

Emily Bartlett (esb38)
Dean's Scholars Summer Research Proposal

Pauline and Irving Tanner Dean's Scholars
Summer Research Proposal
Total Synthesis of Platensimycin
Emily Bartlett

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Faculty Advisor

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Major Advisor: Barbara Baird

I hereby waive my right of access to my letter of recommendation.

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Abstract:

This summer, I plan to continue working on the same project I have been involved in for the past year as part of the Njardarson group in the department of Chemistry and Chemical Biology. The work has centered around the chemical synthesis of the recently discovered antibiotic platensimycin, which is derived from *Streptomyces platensis*, a bacterium collected from soil samples in South Africa and isolated by a Merck research group that worked on screening natural products^[1]. This new antibiotic is of particular importance because it works by inhibiting bacterial fatty acid biosynthesis, which is a mode of action completely different from any other known antibiotic. This means that platensimycin is an effective agent against strains of bacteria with multiple antibiotic resistance.

Due to the complexity of the molecule, I have been working on the project in conjunction with one of the graduate students in the research group. However, I have been working independently on portions of the project, including synthesizing the aromatic ring component of platensimycin, which will be joined via an amide linkage to the second substructure of the molecule to complete the total synthesis of this product. This coming summer, work on the project would include completing the synthesis of the central cage-like structure of platensimycin as well as fully characterizing each compound in our synthetic route using mass spectroscopy (MS) and nuclear magnetic resonance spectroscopy (NMR) to prepare for publication.

References

[1] Singh, S.B. *et. al. Nature*. 2006, 441, 358.

Biography:

I was born in Guatemala City, Guatemala in 1987 and lived in the Antigua Valley for five years before moving to the United States. My parents were both working in Guatemala at the time; my mother carrying out research as an archaeologist and my father working for the U.S. Agency for International Development in maternal and children's health programs. While growing up in Guatemala, I learned Spanish and English simultaneously and after moving to my new home in Chevy Chase, Maryland maintained my fluency in Spanish by attending a Spanish immersion elementary school. Despite living in the U.S., I returned to Guatemala on a regular basis during the summer when my mother traveled there to continue doing research. My time spent abroad incited in me a love of travel and of learning about new cultures and languages, which has continued to affect my worldviews today.

My interest in chemistry began with a fabulous high school AP chemistry teacher, who made the topic both stimulating and challenging. I entered Cornell with an intent to pursue a major in chemistry, but my interest in the topic has evolved and matured during my time here. I particularly enjoyed gaining knowledge at a high enough level to engage productively in research. I take pleasure in being able to draw connections from many

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different areas of chemistry and applying them to a problem or challenge presented in the laboratory.

I was able to combine my interests in chemistry and world travel during a summer internship last year at the Phillips University in Marburg, Germany. I spent most of the week carrying out research in a laboratory group in the chemistry department there, but also traveled by train throughout Germany almost every weekend. Another thing that made the experience particularly interesting was that I spoke virtually no German when I applied for the internship. In many ways, Germany seemed more foreign to me than anywhere in Latin America because the language was completely incomprehensible at first. However, I took individual language courses and studied German on my own while I was there and also took every opportunity to speak to people in my rudimentary German, no matter how self-conscious I was to begin with and at the end of the summer had acquired a respectable degree of competency in the language. Aside from the language, my time in Germany was eye-opening because the country has devoted a lot of resources to "green" technology such as producing clean sources of energy and improving transportation efficiency, which is an application of chemistry I would be particularly interested in pursuing in the future. Overall, I found the experience to be both wonderful and challenging, as it forced me to learn about another culture and also to see my life in the United States with new eyes.

