Design and Synthesis of 6-Substituted Uridine Derivatives as Mechanistic Probes and Potential Chemotherapeutic Agents

Yu-Chiao Shih (史諭樵), Jian-Bang Lin (林建邦), Ying-Shun Liao (廖英舜), Chen-Chieh Liao (廖振傑), Jhih-Li He (何智豐), Yuen-Jen Wu (吳元仁), Cheng-Hung Jen (任政宏), and Tun-Cheng Chien (簡敦誠)*

Department of Chemistry, National Taiwan Normal University, Taipei 11677, Taiwan
tcchien@ntnu.edu.tw

Orotidine 5'-monophosphate decarboxylase (ODCase) catalyzes the decarboxylation of orotidine 5'-monophosphate (OMP, **1**) to uridine 5'-monophosphate (UMP, **2**) in the final step of the *de novo* pyrimidine nucleotide biosynthesis. ODCase has been identified as a potential target for the new drug discovery. Inhibition of ODCase results in depletion of the pyrimidine nucleotide pools, which can be correlated to antiviral, antiparasitic, and anticancer activities. ODCase is one of the most proficient enzymes known. Unlike most of the other decarboxylases, ODCase contains no metal ions or small molecule cofactors, and there is no evidence for the existence of a covalent intermediate during the catalysis. These facts suggest that the proficient catalyst operates by a novel chemical mechanism.

The research has been focusing on developing effective mechanistic probes to study the possible mechanisms for the enzymatic catalysis of ODCase. The research includes the design and synthesis of the structural models (**3**) of natural and alternative substrates to explore the chemistry occurring at the 6-position of uridine derivatives in order to elucidate the possible enzymatic mechanisms by chemical model reactions. In addition, the research has also investigated the chemistry generally applicable to the modification at the 6-position of uridine to synthesize a series of OMP analogs (**4**) that were designed by bioisosteric replacement of the characteristic OMP functional group. Our effort toward the synthesis of mechanistic probes for ODCase provided a better understanding of the mechanism of the OMP decarboxylation process. The 6-substituted uridine derivatives are potential ODCase inhibitors as well as chemotherapeutical agents which are currently under evaluation.