Project 2. Computer-aided design and development of selective matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, and 24 MMPs are present in mammals. MMPs have been important therapeutic targets due to the pathological roles in various human diseases, particularly in cancer progression, inflammatory processes, and pulmonary diseases. Thus, more than 50 MMP inhibitors entered clinical trials for the treatment of cancers, but all of these studies failed possibly due to the lack of inhibitor specificity and insufficient knowledge of pathological roles related to MMPs. These broad-spectrum MMP inhibitors displayed undesired side effects in clinical studies, particularly musculoskeletal pain and inflammation. Therefore, it is highly demanded to develop highly specific MMP inhibitors as therapeutic candidates for the treatment of human diseases.

In my research at Scripps Florida, we developed highly potent and specific MMP-13 inhibitors by applying structure-guided drug design techniques (*J. Med. Chem.*, **2017**, 5816-5825). A high-throughput screening hit (**5**, IC_{50} = 2.4 μM) from a MLPCN probe development project was optimized, and potent and selective inhibitors were developed through comparative analysis and computational molecular design approaches ((*S*)-**17b**, IC_{50} = 2.7 nM, 1,000-fold improvement). The protease selectivity of (*S*)-**17b** was evaluated, and it showed entirely no activity against other MMPs and proteases tested at 5 μM and moderate inhibition to MMP-3 and MMP-12 with IC_{50} = 4.4 and 1.8 μM, respectively.

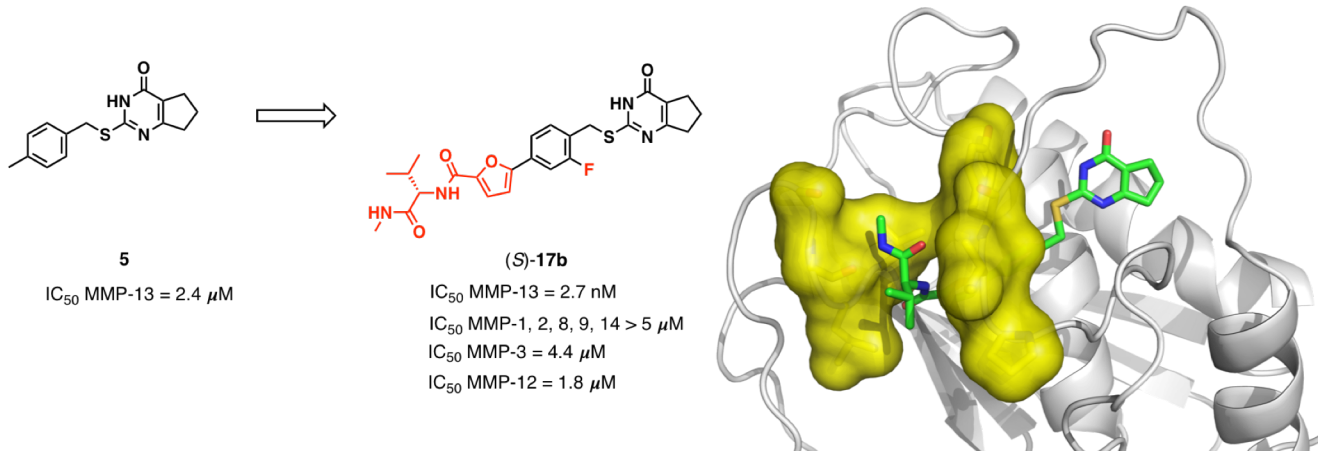

Figure 2. Structure-guided design and development of highly potent and selective MMP-13 inhibitors

Currently, we are conducting design and synthesis of specific MMP inhibitors by applying our expertise obtained from the development of MMP-13 specific inhibitors. Potent and specific MMP inhibitors developed in our laboratory will be utilized to investigate biological and pathological functions of individual MMP in animal models of human diseases with collaborators at Columbia Medical Center, Georgia Tech/Emory Medical School, and Florida Atlantic University.