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Antimicrobial Resistance: Public Health Review of Policy, Education, and Treatment [senior thesis]

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"Antimicrobial Resistance: Public Health Review of Policy, Education, and Treatment"

The following thesis is broken into two sections. Part 1 is public health focused, utilizing a literature review(part 1a) and a population based survey(part 1b). Part 2 looks at the synthesis of natural product, (R)-Dysidazirine.

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Part 1: Public Health Study

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Introduction:

Antimicrobial resistance (AMR) is a massive global public health crisis. Known as the "silent pandemic", AMR has been around since the discovery of the first penicillin resistant bacteria in 1947, just five years after the discovery of the first antibiotic in 1942[1]. Since 2001, AMR has been one of the World Health Organization's(WHO) top 10 global public health crises. AMR is directly responsible for roughly 5 million deaths per year globally, though this number does not include the many other deaths correlated to resistant infection. There is a stigma associated with AMR that causes it to be associated with developing nations due to certain countries limited access to healthcare and varying medication regulations. AMR is, however, an issue that is very present in all countries throughout the world[2]. In the United States, 2.8 million drug resistant infections are recorded annually, though the number of total drug resistant infections is expected to be much higher because the 2.8 million only includes the infections of those seek medical treatment at a location that carries out resistant infection surveillance protocols. Of those recorded drug resistant infections, 35,000 people die directly due to resistance, though there are many others who die of complications exacerbated by drug resistance.

AMR is defined as the development of resistance by a pathogen to antimicrobial agents[3]. These antimicrobial agents include antibiotics, antivirals, antifungals and

[1] *The discovery of antibiotics – Part 1*. (n.d.). ReAct. Retrieved April 27, 2023, from https://www.reactgroup.org/antibiotic-resistance/course-antibiotic-resistance-the-silent-tsunami/part-1/the-discovery-of-antibiotics/

[2] Ayukekbong, J. A., Ntemgwa, M., & Atabe, A. N. (2017). The threat of antimicrobial resistance in developing countries: Causes and control strategies. *Antimicrobial Resistance & Infection Control*, *6*(1), 47. https://doi.org/10.1186/s13756-017-0208-x

[3] *Antimicrobial Resistance—PAHO/WHO | Pan American Health Organization*. (n.d.). Retrieved April 28, 2023, from https://www.paho.org/en/topics/antimicrobial-resistance

antiparasitics. This increased resistance has made it difficult to treat common infections, which contributes to disease spread and increased hospitalization. Antibiotic resistance is exacerbated by the overuse of antimicrobial medications and while new medications are needed to treat these resistant infections, other methods of treatment and further regulation of prescriptions are needed to minimize antimicrobial resistance pathogens.[4]

The spread of antimicrobial resistance is a global concern because of the role antimicrobial drugs play in our society. Antibiotics are both overused and overprescribed. According to the CDC, 30% of prescribed antibiotics are not necessary. There is little regulation on the prescriptions of medications, dosage, and correct usage of antibiotics. In 2015, the White House set a goal to decrease the unnecessary usage of antibiotics by 15% by 2020, however, the demand and percent usage of antibiotics has only increased following the COVID-19 pandemic[5].

Moreover, in the meat and agriculture industries, there has been a rise in the usage of antibiotics to maintain healthy and abundant food sources to keep up with high demand[6]. This usage has seeped into waterways, which have impacted human antibiotic consumption, as well as consumption by ocean life.[7] The normalized antibiotic use in life-sustaining processes have created a cycle of antibiotic spread, which has contributed to increased resistance.

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[4] *Antimicrobial resistance*. (n.d.). Retrieved April 28, 2023, from https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

[5] *CDC Newsroom*. (2016, January 1). CDC. https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html

[6] Medicine, C. for V. (2022). FDA Releases Annual Summary Report on Antimicrobials Sold or Distributed in 2021 for Use in Food-Producing Animals. *FDA*. https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2021-use-food-producing

[7] Manyi-Loh, C., Mamphweli, S., Meyer, E., & Okoh, A. (2018, March 30). Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential Public Health Implications. Retrieved December 17, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6017557/

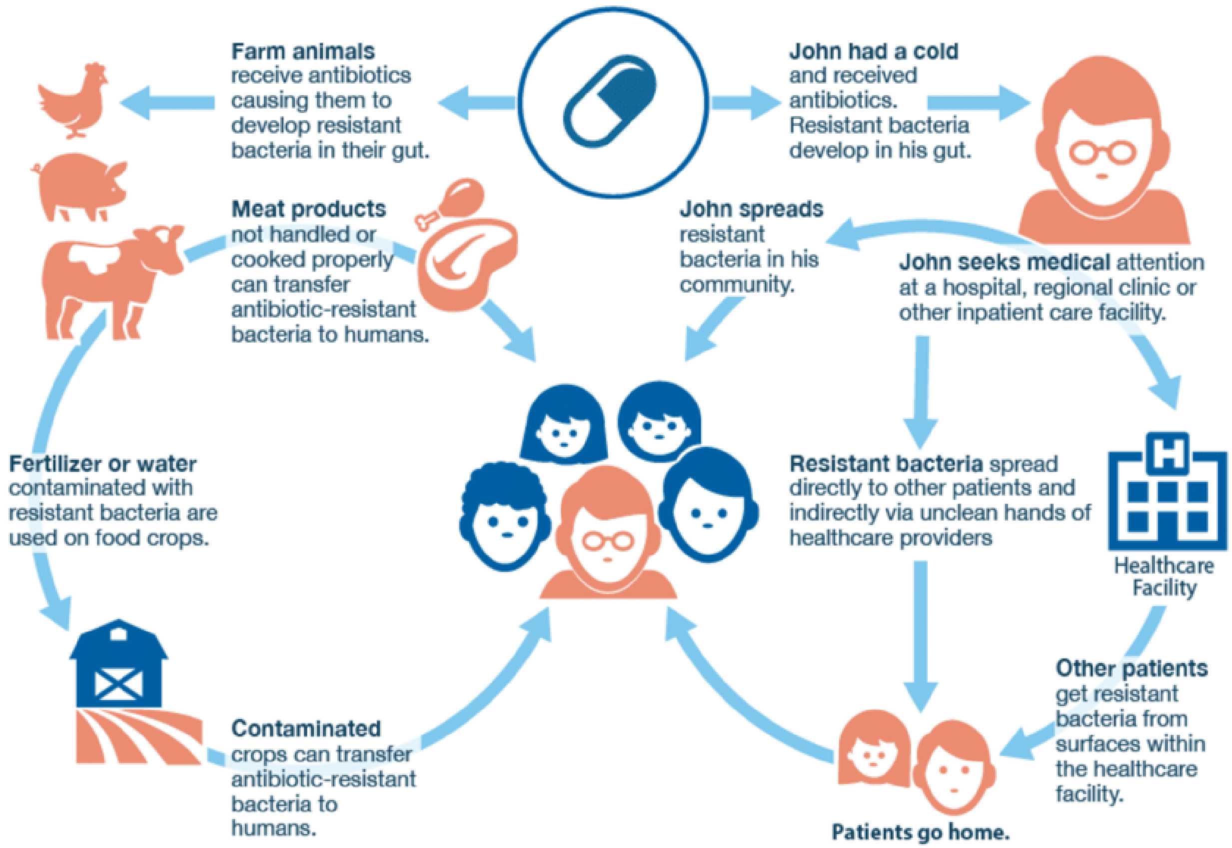

Figure 1. This diagram, adapted from literature,[8] shows the spread of antibiotic resistance throughout people.There are two main contraction spheres pertaining to interpersonal transmission and food and water consumption. The overuse of antibiotics can cause a snowball effect that results in the spread of resistant bacteria to treatment.

Antibiotic resistance spreads through five key groups: healthcare sites, communities, water/soil, food, and travel **(Fig. 1)**. In the United States, antibiotic resistance has become a major concern, especially following the COVID-19 pandemic. During the pandemic, there was an increased interest in public health initiatives, with an emphasis on infectious diseases. Infectious diseases, oftentimes, are treated with

[8] Kong, C., Neoh, H., & Nathan, S. (2016). Targeting staphylococcus aureus toxins: A potential form of anti-virulence therapy. *Toxins, 8*(3), 72. doi:10.3390/toxins8030072

antimicrobial medications. If mass amounts of populations develop resistance to medications used to treat infectious diseases, it can greatly impact the health of the nation and the globe. Health infrastructure will be harmed due to the nation's hindered ability to treat common illnesses, such as the flu, which hurts the nation's ability to protect people against more serious or new illnesses, such as covid-19. Some of the most common bacterial infections in the United States are urinary tract infections (UTIs) and sexually transmitted diseases (STDs). In the past few years, there has been an increase in the number of reported cases of these infections, along with an increased difficulty for physicians to treat these illnesses[9]. While all communities are at risk of developing antibiotic resistance, some communities have increased exposure due to a lack of resources. Low-income populations, as well as people of color, are at a higher risk of developing resistance to medications[10].

The risk that is imparted on these communities are related to public health-based social determinants of health, which are defined as nonmedical related factors that impact a person's health. Race, ethnicity and socioeconomic status are a few social determinants that can impact the health of a person due to systems and structures in society that intrinsically allow white and higher income individuals more access to resources and privileges. Not only are those from underrepresented backgrounds at a disadvantage due to social determinants of health, they are also often disproportionately blamed for many health crises. For example, the LatinX community is regularly the target of blame

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[9] Behzadi, P., Behzadi, E., & Pawlak-Adamska, E. A. (2019). Urinary tract infections (UTIs) or genital tract infections (GTIs)? It's the diagnostics that count. *GMS Hygiene and Infection Control*, *14*, Doc14. https://doi.org/10.3205/dgkh000320

[10] Nadimpalli, M. L., Chan, C. W., & Doron, S. (2021). Antibiotic resistance: A call to action to prevent the next epidemic of inequality. *Nature Medicine*, *27*(2), 187–188. https://doi.org/10.1038/s41591-020-01201-9

regarding the AMR crisis in the United States. Headlines and media coverage often center AMR around the cultural practices of LatinX people, not recognizing that these practices and behaviors are based out of necessity arising from lack of access to resources including: healthcare, food, housing and livable wage(**Image. 2**).

<u>Headlines villainizing LatinX populations for spread of AMR in the US:</u>

MEDICATIONS · **Published** January 2, 2017 11:29am EST

Many Hispanic adults still believe antibiotics will treat a cold

ARE LATINO CULTURAL BELIEFS INCREASING ANTIBIOTIC RESISTANCE IN THE US?

June 8, 2018

Image 1. This image shows headlines from news articles that related antibiotic usage to LatinX populations[11,12]. The headlines target both LatinX knowledge and cultural practices. The messages are harmful because they create a narrative that villainizes LatinX populations, which can lead to social panics that further perpetuate racism and harm support for public policies that can help increase communities' access to resources.

To support the marginalized communities, additional policy, education, and research are needed to create a multifaceted solution plan for the prevention of antibiotic resistance. Education about antibiotic resistance is dependent on social determinants of

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[11] *Many Hispanic adults still believe antibiotics will treat a cold*. (2015, August 19). [Text.Article]. Reuters; Fox News. https://www.foxnews.com/health/many-hispanic-adults-still-believe-antibiotics-will-treat-a-cold

[12] *Are Latino Cultural Beliefs Increasing Antibiotic Resistance in the US? – Clinical Correlations*. (n.d.). Retrieved April 29, 2023, from https://www.clinicalcorrelations.org/2018/06/08/are-latino-cultural-beliefs-increasing-antibiotic-resistance-in-the-us/

health that create inequity contributing to racial, ethnic and income divides in at-risk communities. A big component of a person's ability to protect themselves against AMR is through access to knowledge about how to keep oneself safe. Due to a variety of barriers facing marginalized communities, access to health education is hindered on multiple fronts. Preliminary research that gauges the level of awareness around the topic of resistance within different demographics is needed to better understand the current state of antibiotic resistance education. Research gauging awareness and knowledge can identify how different communities and intersecting identities are being impacted by health disparities. This data, along with knowledge of other social determinants impacting these communities, can then be used to inform policy changes that better support the health of marginalized communities.

Currently, the research related to antibiotic resistance is focused on the containment of hot spot locations, with little to no record of demographics such as populations, race, ethnicity, income, or citizenship status, all of which could reveal underlying faults in community health systems that played a role in breakout cases of resistant strains of bacteria. To better understand the state of antibiotic resistance education, I am conducting a survey and literature-based study examining the state of knowledge surrounding safe antibiotic usage and antibiotic resistance in different communities. The survey aims to bolster data around different demographics' access and use of antibiotics, as well as their access to and sources of medical information. I anticipate the survey results will illuminate disparities in access to medication and information. I have chosen to use the survey format, supported by a literature review, because of the need for more quantitative data that focuses on demographics like income status, race and ethnicity, all of which can be associated with the social aspect of antibiotic resistance spread.

In low-income communities, access to healthcare is limited[13]. Based on current literature, I hypothesize that low-income communities and non-white communities will have the least access to trusted sources of information and support around antibacterial resistance. In order to have an informative understanding of antibiotic resistance, proper usage of medications, and ways to minimize spread, patients need access to strong healthcare support systems, including primary physicians and pharmacists who monitor each patient's prescriptions and discuss all health options and interventions with patients. This strong healthcare support system is important on both the individual and community level. Community healthcare support systems are crucial to preventing AMR spread. Equity in community health mitigates the need for communal sharing and outsourcing of antibiotics. This survey is intended to reveal more information on where exactly patients are receiving medication, and it is expected that, overall, the less access there is to adequate healthcare, the more reliant providers and patients become on antibiotics. This reliance can blur the lines between safe usage and acquisition of medications. For BIPOC(Black, Indigenous, and people of color) communities, there is an added component of injustice that has been historically present throughout medicine[14]. Mistrust in science and medicine, I anticipate, will be more apparent through the survey.

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[13] Lazar, M., & Davenport, L. (2018). Barriers to Health Care Access for Low Income Families: A Review of Literature. *Journal of Community Health Nursing*, *35*(1), 28–37. https://doi.org/10.1080/07370016.2018.1404832
[14] Byrd, W. M., & Clayton, L. A. (2001). Race, medicine, and health care in the United States: A historical survey. *Journal of the National Medical Association*, *93*(3 Suppl), 11S-34S.

<u>Method:</u> Part 1A - Literature Review

A literature review was conducted using a variety of peer-reviewed journals, as well as news articles to gather information in regards to antimicrobial resistance in the United States. The key terms used to conduct the literature review are listed in **Table 1**. Six databases were used to find articles: google scholar, NIH, pubmed, Haverford College trico institutional database and BioMed central. The literature search resulted in 33 articles reviewed with publishing dates from 1990 to 2023.

Population Key Words:	**Medical related Keywords:**	**Education/Policy Key Words:**
LatinX	Antimicrobial	Family Use
Low-Income	Antibacterial	Population Use
United States	Resistance	Improper Usage*
Minority	Overuse	Physician Policy
Underrepresented	Overprescription	Media

Table 1. This table shows the key words used to find articles related to antimicrobial resistance. The words are separated into three main categories: population, medical terms, and education/policy. Any word, or combination of words, from the three columns was searched to find articles related to antimicrobial resistance.