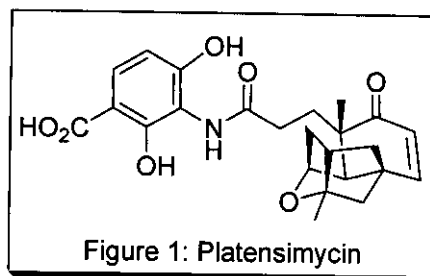
Statement of Purpose:

The search for new antibiotics and their development as marketable drugs have been increasingly important issues because of the emergence of several strains of bacteria with resistance to multiple antibiotic classes. However, antibiotic research has been lagging because of the high cost associated with targeting and preparing new antibiotics as marketable drugs as well as the relatively low levels of return generated by antibiotics for pharmaceutical companies. In comparison with drugs for chronic conditions like hypertension or HIV/AIDS, antibiotics tend to not be very profitable investments for drug companies because they are generally effective within a few days, thus eliminating their own need. Additionally, they have an inherent limit to their life span as a drug because of the eventual development of resistance of bacteria to new antibiotics^[1]. Especially troubling is the fact that some strains of bacteria are now resistant to Vancomycin, which is generally regarded as one of the last lines of defense against some microbes, including *Staphylococcus aureus*^[2]. Vancomycin and other glycopeptide antibiotics that inhibit bacterial cell-wall biosynthesis are usually the preferred treatment for strains of bacteria with multiple resistance because of the low levels of cross-resistance between these and other classes of antibiotics, which function via other mechanisms. However, as even these glycopeptide antibiotics have not proven invincible, the necessity of identifying and developing new antibiotics which are effective against strains resistant to even the most potent known antibiotics becomes very clear. In particular, there is a critical need for new structural classes of antibiotics that pinpoint novel and valid targets, since the antibiotics available today use only a limited array of mechanisms^[3].

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In 2006, a Merck research group that worked on screening natural products^[4] identified platensimycin (Figure 1), which is a natural product derived from *Streptomyces platensis*, a bacterium collected from soil samples in South Africa. Platensimycin is a structurally novel natural product that was discovered to have potent antibiotic properties. It is of particular interest because it has been shown to kill bacterial cells by blocking bacterial fatty acid biosynthesis, specifically by inhibiting the elongation condensing enzyme FabF. This is a mode of action that is completely distinct from previously known classes of antibiotics, meaning that platensimycin has great promise as a new antibiotic because its novel mechanism of action prevents current "superbugs" from having developed any sort of resistance to it^[1].



Before platensimycin, or any new pharmaceutical, can be made available as a drug, it must pass a series of tests in both animals and humans in order to verify its potency and safety as a prescription drug for the FDA. Because of the biological importance of platensimycin, synthesizing the molecule for further development and testing is very important. Additional reasons for synthesizing this molecule include evidence that platensimycin may be unstable *in vivo*, since researchers had to infuse it continuously into mice infected with *S. aureus* in order to achieve a bacteriologic cure. Additionally, clinical tests must be performed in order to determine if platensimycin has significant toxic side effects. Therefore, it is possible that the structure of platensimycin might have to be significantly modified before it can be approved for use a drug^[5].

As a research project, I propose to extend work on the total synthesis of platensimycin, in which I have been involved for the past year in collaboration with Nicholas McGrath, a Ph.D. student in the Njardarson group at Cornell University. We will aim to complete an enantioselective synthesis of the molecule using a route that is both efficient and elegant. Aside from potentially providing a viable way to produce larger quantities of platensimycin for drug development, once a synthesis of the molecule has been completed, the general synthetic blueprint could then be used to systematically alter the framework of the molecule. This would allow us to create a collection of otherwise inaccessible hybrid structures that could be used to obtain a better understanding of platensimycin's biological function as well as to identify new and improved antibiotics derived from the original molecular model provided by platensimycin. This is particularly important because in the past many commercially available antibiotics have been the result of synthetic modifications of naturally occurring compounds that have greater stability, potency, selectivity or antibacterial spectrum than the original natural product.^[1] Carrying out a total synthesis of natural products such as platensimycin has additional importance because it provides a basis on which to develop new methodology in organic synthesis, which could then later be applied to other synthetic challenges. Also, an ideal route to the synthesis of platensimycin would be cost effective, be capable of being scaled-up for potential use by industry, and utilize reagents that represent little or no threat to the environment. Therefore, in this synthesis, we will seek to minimize

the use of protecting groups that decrease the efficiency of the synthesis and also to use environmentally acceptable reactions.

