

## Design and Synthesis of Novel Antibacterial Agents Targeting Bacterial Topoisomerases

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This summer, our research team focused on synthesizing a new generation of fluoroquinolones, an antibacterial agent that mainly target on the type II bacterial topoisomerases. This project is important for researching because the continue growing of antibiotic resistance has caused more than 20,000 deaths and 250,000 illnesses each year, and there has been an urgent shortage of treatment for gram-negative infections. In addition, as the medical companies have shifted their focus on developing new antibiotics to anticancer drugs, academia is trying hard to fill the need. Fluoroquinolones have been known for their

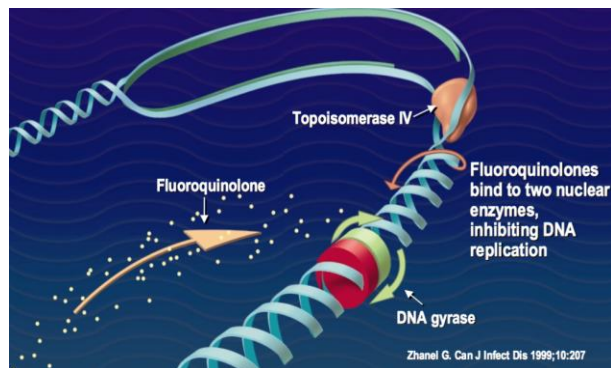


Figure 1: Fluoroquinolones attack bacterial topoisomerases

effectiveness on kill the bacteria by targeting on the topoisomerases (Figure 1). Topoisomerases are important enzymes because they control both the winding and unwinding of the DNA. As the drugs bind to the enzymes through non-covalent bonds, they form a physical blockage and prevent the DNA to pass through the enzyme and reconnect. To synthesize a new generation of fluoroquinolones, we started with making the

known fluoroquinolone intermediate derivatives from related keto ether and went

through a three steps synthesis (Figure 2). Next, a step of direct amination was applied at the C-7 positions the quinolone ether, and two amines with piperazine attached have been proven to be workable with the confirmation of the spectra of Nuclear Magnetic Resonance (NMR) Spectroscopy (Figure 3). In addition, we extended our research by exchanging the cyclopropylamine with 3,4,5-trimethoxy aniline. The exchange of the functional group has also been successfully worked out with decent yield.

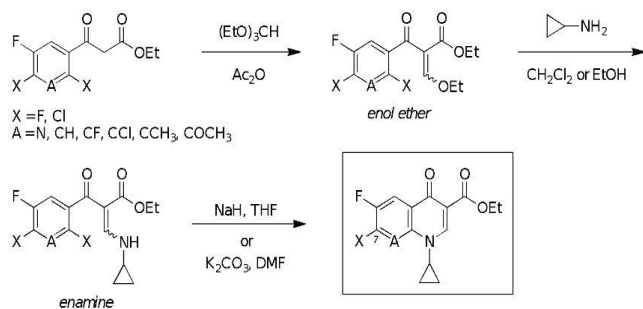
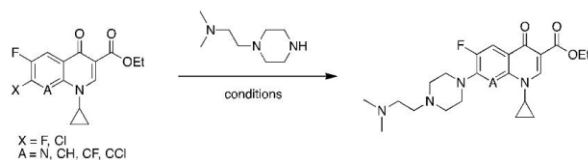


Figure 2: mechanisms of 3-steps fluoroquinolones

My research focus in this summer was on the fluoroquinolone derivative with chlorine at X position, and nitrogen at A (Figure 2). First, the enol ether intermediate was prepared by adding an ethyl ether to the keto ether with a double bond created on the ether. The completion of each reaction was tested with Thin Layer Chromatography

(TLC). Usually, the reactions took about four to five hours to achieve the completion. Second, added the ethyl ether was exchanged with cyclopropylamine through a substitution reaction in ethanol. Third, to close the ring by

deprotonating the nitrogen, and the reaction was run under condition of potassium carbonate and DMF. The completed reaction mixture was quenched with deionized water, and the product was filtered. The product was purified under the Flash Chromatography. The yields of fluoroquinolone intermediate preparation were high and promising. However, as the piperazine



was added at the C-7 position, no further alkylation on the piperazine could be run completely that it was always a mixture of both starting material and product, as well as some unknowns. The yields for the reaction were below 10% under various conditions.

Moreover, the solubility for the piperazinyl quinolones were poor due to their polarity and hard to work with the compound. For these reasons, direct amination of the amine derivatives was used to replace the alkylation, and it was more favorable that the reactions were able to be completed, and the yields rose from below 10% to 68%. At the end of the summer, the cyclopropylamine was replaced with 3,4,5-trimethoxy aniline by using the same conditions as the cyclopropyl reactions, and they had run smoothly with the confirmation of the NMR spectra.

This summer was a valuable experience for me because I have not only improved my laboratory skills, but also my life skills. On one hand, I improved the using of the techniques that I had learned from the past, such as NMR and flash chromatography, and can now run them more efficiently. Although still not a master of NMR spectral interpretation, I am now able to analyze the spectra data much better than in the past. On the other hand, I have also learned to be more perseverant and patient. Having now worked with a variety of chemical transformations on a daily basis, I have had the opportunity to practice all of my learned techniques in a controlled, careful and scientifically rigorous setting.