Title: Synthesis and Evaluation of Protein N-terminal Acetyltransferase D Inhibitors

N-terminal acetylation is an essential protein modification, and it is involved in protein-protein interactions, protein complex formation, cellular apoptosis, rDNA transcriptional regulation, and protein subcellular localization. This modification is catalyzed by Protein N-terminal acetyltransferases (NATs). NatD is a highly selective NAT because its only known substrates are histones H2A and H4. Inhibition of NatD has appeared as a new therapeutic target due to its oncogenic activity in primary human lung and colorectal cancer. This study aims to discover potent and selective small NatD inhibitors. Previously, we established a ThioGlo4 fluorescence assay to conduct high throughput screening and identified a hit compound YH086 with IC_{50} of 150 μM. To understand the structural relationship activity of YH086 and optimize the inhibitory activities, we applied a medicinal chemistry approach and synthesized more than 40 analogs using Curtius rearrangement reaction. We have improved the IC_{50} from 150 μM to a single-digit micromolar in biochemical Thioglo4 fluorescence assay. Our ongoing work will validate our inhibitors with thermal shift assay, cellular thermal shift assay, and cellular inhibitory activities against lung and colorectal cancer cells. We anticipate that discovering inhibitors can help us further understand the biological roles of NatD.