Ian Diccion MacDonald
FURSCA
Elizabeth Palmer, Renee Kreger
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End of Summer Report

Hello all, my name is Ian Diccion MacDonald. I am a rising Junior here at Albion College majoring in both Music (piano), and Biochemistry. Over the course of these past eight weeks or so, along with the rest of the team (pictured below) we aimed to develop upon the synthesis of a novel BCR-ABL1 inhibitor.

Pictured Above (left to right): Senior Payton Baker, Junior Ian MacDonald, Faculty Advisor Craig Streu, Senior Tejal Richardson

The faculty advisor who helped to guide us through the challenges and more was none other than the wonderful Craig Streu, Professor of Biochemistry. By the end of the eight weeks, via forms of analysis, the group intended to both see whether the target molecule was made, and

whether or not the target molecule had the intended effects on cancer cells. The lab where the group spent the majority of our time was the third floor biochemistry research lab (rm. 371) and the second floor biochemistry teaching lab. The science complex became a secondary home throughout the summer

The summer was incredibly successful as in the end, I successfully was able to synthesize two BCR-ABL1 inhibitors. I made a first generation inhibitor followed shortly thereafter by the second generation inhibitor; the need for multiple generations of inhibitors is found in evolution. The BCR-ABL1 protein complex is formed when chromosomes 9 and 22 in the human genome experience a translocation creating a fusion on chromosome 9 called the BCR-ABL1. The translocation is responsible for approximately 90% of all patients diagnosed with Chronic Myeloid Leukemia (CML). Before the invention of these tyrosine kinase inhibitors (the chemotherapies in question) had a mortality rate of 90-95%. With the invention of novel tyrosine kinase inhibitors in 2001, and generations following, the life expectancy of individuals with CML now hover around 90-95%.

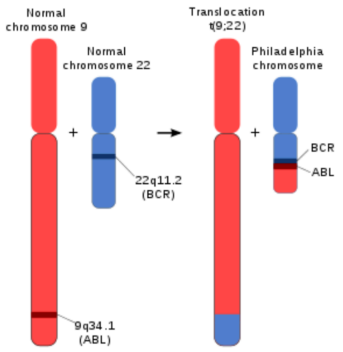

Figure 1. Philadelphia Chromosome Translocation

The research which the group conducted this summer focused on the conversion of these already known molecules into a photoswitchable version; this photoswitchable version of the molecule allows for the molecule to change its conformation (its shape). These molecules are known as azologue molecules (representing the name of the nitrogen-nitrogen double bond found between the two parts of the molecule).

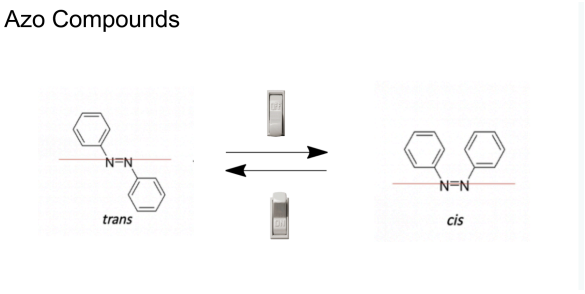

Figure 2. The Properties Demonstrated of an Azologue Molecule Changing Conformation.

This change in molecular conformation allows for the specific activation of the target molecule to the corresponding binding site.

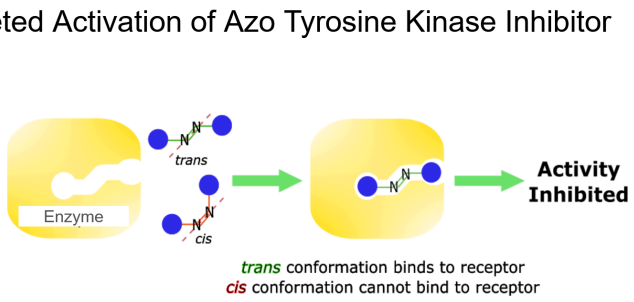

Figure 3. The Targeted Activation of an Azologue Molecule Leading to the inhibition of the Cellular Signalling and Pathways.

