Hello, I hope you are all well and having a good day. My name is Juan Canchola I am an undergrad researcher at Illinois State University. I work under Dr. Jonathan mills, in his medicinal chemistry lab. We are currently studying synthesis of interesting natural products for novel antimicrobial drug development. Today I will be presenting to you the synthesis of the and biological evaluation of the Antimicrobial Natural Products Anaephene A and B

The discovery and implementation of antibiotics in the early twentieth century significantly increased human health and conditions. Advancements in organic chemistry lead to the development of many clinically relevant antibiotics, such as, penicillin, streptomycin, tetracycline, and erythromycin. All of which where derived from natural products, chemicals that can be isolated from living organisms. Natural products great options for drug development and I’ll talk more about that in a second. However, what we saw with the clinically relevant antibiotics is that many of them have become ineffective to the bacteria they were meant to treat. These drugs where very effective but because of our misuse overreliance, new strains of antibiotic resistant bacteria are emerging. When antibiotics are misused, bacteria that survive replicate to yield new generations of bacteria that are resistant to those commonly used FDA approved antibiotics.

The problem is that we are running of antibiotics. If you look here at figure 2, it just shows that there has been significant decrease in new drug approval throughout the years. It’s an accurate representation of our situation today, the usual pipeline for drug synthesis and development is running dry. In the past most antibiotics were produced by screening soil microorganisms, but this was a very limited resource and it was overmined in the 1960’s. Antibiotics have also been developed through synthetic and semi-synthetic methods. However, due to economic constraints, development through these routes has proved difficult. If implemented sparingly, antibiotics from natural products can be very effective. Considering that most approved antibiotics are derived from natural products and over 60% of all clinically relevant antibiotics are obtained from terrestrial Gram-positive bacteria. Natural products can serve as molecular templates for novel antibiotic development, Anaephene A (1) and B (2) are antimicrobial natural products isolated from a marine bacterium off the coast of Guam. These compounds were reported to have antibacterial activity against *Bacillus cereus* and *Staphylococcus aureus* with MIC values of 22 μg/mL and 6 μg/mL, respectively.

Driven by the promising biological activity of these compounds, the mills research team set out to report the first synthesis of Anaephene A and B. This would require the development a modular synthetic pathway. Because the natural products were so similar, we were able to obtain them using the same pathway. The general synthesis consisted of a Sonogashira cross-coupling reaction to add the alkyl chain on to the TBS protected iodol-phenol. The terminal alcohol was oxidized to the aldehyde, which would be required for a Julia olefination reaction. We used the Julia olefination reaction to attach our R groups. The sulfone, with our attached R group, would react with the aldehyde to yield the addition of the R group, as well as the incorporation of an E alkene (Scheme 1). The pathway was concluded with a TBS deprotection using TBAF to yield Anaephene A (**1**) and B (**2**) in 5 linear steps and an overall yield of 18% and 12%, respectively (Scheme 4).

Once we had the synthesized natural products in hand, we needed to confirm their biological activity. This was done using Minimum Inhibitory concentration assays, in which we tested our compounds ability to inhibit bacterial growth. We tested our compounds against S. aureus and methicillin-resistant *Staphylococcus aureus* (MRSA). The MIC results confirmed the reported biological activity against *S. aureus,* as our Anaephene A (1) and B (2) produced MICs of 16 μg/mL and 8 μg/mL respectively. In addition, we demonstrated that these compounds are also active against drug-resistant bacterial strains, such as MRSA. As you can see here on (Table 1)6 the compounds displayed identical MIC values for MRSA and *S. aureus.*

To summarize, we have developed an efficient and modular synthetic route to the Anaephene natural products. We have also shown that these natural products are active against *Staphylococcus aureus and* MRSA. Additional research is needed to determine whether it is possible to derive effective, efficient, and economical antibiotics from the Anaephene natural products. We are in the process of synthesizing novel analogs to generate structure-activity relationships. We are also going to test these compounds against additional drug-resistant bacterial strains. The results obtained will guide the development of more potent analogs with improved drug-like properties.

That concludes my presentation. Thank you for listening.

For more information on this research, please visit our recently published article the **Synthesis of the Cyanobacterial Antibiotics Anaephenes A and B.**

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