Identification of Novel Bacterial Topoisomerase Inhibitors Targeting Gram-negative Pathogens

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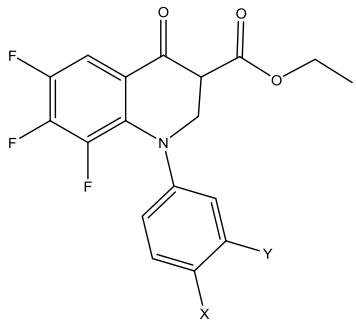
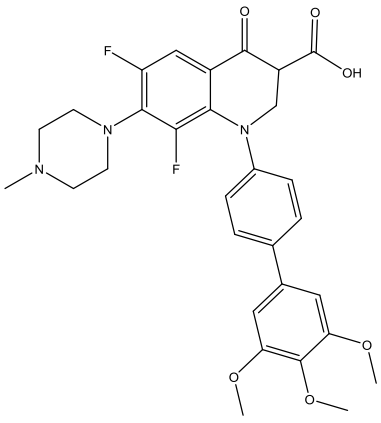
This summer we continued work on a project which the Barbachyn Lab started last year. This project is being done in conjunction with the Walter Reed Army Institute of Research in order to combat the public health threat of widespread antibacterial resistance. Our summer has been specifically focused on synthesizing novel derivatives of fluoroquinolones to target bacterial DNA gyrase and Topoisomerase IV. Our target compound structures were chosen based on a 2015 publication which characterized how other quinolones, such as moxifloxacin and ciprofloxacin, interact with the bacterial DNA gyrase/DNA complex to stop DNA replication. Since interacting with the protein in a different way could combat resistance, knowing how effective antibacterial agents interact with the target protein gave the basis for the design of new antibacterial agents.

All of the target structures in Barbachyn Lab had the same fluoroquinolone backbone, but each one of us had a different combination of R-groups and spacers which we were focused on synthesizing. For the first part of the summer, I worked on producing compounds with a bromine at either the meta or para position of the benzene spacer between the quinolone and the R-group. I spent the second half of the summer optimizing the Suzuki coupling reactions for different R-groups, reducing the terminal ester on the main structure to a carboxyl, and adding a pyrazine to the 7th carbon of the main quinolone body. The Suzuki reactions were done with various boronic acids and worked best when the group being added did not have a hydroxyl group. Boronic acids with a pyrazole group also did not work under the conditions we were using.



Compound used in Suzuki cross-coupling reactions. Synthesized both metabromo (X=H, Y=Br) and parabromo (X=Br, Y=H) variants.



An example of one of my target compounds. In this specific case I got as far as reducing the terminal ester.

This summer I have identified good conditions for the Suzuki coupling reactions and explored their restrictions. Hopefully my work will give people more refined procedural guidelines to start from in the future. More work will need to be done on this project, specifically with regard to the pyrazine addition, to get to the completed target compounds.

This summer has given me an appreciation for how intense organic chemistry research is. Refining a procedure takes a whole lot of time, patience, and attention to detail. Even though some reaction conditions worked very well for one molecule, analogous conditions could produce wildly different results. I have learned how to persevere and find solutions when something is not going my way. This experience has also helped me improve my laboratory skills and given me insight into the complexities behind drug development.