

ABSTRACT

Radiation therapy, utilized in about half of cancer cases, could be even more efficient if combined appropriately with chemotherapy. This approach – radiochemotherapy – allows to lower the radiation dose, while improving the therapeutic effect. One of the radiosensitizer examples (radiochemotherapeutic agents) are the thymidine analogues, which are able to sensitize DNA to the solvated electrons' action. These electrons, especially active in the hypoxic environment which is a common feature of solid tumors, are incapable to damage the native DNA nucleobases, but can lead to dissociation of their analogues. This dissociation can further lead to a cascade of events ending with lethal DNA damage.

Two of the most studied thymidine analogues are 5-iodo and 5-bromo-2'-deoxyuridines. Unfortunately both of them, despite very promising *in vitro* studies, did not prove their potential in clinical studies, hence remaining useless in practice. The aim of my study, performed with the use of computational chemistry methods, was to design and characterize a new potent radiosensitizer, that would be similar in the mode of action to 5-bromo-2'-deoxyuridine, but with a better susceptibility to the dissociative electron attachment process.

This goal was achieved with the use of quantum chemistry calculations, mostly with the density functional theory. In first place, the ability to undergo the dissociative electron attachment process was tested for a series of uracil derivatives. Three of them: 5-trifluoromethanesulfonyl-, 5-selenocyanato- and 5-iodo-4-thio derivatives of 2'-deoxyuridine were shown to possess the desirable radiosensitizing properties.

All the derivatives were synthesized and underwent the experimental procedures, where their dissociation was induced by the electron attachment both in water and gaseous environments. The theoretical predictions remain in good agreement with the experimental results. The resonance thresholds in the gas phase dissociation correspond to the thermodynamic stimuli shown in calculations for the respective products. The computational studies concerning the water phase reactions allowed to explain the products formation mechanisms. These also emphasized the need to consider both the deprotonated forms of substrates (pKa values) and the possibility of radical anions protonation in the primary electron attachment process.