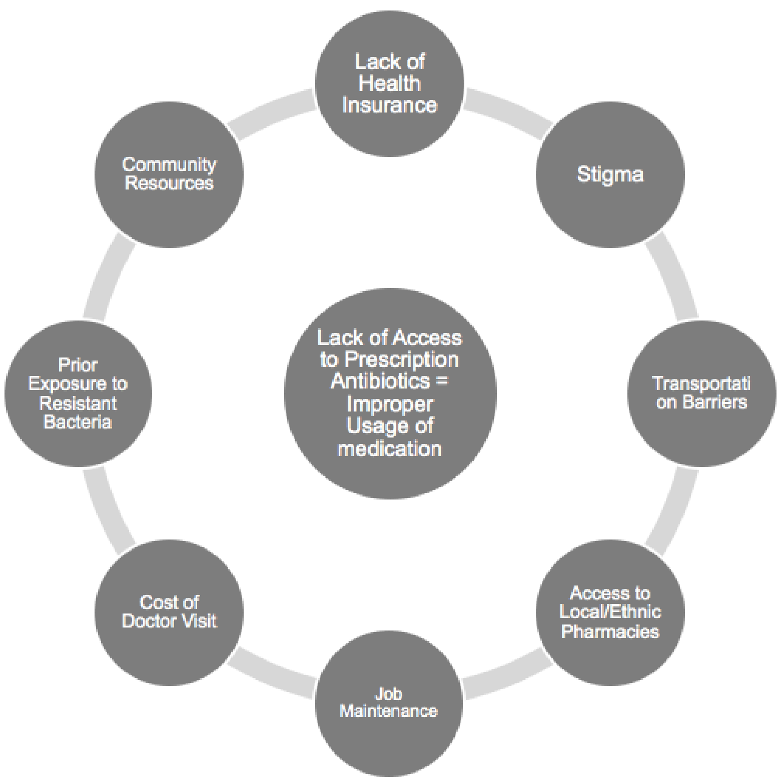
**Improper Usage is defined as usage of medication without a prescription or outside of the bounds of physician regulated prescriptions.*

<u>Results:</u> Part 1A - Literature review

Social Determinants Impacting AMR:

Figure 2. This figure shows the different categories that contribute to racial and ethnic inequalities in antibiotic resistance.[15] All of these categories relate to differences in access and equity barriers. Low-income, LatinX and Black communities are more likely to occupy jobs that increase their exposure to antibiotics[16,17]. Additionally, these communities typically have less access to healthcare resources, creating larger divides in education and proper usage knowledge.

Prescription Antibiotic Accessibility:



[15] Nadimpalli, M. L., Chan, C. W., & Doron, S. (2021). Antibiotic resistance: A call to action to prevent the next epidemic of inequality. *Nature Medicine, 27*(2), 187-188. doi:10.1038/s41591-020-01201-9
[16] *Black, Hispanic Americans are Overrepresented in Essential Jobs* | *School of Public Health* | *University of Illinois Chicago*. (n.d.). Retrieved April 28, 2023, from https://publichealth.uic.edu/news-stories/black-hispanic-americans-are-overrepresented-in-essential-jobs/
[17] *How COVID-19 Is Affecting Black and Latino Families' Employment and Financial Well-Being*. (2020, May 6). Urban Institute. https://www.urban.org/urban-wire/how-covid-19-affecting-black-and-latino-families-employment-and-financial-well-being

Figure 3. This figure shows different reasons that hinder a person's ability to access prescription antibiotics. Majority of these examples disproportionately affect those from underrepresented backgrounds and are correlated with an individual's access to physicians. Due to these barriers, patients often seek other sources for medication, thus, lack of access to prescription antibiotics can result in improper/non-prescription usage of antibiotics.

Correlation between sources of Antibiotics and Information:

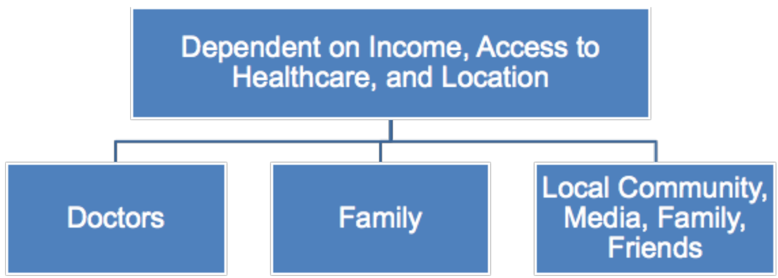


Figure 4. This figure summarizes the 3 main sources people use to get information about medications: doctors, family and community. A person's sources of information are heavily impacted by demographics such as income, location, and race/ethnicity.

<u>**Discussion:**</u> Part 1A - Literature review

There is a duality of need and risk associated with AMR that clash when resources are removed from a community. Risk behaviors pertaining to AMR, such as the saving and sharing of antibiotics, are associated with the need for instant and cheap relief to medical issues. This duality of need and risk really emphasizes the importance accessibility has on health outcomes and the spread of disease.

When looking at the issue of accessibility, there are a few key components that correlate to minority groups using alternative resources for antibiotics (**Fig 3**.). Access to healthcare is a big component. Many of those from low-income and minority backgrounds have less access to healthcare[18]. This can manifest as an individual lacking health insurance. Or this can manifest as life barriers that make seeing a physician more difficult, such as not being able to take off from work or having no accessible means of transportation to see a physician. Additionally, for low-income and minority backgrounds there is a lack of trust in medicine. This lack of trust stems from medical history and systems that have continuously harmed minority communities[19,20]. In response to these circumstances, many minority communities have developed a prescription sharing system. To ensure that everyone has access in the community, there are ethnic pharmacies, known as “tiendas" in the LatinX community, that carry an abundance of medications that community members can use[21,22]. Prescription sharing systems support their community by breaking down the barriers that come from a lack of health insurance by circumventing the prohibitive costs of the doctor’s visit and/or the required medication. This system can also serve to protect individuals from reporting logistics, such as immigration status. While not recommended, these methods are all the results of an accessibility issue. Need for immediate relief of health issues outway the risk of future development of AMR.

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[18] Riley, W. J. (2012). Health Disparities: Gaps in Access, Quality and Affordability of Medical Care. *Transactions of the American Clinical and Climatological Association*, *123*, 167–174.

[19] *Understanding and Ameliorating Medical Mistrust Among Black Americans*. (2021, January 14). https://doi.org/10.26099/9grt-2b21

[20] Smirnoff, M., Wilets, I., Ragin, D. F., Adams, R., Holohan, J., Rhodes, R., Winkel, G., Ricc, E. M., Clesca, C., & Richardson, L. D. (2018). A Paradigm for Understanding Trust and Mistrust in Medical Research: The Community VOICES Study. *AJOB Empirical Bioethics*, *9*(1), 39–47. https://doi.org/10.1080/23294515.2018.1432718

[21] Sleath, B., Blalock, S. J., Bender, D., Murray, M., Cerna, A., & Cohen, M. G. (2009). Latinos’ sources of medication and medication information in the United States and their home countries. *Patient Education and Counseling*, *75*(2), 279–282. https://doi.org/10.1016/j.pec.2008.10.002

[22] Mainous, A. G., Diaz, V. A., & Carnemolla, M. (2008). Factors affecting Latino adults’ use of antibiotics for self-medication. *Journal of the American Board of Family Medicine: JABFM*, *21*(2), 128–134. https://doi.org/10.3122/jabfm.2008.02.070149

Low-income and minority communities do not have the same access to education about AMR, or many other diseases affecting their community, as compared to individuals from other backgrounds. Through the literature it has become clear that people often use three main sources for information about their health and medications. The sources are a physician, family members, and community members such as pharmacists. These main sources of information are very telling of the backgrounds that they are serving. If a physician is a person's main source of information, they are most likely to be from a higher socioeconomic, like in a wealthier neighborhood, usually urban or suburban, and have access to privatized healthcare. If a person's main source of information is their family, they are most likely to be from a medium to low-income background and have variable access to healthcare. Family sources of information could mean that the person has highly educated family members and/or physicians in their family. If community members are a person's main source of information, they are more likely from a lower socioeconomic status.

Method: Part 1B

Link to Survey

The survey was developed to gauge knowledge related to antibiotic usage and education was created using the survey platform Qualtrics. The survey is under IRB exemption due to the extensive anonymity of the survey structure and data collection. The survey (which is ongoing) consists of an overall total of 12 questions divided into three sections. The first section focuses on demographics, prompting users to answer questions regarding their age bracket, race, ethnicity and socioeconomic status. The second section is focused on antibiotic usage of both the user and people in their life. The third section is regarding education and awareness in regards to antibiotic resistance.

All information was collected anonymously and no identifying personal information was gathered using the survey. A secondary survey was created to collect email addresses of survey users wishing to be entered into the raffle for a $45 amazon electronic gift card. The email addresses are hidden from survey users and the Qualtrics platform utilizes an algorithm to randomly select from the emails submitted. When the survey is closed, the Qualtrics platform is set to select two winners who will each receive a $45 amazon gift card.

The survey was opened to anyone equal to or over the age of eighteen years old. The survey was mainly shared through the Haverford College community, which meant that the majority of the data was skewed toward the 18-22 age range. The questionnaire was opened March 9, 2023. The data analyzed in this thesis is preliminary, and the results are based on 173 numbers of respondents. The data will be reanalyzed using analogous methods when the survey closes. All data was analyzed using qualtrics. The data was broken into four groups, low-income, non-low-income, white, and non-white submissions.

Results (Part 1B):

Demographics:

First Generation college student refers to those whose parents did not complete a four-year college or university degree

Analysis was carried out with 179 survey responses. Of the total survey responses, 88% of responses were between the ages of 18-22 years old. Overall survey responses regarding demographics are as follows. Responses identifying as white was 50%, while the other 50% identified as non-white (**Fig. 5**). Of the total survey responses, 69.5% of responses identify as female, 23.2% identify as male, and 6.71% identify as non-binary. Of the total survey responses, 50.3% of submissions reported being on work-study and 49.7% reported not being on work study. Of the total survey responses, 56.5% reported identifying as first generation/low-income*, while the other 43.5% reported not identifying as first generation/low-income.

Specifically of the white identifying submissions, 29% reported being on work-study and 36% identify as first-generation/low-income. In comparison, of the non-white identifying responses, 71% reported being on work-study and 80% identified as first-generation/low-income.

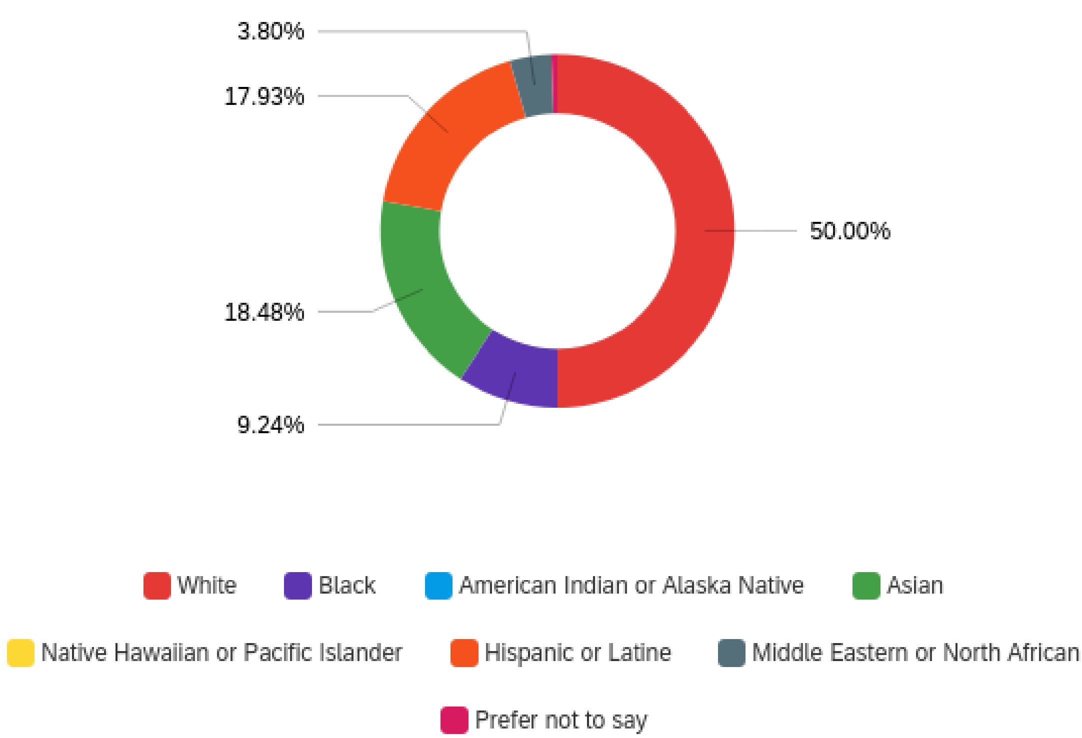


Figure 5. Figure developed through qualtrics software. This pie chart shows the percentage breakdown of race/ethnicity of the survey respondents.

Obtaining Antibiotics and Antibiotic Usage:

Overall, 88.2% of submissions have taken antibiotics and 89.7% reported having been prescribed antibiotics (**Fig. 6**). The sources for obtaining antibiotics included in the survey were physician, family, friends, internet and other. A notable disparity between white and non-white identifying submissions emerged with this survey question. Of white identifying submissions, 87% listed “physician” as their main resource for obtaining antibiotics. In comparison, 61% of non-white identifying submissions listed “physician” as their main resource for obtaining antibiotics. Moreover, 34% of non-white submissions listed “family/friends” as their second source of antibiotics, while only 10% of white submissions listed “family/friends” as their second source of antibiotics. This pattern is similarly seen when comparing low-income vs. non-low-income submissions (**Fig. 7**).

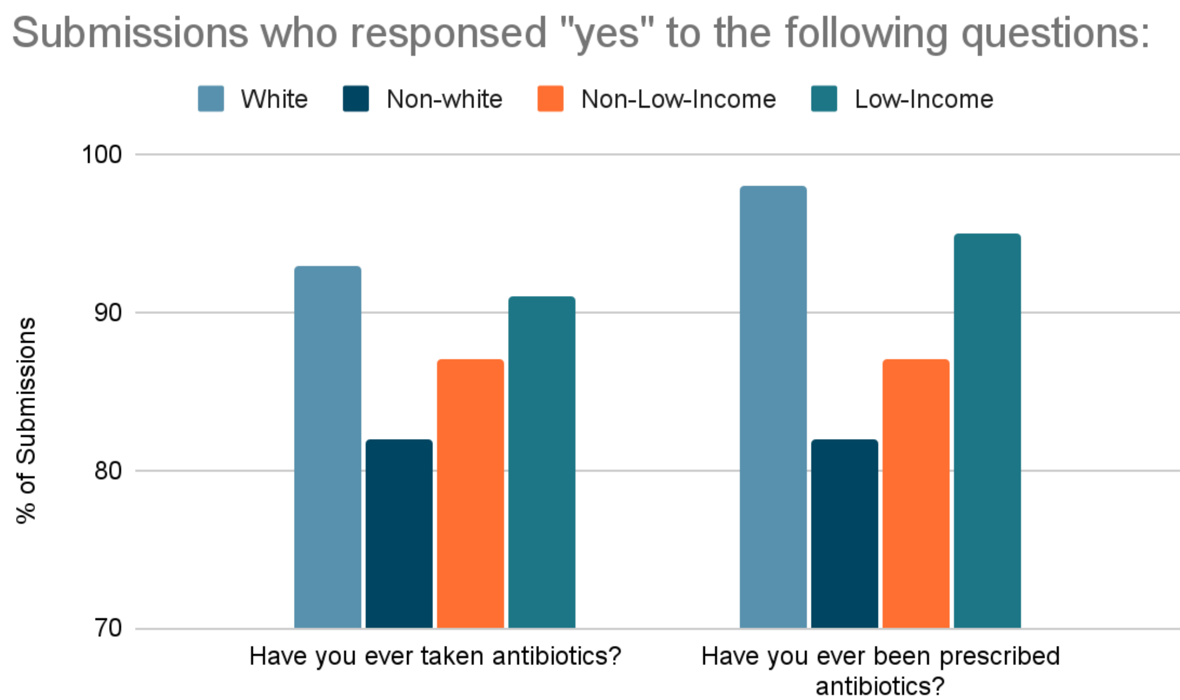

Submissions who responsed "yes" to the following questions:
White
Non-white
Non-Low-Income
Low-Income
100
90
80
70
% of Submissions
Have you ever taken antibiotics?
Have you ever been prescribed antibiotics?

