Development of Chemical and Enzymatic Pathways for Modifying the Amino Group of 6-Aminopenicillanic Acid by Introducing Bacterial-Derived 3-Hydroxyacids into the Molecule

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Semi-synthetic penicillins represent a crucial class of antibiotics globally, often preferred for treating infections due to their efficacy against a broad spectrum of Gram-positive and Gram-negative bacteria. They function by disrupting bacterial cell wall synthesis, specifically targeting peptidoglycan, which is absent in eukaryotic cells, thus ensuring their safety for humans and animals. However, the increasing prevalence of antibiotic-resistant bacterial strains has reduced the efficacy of many β-lactam antibiotics, highlighting the urgent need to develop novel antibiotics and β-lactamase inhibitors or find new modification methods.

This research project explores novel pathways for penicillin synthesis by modifying the side chain at the C6 position. The starting molecule is 6-aminopenicillanic acid (6-APA), which is modified using derivatives of polyhydroxyalkanoates (PHA), a diverse group of chiral (*R*)-3-hydroxy acids. Poly-3-hydroxynonanoate (P(3HN)) and poly-3-hydroxy-5-phenylvalerate (P(3H5PV)) were synthesized *via* bacterial fermentation and then linked to 6-APA benzyl ester through both chemical synthesis with T3P condensing reagent and enzymatic biosynthesis using *Thermomyces lanuginosus* TL-IM lipase. Six 6-APA derivatives featuring side chain modifications were obtained. These PHA-modified penicillins exhibited potent antibacterial activity against Gram-positive and Gram-negative bacteria, particularly of the *Proteus* genus, with a similar spectrum to penicillin G. Furthermore, the new derivatives displayed lower genotoxicity compared to penicillin G and ampicillin.

The pathways developed here utilizing structurally diverse PHA monomers could provide a framework for further modifications of the 6-APA core, leading to the discovery of new, more effective antimicrobial compounds.

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