Summary

Conventional radiotherapy and chemotherapy interfere with the basic functions of dividing cells and are very effective againts rapidly proliferating tumor cells. They are still an indispensable tool in the fight against cancer, but their interventions also affect healthy cells and cause a number of side effects. Due to the instability of the gemone of tumor cells and frequent mutations, increased aggressiveness and resistence to treatment can occur. Tumor resistence to treatment is a very serious problem. There are a number of mechanisms by which cells defend themselves. One of the fundamental causes of resistence is the natural ability of all cells to repair damaged DNA. On the one hand, this is indispensable for cell life. On the other hand, it reduces the effect of chemotherapy or radiotherapy, which are based on the principle of causing DNA lesions. Small interventions in the signaling pathways of the cell´s repair system can contribute to increasing the effectiveness of cytotoxic treatment.

DNA-PK is serine/threonine kinase that is activated by DNA double-strand breaks which are considered the most lethal type of damage caused by radiation and some chemotherapy drugs. Activation of this kinase triggers signaling cascades that can lead to DNA repair, cell cycle arrest, or apoptosis. By inhibiting this kinase, we can block the repair mechanism that was activated by chemotherapy or radiation. Tumor cells are characterized by a high rate of proliferation and a considerable rate of metabolic activity. This fact is probably the way in which the inhibitor is able to target tumor cells and not healthy cells.

The aim of the dissertation was to study the cytotoxic effect of newly synthesized quinazoline and purine derivatives *in vitro* using a panel of tumor cell lines and normal human fibroblasts. Purine derivatives were screened on ten cell lines and tested for their chemosensitizing capabilities. Cytotoxicity of the quinazoline derivatives was tested on a panel of 17 cell lines and the ability to potentiate the effects of the standard chemotherapeutic drug doxorubicin was also investigated. Cell proliferation and viability were monitored using the WST-1 assay. After the basic screening, the most effective inhibitor 14d and the most suitable tumor cell line HT-29 were selected for a more detailed study of the molecular mechanisms of action. By monitoring the activity of caspases (-3/7, -8, -9), an increase in the apoptotic effect was observed when the inhibitor 14d was combined with doxorubicin. The effect on the cell cycle was determined by flow cytometry and the accumulation of cells in the G2 phase of the cell

cycle was registered. Key proteins involved in growth arrest or induction of apoptosis were detected by electrophoresis followed by Western blotting. The aim was to exclude the inhibition of ATM and ATR proteins, which are also involved in repair mechanisms. Protein p53, Chk1 and Chk2 were monitored. The protein p53, which serves as a substrate for ATM, was phosphorylated on Ser 15 after combined treatment. Furthermore, we observed the phosphorylation of Chk1 on Ser 345 and Chk2 on Thr 68. Since these kinases are activated by ATR or ATM, we can state that the tested inhibitor did not affect these pathways. The maximum tolerated dose was determined by *in vivo* research on female outbred mice. The relatively low toxicity of the studied substance was manifested. Inhibitor 14d proved to be a very attractive compound that can serve as a template for the synthesis of other drugs specific for DNA-PK inhibition.