My involvement in this project has proven to be an excellent hands-on learning experience that will be beneficial in pursuing a career in chemistry. Thus far, I have independently synthesized the aromatic ring component of platensimycin, which we plan to join with the cage-like core of the molecule via an amide linkage in the last stage of the synthesis. Additionally, I am and will continue to be involved in synthesizing the core of the molecule by running reactions, purifying compounds and characterizing the structures of all intermediates primarily using Nuclear Magnetic Resonance (NMR) spectroscopy, Mass Spectrometry and Infrared (IR) spectroscopy. Working on this project is an excellent practical application of the knowledge I have gained in my coursework as a chemistry major, because many of the principles and reactions I have learned about are applicable to the process of synthesizing platensimycin. Being involved in this project for the past year has allowed me to develop laboratory skills far beyond what is taught in a typical laboratory course, because our work on the synthesis of platensimycin involves a wide range of different reactions, many of which are not discussed in typical undergraduate courses. Through the exposure to new chemistry I have gained in my laboratory work, I have broadened my range of knowledge in organic chemistry and have made an effort to understand the mechanisms behind each reaction I set up, making the laboratory work a gratifying intellectual endeavor rather than mere busywork. Also, in order to become more self-sufficient and productive in my research, I have taken training courses to become certified to use Cornell's NMR facility without the supervision of a graduate student. I now perform NMR experiments independently on a regular basis in order to characterize the compounds synthesized in the laboratory. Therefore, being involved in this project has and will continue to be a worthwhile experience that equips me with skills that will serve me well, no matter what research I choose to pursue in the future.

Bibliography

- [1] F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich, *Angew. Chem. Int. Ed.* **2006**, *45*, 5072.
- [2] H. Pearson, *Nature* **2002**, *418*, 469.
- [3] D. Häbich, F. von Nussbaum, *ChemMedChem.* **2006** Aug 3;1(9):951-954
- [4] J. Wang *et. al.* *Nature.* **2006**, *441*, 358.
- [5] H. Pearson, *Nature* **2006**, <<http://news.nature.com/news/2006/060515/441260a.html>>

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Proposed Budget:

Item	Purpose	Price per Unit	Quantity expected to be used for summer	Total Price
Time using Cornell's NMR facility	Obtain spectra to characterize organic compounds	\$10 per hour ^[1]	3 hours per week	\$360.00
Analytical Thin Layer Chromatography (TLC) plates	to monitor reaction progress and identify fractions from columns containing target compounds	\$106.00 per package ^[2]	1 package of 20x20cm plates with fluorescent indicator	\$106.00
Preparative Thin Layer Chromatography (TLC) plates	purifying small amounts of compounds to obtain analytically pure samples	\$194.70 per package of 25 ^[3]	1 package	\$194.70
NMR tubes	used to insert samples into NMR spectrometer	69.40 per pack ^[3]	1 package of 5 reusable tubes	\$69.40
Deuterated Chloroform (99.8 atom% D)	Solvent for preparing NMR samples	\$68.30 per 250g ^[3]	2x250g	\$136.60
Silica gel	Used for packing columns for flash chromatography	\$188.43 per kg ^[3]	4 kg	\$753.72
Ethyl Acetate	Solvent for running columns and reactions	\$22.16 per 4 L ^[4]	6x 4L	\$132.96
Hexane	Solvent for running columns and reactions	\$18.33 per 4L ^[4]	6x 4L	\$109.98
Diethyl Ether	Solvent for running columns and reactions	\$37.21 per 4L ^[4]	6x 4L	\$223.26
Dichloromethane	Solvent for running columns and reactions	\$23.56 per 4L ^[4]	6 x 4L	\$141.36
Assorted Lab Supplies	Reagents, Gloves, Test Tubes, Syringes, Filter Paper, etc.	N/A	N/A	\$275.00
			Total	\$2502.98

Sources for Price Quotes:

- [1] <http://nmrscheduler.chem.cornell.edu/rates.shtml>
 [2] <http://www.saiadsorbents.com/pricelisttlc.htm>
 [3] <http://www.sigmaaldrich.com/catalog>
 [4] <http://www.chem.cornell.edu/kda1/stock/CatalogPage.html>

All major lab equipment, such as glassware will be provided by the Njardarson group at Cornell. Living expenses such as rent, utilities and food will be covered by a living expense grant taken from my Research Support Account (RSA) from the Cornell Presidential Research Scholars. The remaining funds available from the RSA will be used to cover the costs of research during the school-year.