Abstract

Cancer is the second leading cause of death in developed countries, surpassed only by cardiovascular diseases. As a result, intensive research efforts are underway to develop novel and more effective oncological treatment strategies. More than 80% of cancer cases are classified as solid tumors, which are often characterized by pronounced hypoxia. This hypoxic environment reduces the effectiveness of ionizing radiation used in radiotherapy, thereby contributing to the development of tumor radioresistance.

One promising strategy to overcome this limitation is the use of radiosensitizers – compounds that enhance the sensitivity of cancer cells to radiation. Modified nucleosides, which, due to their structural similarity to natural nucleosides, can be efficiently incorporated into the genomic DNA of cancer cells, are particularly interesting in the context of radiosensitization. Their mechanism of action involves capturing of hydrated electrons generated by the radiolysis of water. Incorporation of such compounds into genomic DNA renders the biomolecule more susceptible to radiation-induced damage, ultimately leading to cancer cell death.

The objective of this doctoral dissertation was the synthesis of novel adenine and 2'-deoxyadenosine derivatives, evaluation of their susceptibility to radiolysis, and in vitro assessment of their radiosensitizing properties at the cellular level. Five novel compounds were designed and synthesized: 8-methylthioadenine, 8-trifluoromethylthioadenine, 8-trifluoromethoxybenzylamino-2’-deoxyadenosine, 8-trifluoromethylthiobenzylamino-2’-deoxyadenosine, and 8-trifluoromethylbenzylamino-2’-deoxyadenosine.

All compounds were exposed to ionizing radiation, and the resulting radiolysis products were analyzed using high-performance liquid chromatography and mass spectrometry. The identified products were in good agreement with theoretical predictions.

Due to their higher susceptibility to radiation-induced degradation in aqueous solutions and their closer structural resemblance to natural DNA components compared to adenine derivatives, adenine nucleoside derivatives were selected for further in vitro studies. Cytotoxicity was evaluated using the MTT assay on two cancer cell lines and one normal cell line. In addition, clonogenic assays were conducted, confirming the radiosensitizing potential of these compounds at the cellular level.

Subsequent investigations concerned the most promising derivatives, dA-NHbenzylOCF_3 and dA-NHbenzylSCF_3. A series of experiments, including flow cytometric analyses of cell cycle progression and induction of DNA double-strand breaks, was performed to elucidate their mechanism of action. Furthermore, the compounds' ability to penetrate cells, their subcellular localization, phosphorylation, and incorporation into DNA were examined.

The research presented in this dissertation is of significant relevance for the potential application of the synthesized compounds as radiosensitizers. Following successful in vivo validation and clinical evaluation, these derivatives may contribute to improving the efficacy of radiotherapy in the treatment of solid tumors.