Novel Sugar-Based Gold Inhibitors of *Helicobacter pylori*

Tessa Epstein, Class of 2019

I am a senior biochemistry major currently pursing honors and will begin a PhD program in Chemical Biology at the University of Michigan in the fall. The Grua O'Connell mini grant funded my attendance at the American Chemical Society (ACS) national meeting from March 31st to April 4th in Orlando, Florida. The opportunity to attend the ACS national conference as an undergraduate alongside experts in my field of interest was incredibly impactful on the development of my honors project, decision on which graduate program to attend, and future career.

My research has focused on a class of compounds that could serve as an alternative treatment for infection of the pathogenic bacterium *Helicobacter pylori*. *H. pylori* is a gram-negative bacterium that infects over 50% of the world population.[1-2] *H. pylori* infection often leads to the development of duodenal and gastric ulcers and cancers along the gastric tract.[1] Current treatment methods of *H. pylori* consist of a triple therapy of potent antibiotics, which have toxic physiological effects, most notably on the healthy gut microbiome.[1, 3] Additionally, there is an increasing presence of antibiotic resistant strains of *H. pylori*, meaning that these toxic treatments are unable to successfully eradicate *H. pylori* infection for a growing population of patients.[1, 3] As antibiotic resistance continues to grow, the discovery of alternative treatment methods is of urgent necessity.

Auranofin, a gold containing sugar-based molecule, is a potential alternative therapeutic for the treatment of *H. pylori* infection. Auranofin received FDA approval for the treatment of rheumatoid arthritis in 1985 but has recently been discovered to have inhibitory properties against a range of human diseases such as cancer, Alzheimer's and bacterial infection.[4] Auranofin initiates cellular death through the inhibition of thioredoxin reductase (TrxR), which disrupts cellular thiol redox balance, leading to cellular death.[5-6] While auranofin is a promising drug candidate, it causes a range of harmful physiological side effects.[4] A compound that resembles auranofin in its interaction with pathogens but that has a decreased toxicity against mammalian cells would be an ideal alternative therapeutic.

My honors project has focused on a novel series of auranofin derivative compounds, synthesized by Mingdi Yan at the University of Massachusetts, Lowell, in the hope of developing new small molecule drug inhibitors of *H. pylori*. These compounds all resemble auranofin through their gold side chain and sugar-base but vary by the side chain attached to the second carbon on the glucose ring (Figure 1). Dr. Yan's lab has established that one of the analog compounds is five times less toxic against mammalian cells than auranofin, making the analogs promising candidates for treatment against *H. pylori*.

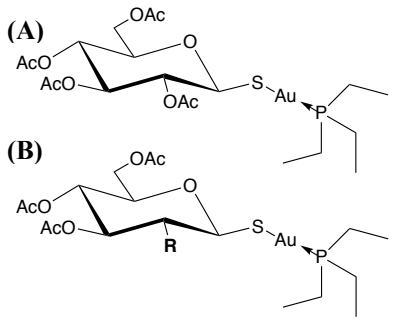

Figure 1. *(A)* Chemical structure of auranofin. *(B)* The auranofin derivatives vary in structure at the second carbon of the sugar ring.

I have established the minimum inhibitory concentration (MIC) against *H. pylori* of each compound. While all compounds successfully eradicated *H. pylori* growth, three of the compounds, including the compound determined to have decreased toxicity against mammalian cells, inhibited *H. pylori* growth at a concentration lower than auranofin. Additionally, I determined that the novel compounds obstruct *H. pylori* growth in the same manner as auranofin, through the inhibition of free thiol residues on TrxR. I established the half maximal inhibitory concentration (IC_{50}) for each compound against TrxR to discover that the same three compounds that decreased MIC values from auranofin also had decreased IC_{50} values.

Future work on this project will focus on understanding why the chemical variations between the compounds yield differences in inhibitory properties. My hypothesis is that modulation of the sugar ligand impacts the ability of the compounds to enter the cells. Gaining insight into why changes in chemical structures yield more promising therapeutics will provide us with greater rationale for the design of future analog compounds.

As a biochemistry major and sociology minor, I am interested in applying chemical and biological concepts and tools to solve public health issues. I have gained conceptual and laboratory skills in my science classes and studied issues of global health and health inequality in my sociology classes at Bowdoin. My honors project in the Dube research group has allowed me to use my chemistry skillset to further understand and solve issues of public health. The opportunity to attend the ACS national conference provided me with the opportunity to present my research to peers and leaders in the field and conceptualize my honors project within the context of preeminent research in the country. This conference also provided a critical opportunity for me to identify research areas to pursue in the next stage of my training as I enter the PhD Program in Chemical Biology at the University of Michigan in the fall.

Faculty Mentor: Danielle Dube

Funded by the Grua/O'Connell Research Award

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