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Use of Aryl Isonitrile Antibiotics to Combat Multi-drug Resistant *Staphylococcus aureus*

Author: Troy M. King Jr.
Major: Microbiology and Biochemistry
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

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Methicillin- and Vancomycin-resistant Staphylococcus *aureus* (MRSA and VRSA) are of significance due to their mortality rates and the limited success in the development of new therapeutic treatments. Modern treatment options are limited in their diversity to treat specific trains. Additionally, certain strains of *S. aureus* have developed multi-drug resistance (MDR). These developments require a new bactericidal compound that would not likely favor evolutionary resistance. Aryl isonitriles have shown potential to be quality candidates, but they possess structural limitations. In order to utilize these compounds, scientists and synthesized different variants in an effort to clarify their effectiveness and justify isonitriles as treatment candidates. The question that can be imposed from this study is how viable isonitrile antibiotics and why should we use it as a candidate for MRSA and VRSA infections. This research could be applied to future methods with utilizing these drugs with additional modifications and for use in MDR bacteria.

Introduction

Antibiotics are a broad category of drugs that function to inhibit growth of bacterial strains through treatment and prevention of bacterial infections[6]. Antibiotics, such as methicillin and vancomycin are popular forms of treatment for gram-positive bacterial infections, some stemming from *Staphylococcus* (*S.*) *aureus*. In 1961, a strain of *S. aureus* was shown to possess the ability to grow in the presence methicillin from an increase in resistance[2]. Methicillin-resistant *S. aureus* (MRSA) is culturally significant due to the sheer number of casualties that arises from chronic infection (more than 10,000 deaths per year) [5]. The mechanism for resistance acquisition to methicillin is derived from the bacterial production of a penicillin-binding protein 2a (PBP 2a), which is highly conserved in staphylococcal species. PBPs are known for their high affinity towards binding to penicillin. Due to the prominence of PBP producing bacteria, β-lactam antibiotics were utilized to bind to PBPs and in turn inhibit cell growth via bacterial cell wall degeneration[4]. The problem with penicillin- (a β-lactam antibiotic) based agents is their overuse in healthcare which has led to an increase in occurrence of multi-drug resistant (MDR) bacteria[8].

Due to the emergence of MRSA, vancomycin was the next logical choice for treatment due to the drug possessing peripheral target for inhibiting cell wall synthesis in gram-positive bacteria[9]. Vancomycin is a glycopeptide antibiotic is significant due to its low minimum inhibitory concentration (MIC) [3]. A low MIC is important for treatment of patients with bacterial infections because, in high concentrations, drugs can conflict serious to the liver[3]. Due to overuse of antibiotics in hospitals, similarly to methicillin, a strain of *S. aureus* inevitably acquired resistance to

vancomycin to become vancomycin-resistant *S. aureus* (VRSA[9]).

Lack of available treatments for these ailments would require chemotherapy for limiting the growth of resistant cells[9]. New forms of antibiotics are needed to combat MDR strains of bacteria or history will repeat itself, and we will have another outbreak of deaths due to drug resistant bacterial infection[1]. To combat the rise of MDR bacteria, scientists have attempted to chemically modify current antibiotics to increase their efficacy and have recently made significant progress. Isonitrile agents have been of significance for their potential as antibiotics since isonitrin isolation from *Trichoderma* fungal species in 1982[7]. Of the isonitrin discovered from the *Trichoderma*, isonitrin A (Fig. 1) was of the utmost importance with its possession of a low MIC (1.56 µm/ml) [7].

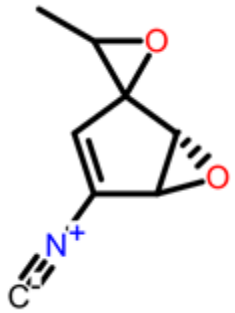

Figure 1: Structure of Isonitrin A

Further studies have shown that isonitriles isolated from a marine sponge, *Cymbastela hooperi*, can exhibit anti-malarial and anti-bacterial activity[10]. From *C. hooperi*, the antibiotic of significance was axisonitrile-3 (Fig. 2) which showed promise by limiting the growth of *Plasmodium* strains (MICs of 0.142 and 0.165 ppm) [10]. These studies show that there is potential for use of isonitrile antibiotics to treat bacterial infections. The purpose of this review is to present recent scientific advancements by Wright and collaborators. that will exhibit new forms of antibiotics that should be modified to make them more effective[10].

