Abstract

Cancer is one of the leading cause of death, especially in highly developed countries. One of the most commonly used treatment modality, apart from surgery and chemotherapy, is radiotherapy. During radiotherapy, patients are exposed to ionizing radiation, which is not indifferent to human body, and when used in high doses, it leads to a number of serious side effects, including the appearance of a secondary tumor.
A particularly important feature characterizing the cancer cells of solid tumors is hypoxia, which is responsible for the low effectiveness of radiotherapy, due to radioresistance of cells at the low concentration of oxygen. This situation calls for introducing of the so-called radiosensitizers, i.e. compounds which can sensitize cancer cells to ionizing radiation. The well-known classes of these compounds include the nitroimidazole oxygen mimetics and thymine analogues. A derivative with an *in vitro* and *in vivo* confirmed radiosensitizing effect, is 5-bromo-2'-deoxyuridine. It has not been used in clinical practice so far due to its swift metabolism. Nimorazol, an oxygen mimetic, is the only radiosensitizer approved in Denmark and Norway as a radiotherapeutic agent in the treatment of head and neck cancer. Due to the limited use of radiosensitizers in anti-cancer therapy, the understanding of their mechanism of action seems to be necessary for the development of new, better-performing compounds.

This doctoral dissertation presents the results of research on the mechanisms responsible for the radiosensitizing properties of selected uridine derivatives and oxygen mimetics from the nitroimidazole group. For this purpose, quantum-chemical calculations and chemometric analysis were used.

Uracil derivatives - uracil-5-yl *O*-sulfamate (SU) and uracil-5-yl *O*-(*N*,*N*-dimethylsulfamate) (DMSU) was tested using crossed electron-molecular beam experiments in the gas phase. For the obtained experimental results, the process of degradation induced by low-energy electrons of registered fragmentation anions was described. In the case of the SU derivative, theoretical studies of the dissociative electron attachment (DEA) in aqueous solution were additionally carried out with the stationary radiolysis experiment. SU does not show radiosensitizing properties despite encouraging results of theoretical calculations of its DEA profile. The recalculation of the DEA process with the chemical accuracy method, G2MP2, allowed to demonstrate that the previously adopted DFT model possesses too low accuracy. On the other hand, in case of DMSU, the degradation paths in the gas phase were similar to those

obtained for SU and support the conclusion that methylation of the derivative does not qualitatively affect the DEA process.

Another aspect studied within this dissertation was the determination of the stability in an aqueous solution of the 6-iodouridine (6IUrd) and selected iodo- derivatives of 2'-deoxyuridine: 5-iodo- (5IdU) and 6-iodo-2'-deoxyuridine (6IdU). For this purpose, the mechanism of the hydrolysis of these compounds was analyzed computationally, as well as kinetic simulations were performed in order to obtain the concentration-time plots and respective half-lifetimes. Research has shown that 6-iodo-2'-deoxyuridine is unstable in the aqueous environment and, different form the literature suggestions, cannot be used as a radiosensitizer. Its low stability, compared to the 5IdU derivative, may result from the steric hindrance of the iodine atom at the 6 position with the sugar residue.

Finally, an interdisciplinary research, in order to identify a possible mechanism of the radiosensitizing effect of nitroimidazoles was carried out. The stationary radiolysis, as well as computational studies were employed to verify one of the mechanisms of action of oxygen mimetics presented in the literature - the radical mechanism – using the 5-hydroxypyrimidine radical-metronidazole model. The quantum chemical studies was supplemented by the quantitative structure-activity relationship (QSAR) based on the known compounds from the nitroimidazole group and their radiosensitization efficiency, expressed as the experimentally measured parameter C1.6. The carried out studies indicate that the commonly assumed radical mechanism is not operative. The obtained QSAR models based on quantum chemical descriptors related to the two mechanisms –radical mechanism or electron attachment based mechanism – show that the model based on the electron attachment descriptors possesses much better prognostic abilities.