Figure 6. This bar graph shows how different demographics responded "yes" to questions regarding antibiotic use and prescription antibiotic use. This figure was developed using Google Sheets.

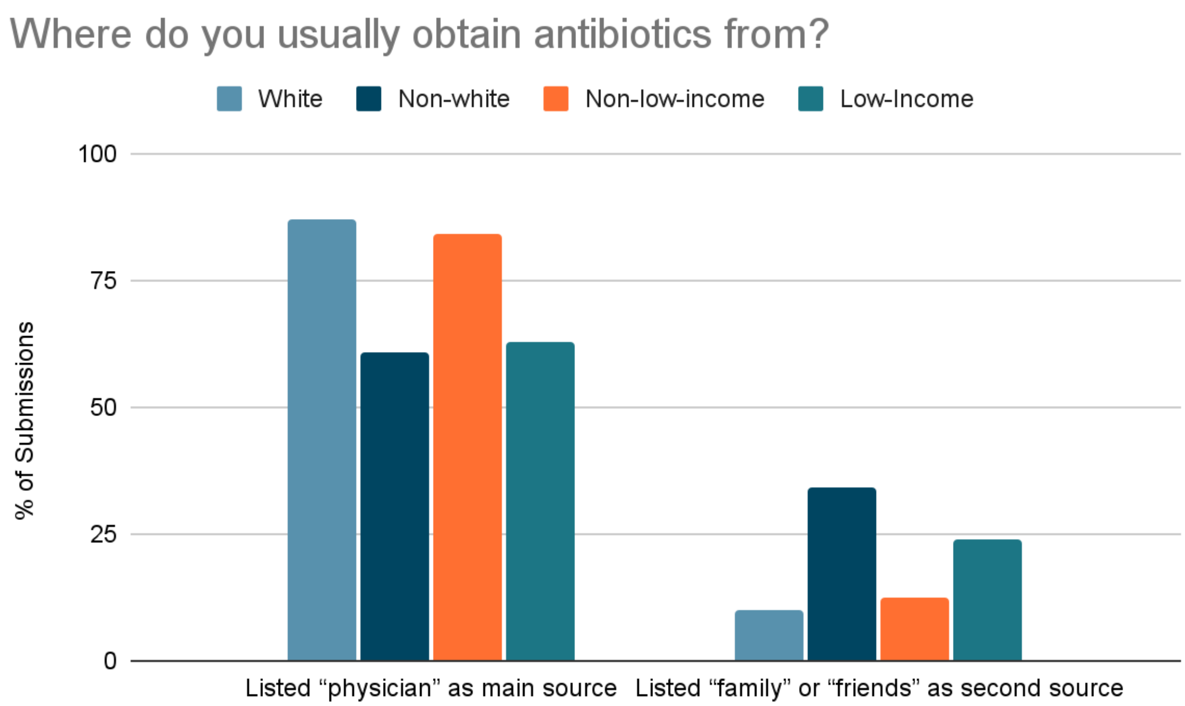


Figure 7. This bar graph shows where different demographics obtain antibiotics from. This figure was developed using Google Sheets.

When examining antibiotic usage, overall 40% of submissions reported having saved antibiotics for later usage and 21% of submissions reported sharing antibiotics with others. With regards to antibiotic sharing, 40% of white submissions reported saving antibiotics and 20% of white identifying submissions reported sharing antibiotics. When comparing white identifying submissions to non-white identifying submissions, a higher percentage of non-white identifying submissions reported saving antibiotics and a significantly higher number of non-white identifying submissions reported sharing antibiotics. Notably, 57% of non-white identifying submissions reported that they have saved antibiotics for later usage and 41% reported having shared antibiotics (**Fig. 8**).

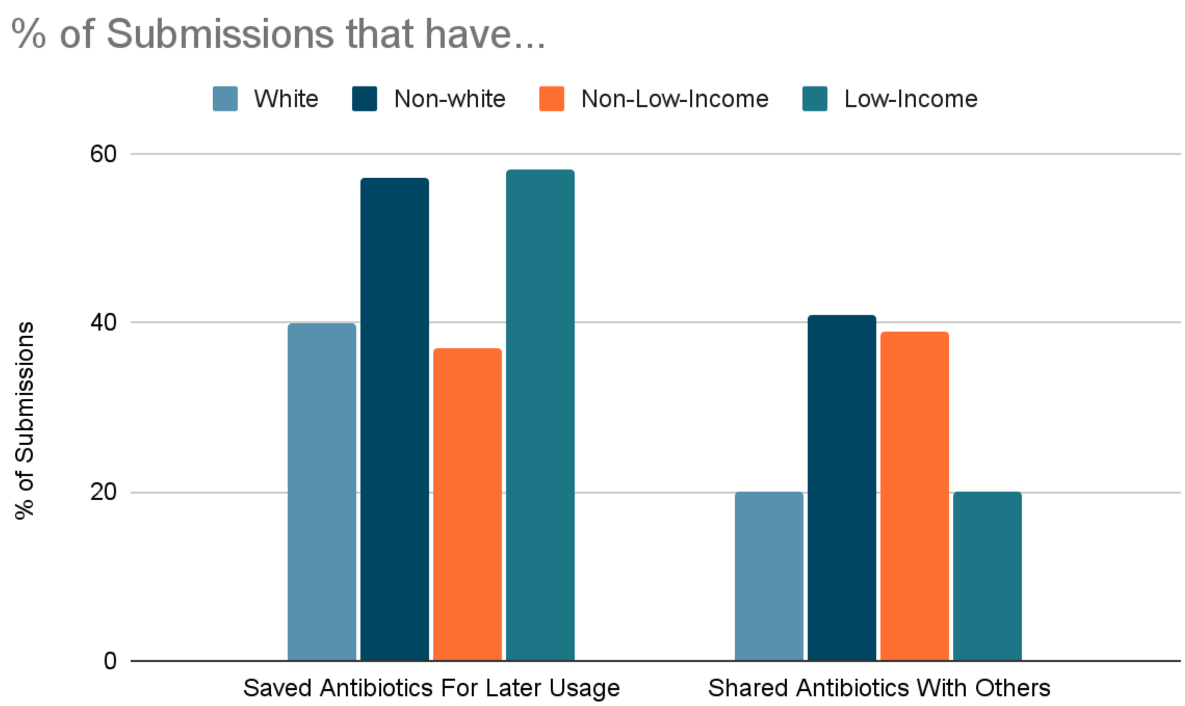


Figure 8. This bar graph shows how different demographics responded to questions regarding saving antibiotics and sharing antibiotics with others. This bar graph was developed using google sheets.

Family Antibiotic Usage:

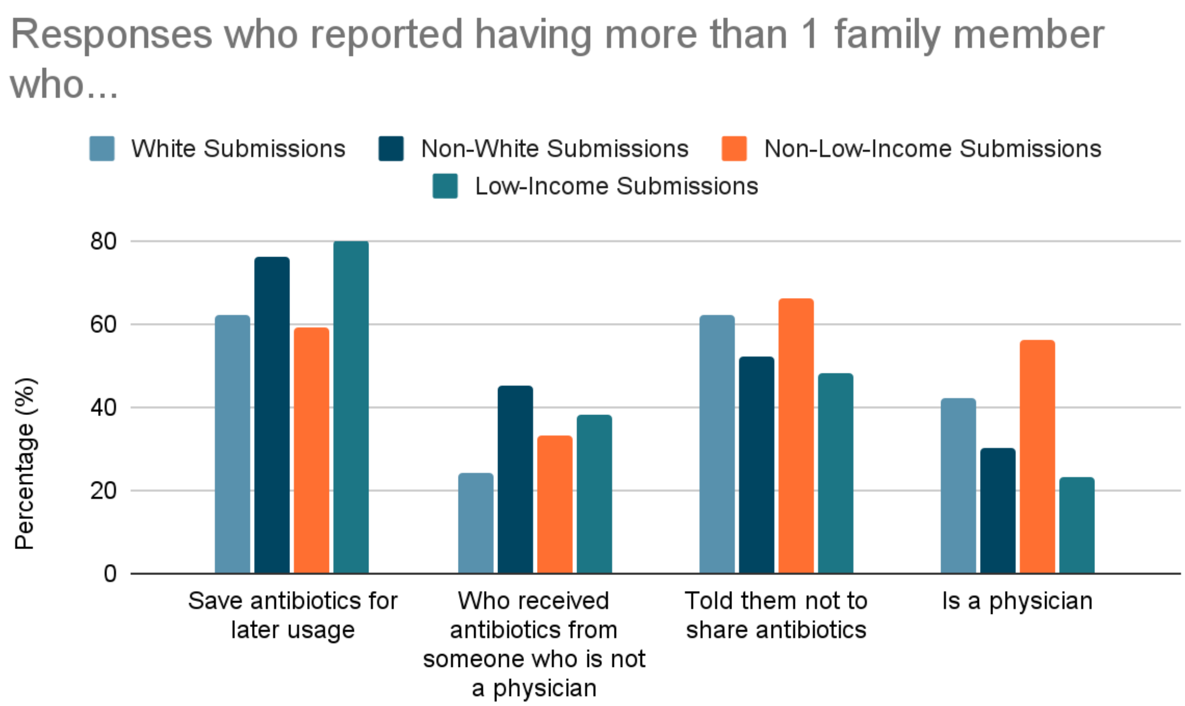


Figure 9. This bar graph shows how different demographics responded to questions about antibiotics usage, pertaining to saving antibiotics and sharing antibiotics with others. This bar graph was developed using Google Sheets.

When examining antibiotic usage within a family, across all income and race, there were alarming trends regarding saving antibiotics for later use; 62% of white identifying submissions reported having a family member who saved antibiotics for later usage, and similarly 59% of non-low-income submissions reported having a family member who saved antibiotics for later usage. These percentages were even higher for non-white identifying individuals and low-income individuals; 76% of non-white submissions and 80% of low-income submissions reported having at least 1 family member who saved antibiotics for later usage.

24% of white identifying submissions reported having at least 1 family member who has received antibiotics from someone who is not a physician. This was followed by 33% of non-low-income submissions, then 38% of low-income submissions. Non-white submissions had the highest percentage to report having at least 1 family member who has received antibiotics from someone who is not a physician, 45%.

Looking at how many submissions had at least 1 family member who advised them not to share antibiotics, non-low-income submissions had the highest percentage with 66%. This was followed by 62% of white submissions. Then non-white submissions reported 52% and low-income submissions had the lowest percentage, 48%.

Finally, when looking at how many submissions reported having at least 1 family member who is a physician, non-low-income submissions had the highest percentage with 56%. Then white submissions came next with 42%. Non-white submissions reported 30% and then low-income submissions reported 23%.

Knowledge about AMR:

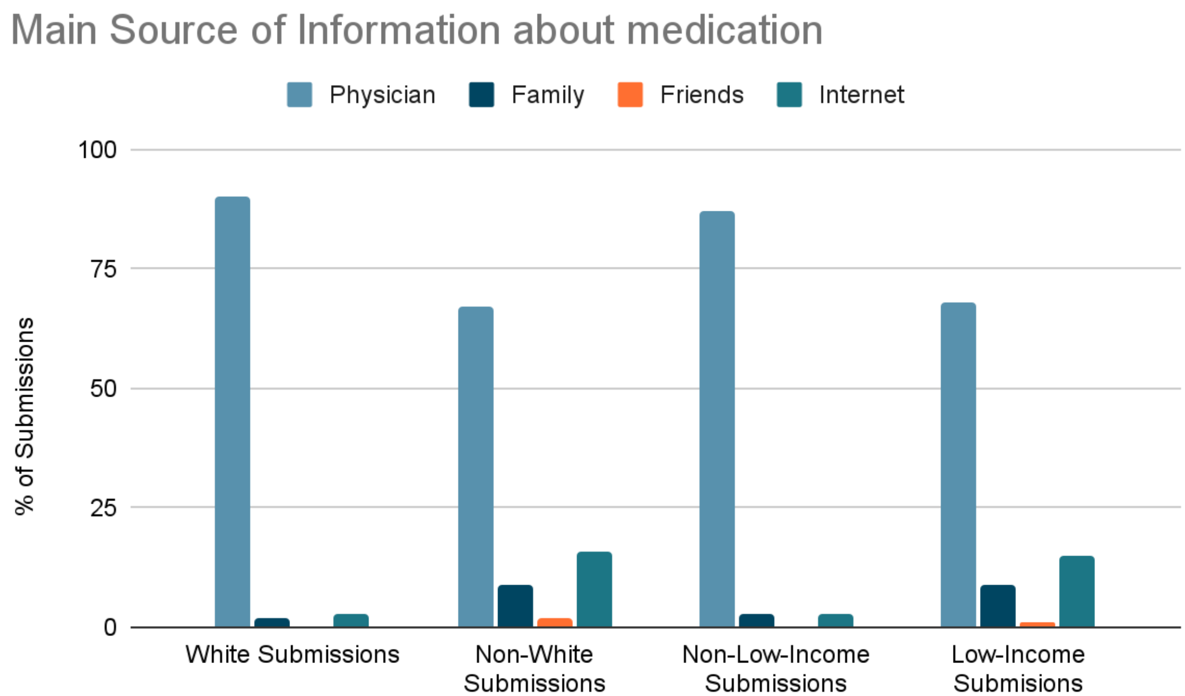


Figure 10. This bar graph shows who different demographics' main source of information about antibiotics are. This figure was developed using Google Sheets.

When examining knowledge about AMR, all demographics' main source of information was from their physician. The % breakdowns are: 90% white submissions, 87% non-low-income submissions, 68% low-income submissions, and 67% non-white submissions. Both non-white submission and low-income submissions had the highest diversity in responses of main sources of information.