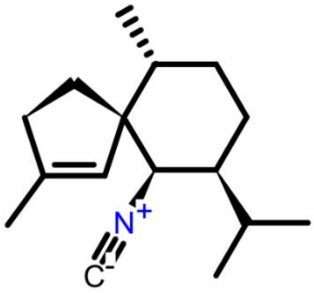

Figure 2: Structure of Axisonitrile-3

Recent Progress

Isonitrile drugs have been shown to be effective, but the addition of functional groups were not previously fully characterized. In an effort to generate more variants of isonitriles, about 250 molecules were synthesized and screened for bactericidal activity. From these molecules, Davis and collaborators created an isonitrile backbone that possessed bacteriostatic, inhibiting growth, activity (32 µM) and could be further modified via addition of function groups to generate many variations of isonitrile compounds (Fig 3). These new isonitrile compounds were then quantified via effectiveness. The varying functional groups were attached to the backbone and their quality was determined by whether or not the new conformation was a benefit, lowering the MIC, or an impediment, increasing the MIC from the backbone[10].

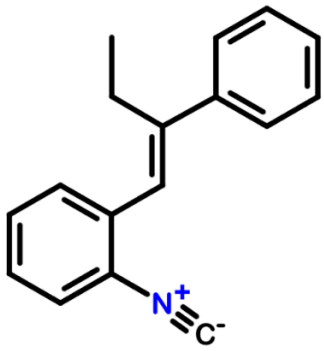

Figure 3: Structure of Aryl Isonitrile backbone

The test for effectiveness involved treating the compounds against six strains of MRSA and a single strain of VRSA. Each compound was tested against the strains each possessing broad variations in effectiveness (MICs between 2 and >128 µM). A particularly significant variation that changed effectiveness of the potential antibiotic is the position of functional groups on the benzene ring[10].

One of the compounds generated, currently named compound 13, was comparatively simple in

that it was a version of the backbone (Fig. 4) with deletions of functional groups, instead of additions, that increased effectiveness[10]. In an effort to confirm the active isonitrile group as the active site on 13, the isonitrile group was replaced by an isosteric nitrile (cyano-) group to exhibit a complete loss in bactericidal activity. The compound was also tested for toxicity to mammalian cells to display no damage at MIC 64 μM, while simultaneously possessing bactericidal activity at 2μM. A potential limitation of 13 is that is lack permeability properties that would limit how the antibiotic could be applied for treatment[10].

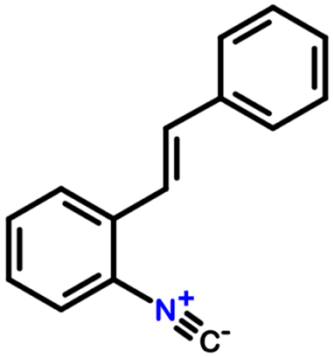

Figure 4: Structure of backbone-generated isonitrile, compound 13.

Discussion

The new isonitrile compounds proposed were indeed significant and show potential for medical use. Before implementation, I hope to see modifications done to the compounds to allow for better solubility without compromising function. Because compound 13 was significant, it would be interesting to confirm the effectiveness of the compound within MRSA or VRSA models in order to have an observation of an actual infection possessing susceptibility to isonitrile drug treatment instead of on a plate[10]. As the compound exists currently, compound 13 requires solubility modifications to get the most out of the effectiveness of the drug. Possible antibiotic, compound 13, would have to be applied topically because it is unable to spread regularly because the drug currently lacks the ability to cross over to neighboring tissues. The applications of this experiment is impressive and very detailed in how each compound was synthesized. Adequate comparisons between synthesized compounds and current drugs indicate comparatively lower MIC, demonstrating wider margins of treatment applications than linezolid and vancomycin[10]. Once the compound overcomes these limitations, doctors would be able to fully employ the qualities of isonitriles and treatment can effectively be performed as a dialysis.

There are also some inevitable concerns with these necessary modifications of compound 13 such as the impact on functionality. In the Davis paper, it is proposed that solubility attachments may aid in potential treatments, but they fail to explain which modifications may aid in solubility and whether or not these modifications go against the conservative nature of compound 13. Compound 13 appears to be of significance due to its attribute to not have many side groups on its backbone. This is important information because an explanation for the effectiveness of this aryl isonitrile compound may stem from its simplicity versus others of its type that appear in the Wright paper. However, if scientists were to overcome this obstacle, drug resistant bacterial complications will, in theory, decrease drastically because it is less probable for MRSA- and VRSA-like strains to develop resistance to compounds that are not found readily in nature.

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