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Dissertation

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„Assessment of the anticancer component of acridine in systems containing iodobenzoic acid"

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Cancer is one of the most serious civilization threats of the 21st century. An increase in cancer mortality has been reported worldwide. Nine new tetrahydroacridine derivatives (1,2,3,4-tetrahydro-9-aminoacridine) were synthesized for the first time at the Department of Pharmaceutical Chemistry of the Medical University of Lodz.

The aim of this dissertation was to evaluate the anti-cancer component of nine new tetrahydroacridine derivatives containing iodobenzoic acid on non-small cell lung (A549) and colorectal cancer cells (HT-29) by examining their effects on cell viability, mechanism of anti-tumour activity and antioxidant properties.

Basic screening studies were conducted on a group of nine compounds to select the molecules that most strongly reduce cell survival. Studies have confirmed that all compounds **1a-1i** strongly reduce cell viability. In addition, compounds **1a-1i** had weak anti-inflammatory properties. Almost all parameters of the compounds were in line with Lipinski's rule. Based on the results of cell viability, five compounds were selected, which most strongly reduced the viability of cancer cells (compounds **1b**, **1c**, **1e**, **1f**, **1i**) were selected. The selection of derivatives was made within individual groups - the three best derivatives (one for *ortho*, *meta* and *para*) were selected for lines - A549 and HT-29. Based on the comparison of survival of colorectal, lung and vascular endothelial cancer cells, compounds **1c**, **1f**, **1i** may be safer to use. The compounds had DNA intercalating properties, which is a desirable anti-tumour activity and counteracted cisplatin resistance in bladder cancer cells. However, the substances were not able to capture free radicals. Studies have shown that compounds at concentrations below IC_{50} may have antioxidant activity against endogenous free radicals. Only compound **1c** can protect cells against exogenous free radicals. On three selected compounds **1b**, **1e**, **1i** - the most reducing the survival of A549 cells and on three compounds **1c**, **1e**, **1i** - the most reducing the survival of HT-29 cells, detailed studies on their mechanism of anti-tumour activity were conducted. These compounds inhibited the cell cycle in the G0/G1 phase and strongly induced apoptosis. In addition, the compounds activated the apoptotic pathway by cleaving PARP-1 protein and weakly damaged DNA by histone H2AX phosphorylation. At IC_{50} concentrations, they induced oxidative stress, which could then have an effect on the induction of apoptosis in cancer cells.

Based on the obtained research results, the most promising compounds with potential significance in medicine and pharmacy were selected. Compound **1i** may form the basis for further research for lung and colorectal cancer; compound **1f** for studies on cisplatin resistance bladder cancer and compound **1c** for studies on substances with potentially lower side effects than currently used preparations in the treatment of cancer (lung and colorectal cancer).