Awareness and Concern in regards to AMR:

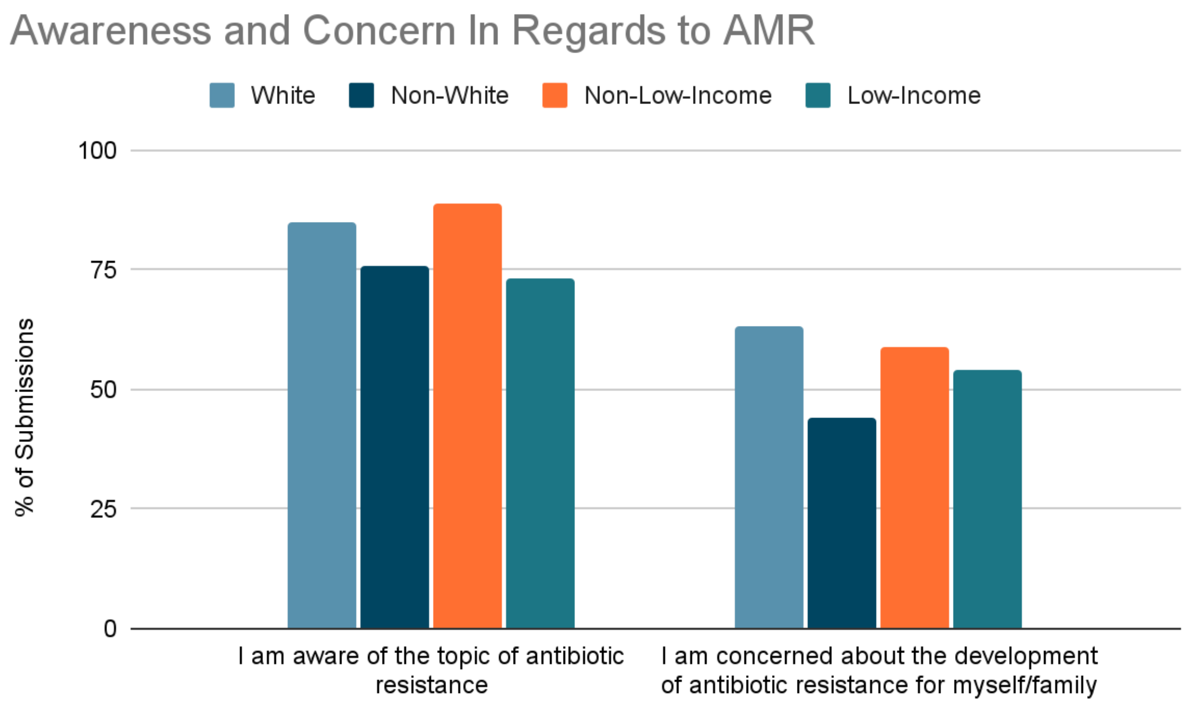


Figure 11. This graph shows how different demographics responded to questions regarding awareness and concern about AMR.

When examining awareness and concern around AMR, 89% of non-low-income submissions felt they were informed about the topic of antibiotic resistance. This was followed by a 85% rate of white submissions who agreed, then 76% of non-white submissions, and then 73% of low-income submissions having the lowest percentage. Moreover, 63% of white submissions responded that they were concerned about the development of antibiotic resistance for themselves/family. This number was followed by 59% of non-low-income submissions, 54% of low-income submissions and then 44% of non-white submissions.

Comfortability with Physician:

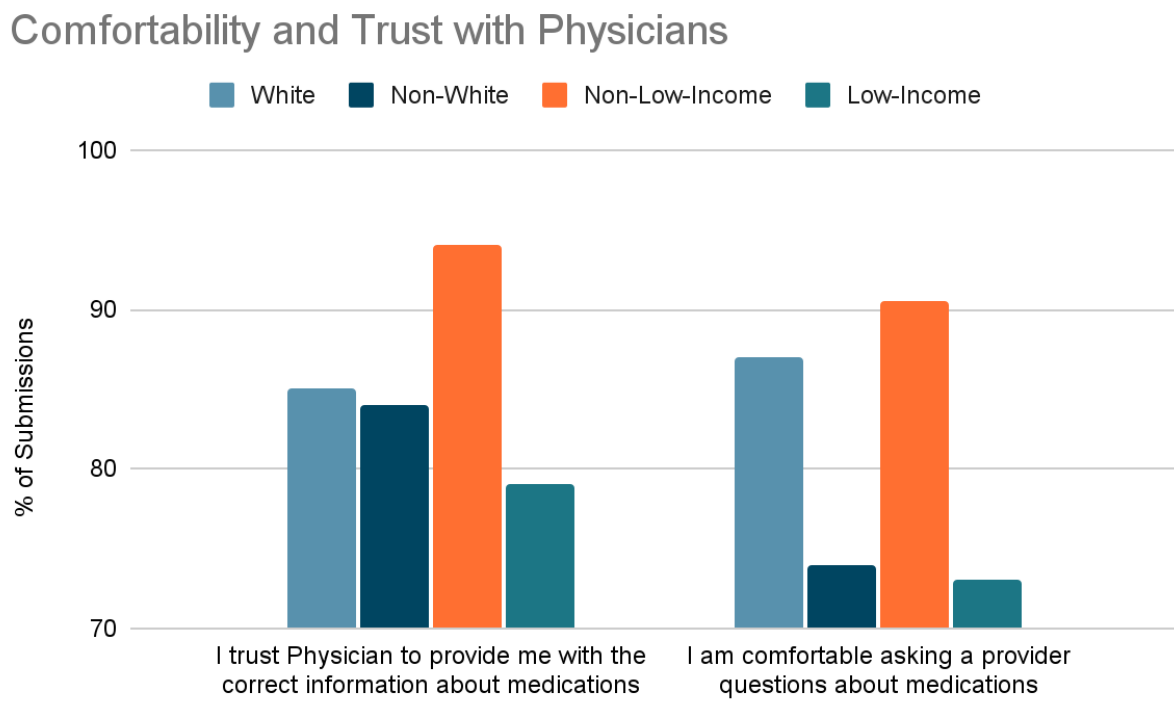


Figure 12. This figure shows how different demographics responded to questions about how comfortable they are and how much they trust their physicians.

When examining how demographics felt about their comfortability and trust with physicians, non-low-income submissions had the highest percentage of responses who said they trusted their physicians to provide them with the correct information about medications(94%). This was followed by 85% of white submission respondents, then 84% of non-white respondents, and low-income responses had the lowest percentage(79%). Looking at how comfortable respondents felt asking their physicians questions about medications, non-low-income identifying responses had the highest percentage with 91%. This was followed by white respondents with a percentage of 87. The next percentage was of non-white responses with 74%. Low-income responses then had the lowest percentage with 73%.

Discussion:

Demographics:

While the survey responses were evenly split between white and non-white submissions, it is important to note that the majority of submissions were white identifying people, with various ranges of non-white demographics being represented in the survey. I chose to do preliminary data collection to examine white vs. non-white submissions in order to understand how racial privilege impacts a person's access to adequate information about their health and the appropriate tools to help reduce their risk of developing AMR.

Moreover, when examining the demographics of the survey there is a stark divide between how many white identifying submissions are low-income and how many non-white submissions are low-income. In the study 50% of submissions were white-identifying and the other 50% were non-white identifying. Of the white-identifying submissions, 36% identified as first generation college students/low-income. Of the non-white identifying submissions, 80% identified as first generation college students/ low-income. It is also important to note that the majority of survey responses were from students at Haverford College, which is a predominantly white private institution(PWI). Of the current class years at Haverford College, 2023-2026, 68.2% of the student body identify as white, with the remaining percentages identifying as Black/African-American, Hispanic/LatinX, Asian, American Indian/Alaska Native, or Native Hawaiian/Pacific

Ilander[23]. While there is a correlation between race and socioeconomic disparities, this correlation is even more prevalent at a predominantly white institution(PWI).

Obtaining Antibiotics and Antibiotic Usage:

When examining who has taken and/or been prescribed antibiotics, white identifying submissions had a higher percentage of responses that had been prescribed antibiotics than those who reported having taken antibiotics. In the data, of white submissions, 93% reported taking antibiotics, but 98% have been prescribed. This suggests that this demographic has access to prescriptions and does not always take them. This could mean that the prescriptions are not always important to the immediate resolution of a person's health or they have access to other resources that they feel will improve their health. In comparison. Non-white identifying responses have the same percentage of those who have been prescribed antibiotics than those who have taken antibiotics. This percentage, however, is lower than that of white identifying submissions, which, I believe correlated to access to prescription medications.

When looking at where people obtain antibiotics, the top two responses were "physician" and "family/friends". Physician was the top first choice response for all demographics, but the ranges in percentage of those who selected physician as their top choice varied. Non-white and low-income identifying submissions had significantly lower percentages, 63% and 61%, than white and non-low-income submissions, 87% and 84%. If white and non-low-income submissions look to physicians at a higher rate than those from other identities, this correlates to their increased access to a physician. Having a

[23] *Demographic Data*. (n.d.). Retrieved April 29, 2023, from https://www.haverford.edu/institutional-diversity-equity-and-access/demographic-data

physician as a main source requires having access to a physician. Moreover, non-white and non-low-income responses had a higher percentage of responses who reported their family or friends as their second source of antibiotics, this speaks to the outsourcing of medications when access to prescription antibiotics is hindered. Additionally, non-white submissions had the highest percentage to use family or friends as a source. This speaks to the communal aspect of sharing antibiotics that was seen in the literature. Having established networks and resources like that of “tiendas” is the result of communities recognizing that the healthcare system is not supporting them and they must do that for themselves. This is further gleaned by the data of non-white responses having the highest percentage of responses who report having people in their life who have shared antibiotics. In contrast, low-income responses, which include white identifying people, had the highest percentage of submissions who reported having people in their life who save antibiotics for later usage. This speaks to the necessity of having access to prescription antibiotics, but also potentially not having alternative sources to receive them from.

Family Antibiotic Usage:

Looking at family antibiotic usage, non-white submissions(76%) had a higher percentage of family members saving antibiotics for later than white submissions(62%). Low-income submissions(80%) also reported having a higher percentage of family members saving antibiotics than non-low-income submissions(59%). There is a greater difference in percentages between low-income and non-low-income submissions, compared to white vs. non-white submissions. Low-income submissions also report having a higher percentage of family members saving antibiotics than non-white submissions, which suggest that saving antibiotics for later usage is correlated to the affordability of prescription antibiotics. Those from low-income backgrounds have less access to affordable healthcare, which impacts their access to physicians and thus prescription antibiotics. Due to the limited access to prescriptions, those from low-income backgrounds save antibiotics out of necessity.

Moreover, low-income families have also been proven to be the group least likely to have a physician in their family and least likely to have a family member that advises them on proper antibiotic usage. When looking at those whose family members have advised them not to share antibiotics, low-income submissions were the group with the lowest percentage of people who reported having at least one family member advise them not to share antibiotics(48%). The second lowest group was non-white submissions(52%), followed by white submissions(62%) and non-low-income submissions(66%). The results for those who reported having 1 or more family members who is a physician are similar, with non-low-income submissions having the highest percentage of people who have at least one physician in their family(56%), followed by white submissions(42%), then non-white submissions(30%), and low-income submissions(23%). These results are consistent with the fact that those with a higher income have more social mobility and access to professions, such as a physician. Being low-income hinders this social mobility and limits access to physicians, which also impacts access to information that can protect someone's health.

When looking at how many submissions family members receive antibiotics from someone who is not a physician, non-white submissions had the highest percentage of family members who have done this (45%). The next highest percentage are low-income submissions with a percentage of 38%, followed by non-low-income submissions(33%), and white submissions(24%). This suggests that there is a cultural component to the sharing of antibiotics. There is a communal component to the sharing of antibiotics that is correlated to different ethnic groups. For example, there are ethnic community pharmacies that provide community members access to non-prescription antibiotics. This theory is also supported by the fact that of the more privileges submissions(i.e. Non-low-income and white), the non-low-income, which contains answers from both white and non-white identifying people, has a higher percentage of those with family members who have received antibiotics from someone who is not a physician.

Moving over to those whose family members have advised them not to share antibiotics, low-income submissions were the group with the lowest percentage of people who reported having at least one family member advise them not to share antibiotics(48%). The second lowest group was non-white submissions(52%), followed by white submissions(62%) and non-low-income submissions(66%). The results for those who reported having 1 or more family members who is a physician are similar, with non-low-income submissions having the highest percentage of people who have at least one physician in their family(56%), followed by white submissions(42%), then non-white submissions(30%), and low-income submissions(23%).

Knowledge about AMR:

When examining where people are getting their information from about AMR, 90% of white submissions and 87% of non-low-income submissions reported their physician as their main source of information about antibiotic resistance. In comparison, 67% of non-white submissions and 68% of low-income submissions reported their physician as their main source of information about AMR. This result indicates that those from white and higher income backgrounds rely more heavily on their physician to provide them information about their health. Low-income and non-white identifying submissions used a wider range of resources as their main source of information. This range included pharmacists(7%), family(9%), and the internet(16%). These results suggest that low-income and non-white identifying groups have less trust in their physician or do not readily have access to a physician that can provide information. With the internet being the highest source of information outside of physicians, it is apparent that low-income and non-white submissions utilize this resource the most out of the different demographics. This speaks, again, to the issue of accessibility and what trusted sources people seek out when physicians are not available.

Awareness and Concern in regards to AMR:

Looking at awareness about AMR, non-low-income groups had the highest percentage of submissions(89%) that felt they had knowledge about the issue of antibiotic resistance. White identifying groups came second with (85%) confidence. Non-white submissions then reported (76%) and low-income submissions reported the lowest, with (73%). Moreover, when looking at the percentage of submissions that reported being concerned about the development of antibiotic resistance in themselves or family members, white submissions had the highest percentage with 63%. Non-white submissions were the next highest with 59%. The low-income responses resulted in 54% concerned submissions and non-white submissions reported 44% concern.

This data highlights that knowledge is a privilege. As seen in the data set related to knowledge about AMR, white and non-low-income identifying submissions have greater access to physicians, have more physicians in their immediate family circle, and are more informed about the issue of AMR. These are a few pieces that allow for these groups to be able to protect themselves from the spread of AMR because they have needed knowledge about the risk of AMR, as well as resources to mitigate those risks. These privileges are not imparted on those from low-income and non-white backgrounds. While low-income and non-white demographics reported being less concerned, results from previous data sections show that these groups have less access to resources that would inform them of the risk associated with AMR.

Comfortability with Physician:

Finally, when examining the trust between physician and patient, 94% of non-low-income submissions reported trusting their doctor to provide them with adequate medication for treatment and 90% of non-low-income submissions said they felt comfortable to ask their physician questions about medication that are prescribed to them. These high rates of comfortability correlate with the trend for higher income individuals to have access to better healthcare options, which could have a positive impact on how they perceive their relationship with their physician.

85% of white submissions reported trusting their doctor to provide them with adequate medication for treatment and 87% of non-low-income submissions said they felt comfortable to ask their physician questions about medication that are prescribed to them. This percentage is not far off from the non-white percentage which reported 85% of responses trusting physicians and 74% of responses feeling comfortable to ask their physician questions. While white and non-white submissions had the same percentage of those who trusted their physician to provide the right medication, there is a big difference in the percentage of non-white submissions to feel comfortable asking their physician questions compared to white submissions. It is important to note that medical doctors are majority white and this creates a racial power dynamic between patient and physician. Additionally, because of malpractice in science and medicine people of color often have less trust in science because of the harm they've done to communities of color. These are some of the reasons that would have resulted in people not feeling as comfortable as white patients when it comes to talking to their physician and asking questions.

