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The in vitro Biosythesis of Obafluorin ß-Lactone Analogs for Use in a Biological System

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The *in vitro* Biosynthesis of Obafluorin β-lactone Analogs for Use in a Biological System

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Since the discovery of penicillin in the 1940s, microbial resistance to antibiotics has been a widespread issue in the medical community. This problem has been exacerbated by the overuse of antibiotics, exploitation of the same molecular targets, and the natural ability of microbes to defend themselves when put under evolutionary pressure. In order to combat the rise of microbial resistance, researchers are constantly searching for new molecular scaffolds to use against pathogens and new biological targets to pursue. The β-lactam containing antibiotics make up over 50% of the antibiotic prescriptions worldwide. Obafluorin (obi) is a molecule with a novel antibiotic scaffold containing a β-lactone ring that is similar to the β-lactam. This new molecule is hypothesized to disrupt quorum sensing between bacteria. The mechanism of action is bacteriostatic, not bactericidal like most other antibiotics. While seemingly counterintuitive, halting the growth of a pathogen and allowing the infected organism's innate immune response to clear the bacteria is gaining ground in the research community because bacteriostatic antibiotics have shown lower incidences of resistance. The lab has recently fully characterized the biosynthetic gene cluster of obi in the producer organism *Psuedomonas fluorescens* and has performed an *in vitro* reconstitution of the biosynthetic enzymes. This project explored the possible unnatural substrates that were commercially available and relatively inexpensive, by feeding them through enzymes in the gene cluster. The substrates that had high product concentration were fed through to make obi analogs, which were quantified by LCMS to determine product content. These obi analogs synthesized as part of this project will help to elucidate the natural mechanism of β-lactone formation and the viability of targeting the quorum sensing abilities of bacteria as an antibiotic target.