Synthesis of Ciclopirox and its Analogues

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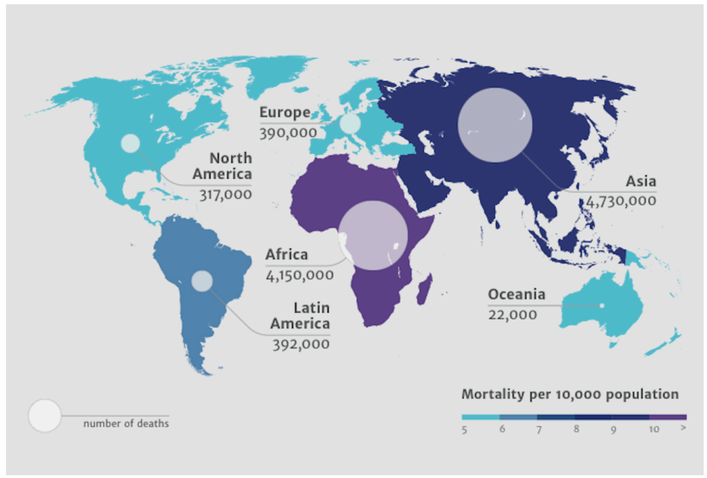
Abstract

The wide spread overuse of antibiotics around the world have led to the rise of bacteria resistance against conventional antibiotic treatments. One likely way to combat this issue is by repurposing previously well known established drugs to develop new antibiotics which can fight off the resistant bacteria once more. One of these said drugs, ciclopirox, an antifungal agent, is a hydroxypyridone which has activity derived from its ability to bind metal.[1] The overall goal of my research is to repurpose ciclopirox into an antibacterial agent and determine it's mode of inhibition. To accomplish this goal I have worked on synthesizing ciclopirox in order to study it in biological systems.

Antibiotic Resistance



Deaths attributable to antibiotic resistance, annually, by 2050. From AMR-Review.org;

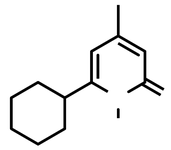
Statistics show that there have been a minimum of at least 2,049,442 illnesses and 23,000 deaths in 2013 from bacterial resistance in the United States alone.[2] It is essential for scientists to keep on developing new ways to fight against drug resistant bacteria or else the death toll will continue to increase over the years. That is why scientists have been using different methods to confront this issue and slow the processes of bacterial resistance down.

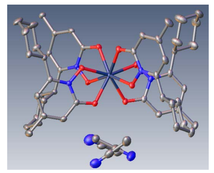
Strategies against Resistance

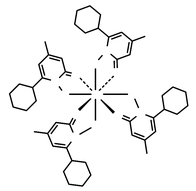
Below are several strategies utilized to fight against drug resistance:[3]

- New classes of antibiotics, particularly against Gram-negative bacteria, are in great demand. However, the development of new antibiotics is never in parallel with the microbial to acquire resistance.
- Co-administer appropriate non-antibiotic drugs with failing antibiotics, which restores sufficient antibacterial activity. The use of such antibiotic resistance breakers (ARBs) to salvage antibiotics is exemplified by the long-standing, successful and widespread co-administration of β-lactamase inhibitors, such as clavulanic acid, with β-lactam antibiotics, such as amoxicillin.
- Novel combinations of existing classes of antibiotics could also be investigated; for example, macrolides may be able to synergize with β-lactams and fluoroquinolones.
- Repurposing previously known drugs, the method I am using, is a more favorable approach because the drug has already been well studied and established, so that the pharmacokinetic properties are already known.

Ciclopriox

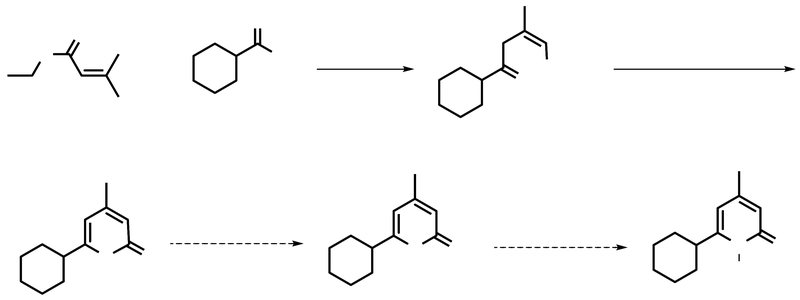






- Ciclopirox is a topical antimycotic agent belonging to the chemical class of hydroxypyridones and not related to azoles or any other class of antifungal agents. Its antimicrobial profile includes nearly all of the clinically relevant dermatophytes, yeasts and moulds, and is therefore broader than that of most other antimycotics.
- The high affinity of ciclopirox for trivalent metal cations, resulting in inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell, appears to be the major determinant of its antimicrobial activity, affect active transport, cell respiratory processes, autophagy and membrane integrity.

Synthesis



Scheme 1. Synthetic route to ciclopirox **1**[4]

Entry	2 : 3	Yield/%
1	1 : 1.2	0
2	1 : 2	0
3	1 : 1	54

Table 1. Optimization of the synthesis of compound **5**

Characterization of the product 5

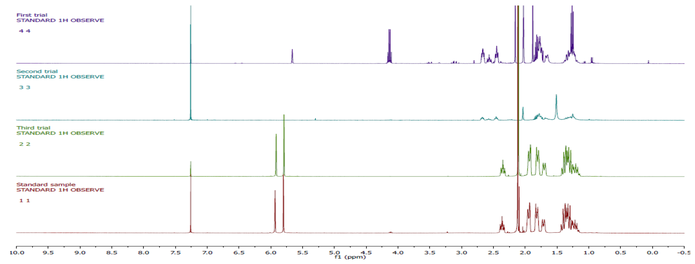


Figure 1. ^{1}H NMR characterization of the obtained products

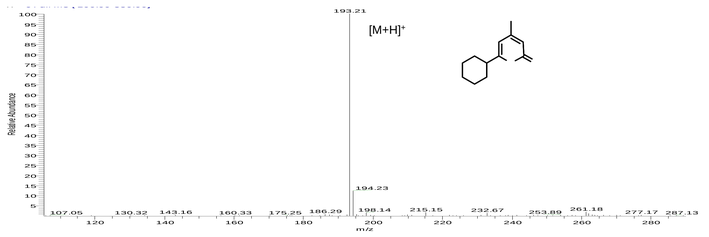


Figure 2. Mass Spectrum of the compound 5

Discussion and Conclusions

Ciclopirox is a widely used topical drug, so it is important to study the SAR (Structure Activity Relationship) and develop it into a more potent drug. Here we developed a method to prepare compound 5 which was well characterized by the NMR and MS.

We found that the ratio between 3 and 4 is very important for the success of this reaction. With this compound in hand we can make ciclopirox and a library of its derivatives. The activities of these compounds will be evaluated by our collaborators Future research will still need to be done to determine ciclopirox's mode of inhibition.

References

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4. Z. Liu, Y. Yao, M. Kogiso, B. Zheng, L. Deng, J. Qiu, S. Dong, H. Lv, J. M. Gallo, X. Li, and Y. Song, J. Med. Chem. 2014, 57, 8307−8318

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