

Pharmaceutical industry is one of the fastest growing and the most profitable branches of the global economy. Every year treatment of more and more diseases becomes possible as new techniques develop and are applied to the problem of disease emergence. This fact evokes the need for the development of modern science in the world, especially the one concerning the searching for new chemotherapeutics.

Cancer is the second leading cause of death in Poland after cardiovascular diseases. Application of chemotherapy seems to be crucial in the fight against tumour diseases. Nowadays many different active substances are used to inhibit the proliferation of cancer cells, but still there is a need to find substances, which act specifically as anticancer factors. The common characteristics of many antineoplastic drugs is their limited effectiveness as well as extensive side effects, which prevent the continuation of the therapy.

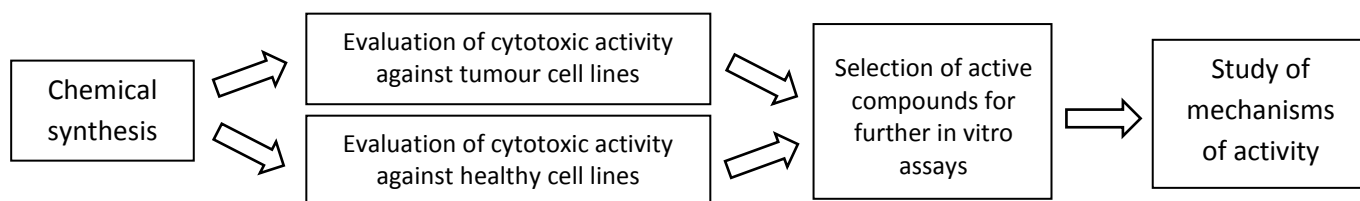
Screening for new active substances serving as antiproliferative agents, but affecting only cancer cells, therefore becomes one of the main targets in pharmaceutical researches. Availability of new technologies related to research development of tumour pathogenesis designated new strategies of searching active compounds, which can be used as medications. One of these pathways is to use natural occurring substances, which in the native form or after modifications show high antiproliferative activity against tumour cells. These compounds can act independently or in combination with other medicines (complex therapy) and can be used in treatment of w cancer diseases.

In the worldwide literature there are more and more reports about new active substances that exhibit strong antimicrobial, antifungal or anti-tumour effects, but in spite of this, the search for compounds that are highly effective in inhibiting the proliferation of tumour cells, but do not adversely affect the function of healthy cells, is still in progress.

It is worth noting that there are more difficulties than one would expect. The very complicated chemical synthesis causes many problems during the production of a substance itself, with its modification or purification in order to obtain a product of high quality. Another problem concerns the solubility of substances. Chemical compounds have different chemical and spatial structures as well, which affect their behaviour in solvents, including the body fluids. It must be borne in mind that the undissolved compound will not be able to penetrate into the cells and cause the desired effect. It is therefore not only to design the structure of a proper compound, its chemical synthesis (or modification of existing natural substance), but also to provide good solubility of the product. Many organic substances are soluble in organic solvents, while body fluids, to which these substances will be applied to, contain water which unfortunately do not dissolve organic molecules.

The aim of this project is to search for new plant-derived derivatives (alloxanthoxyletins) that will exhibit high antiproliferative activity against tumour cells, comparable to leading cytostatics, and reduced cytotoxicity to healthy cells. Fatty acids are commonly known substances showing high lipophilicity and therefore having high affinity to biological membranes. They can incorporate into phospholipid bilayers and affect their structure, permeability and selectivity. Modifications of alloxanthoxyletin, by combining it with selected fatty acids, will alter lipophilic properties, which will result in an increase in the cytostatic activity of these substances.

The project consist of several, complementary to each other areas:



#### 1. **Synthesis of alloxanthoxyletin and fatty acid derivatives.**

The first stage of studies will be to obtain a varied group of alloxanthoxyletin and fatty acid derivatives.

#### 2. **Evaluation of cytotoxic effect of newly synthesized compounds** against cancer and healthy cell lines.

#### 3. **Evaluation of cells viability, level of proliferation (MTT assay, incorporation of BrdU into DNA) and their mortality (LDH assay).**

#### 4. **Selection of these derivatives, which show a high antiproliferative activity** against cancer cell lines and the evaluation of their impact on apoptosis induction, apoptosis related gene expression, caspase 3/7 activity and on the level of active NF-cappaB form.