

According to the Central Statistical Office of Poland, in 2009 malignant neoplasms were the second, next only to the cardiovascular diseases, cause of the death cases in Poland. They were responsible for 24% of deceases, what means that in Poland, every day due to a kind of cancer circa 250 men, women and children dies. What makes situation even worse, despite the progress in prophylactics and the growing awareness of the society, a number of new cases steadily increases.

Of course, a death rate strongly depends on the kind of a disease, and new drugs cause that slowly but systematically the survival rate grows. The number of patients surviving for at least 5 years after diagnosis, has grown during the first decade of 21st century: for women from 51.2% to 53.5%, for men from 32.9% to 37.3%.

That means that it is very important to look all the time for new drugs, new therapies, which could help in solving this very serious social problem. To this end it is necessary to work towards a better understanding of the factors that are crucial in the cancerogenesis, because this may help in pinpointing these stages of the process at which newly projected drugs can interfere.

One of such fragile stages is a process of creating of the spindle apparatus, which allows chromosomes (during mitosis) to separate and to go to the opposite ends of the cell. This spindle structure is built of microtubules, protein fibers which are created during polymerization process of tubulin – specific globular protein.

Drugs which are currently used in chemotherapy usually act by means of the suppression of the cancer cell divisions (unfortunately, also of the healthy cells). There is a number of possible mechanisms of such action; one of them, relatively recently exploited, is the inhibition of formation of microtubules – this causes perturbations in a process of mitosis and therefore stops the cancer growing.

Compounds that can interact with tubulin and inhibit creation of microtubules are traditionally divided into three classes, depending on the binding site on the receptor molecule: Vinca alkaloids, paclitaxel and colchicine. Our project is devised to select the compounds which will interact with colchicine binding site (or domain) of the tubulin molecule.

Literature data and our previous experience caused that we turn our attention to the derivatives of chalcone, relatively simple chemical compound which systematical name is 1,3-diphenyl-2-prop-1-one.

In our opinion the success in such an endeavor demands a multidisciplinary team, we are going to connect the efforts of few specializations, starting from a synthetic chemist, through people who can perform quantum-mechanical calculations (in particular, docking a drug molecule to the structure of a receptor protein molecule), experts in biological studies, who can in the lab determine the influence of a given molecule on different cancer cell lines and compare this with the effect on healthy cells (because the medicine can not make them more harm), to an X-ray crystallographer, who in turn can determine the positions of atoms in the molecules (so in a sense, show the real molecules), or even can study the very tiny details of electron density distribution and look at e.g. the electrons which make a chemical bonds or calculate the details of electrostatic potential. The last characteristics is of a special interest as it decides about the interactions of molecules with other objects, for instance with receptor molecule.

Our work schedule assumes iterative application of a certain procedure, which will be refined on a fly. We are going to start from picking a pool of chalcone derivatives with a possibly wide range of substituents (they can be either commercially available or easily synthesized). These compounds will be characterized by means of spectroscopic methods (UV VIS, IR, NMR etc.), and their crystal structures will be determined by means of X-ray diffraction. For those compounds for which we will be able to obtain the crystals of high quality, the high resolution diffraction data will be collected, and their electron density distribution will be described. Then, all these compounds will be analyzed, by means of computer-aided docking to the receptor molecule and their potential biological activity will be estimated, based on previously created procedure and scoring scheme. At the same time, the biological activity against cancer and healthy cell lines will be determined experimentally, in the lab. A comparison of both these results should allow to assess how good, or how bad, our computer procedures work. We hope to be able to modify these procedures on a basis of correlations between biological activity and different structural parameters, from the geometry of molecules to the results of high resolution diffraction, e.g. electrostatic potential or dipole moments.

A new, refined procedure will be then used to make a selection of the next pool of compounds, for which all the stages –synthesis, characteristics, structure determination, biological activity - will be repeated. Because one can expect that the compounds will be more and more complicated, the crystals of appropriate quality might be hard to obtain. To help, a databank will be created which will allow to transfer the results for smaller molecules to the more complicated systems. Thus even for those latter ones the details of the electron density should be available.

A final effect of our project should be, first, a group of compounds with high anticancer activity, which can be directed to the further studies, second, the understanding of the mechanism of action of chalcones, and the better pharmacophore model. Additionally, our research should influence the progress in advanced experimental and computational methods.