

Discovery of novel selective modulators of selected therapeutically relevant biological targets

Abstract

My doctoral research mainly consists of two medicinal chemistry projects focused on development of new biologically active small organic molecules. These small organic molecules might find utilization as probes for chemical genetics, molecular/chemical biology or as leads for development of compounds for clinical testing.

In the first project we report the identification of the furo[3,2-*b*]pyridine (FP) core as a novel scaffold for potent and highly selective inhibitors of cdc-like kinases (CLKs) and efficient modulators of the Hedgehog signalling pathway. Initially, a diverse target compound set was prepared by synthetic sequences based on chemoselective metal-mediated couplings. Optimization of the subseries containing 3,5-disubstituted furo[3,2-*b*]pyridines afforded potent, cell-active and highly selective inhibitors of CLKs. It has been published that CLKs could be promising targets for treatment of neurodegenerative diseases (Alzheimer, Parkinson) or breast cancer. Profiling of the kinase-inactive subset of 3, 5, 7-trisubstituted furo[3,2-*b*]pyridines revealed sub-micromolar non-toxic modulators of the Hedgehog pathway. Inappropriate activation of Hedgehog signalling has been found in various cancers.

Second project is focused on the synthesis and biological evaluation of inhibitors of Casein kinase 1 (CK1). In collaboration with colleagues from the Department of Experimental Biology we have identified a new central pharmacophore, explored the structure-activity relationship (SAR) and thereby discovered highly selective and potent CK1 inhibitors. Some inhibitors exhibit also high activities in cells and promising *in vivo* profile. We are mostly focused on utilization of these compounds in the treatment of chronic lymphocytic leukemia (CLL), but CK1 inhibition is promising also for treatment of additional malignancies and other diseases such as insomnia or obesity.