Proteasome inhibitors (PIs) have become an effective class of targeted therapeutic agents for the treatment of multiple myeloma (MM) in the last couple of decades. However, MM remains incurable, and most patients experience relapse and are treated with multiple agents in their disease course. Therefore, our lab has continued to investigate alternative proteasome inhibitors based on two peptidic β-lactone-containing natural products, Cystargolides A and B. Based on the cystargolide scaffold, our PIs are comprised of a dipeptide moiety and a β-lactone moiety. Following on our previous studies, the β-lactone fragment can be prepared stereoselectively using an asymmetric alkylation and a one-pot chlorination-lactonization as key steps. The syntheses of the dipeptide fragments of our PIs were achieved by a series of standard amino acid coupling and acidic/basic deprotection steps. Alternative synthesis sequences were adopted to circumvent unexpected cyclization byproducts.

Our current studies focus on the optimization of our most recent drug lead 1 in order to enhance its efficacy \textit{in vitro} and its drug-like properties. To increase the chemical and/or metabolic stability of 1, we replaced an ester moiety with an amide moiety. We hypothesize that the amides will be more stable than the esters due to their lower tendency to hydrolyze. We also investigated isosteric replacement of one of our phenyl groups for a pyridyl group in hopes of increasing its water solubility and improving its pharmacokinetic profile. Herein, we report the syntheses of amide/pyridyl-Cystargolide analogs along with their preliminary biological results as proteasome inhibitors.