Low-income submissions had the lowest percentage of those who trusted their physician to provide them with the right medication(79%) and felt comfortable to ask questions(73%). This correlates to low-income communities having limited access to healthcare and quality physicians, thus hindering confidence in physicians and feeling comfortable enough to ask questions. Overall, this study shows the impact race, ethnicity, and socioeconomic status have on antimicrobial resistance and antibiotic usage.

Conclusions:

When looking at the problem of antibiotic resistance, there is a need for more transparency around the topic, how resistance is transmitted, and how people can keep themselves safe. While this information is crucial for all people to protect themselves, social determinants relating to race and income disparities have kept people from marginalized backgrounds from being able to protect themselves in the same way as those from more privileged backgrounds. Low-income and non-white identifying groups have a higher chance of developing antibiotic resistance due to exposures not related to taking antibiotics, such as working at sites with higher rates of resistance transmissions. While switching jobs may not be as feasible for people, everyday protections such as information surrounding proper antibiotic usage and education on transmissions of resistance are sources of patient agency that are also being hindered.

With this already increased exposure to AMR, those from marginalized backgrounds then face systemic barriers that hinder their ability to treat illnesses, causing them to seek alternative resources to attempt to meet their healthcare needs. These alternative resources include outsource to non-physician locations and conserving medications to ensure they maintain their access to much needed prescriptions. Though done out of necessity, these behaviors can also further increase communities exposure and risk to the development of AMR.

As seen through the literature review and survey, AMR is a health crisis that disproportionately affects minority communities. The driving force of these disparities are fundamental breakdowns in the healthcare system of the United States and its inability to support the health of those from underserved backgrounds. Future plans for this project include researching how location and region fit into the disparities seen in the survey. Following research on location, next steps include translating the results to policy plans and how this research can be used to impact policy on both AMR and general healthcare advocacy.

Future Directions:

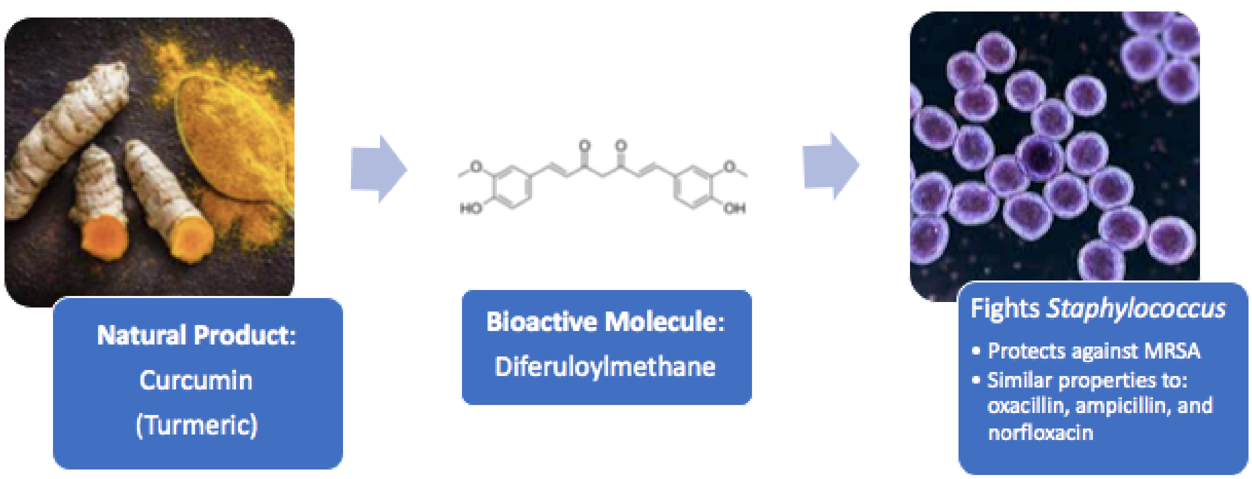
If this research is reproduced, in the future it is important to specify oral antibiotics. Moreover, it would be very impactful to send the survey to a broader range of people throughout Philadelphia to get a more diverse perspective, beyond that of the college student.

Part 2: Natural Product Synthesis

Figure Legend for Part 2:

Introduction:

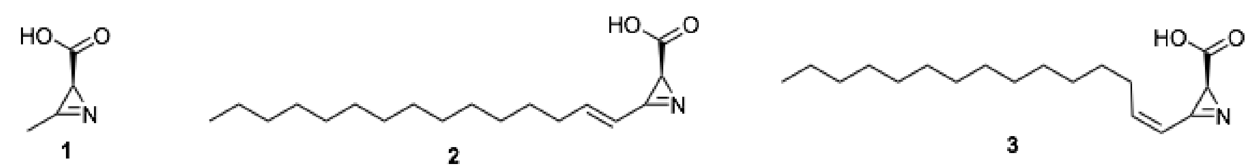
To combat antibiotic resistance, research regarding novel inhibitors and new drug targets is necessary to continue to provide patients with adequate treatment for their medical concerns. Pharmaceutical development of antibiotics has been difficult because there is a risk those medications will also be rendered ineffective with the ever growing pools of resistant bacteria[24]. For years, natural products have been a source of inspiration for therapeutic development. Natural products bioactive compounds are used to fight various diseases, including microbial diseases and infections. Curcumin, for example, is a natural product that has antimicrobial properties and can be used to fight against *Staphylococcus* related infections, such as MRSA(**Fig. 1**). While the best form of treatment would include a combinatorial approach, the urgency of much-needed medicine makes the engineering of strong natural product-based drugs a better time-sensitive solution.[25]



[24] *Why is it so hard to develop new antibiotics?* (2020, January 21). Wellcome. https://wellcome.org/news/why-is-it-so-hard-develop-new-antibiotics
[25] Rossiter, Fletcher, M. H., & Wuest, W. M. (2017). Natural Products as Platforms To Overcome Antibiotic Resistance. Chemical Reviews, 117(19), 12415–12474. https://doi.org/10.1021/acs.chemrev.7b00283

Figure 13. This figure shows the bioactive ingredient in the natural product curcumin(turmeric) which has antimicrobial properties and can be used as a template for antimicrobial drugs similar to the ones listed[26].

Naturally occurring *2H*-azirine products contain the smallest of unsaturated nitrogen heterocycles.[27] This category of natural products **(Fig. 14)** has demonstrated to have potent antimicrobial properties, this includes inhibiting growth of resistant strains of *Candida albicans* and *Saccharomyces cereVisiae* as measured by standard broth microdilution assays[28]. The mechanism of inhibition has not yet been elucidated, but its inhibition is suspected to arise from the combination of the chemically reactive *2H*-azirine moiety with a sphingolipid structure that contributes to the antifungal properties.[29][30] Azirinomycin is the smallest of the 2*H*-azirine containing natural products, and also demonstrates similar antibiotic properties.



[26] Stan, D., Enciu, A.-M., Mateescu, A. L., Ion, A. C., Brezeanu, A. C., Stan, D., & Tanase, C. (2021). Natural Compounds With Antimicrobial and Antiviral Effect and Nanocarriers Used for Their Transportation. *Frontiers in Pharmacology*, *12*, 723233. https://doi.org/10.3389/fphar.2021.723233

[27] Kadam, V. D., & Sudhakar, G. (2015). Total synthesis of motualevic acids A–F, (e) and (z)-antazirines. *Tetrahedron, 71*(7), 1058-1067. doi:10.1016/j.tet.2014.12.092

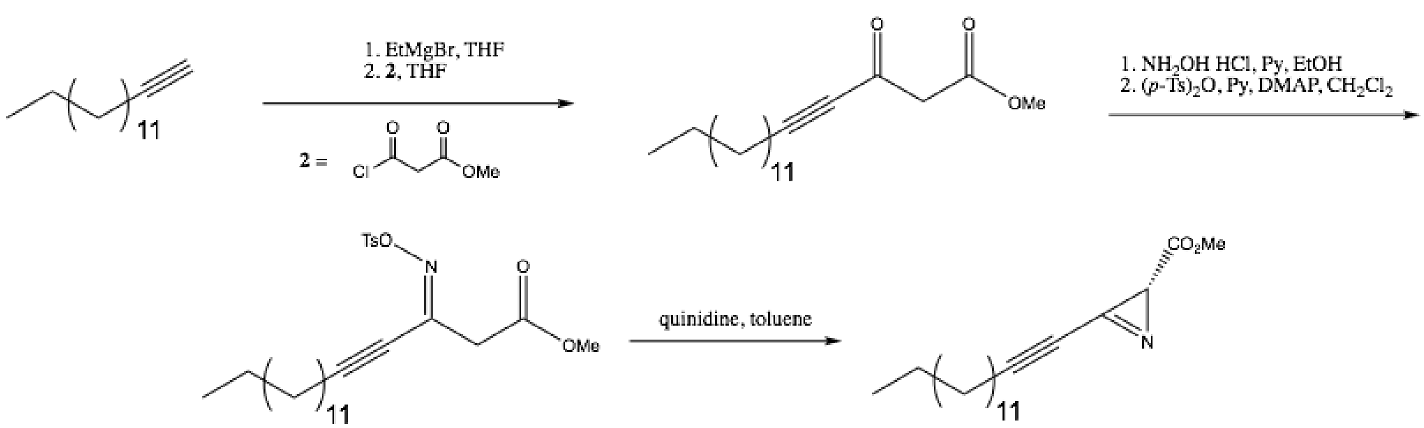
[28] Sakharov, P. A., Novikov, M. S., & Rostovskii, N. V. (2021). 2H-Azirines in medicinal chemistry. *Chemistry of Heterocyclic Compounds*, *57*(5), 512–521. https://doi.org/10.1007/s10593-021-02934-2

[29] Sudhakar, G., Kadam, V. D., & Reddy, V. V. (2010). Total synthesis of motualevic acids A–E. *Tetrahedron Letters, 51*(7), 1124-1125. doi:10.1016/j.tetlet.2009.12.113

[30] Cheruku, P., Keffer, J. L., Dogo-Isonagie, C., & Bewley, C. A. (2010). Motualevic acids and analogs: Synthesis and antimicrobial structure–activity relationships. *Bioorganic & Medicinal Chemistry Letters, 20*(14), 4108-4111. doi:10.1016/j.bmcl.2010.05.073

Figure 14. This figure shows 3 examples of the family of *2H*-azirine containing natural products that exhibit antifungal properties. Other members of this natural product family include geometric isomers, and terminal vinyl halogenation.

(R)-Dysidazirine is another *2H*-azirine-containing natural product found in the marine sponge *Dysidea Fragilis* in 1988[31]. The molecule contains a *2H*-azirine ring with a carboxylic acid and a long carbon chain. (R)-Dysidazirine, like other natural products comprising of a *2H*-azirine heterocycle, has exhibited antifungal properties against varying drug-resistant strains of *Candida albicans* and *Saccharomyces cereVisiae*[32]. It is cytotoxic to L1212 cells and inhibits the growth of gram-negative bacteria, as well as yeast. (R)-Dysidazirine was first synthesized in 1995, where (E) and (Z) enantiomers were isolated. The E configuration is the target structure for synthesis. In order to further study the antifungal properties of (R)-Dysidazirine, I am working towards synthesizing this natural product. In addition, I am investigating the use of azirinomycin, which will further inform the synthesis and applicability of (R)-Dysidazirine.

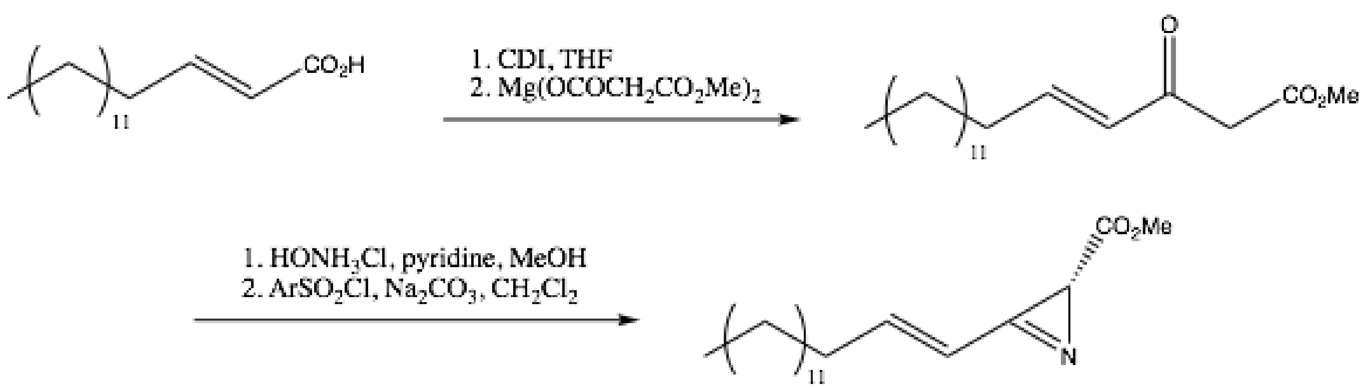


[31] (r)-dysidazirine. (2022, May 9). Retrieved December 17, 2022, from https://www.acs.org/molecule-of-the-week/archive/d/r-dysidazirine.html
[32] Skepper, C. K., Dalisay, D. S., & Molinski, T. F. (2008). Synthesis and antifungal activity of (−)-(*z*)-dysidazirine. *Organic Letters, 10*(22), 5269-5271. doi:10.1021/ol802065d

Scheme 1. The published route to produce (R)-Dysidazirine[33].

To synthesize (R)-Dysidazirine, there is a published four step synthesis that begins with a Grignard coupling between a terminal alkyne and a methyl malonyl chloride, followed by formation of an oxime (**Scheme 1**). Subsequent treatment with a base, in this case quinidine, will drive the Neber rearrangement to form the 2*H*-azirine.

An alternative route has also been published (**Scheme 2**). The synthesis commences with activation of the carboxylic acid with carbonyl diimidazole (CDI) for nucleophilic attack with an organomagnesium reagent. The following step involves forming the oxime with hydroxylamine hydrochloride. The reaction then proceeds with a base promoted (Na_2CO_3) Neber rearrangement to form the *2H*-azirine.



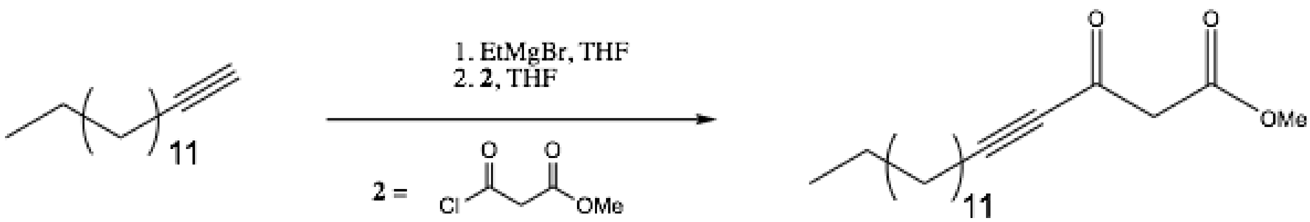
Scheme 2. This shows an alternative published route for the synthesis of (R)-Dysidazirine.[34] The 5% mol catalyst was used for stereoselective control over the Neber rearrangement, and will not be utilized in this thesis.

