Construction of Trimodular Pikromycin Polyketide Synthase

~~Won Seok Jung~~*, Eung Soo Kim**, Han Young Kang***, Cha Yong Choi*, Yeo Joon Yoon****

Interdisciplinary Program for Biochemical Engineering and Biotechnology, Seoul National University. Seoul 1512-742*

School of Chemical Engineering and Biotechnology, College of Engineering, Inha University. Incheon 402-751**

Department of Chemistry, College of Natural Science, Chungbuk National University. Cheongju, Chungbuk, 361-763***

School of Chemical Engineering and Bioengineering, University of Ulsan. Ulsan 680-749****

Abstract

Macrocyclic polyketides exhibit an impressive range of medically useful activities, and there is a great interest in manipulating the genes that govern their synthesis. The pikromycin polyketide synthase (Pik PKS) of *Streptomyces venezuelae* can synthesize two macrolactone structures, 12- and 14-membered ring. This unusual nature of Pik PKS provides a potentially useful tool for generating multiple products from a single hybrid modular PKS by combinatorial biosynthesis. However, there is only a limited knowledge about the molecular mechanism of generating multiplicity, which has placed a restriction on its application. In this study, in order to understand the molecular mechanism of generating structural multiplicity, we propose to develop the hybrid three modular Pik PKS as a model system, which has been constructed by deleting the region between acyltransferase (AT) domain of module 2 and ketoreductase (KR) domain of module 5. The resulting hybrid Pik PKS in *S.venezuelae* is expected to catalyze the formation of two different lactone compounds, triketide and tetraketide lactones. Understanding the mechanism involved in the formation of the two different macrolactone ring sizes will enable us to generate a diverse range of polyketides by combinatorial biosynthesis and to develop novel drugs for therapeutic usage.