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Kosuke Ohsawa

Total Synthesis of Thielocin B1 as a Protein–Protein Interaction Inhibitor of PAC3 Homodimer

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Total Synthesis of Thielocin B1 as a Protein–Protein Interaction Inhibitor of PAC3 Homodimer

Doctoral Thesis accepted by
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Supervisor's Foreword

It is my pleasure to introduce Dr. Kosuke Ohsawa's study for publication in the Springer Thesis series as an outstanding original work from one of the world's top universities. Dr. Ohsawa was born in Japan in 1987. After graduation in 2009 from the Department of Pharmaceutical Sciences, Tohoku University, he received a license to practice pharmacy. He studied Organic Chemistry in the Ph.D. course at the Graduate School of Pharmaceutical Sciences of Tohoku University and received his Ph.D. in 2014. He moved to Dortmund, Germany, as a postdoctoral fellow under the guidance of Prof. Dr. Herbert Waldmann in Max-Planck Institute of Molecular Physiology.

Protein–protein interactions (PPIs) have recently attracted attention as novel therapeutic targets because they play vital roles in numerous cellular functions. However, conventional methodology based on lock-and-key theory is usually difficult to apply for large and flat interfaces of PPIs. Dr. Ohsawa focused on thielocin B1, which was found to be a PPI inhibitor of a proteasome assembling chaperone (PAC) 3 homodimer, and he has achieved the first total synthesis of thielocin B1 and its molecular probe. In the process, he developed the synthetic methodology for highly functionalized aromatic compounds, e.g., the synthesis of unique 2,2′,6,6′-tetrasubstituted diphenyl ether and the formylation of aromatic compounds at sterically hindered position. Compounds that he synthesized were utilized for NMR studies to validate the interaction model of a thielocin B1/PAC3 complex, and further in silico docking study suggests that thielocin B1 promotes the dissociation to monomeric PAC3 after approaching PAC3 homodimer.

I hope that Dr. Ohsawa's Ph.D. thesis will help many readers to reconfirm the potential of complicated natural products as drug seeds.

Sendai, October 2014 Prof. Takayuki Doi

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