Scheme 1 was the first plan to make the target compound, and **Scheme 2** was intended to be an alternative plan if the synthesis in **Scheme 1** was unsuccessful.

[33] Skepper, C. K., Dalisay, D. S., & Molinski, T. F. (2008). Synthesis and Antifungal Activity of (−)-(Z)-Dysidazirine. *Organic Letters*, *10*(22), 5269–5271. https://doi.org/10.1021/ol802065d
[34] Sakamoto, Inokuma, T., & Takemoto, Y. (2011). Organocatalytic Asymmetric Neber Reaction for the Synthesis of 2H-Azirine Carboxylic Esters. Organic Letters, 13(24), 6374–6377. https://doi.org/10.1021/ol2026747

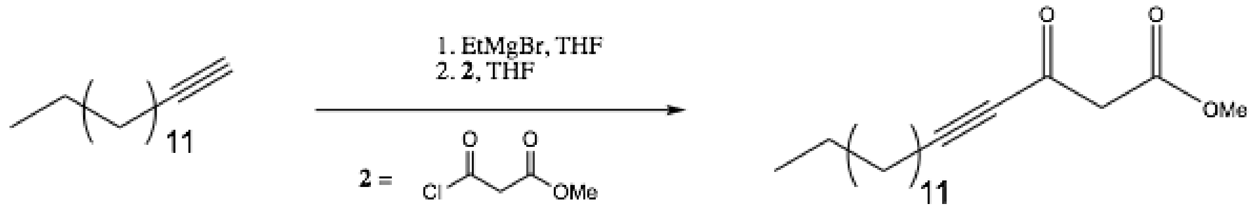
Methods:

Synthesis of *Methyl 3-oxooctadec-4-ynoate*:



EtMgBr (0.1600 g, 0.0012 mol) was added to a solution of *1-pentadecyne* (0.2500 g, 0.0012 mol) in THF (3.509 mL) at 0 ℃ in a 25.00 ml r.b.. The solution was warmed to RT and stirred for 2.50 hours. *Methyl malonyl chloride* (0.1230 g, 0.0090 mol) in THF (0.5000 mL) was added dropwise to the solution. The mixture was stirred for 1 hr at 0°C. The reaction was quenched with sat. NH_4Cl (10.00 mL) and H_2O (10.00 mL). The product was extracted with hexanes and washed with brine. The organics were dried with Na_2SO_4 and concentrated under reduced pressure. The NMR spectrum of the isolated compound showed only starting material and no product (**Fig**. 16). TLC was not performed. The hydrophobicity of the long alkyl chain present in both the starting material and the product would not be able to be separated by standard silica TLC plates.

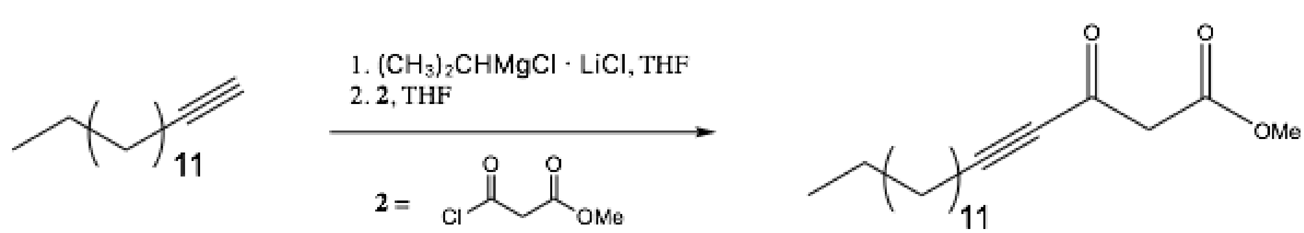
Synthesis of *Methyl 3-oxooctadec-4-ynoate* with fresh Grignard:



Magnesium metal (0.1800 g) and 1 crystal of iodine were added to THF (3.000 mL) in a 25.00 mL 3-neck flask under an inert atmosphere. *Ethyl bromide* (0.4500 mL) was added dropwise to maintain reflux. The reaction was stirred for 20 min to produce EtMgBr.

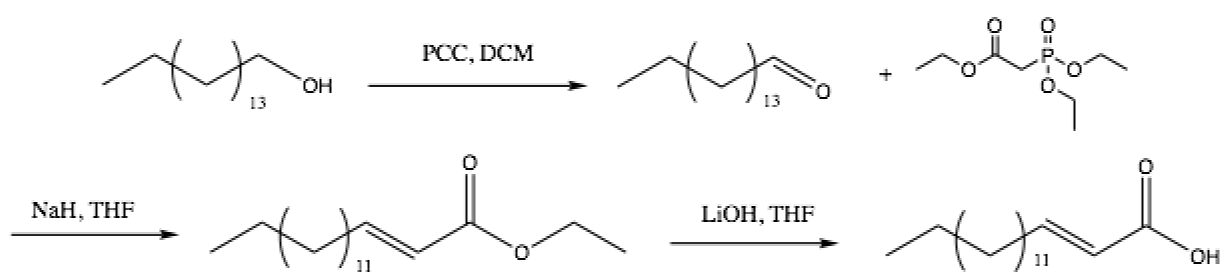
EtMgBr (0.1580 mL, 0.0012 mol) was added to a solution of *1-pentadecyne* (0.2500 g, 0.0012 mol) in THF (3.500 mL) at 0℃ in a 25.00 ml r.b.. The solution was warmed to RT and stirred for 2.5 h. *Methyl malonyl chloride* (0.1230 g, 0.0009 mol) in THF (0.5000 mL) was added dropwise to the solution. The mixture was stirred for 1 hr at 0 °C. The reaction was quenched with sat. NH_4Cl (10.00 mL) and H_2O (10.00 mL). The product was extracted with hexanes and washed with brine. The organic layers were combined and dried with Na_2SO_4. Solvent was removed under reduced pressure. The NMR spectrum showed only starting material, with no indication of product. TLC was not performed (**Fig.** 17). The hydrophobicity of the long alkyl chain present in both the starting material and the product would not be able to be separated by standard silica TLC plates.

Synthesis of *Methyl 3-oxooctadec-4-ynoate* with Turbo Grignard:



Isopropyl magnesium chloride lithium chloride complex, also known as Turbo Grignard (0.9230 mL, 0.0012 mol) was added to a solution of *1-pentadecyne* (0.2500 g, 0.0012 mol) in THF (3.500 mL) at 0 °C in a 25.00 ml r.b.. The solution was warmed to RT and stirred for 2.5 h. The mixture was then cooled to 0 °C and *methyl malonyl chloride* (0.1230 g, 0.0009 mol) in THF (0.5000 mL) was added dropwise to the solution. The mixture was stirred for 1 h. The reaction was quenched with sat. NH_4Cl (10.00 mL) and H_2O (10.00 mL). The product was extracted with hexanes and washed with brine. The organic layers were combined and dried with Na_2SO_4. The solvent was removed under reduced pressure. The NMR spectrum of the crude material showed no conversion of starting material to product (**Fig.** 18). TLC was not performed. The hydrophobicity of the long alkyl chain present in both the starting material and the product would not be able to be separated by standard silica TLC plates.

*NOTE: The starting material of **Scheme 2** was synthesized using the following mechanism:

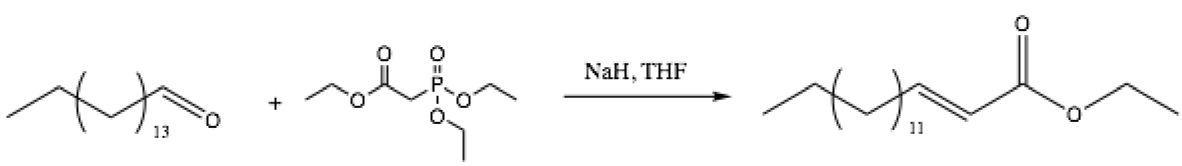


Synthesis of *Tetradecanal*:

Added *1-tetradecanol* (1.0200 g, 0.0047mol) to a stirred suspension of *pyridinium chlorochromate* (1.414 g, 0.0071 mol) in dichloromethane (8.750 mL) in a 25.00 mL r.b.. The reaction was stirred for 4 h at RT. Diethyl ether (10.00 mL) was added to the reaction mixture and stirred. The contents were filtered through silica gel (a silica plug) and concentrated. TLC was conducted to test for the presence of the product. TLC conditions: 1:1 Diethyl Ether: Hexanes, test under UV and stained using $KMnO_4$. The product was purified with flash chromatography with a 50% ether/hexane gradient hold. Product was formed as a colorless oil. NMR results analyzed in **Fig.** 19. H^1 NMR(400 MHz, $CDCl_3$) δ 9.76 (t, 1H), 2.42(td, 2H), 1.62 (m, 2H), 1.26 (m, 24H*), 0.88 (t, 6H*). Yield of isolated product: 0.7265 g, 72.65%.

*The multiplet and tripled at 1.26 and 0.88 ppm are supposed to integrate from 12H and 3H. However, these regions are over saturated with solvent, causing the inaccuracy in proton integration.

Synthesis of *Ethyl-hexadec-2E-enoate*:

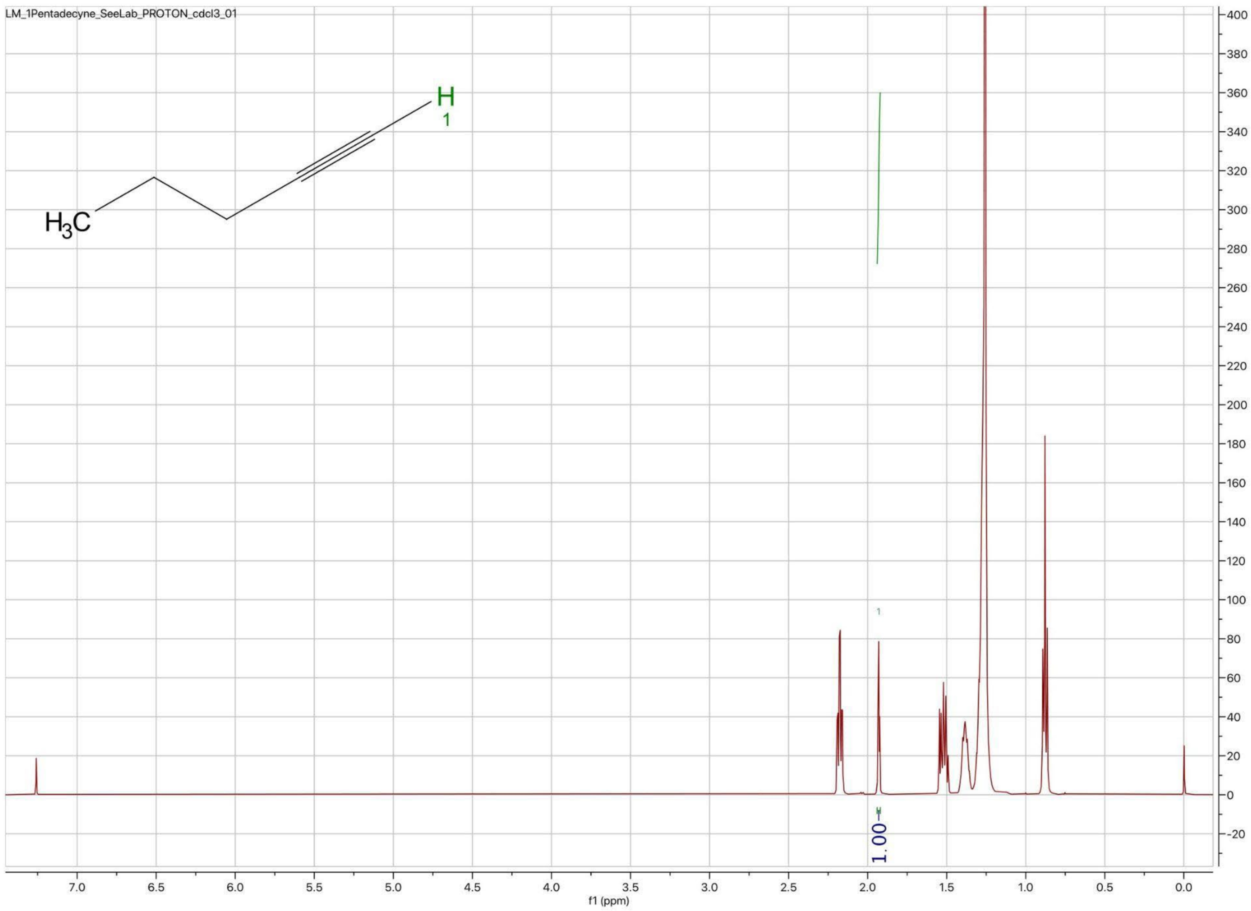


In a 25.00 mL r.b. triethyl phosphonoacetate (1.660 mL, 2.354 mmol) was added dropwise to a suspension of NaH (0.0689 g, 2.872 mmol) in anhydrous THF (3.000 mL) cooled to 0 ℃. The reaction was stirred for 30 minutes holding at 0 ℃. After 30 minutes, tetradecanal (0.5000 g, 2.354 mmol) was added to the mixture and stirred vigorously. The mixture was allowed to rise to RT, then poured into a mixture of brine (2.500 mL) and diethyl ether (5.000 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated under reduced pressure. TLC was conducted to test for the presence of the product. TLC conditions: 1:1 Diethyl Ether: Hexanes, test under UV and stained using $KMnO_4$. The resultant material was purified via flash column chromatography with a 50% ether/hexane isocratic hold. Product was formed as a pale yellow oil. NMR results analyzed in **Fig. 20**. H^1 NMR(400 MHz, $CDCl_3$) δ 6.97 (dt, 1H), 5.79 (dt, 1H), 4.12 (q, 2H). Alkyl chain and methyl groups were unidentifiable because of the presence of hexanes. Yield: 0.2345 g, 46.90%

Synthesis of *E-hexadec-2-enoic acid*:

LiOH (aq) (0.9400 mL, 0.9905 mmol) was added to a solution of ethyl-hexadec-2E-enoate (0.2345 g, 0.8302 mmol) in THF (1.550 mL) and MeOH (0.8200 mL) at RT. The reaction was stirred overnight. The organic solvents were removed with reduced pressure and the resultant aqueous mixture was poured into EtOAc. The mixture was acidified with 5% HCl (aq) to a pH of 3. The resultant solution was extracted with EtOAc and washed with water and brine. TLC was conducted to test for the presence of the product. TLC conditions: 1:0.5 Diethyl Ether: Hexanes, test under UV and stained using $KMnO_4$. The organic layers were combined and were dried with $MgSO_4$ and then concentrated under reduced pressure. The product was then purified by recrystallization from hexane. Product formed as a white solid. NMR results analyzed in **Fig.** 21. H^1 NMR(400 MHz, $CDCl_3$) δ 7.06 (dt, 1H), 5.82 (d, 1H), 2.21 (q, 2H). Alkyl chain and methyl groups were unidentifiable because of the presence of hexanes. IR: 3400(m), 3000(m) cm^{-1} (**Fig.** 22). Yield: 0.1935 g., 82.52%

Results:



LM_1Pentadecyne_SeeLab_PROTON_cdcl3_01
H
1
H3C
1
1.00
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2.0
1.5
1.0
0.5
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f1 (ppm)
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20

Figure 15. This figure shows the NMR of the starting material used in the attempted synthesis of *Methyl 3-oxooctadec-4-ynoate*. H_1 labeled in the NMR at 1.9 ppm shows the proton that is expected to be removed in the first step of the synthesis.

