Design and Synthesis of Novel Antibacterial Agents Targeting Bacterial Topoisomerases

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This summer research was the beginning of a new project in the Barbachyn Lab: researching the antibacterial activity of novel agents specifically in the family of the fluoroquinolones. Antibiotic resistance continues to be a large concern for public health. The search for antibiotics that target bacteria, particularly Gram-negative bacteria, has become a focus of the pharmaceutical industry backed by an executive order from the White House.

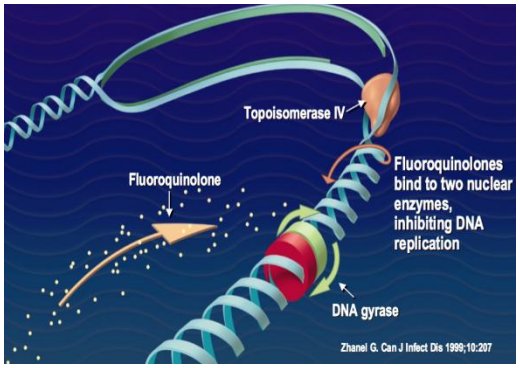


Figure 1. Topoisomerase II and IV positions

Fluoroquinolones are of particular interest because they target two particular enzymes in bacteria that are responsible for DNA replication: DNA gyrase (topoisomerase II) and Topoisomerase IV.

DNA gyrase is responsible for supercoiling DNA ahead of the replication fork and therefore relieves torsional strain and allows the fork to keep moving. Topoisomerase IV relaxes and decatenates behind the replication fork, where crucial work takes place (**Figure 1)**. Examples of fluoroquinolones that already have been marketed are ciprofloxacin, levofloxacin, and moxifloxacin. (**Figure 2)**.

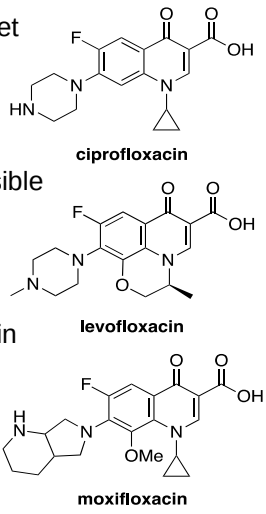
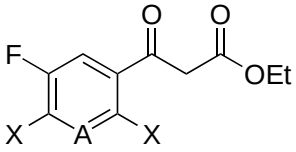


Figure 2. Fluoroquinolone examples

This summer the Barbachyn lab commenced synthesizing novel fluoroquinolones that will be sent to the Walter Reed Army Institute of Research for testing, starting with a MIC test of the compounds.



X = F, Cl
A = N, CH, CF, CCl, CCH_3, $COCH_3$

Figure 3. Starting materials

There were a total of six starting materials (**Figure 3)** split between the four student lab members, two of which I started with. The two compounds that I started with were where A = CH and CCH_3, both of which had X = F. These compounds were progressed through a series of reactions first forming an enol ether, then an enamine, and finally the cyclized 7-desamino quinolone. Nucleophilic aromatic substitution with a variety of piperazine derivatives then led to the targeted penultimate compounds shown in **Figure 4**.

The only remaining reactions for these compound are ester hydrolysis, under either basic or acidic conditions, and the removal of the Boc protecting group.

This research has greatly improved my skills in the organic chemistry lab setting, whether by working with a specific kind of reaction or learning how to run and interpret the NMR data. It has particularly reinforced my knowledge of chemistry on the molecular level.

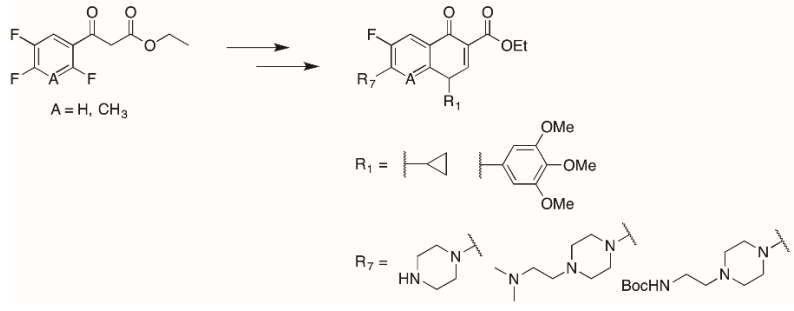


Figure 4. Final synthesized compounds