

## Abstract

Begnini, F. 2019. Development of Novel Macrocyclic Inhibitors of Protein-Protein Interactions: Applied to the Keap1-Nrf2 Complex.

The Keap1-Nrf2 protein-protein interaction is well characterized, but development of ligands for the binding site on Keap1 is challenging due to its polar and charged nature. Activation of Nrf2 through inhibition of the complex with Keap1 offers opportunities to reduce oxidative stress, which is involved in a number of diseases.

The natural product cyclothialidine, which contains a 12-membered lactone, was identified as a ligand for Keap1 in a virtual screen of a set of natural product derived macrocyclic cores. More than 30 simplified analogues of cyclothialidine were synthesized and evaluated as inhibitors of the binding of a peptide from Nrf2 to Keap1. This provided an optimized lead compound that showed a 100-fold improvement in potency as compared to cyclothialidine. In addition, the lead compound had good solubility, moderate cell permeability but a somewhat high metabolism. The employed synthetic strategy proved to be reproducible and robust and allowed significant modifications of the macrocycle and its substituents.

Additionally, preliminary experiments of late-stage functionalization of the lead compound were carried out to support a more efficient exploration of the structure-activity relationship. In particular, an efficient method to selectively modify the aromatic moiety through C–H borylation was developed.