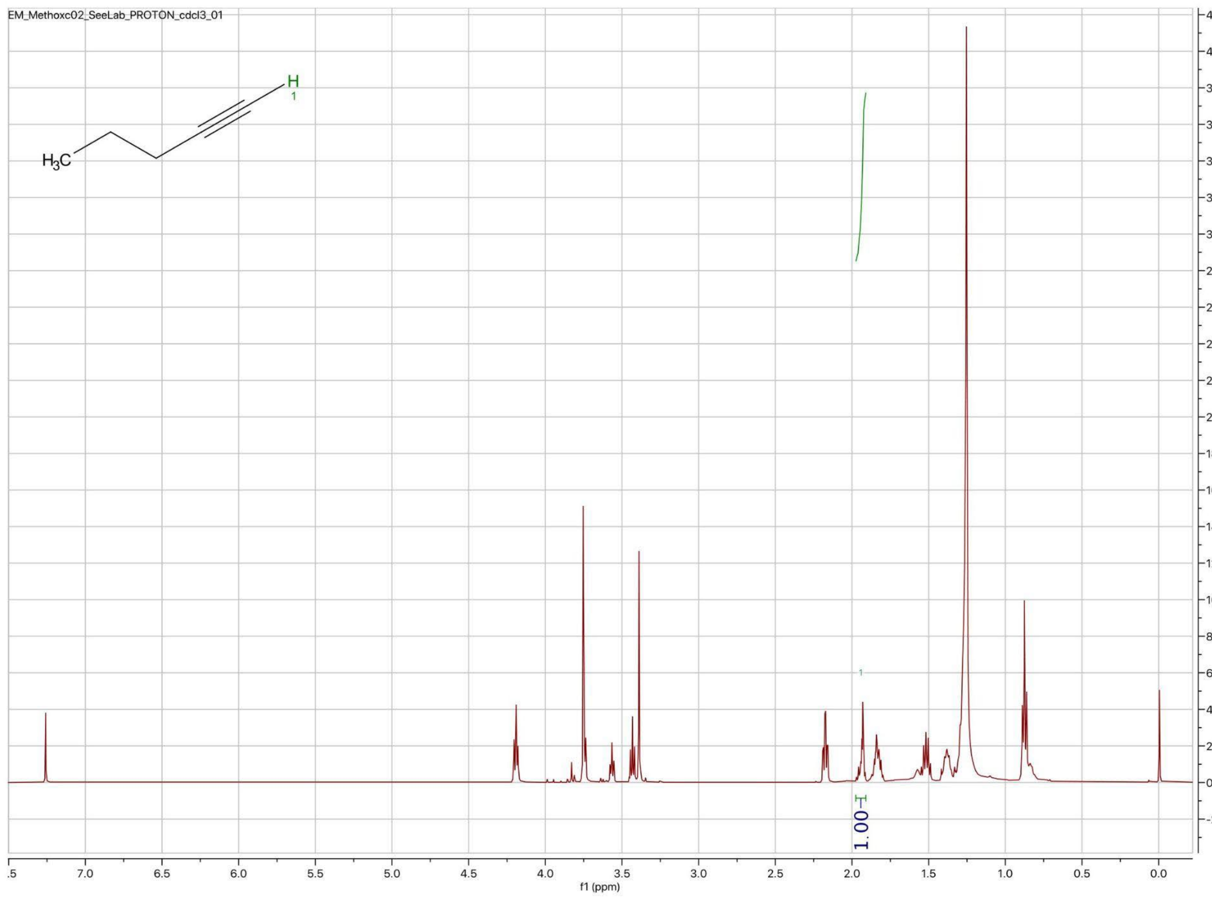
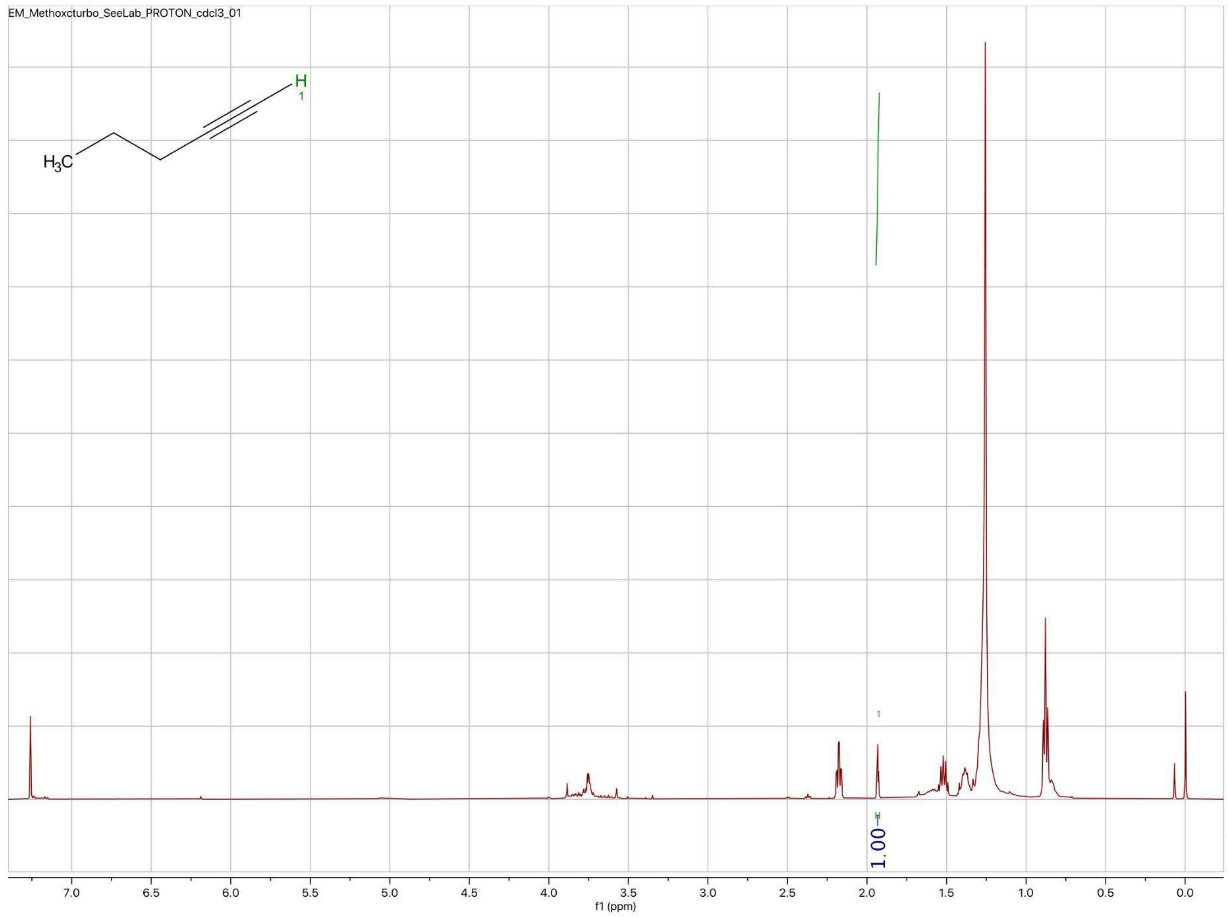


Figure 16. NMR of synthesis of *Methyl 3-oxooctadec-4-ynoate*. The NMR shows the presence of H_1 at 1.93 ppm, indicating that the carbon-carbon bond, and therefore *Methyl 3-oxooctadec-4-ynoate*, was not made.



EM_Methoxcturbo_SeeLab_PROTON_cdcl3_01
H
1
H_3C
1
1.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
500
450
400
350
300
250
200
150
100
50
0

Figure 17. NMR of *Methyl 3-oxooctadec-4-ynoate* made with Turbo Grignard. The NMR shows the presence of H_1 at 1.93 ppm, indicating that the carbon-carbon bond, and therefore *Methyl 3-oxooctadec-4-ynoate* was not made.

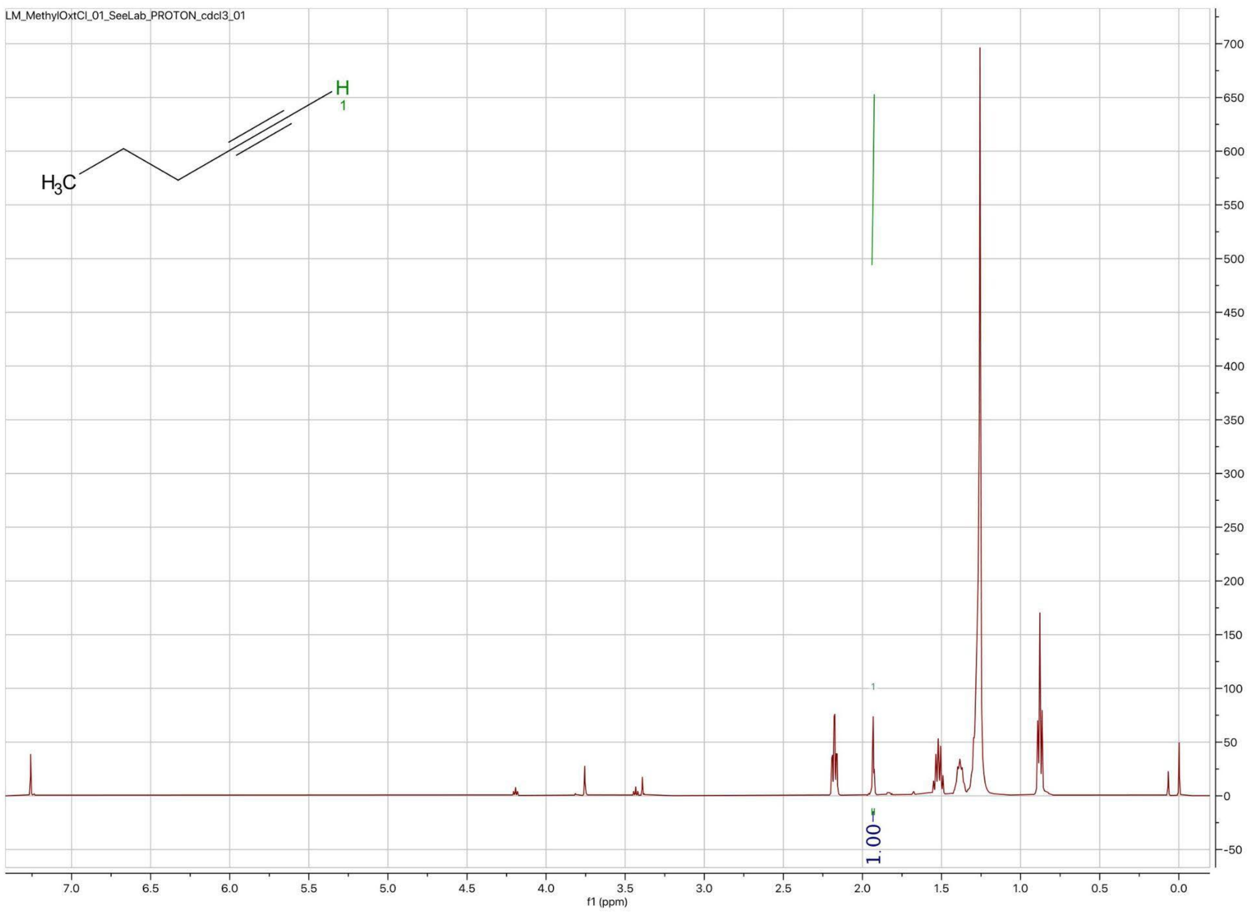


Figure 18. NMR of *Methyl 3-oxooctadec-4-ynoate* with Fresh Grignard. The NMR shows the presence of H_1 at 1.93 ppm, indicating that the carbon-carbon bond was not made.

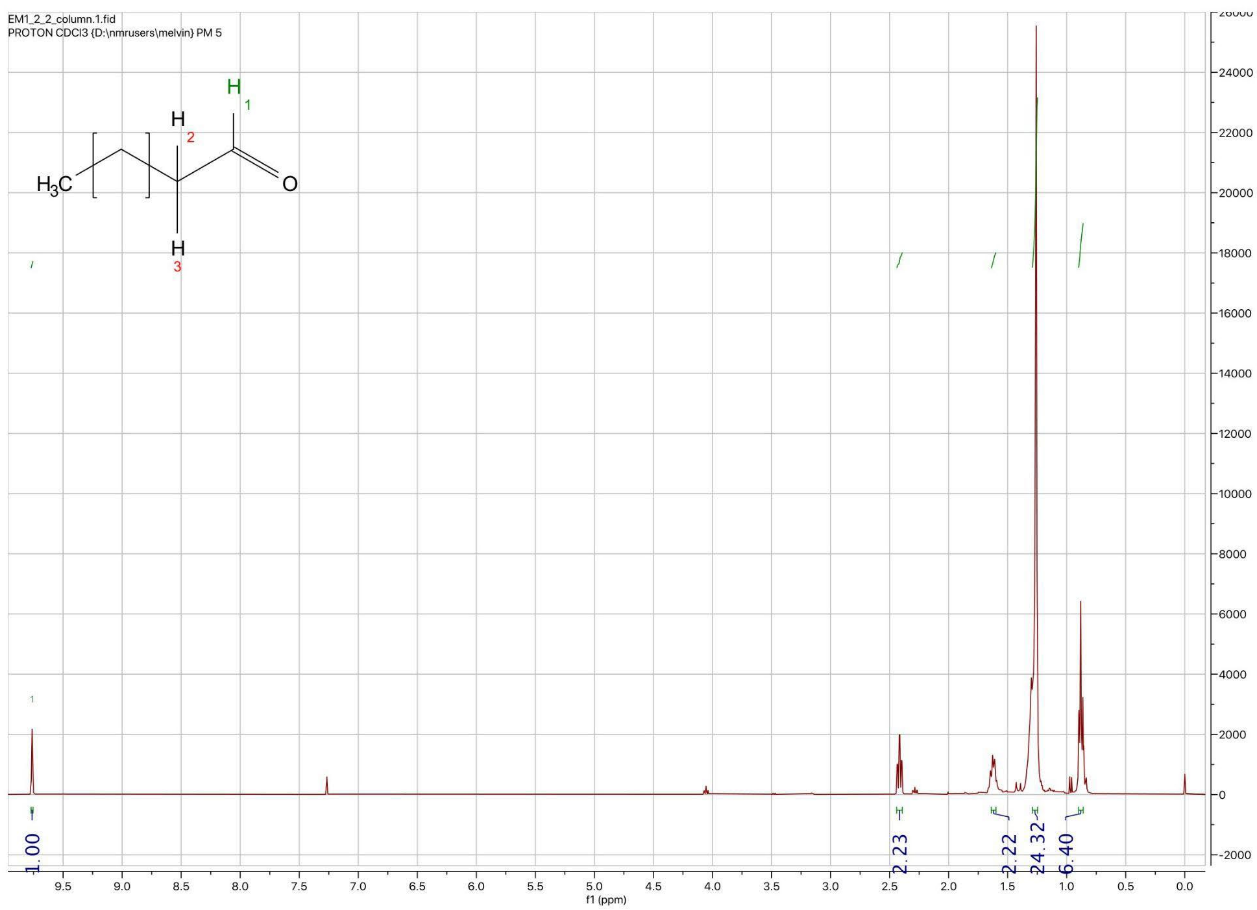


Figure 19. NMR of *Tetradecanal*. The triplet at 9.76 ppm indicated the presence of the aldehyde, which shows that *Tetradecanal* was synthesized.

