

Introduction

Cholestanol glycosides compounds have shown significant anticancer properties. These antitumor effects are still being discovered, but it is difficult due to the complicated synthesis process. My project proposed a novel synthesis of cholestanol glycosides. A simpler synthetic pathway would create opportunities to modify and test these compounds against different cancer strains. The basis of this project was to modify cholesterol by adding various carbohydrate groups from tetraazidokanamycin (kanamycin A). Our hypotheses were 1) that kanamycin A can be selectively cleaved using a Lewis acid, and 2) that the amino sugars from kanamycin A can function as glycosyl donors.

Challenges and Outcome

Several challenges arose as we tested our hypotheses. Some of these problems were solved, and others became stumbling blocks throughout the project.

First, a Lewis acid strong enough to hydrolyze kanamycin A was needed. BF_3 was the first Lewis acid tested, and this showed no hydrolysis of kanamycin A in two solvents, dichloromethane and acetonitrile. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was also tested and successful hydrolysis was achieved using acetonitrile as the solvent.

Second, the hydrolysis of kanamycin achieved using TMSOTf was not specific as to which glycosidic bond was hydrolyzed. This led to a mixture of the amino sugars in the reaction for the glycosylation, which also led to complications.

Third, after the hydrolysis of kanamycin A using TMSOTf, the glycosylation was not achieved. Several modifications were made to potentially allow for the reaction to occur. The first attempt was to add a 2,4,6-trimethylpyridine to function as a leaving group for the glycosylation of cholesterol. There was no evidence that the leaving group was successfully added to the hydrolyzed amino sugars. The hydrolysis was then attempted with cholesterol dissolved into the solvent, eliminating the need for a leaving group.

Fourth, the challenge of finding a solvent that cholesterol was soluble in and also allowed for the hydrolysis of kanamycin A to occur was difficult. Alcohols were not suitable because they would potentially become glycosylated as easily as cholesterol, leading to a very small amount of product to be formed. Many solvents, including acetonitrile, were too polar for cholesterol to be dissolved to any reasonable degree. Dioxane was selected as a solvent because it was polar enough

to dissolve kanamycin A for successful hydrolysis and not too polar that cholesterol would not dissolve. However, after this approach was taken there was still no evidence that any successful glycosylation occurred. The same reaction was attempted with benzyl alcohol, due to the comparable structure to cholesterol, but no glycosylation was measured.

At this point, the project was considered failed. Neither hypothesis--that selective hydrolysis could be achieved or that the amino sugars from kanamycin A could be used as glycosyl donors--was confirmed during our experiments. In further experiments, better leaving groups on the amino sugars could possibly lead to an intermediate that would allow cholesterol to become glycosylated.

Learning Objectives

At the start of my project, my learning objectives were to 1) become more able to think critically, 2) learn the process of preparing and writing research publications, 3) improve my ability to work as part of a team and 4) improve my laboratory skills. Overall I feel very accomplished in each of these learning objectives.

There were many times throughout the project where critical thinking was required. At the beginning of the project, I relied a lot on my graduate student mentors, but as time went on, I was able to predict ways to improve reactions or analyze TLC plates on my own.

While my project did not lead to a publication at this time, I was able to gain some exposure to the papers that my mentors were writing. I also wrote a report for this project while getting class credit for the CHEM 4800 course. These opportunities gave me a better idea of what a professional paper requires.

I believe that I especially became better at working in a group from this experience. There were several times when I did not communicate as clearly as I should have, and my mistakes delayed my project at times. After these mistakes, I made a more conscious effort to talk with my mentor and become a better communicator. By the end of the project, I was able to work with my team effectively and we understood each other well.

Lastly, I improved various lab techniques during my project. There were many processes that were used in my experiment, such as column chromatography, extractions, taking NMR spectra and thin-layer chromatography.

Future Endeavors

I am very grateful for the research experience I have gained through the URCO grant project. Despite the unsuccessful project, I was able to develop skills that I hope will help me throughout my career. I hope to attend medical school starting in 2019, after my graduation from Utah State. I will make research a part of my future practice and have become particularly interested in autoimmune diseases. As I look forward to future research in the medical and public health fields, I am confident that the experience I have gained through this project has prepared me to be successful in the future.