

Design and Synthesis of Novel Antibacterial Agents Targeting Bacterial Topoisomerases

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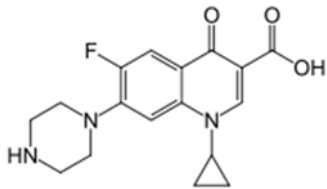


Figure 1: An example of fluoroquinolone known as Ciprofloxacin

This summer we worked on synthesizing new antibiotics that may be useful in fighting bacterial resistance in gram negative bacteria. This is a growing problem as it is estimated 2, 049, 442 infections a year are caused by antibiotic resistant bacteria. We focused on a specific class of antibiotics known as the fluoroquinolones (**Figure 1**). These antibiotics have been used against both grams positive and negative bacteria since their introduction into the market.

The fluoroquinolones work by targeting two enzymes, DNA gyrase and Topoisomerase IV, that bacteria use in replicating DNA. These enzymes allow the DNA to be unwound and replicated (**Figure 2**). The antibiotics bind to a subunit of the enzyme disabling its function. This does not allow the bacteria's DNA to be replicated and therefore the bacteria cannot multiply.

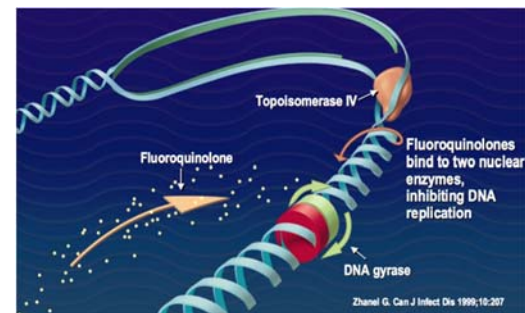


Figure 2: Diagram explaining where fluoroquinolones and the enzymes interact

We are primarily focused on discovering new antibiotics for gram negative bacteria. We are running out of antibiotics to use against gram negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Gram negative bacteria differ from gram positive bacteria in

the composition of their cell wall. Gram negative bacteria have an inner and an outer membrane. The inner membrane is composed phospholipids and membrane proteins. There is a periplasmic space composed of peptidoglycan. The outer membrane is composed of lipopolysaccharides and phospholipids. Gram positive bacteria have one thick peptidoglycan layer (**Figure 3**). Synthesizing antibiotics that are effective against gram negative bacteria is harder due to making sure the antibiotic has the ability to penetrate both membranes.

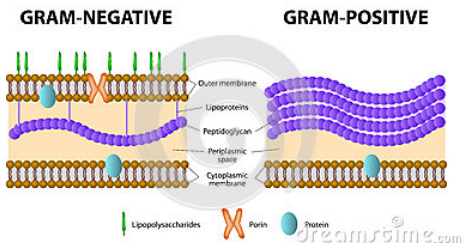


Figure 3: Diagram explaining difference between grams positive and negative bacteria

I specifically looked at a fluorquinolone that started with Ethyl (2,3,4,5-Tetrafluorobenzoyl) acetate (**Figure 4**). After the addition of cyclopropoyl amine, we deprotonate the Nitrogen which causes the ring system to snap shut. After this, we began to make additions to the seventh Carbon. These additions included adding Piperazine, Boc-Pyrrolidine, Dimethyl Ethyl Piperazine, etc (**Figure 4**). We believed directly alkylating the piperazine ring would work, but we ran into trouble with those reactions going to completion. Therefore, we moved into adding the side chains already attached to the piperazine ring via direct amination. We discovered those reactions worked and ran to completion. The last step is converting the ester into the carboxylic acid to give the definitive Fluoroquinolone.

Another series we worked on was adding 3,4,5-Trimethoxyaniline (**Figure 4**) instead of cyclopropyl amine. After proving we could run cyclozation reactions with the Trimethoxyaniline using similar chemistry, we focused again on adding similar substituents to the seventh Carbon. Those reactions are still currently being ran and optimized.

Once these compounds are finished, they will be sent to Walter Reed National Military Medical Center for antibiotic testing. They will be from both the cyclopropyl series and the trimethoxy series.

My second summer working here has been a lot different than my first. Last summer, I felt as if I was getting my feet wet. This summer I felt much more experienced. With Jacob and Lea being new to the lab, it has been awesome getting to help them learn the ropes. I did not have as big of a learning curve this summer even though we started an entirely different project. After a few days, I felt back in the swing of things running totally new reactions.

I have also decided to that I will most likely be pursuing a Ph.D in medicinal chemistry and pharmaceutical sciences after Calvin. Working in the lab setting for two summers has been great experience. It has given me an idea of what to expect in the future. I am greatly honored to have had this opportunity and would highly recommend it to other students.

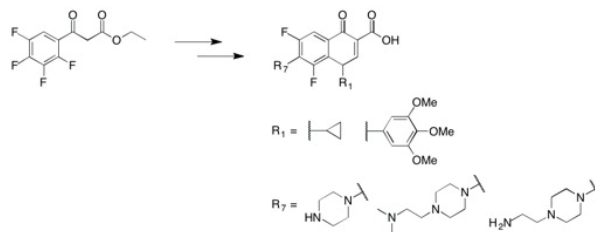


Figure 4: A summary of the chemistry from this summer