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Chemical Synthesis of Klebsazolicin, A Novel Antibiotic against Gram Negative Bacteria

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Abstract

Appearance of resistant strain in gram negative bacteria decreased the treatment effect of colistin, the last-resort treatment for multidrug-resistant gram-negative infections and cast new challenges to medical treatment. Klebsazolicin with characteristic amidine and azole structure, was discovered as a novel antibiotic against gram-negative bacteria, which may serve as a new option besides colistin. Klebsazolincin was successfully synthesized by biotechnology but its diversity is restricted because of the limitation of biosynthesis such as post translational modifications. We designed a chemical strategy to synthesize klebsazolicin and expand its assortment. Klesazolicin was divided into four building blocks including two thiazoles, one oxazole, and one nitrobenzotriazolide, which were obtained by solution synthesis. Amidine is formed directly by chemical reaction on resin. Four building blocks and other normal amino acids were combined by solid phase peptide synthesis and klebsazolincin was synthesized after subsequent amidine formation on resin.

Introduction

Gram-negative bacteria contain one more outer membrane as an extra layer of protection compared with gram-positive bacteria, which posts more challenge to the treatment. Four of gram-negative bacteria are on the list of most urgent threats highlighted by Infectious Disease Society of America[1]. The last-resort treatment for multidrug-resistant gram-negative infections, colistin, also started to fail in the treatment of resistant strains[2].

The development of new antibiotics against gram-negative pathogens is urgently desired. With the new methodologies such as genome mining, high-throughput screening, there are some promising candidates developed and klebsazolicin is one of them[3-4]. However, there are still some drawbacks of klebsazolicin such as narrow spectrum and uptaking limitation needed to overcome[5-6]. As an optional method to solve these problems, biosynthesis achieved a great success in synthesizing klebsazolicin, but it showed inadequacy in post-translational modification, which limits development of mutated klebsazolicin. However, another optional method, chemical synthesis, has fewer limitations in modification and has achieved lots of success in synthesizing and modifying polypeptide and protein especially with the development of solid phase peptide synthesis(SPPS) and chemical ligation, which is another option for the synthesis and modification of klebsazolicin. Accordingly, we designed a chemical strategy to synthesize and modify klebsazolicin based on its antibacterial mechanism. Klebsazolicin is made up of normal amino acids, one amidine, three thiazoles and one oxazole, we split it to four kinds of building blocks. After SPPS and amidine formation on resin, klebsazolicin was synthesized.

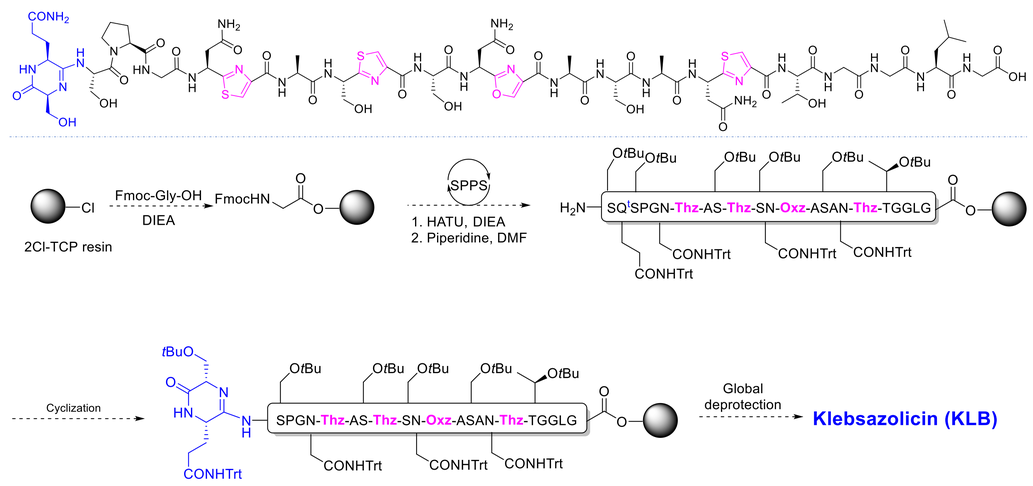

Figure 1 The structure and synthetic strategy of klebsazolicin

Results and Discussion

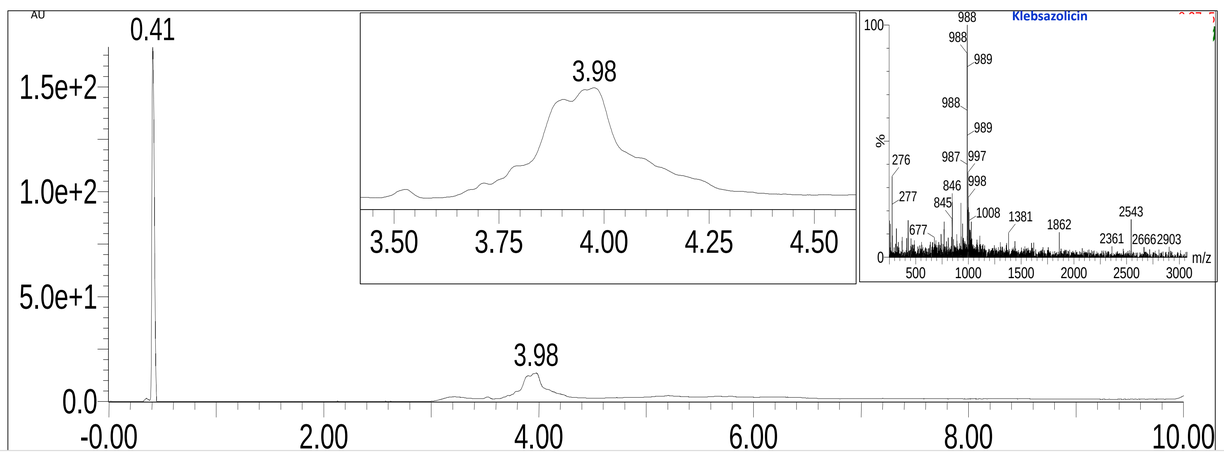

Figure 2 UV and MS spectra of klebsazolicin

Following designed chemical synthetic strategy, two thiazoles, one oxazole, and one nitrobenzotriazole were combined with normal amino acids by solid phase peptide synthesis after solution synthesis. Klebsazolincin was synthesized with subsequent amidine formation on resin, which was confirmed by the MS spectrum in figure 2. However, several peaks with identical MS value of klebsazolincin appeared in the UV spectrum, which indicated that the synthesized klebsazolincin is a mixture. After checking every building block, we found some of them are racemized during solution synthesis, which is responsible for the formation of klebsazolincin mixture. We have been synthesizing these building blocks with new methods to avoid the racemization problem.

Reference

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