Abstract

Synthetic kinase inhibitors are chemical tools to investigate cellular roles of kinase enzymes and, potentially, find new treatments for various diseases that are connected with their dysregulated expressions and activities. This thesis focuses on two projects that were devoted to design, synthesize and evaluate novel compounds as kinase inhibitors.

In a first project, employing structure-based docking methods, novel 7-aryl- or 7-heteroaryl-substituted 4-aminoquinazoline-6-carboxamide compounds were developed as inhibitors of class II phosphatidylinositol 4-kinases (PI4K2A/2B). A simple synthetic approach enabled the preparation and the functionalization of the 4-aminoquinazoline scaffold in six steps. Enzymatic evaluation for activity and selectivity against PI4Ks (i.e., PI4K2A and class III PI4Ks) highlighted several compounds with low micromolar potency and good selectivity against PI4K2A. Moreover, the binding mode of the new compounds in the conserved ATP-binding sites of class II PI4Ks was corroborated by X-ray crystallography. This suggests the applied rationale of the design can be a strategical option to obtain more potent and selective PI4K class II inhibitors, to conduct additional investigations on these kinases.

In a second project, novel 4,6- and 4,6,7-substituted quinazoline compounds were developed and evaluated as inhibitors of receptor-interacting protein kinases 2 and 3 (RIPK2/3). The design of the molecules was guided by structural analyses of documented RIPK inhibitors. These precedents and new docking studies led to installation of an aminobenzothiazole moiety at position 4 of the quinazoline. In the meantime, multiple diversifications were introduced at positions 6 and 7 of the central scaffold, providing three series of structurally correlated compounds. These were synthesized employing a convergent cyclization methodology and palladium-catalyzed reactions. Enzymatic analyses of the molecules against the RIPK1-4 isoenzymes led to identification of various inhibitors selective for RIPK2, or for both RIPK2/3 kinases. In cell-based assays against RIPK2, most of the compounds exerted nanomolar inhibition of the NOD1/2 pro-inflammatory pathways. Surprisingly, for selected dual RIPK2/3 inhibitors, evaluation against RIPK3-mediated necroptosis showed only a limited cellular efficacy. For several lead compounds, assessments in human and mouse liver microsomes and plasma showed high metabolic stability in both species. Lastly, some of the best compounds also exhibited outstanding RIPK selectivity profiles in evaluations against other 58 human enzymes of the kinome. Thus, diversifying substitutions at positions 6 and 7 of the developed quinazoline derivatives enabled to explore significant differences in potency and specificity against RIPK2 and RIPK3. These discoveries could aid further development of new compounds with increased efficiency against these isoenzymes.