I successfully synthesized two target molecules; the first, is a first generation TKI focusing on the BCR-ABL1 fusion protein and the second, is a second generation TKI focusing on the BCR-ABL1 fusion protein as well. Each of the molecules used a three part synthesis whereby each time, I had to follow a similar workflow as seen in the figure below:

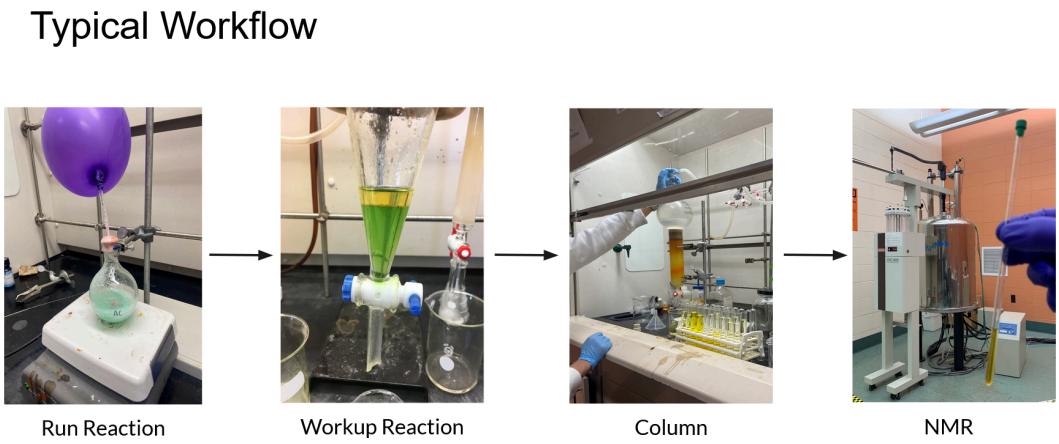

Figure 4: A Typical Workflow for Each Reaction Within a Given Synthesis.

First, a reaction was run combining chemicals together to form a new intermediate or product. Second, the reaction was worked-up in order to remove any water soluble impurities left over in the reaction solution. Third, the specific chemical of interest was isolated using column chromatography; through this purification technique, different molecules separate in accordance with their given polarity. Utilizing thin layer chromatography (TLC) researchers can determine how the different chemicals will run in comparison to one another. This can be seen in the figure above via the different colored bands present in the column. Each band in the column represents a different molecule; extracting those bands individually can be achieved by collecting them in a series of test tubes, and then subsequently combining them in a larger flask. Not pictured is the concentration of these isolated compounds via a rotary evaporator or distillation apparatus (in vacuo).

Figure 5: Pictured Above is a Typical Rotary Evaporator Used to Concentrate Chemical Solutions.

Finally, in workup step four, is confirmation of the molecule's identity through varying forms of chemical analysis. The last step of the work flow is often repeated multiple times, in order to acquire different forms of analysis on the same sample. This allows researchers to be more confident in their assessment of whether or not they have synthesized the intended intermediate or final product.

I found that the greatest lesson learned throughout the course of the summer was never, and I mean truly never, underestimate the small details. My first four or so weeks were plagued by synthetic inefficiencies, where others were having far more success; it was both frustrating and perplexing, seeing as no one in the lab could replicate these same errors. It turned out to be salt buildups in the needles I was using; while it may not seem like a very important detail, these small syringe needles were used in order to “purge” the atmosphere inside of a given reaction flask. This is done typically to remove the reactive oxygen gas, replacing it with the more favorable, less reactive argon or nitrogen gasses. You can see the inert gas being held in the balloon pictured in step one of the reaction workup along with the needle acting as a conduit for the gas. Well, evidently over the years of use in this lab, these needles had been clogged to the point where they no longer allowed for the inert gas to flow through! As soon as I made the small change, the errors disappeared and my desired yields were achieved.

This summer was a lesson in how to precisely execute on a given task. While the above may seem relatively straightforward, getting through the failures with your head up and alert is difficult. Not getting discouraged, but embracing the struggle is necessary at all steps of the synthesis processes, analysis, and subsequent kinetic and biological testing.

Given this wonderful experience, next summer I hope to take my newly found resources and skills to a larger nationally funded lab, or academic environment; there, I would hope to continue my love of learning around more young and bright minds across the country.

After graduating from Albion College, I intend to pursue a career in medicine, following my family's path. This would be not only a great achievement for me, but a meaningful way in which I can both serve the Lord and my community. It goes without saying that while this work at times can be both challenging and difficult, it is rewarding. I do not intend to chase the shadows of fortune or fame, rather I intend on being a faithful and lasting servant both to the community and country which I serve. I am indebted to all of the donors of the FURSCA program, as without your contributions, I would not be able to enjoy the luxuries afforded to our chemistry department.

Thank you all for your time in reading this letter, and I implore you to continue to give; I implore you to continue your dedication to the arts and sciences, as they come under attack from forces both at home and abroad.

P. S. I want to give a special thanks to Craig Streu, our faculty advisor, who has given his unwavering support. He is undoubtedly an incredibly humble and loving mentor to us all. I would also like to thank my big brother, Alex Zoschke; without whom I would not have achieved nearly as much. I stand on the shoulders of giants, and will acknowledge them and their great achievements for as long as I live. Long live Tau Kappa Epsilon.