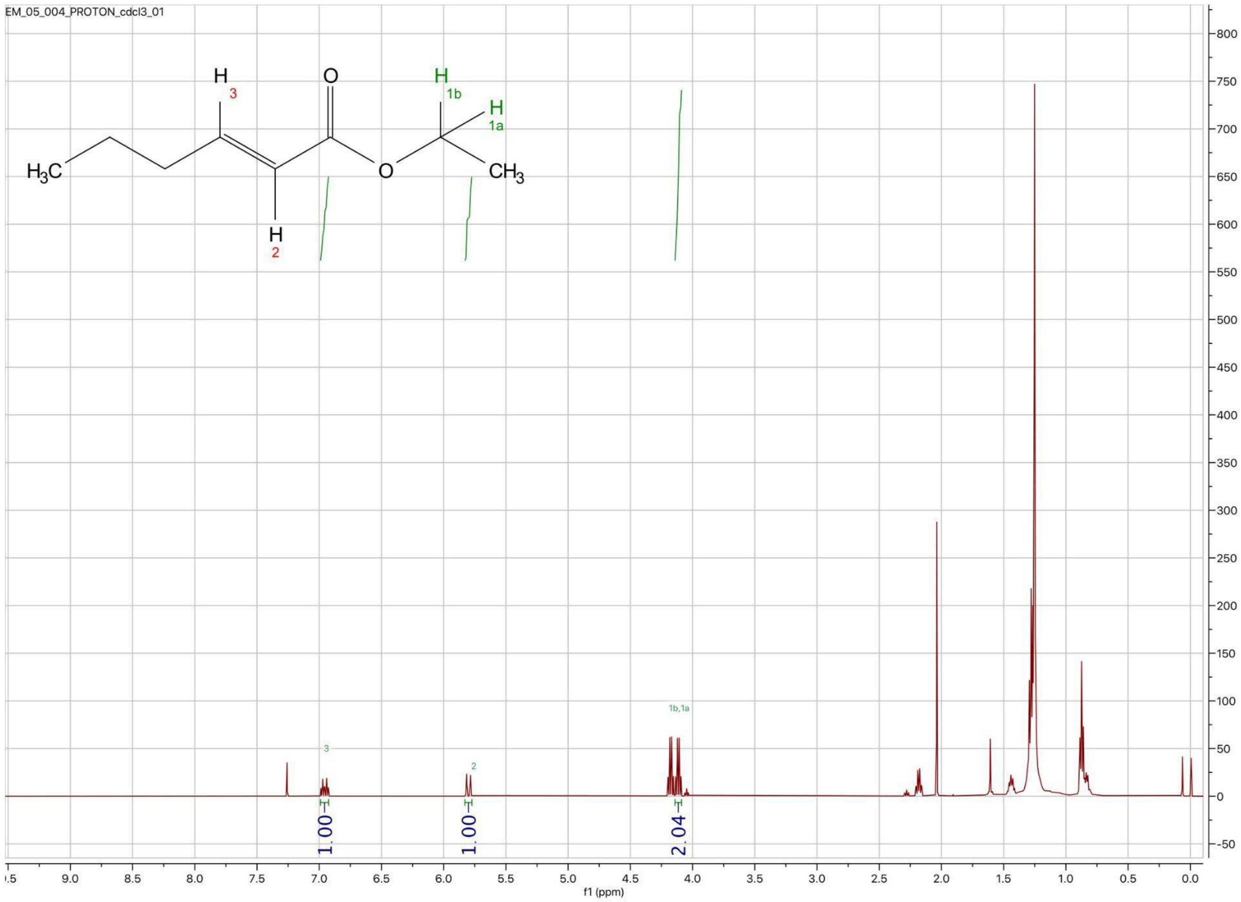


Figure 20. NMR of *Ethyl-hexadec-2E-enoat*e. The loss of the aldehyde peak at 9 ppm indicated starting material consumption. Additionally, the other peaks at 6.98 ppm, 5.79 ppm, 4.11 ppm show the creation of the ester, which is an indicator of the synthesis of *Ethyl-hexadec-2E-enoate*.

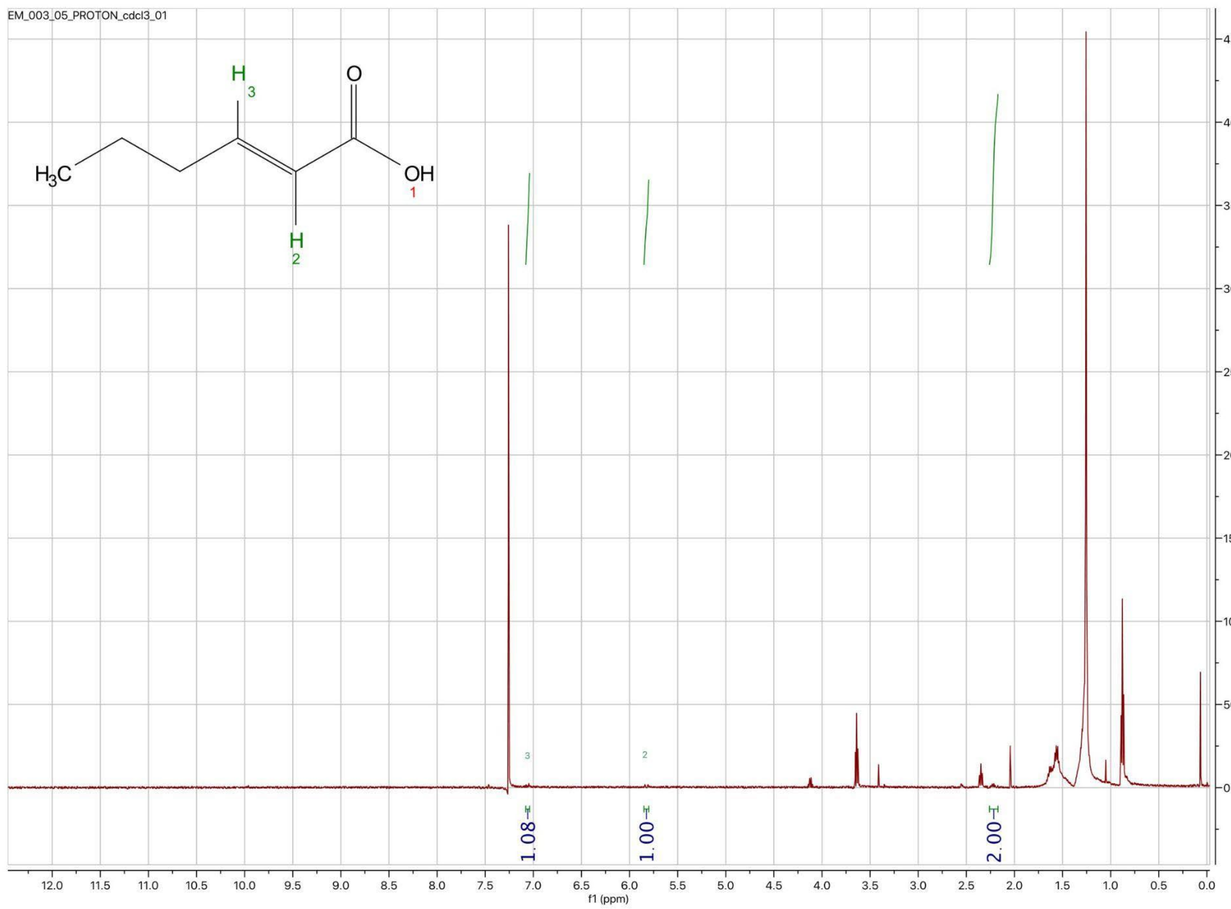


Figure 21. NMR of *E-hexadec-2-enoic acid*. The peak at 7.05 ppm and 5.82 ppm integrating for 1 indicate the presence of the alkene.

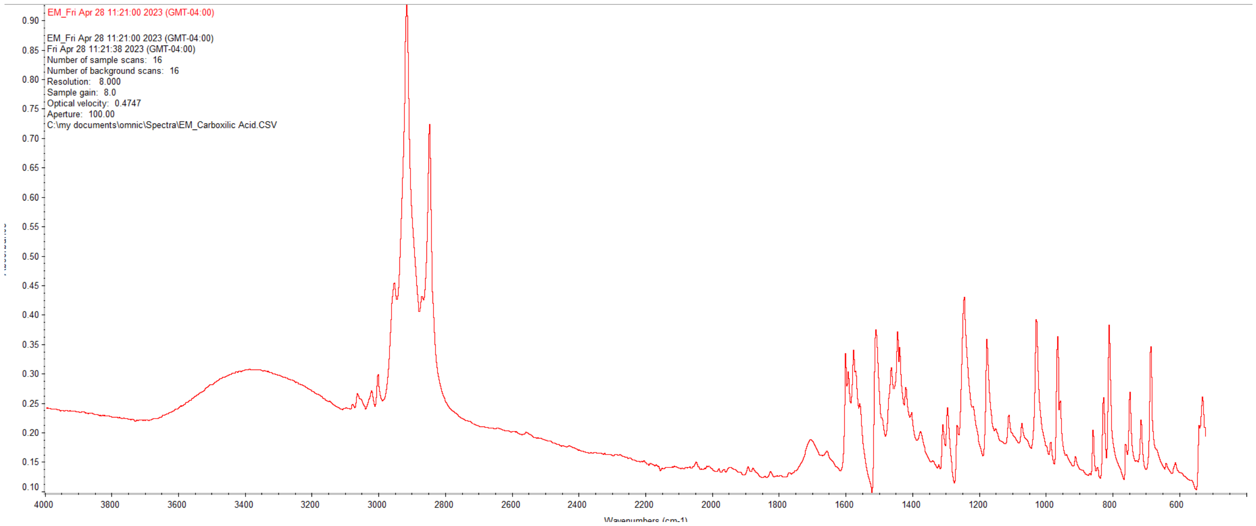
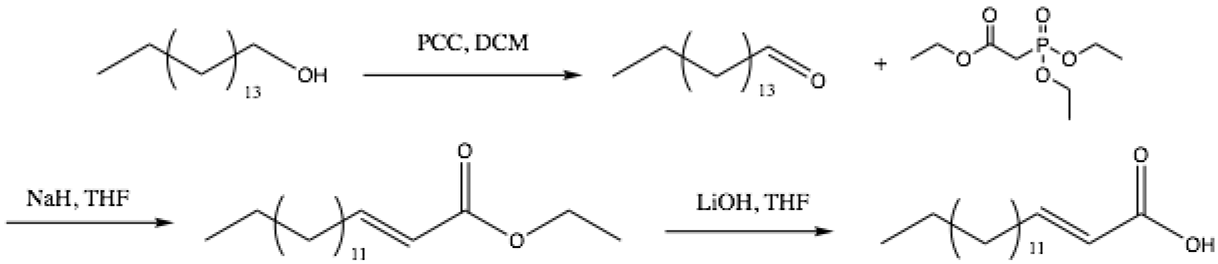


Figure 22. This figure shows the IR for *E-hexadec-2-enoic acid*. The broad peak at ~3400 cm-1 and the sharp peak at ~3000 cm-1 indicate the presence of the carboxylic acid.

Discussion:

Through the proposed synthesis 1 of *Methyl 3-oxooctadec-4-ynoate*, the methoxy wasn't able to be synthesized. The NMR results for the attempted synthesis of *Methyl 3-oxooctadec-4-ynoate*, showed no loss of the H_1 peak at roughly 1.9 ppm, which indicated that the carbon-carbon bond of the alkyne was not made. This is true for the attempts with the turbo grignard and grignard synthesized from scratch. As a result of 4 failed attempts, I moved on to the second proposed synthesis, shown in **Scheme 2**. The starting material of this synthesis, *E-hexadec-2-enoic acid,* however, was too expensive for purchase and had to be synthesized in the laboratory. The proposed synthesis of *E-hexadec-2-enoic acid* is shown in **Scheme 3**.



Scheme 3. This shows the synthesis of *E-hexadec-2-enoic acid*.

The second proposed synthetic scheme involves the starting material, *E-hexadec-2-enoic acid*. This material will be synthesized using scheme 3.

The synthesis of *E-hexadec-2-enoic acid* was successful. The NMR data showed steps 1, 2, and 3 being synthesized, with *E-hexadec-2-enoic acid* as the end result. The synthesis of tetradecanal was successful on the first attempt and there was a clear aldehyde peak at 9.76 ppm supporting this conclusion. *Ethyl-hexadec-2E-enoate* was a less clean synthesis, with optimization needed to ensure the complete consumption and removal of the triethyl phosphonoacetate so it would not carry over to the next reaction. The optimization of *ethyl-hexadec-2E-enoate* showed that maintaining a 1:1 ratio of regents to starting material provided the best yield for the product, and resulted in the most consumption of *triethyl phosphonoacetate*. The NMR results showed the loss of the aldehyde peak around the 9 ppm region, peaks at 6.98 ppm and 5.79 ppm indicating the creation of the alkene, and a peak at 4.11 ppm which indicates the presence of the ester.

The synthesis of *E-hexadec-2-enoic acid*, step 3, was successful, with a yield of 71%. The NMR showed peaks at 7.05 ppm and 5.82 ppm that indicate the maintenance of the alkene from *Ethyl-hexadec-2E-enoate*. The carboxylic acid, which is expected to be in the 10ppm-12 ppm region, was not present. However, carboxylic acid peaks are often very broad and remain at the baseline, making them hard to visualize via nmr. The IR of this product was instead used to support the presence of the carboxylic acid. The broad peak at ~3400 cm-1 and the sharp peak at ~3000 cm-1 indicate the presence of the carboxylic acid.

Conclusion:

I synthesized *E-hexadec-2-enoic acid* on a gram scale. I found literature methods, shown in **Scheme 1**, to not work. The restategized route, shown in **Scheme 2**, is promising. Moving forward all steps show in **Scheme 2** will need to be tested and optimized. I anticipate separating isomers and enantiomers of the *(R)-Dysidazirine* product to be a challenge. Currently the Seebald Lab is investigating methods of separation with analogous products, which will hopefully mitigate the separation challenges anticipated with *(R)-Dysidazirine*. Following the synthesis of *(R)-Dysidazirine*, there is a plan to carry out inhibition studies in collaboration with Eric Miller. The compound will be used as a competitive binding inhibitor for activity based protein profiling assays.

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This endeavor would not have been possible without the mentorship of Dr. Leah Seebald and the support of the Seebald Lab. I would like to extend my gratitude to Terry Synder for continuous assistance and support with the public health portion of my thesis. Lastly, I could not have undertaken this journey without the support of my family(Deborah Candreva and Tyler Mari) and my friends(Andrew Beltran, Hipolito Salazar, Anthony Carrillo, and Sarah Brown).

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