Abstract

AMP-activated protein kinase AMPK functions as a master switch to maintain cellular and whole-body energy homeostasis. Abnormal activity profiles of AMPK cause pathological disorders, and growing evidence supports pharmacological targeting of AMPK as a promising approach to treat human diseases such as metabolic disorders, cancer and neurodegenerative diseases. However, isoform-dependent signaling of AMPK in health and disease remains largely elusive. Therefore, continuous investigations are required as well as new tools to study the physiological functions of AMPK. Previously, the focus has been directed towards development of allosteric AMPK activators whereas only few attempts have been reported describing AMPK inhibitors. Thus, the literature review summarized in **Manuscript I** may provide stimulating starting points to the scientific community to promote AMPK inhibitor development.

To provide novel small-molecule AMPK modulators, a screening campaign was conducted during my environmental exchange at GRIDD, Griffith University, Brisbane, Australia in the group of Prof. Ronald J. Quinn. Chapter 2 discusses the screened compound libraries and highlights selected discoveries of new AMPK modulators, including the hit scaffold which was selected for subsequent optimization.

Chapter 3 outlines the optimization of the promising screening hit scaffold via state-of-the-art medicinal chemistry. The discovered pyrrolo[2,3-*c*]pyridines were altered in an iterative process, including *in silico*-supported ligand-based design, organic synthetic chemistry, and biological testing, to provide the novel pyrrolo[2,3-*c*]pyridine- and thieno[2,3-*c*]pyridine-based AMPK inhibitor series. To our delight, the lead structure TUG-1874 (**3.88**) displays an excellent kinase-selectivity profile while inhibiting activity of all screened AMPK complexes, and was further shown to inhibit AMPK in cells. Moreover, potency and target-selectivity profile of TUG-1874 are superior compared to the commonly used AMPK inhibitor Compound C.

Lastly, Chapter 4 describes the regioselective *N*-alkylation of pyrrolo[2,3-*c*]pyridine intermediates and discusses fluorescent properties of selected compounds in the context of a prospective use in fluorescent tool compounds.