End of Summer FURSCA Report

Scale-Up and Diversification of a Light-Activated PD/PD-L1 Inhibitor Scaffold

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Introduction

My research is focused on the scale-up of the synthesis of a small molecule checkpoint inhibitor drug (immunotherapy) that can be reversibly activated by certain wavelengths of light. Immunotherapy is a type of cancer treatment where an individual's own immune system is boosted or changed to attack cancer cells in the body. Cancerous cells evade the immune system of our bodies by manipulating the checkpoints which are actually engaged in differentiating healthy cells and foreign bodies. By blocking this checkpoint protein with a checkpoint inhibitor, the immune system can be turned "on" to kill the cancerous cells.

Bristol Myers Squibb or BMS has synthesized small molecule compounds targeting the PD-1/PD-L1 interaction. The drug can be easily synthesized and is cost effective because it can be administered orally. However, this drug still has the off-target side effects associated with other checkpoint inhibitors because it has the potential to activate T cells throughout the body as well which leads to the killing of many healthy cells too.

The goal of my project is to create a photo-switchable azo BMS-37 that will drastically reduce the harsh side effects of this drug due to the ability of azo-stilbenes to isomerize in response to light. The drug will be taken in its inactive form and activated by specific wavelengths of light. By doing so it is administered selectively to the cancer cells, thus not harming healthy cells in the body.

Results

Throughout the course of my summer research I was able to complete 5 steps out of the 6 steps in my synthesis. For every step in my synthesis, I start by setting up my reaction and letting it run for the required amount of time. Next I do a workup where I separate my product from the other stuff in the reaction mixture. Then I perform TLC or Thin Layer Chromatography to check how pure my compound is. This is followed by Column Chromatography which is how I purify my compound from its impurities. Once I have my product, I use the rotary evaporator to evaporate the solvent I used in column chromatography to get my product out. After this I use the NMR to check if I actually do have the product that I want.

I have not done Step 6 so far because carbon monoxide is used in the reaction. Carbon monoxide is a poisonous gas so we wanted the reaction to be done once, when we have enough product from the previous step. I also did not get the expected yield in reactions. So most of what I did was to keep repeating Steps 1 to 5 so that I have enough product to carry on with my synthesis.

Figure 1: Photo of the Azo coupling reaction - Diazonium salt is reacting to form an azo compound

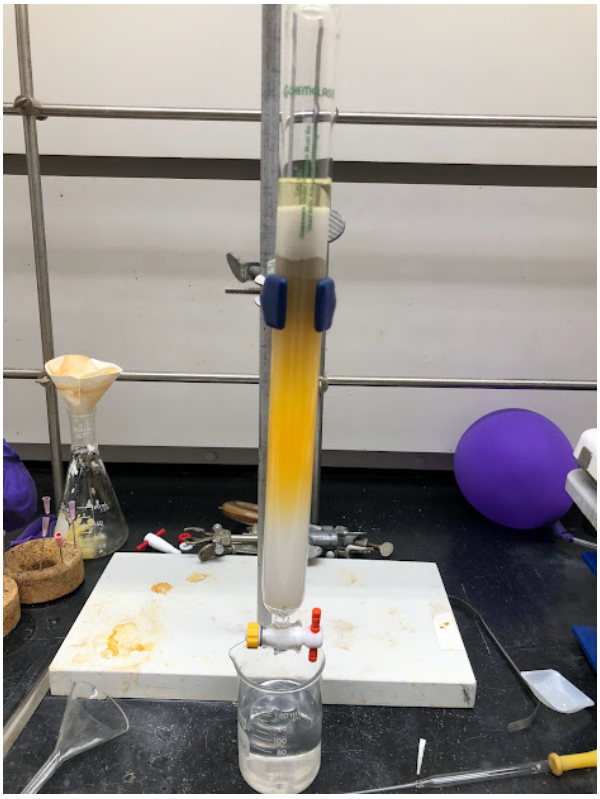

Figure 2: Photo of Column Chromatography - Purification technique use to isolate the product after every reaction

Conclusion

For future work this fall, I would like to make more of azo BMS-37 and test it for photoisomerization. Once I'm done with that I will begin the synthesis of the second molecule, azo BMS-242. I plan to present my research at next year's Elkin Isaac and the American Chemical Society Meeting in Spring 2022.

Over the course of the summer, I have learned various new techniques involved in organic chemistry research. Working in the lab has given me an idea of what a career in research would look like. I feel that this is a valuable experience that can help me decide between going to medical school or pursue a career in research.

I would like to thank FURSCA, Elizabeth Palmer and Renee Kreger for a wonderful summer research experience. I would also like to thank Dr. Streu for teaching me new techniques and guiding me throughout the research.

To the Orpha Leiter Irwin Fellowship

Thank you for giving me the opportunity to participate in Albion's FURSCA program this summer. This summer provided many benefits that will greatly influence my future education and research endeavors. Thank you!