Abstract

This thesis summarizes work carried out in the laboratories of Professor Walid A. Houry and Professor Robert A. Batey at the University of Toronto from September 2016 through March 2018.

Caseinolytic protease P (ClpP) is a serine protease highly conserved in bacteria and eukaryotes. ClpP forms a complex with an ATPase partner whose primary function is to maintain protein homeostasis through the degradation of damaged and misfolded proteins; ClpP is also involved in the regulated elimination of folded proteins. Without its ATPase partner, bacterial ClpP can only degrade small peptides. Recently, novel classes of compounds have been discovered that allow ClpP to non-specifically degrade folded proteins leading to bacterial cell death. One of these classes of compounds are the Activators of Self-Compartmentalizing Proteases (ACPs) discovered using a high-throughput screen. Co-crystal structures with *E. coli* ClpP showed ACPs can bind in two configurations. Improving on these initial hits and to completely fill the binding pocket, 16 new phosphine oxide-based compounds (ACP6) were synthesized and investigated for biological activity. In addition, five new ACP1 analogues were created for biological activity comparison due to structural variations in ACP6. For all of these compounds, their ability to enhance the ClpP peptidase activity was tested. Several of the ACP6 analogs showed increased activity against *E. coli* ClpP compared to the initial ACPs. This work showed that a new class of compounds can also activate bacterial ClpP and can be pursued as chemical leads for the development of antibiotics.