„Synthesis and investigation of the chemical and biological properties of potential topoisomerase I inhibitors interacting with the DNA oligomers”.

Promotor: prof. dr hab. Lech Kozerski
Author: mgr Beata Naumczuk

The PhD dissertation presents a synthesis, studies of basic physicochemical and biological properties of the compounds selected from the series TPT and SN38 from camptothecin family as potential inhibitors of topoisomerase I. The results of the interaction of selected compounds with the DNA oligomer and a model nucleoside provide evidence of spontaneous and UV induced covalent bonding of these compounds to the DNA oligomer.

The Mannich reaction was used to obtain a series of new SN38 derivatives, which are well soluble in water. Evidence of stability (half-life time t ½) of the new derivatives in physiologically solvents used for drugs was presented. The interaction of SN38 derivative with the DNA sequence d $(GCGATCGC)_2$ was investigated. It was confirmed by the largest change of the chemical shifts of DNA protons, that these compounds interact with a terminal base pair GC of octamer.

Using the techniques of NMR and MS it has been shown that the selected SN38 derivatives and induced photochemically quaternary ammonium salt TPT have the ability to alkylate DNA through the intermediate *o*-methylene quinine, QM or nucleophilic substitution mechanism. Studying the kinetics and regioselectivity of the reaction of the selected SN38 derivative with 2'-deoxyguanosine in different conditions, confirmed formation of the thermodynamic product of the reaction, N2 dG adduct.

The results of biological tests show that the novel SN38 derivatives have better biological activity *in vitro* against tumor cells than irinotecan used in clinical chemotherapy for breast cancer. In addition, they do not lead to anti-proliferation of normal cells as it is in the case of SN38. The results of the biological assays showed that the TPT derivative exhibits better biological activity against murine leukemia cells after exposure to UV light as compared to activities obtained without irradiation.