratory setting (as opposed to committing reactions to memory with no sense of context). I have learned how to use an NMR instrument and analyze its output, how to monitor a reaction by TLC, and how to effective record laboratory observations and outcomes. More importantly, however, this summer tested my problem-solving abilities. We encountered a wide array of challenges, from instruments not working like they should, to finding out that some reactions printed in literature don't work quite like the author claimed they would (or in some cases, finding out that they don't work at all). I had to work around low-yield reactions and dead-end synthesis schemes, but eventually I was able to synthesize enough of my final products to submit for testing at Walter Reed Army Institute of Research.

My current plans are to go to medical school after I graduate from Calvin, and this experience has given me a chance to appreciate just how difficult it is to synthesize pharmaceuticals. I can honestly say that I have been challenged by this project in a way that I have never been challenged before. I plan to continue doing research with Professor Barbachyn next summer, and I would whole-heartedly recommend this experience to other students as well!