Abstract

Cyclin-dependent kinase 9 (CDK9) plays a key role in transcriptional regulation. Increased activity of CDK9 is associated with various types of cancer, as well as other (e.g. inflammatory) diseases, and inhibition of this kinase is considered a promising therapeutic target. This thesis deals with a comprehensive *in vitro* evaluation of the biological activity of two original CDK9 inhibitors prepared at the IOCB of the Academy of Sciences of the Czech Republic and their comparison with six commercially available experimental inhibitors in advanced stages of development. To this end, several independent experimental approaches were employed. In addition to the obligatory determination of enzyme inhibition, the phosphorylation of Serine 2 on RNA polymerase II – a direct interaction partner of CDK9 - was determined, the expression of genes regulated by CDK9 and the ability of the substances to induce cell death were also monitored. Furthermore, the pharmacokinetic potential of the substances was evaluated using several *in vitro* ADME tests. The results of this work demonstrated that the new CDK9 inhibitors exhibited promising inhibitory activity against the target kinase, but were less effective compared to the reference inhibitors in most cellular assays. Another shortcoming is their significant efflux, which reduces the bioavailability of substances. Therefore, further optimization of the structure or combination with other drugs is required to maximize their therapeutic effect. Comparing the efficacy and ADME parameters of six reference CDK9 inhibitors under the same conditions side by side also represents a significant contribution to the professional community.

Key words: cyclin-dependent kinase 9, kinase inhibitors, leukemia, cytotoxicity, transcription factors, expression analysis