Cancer is a general name of a group of diseases which common feature is excessive, rapid proliferation of abnormal cells. According to the World Health Organisation, cancer was responsible for an approximate 9.6 million deaths in 2018 globally. Despite the great effort of many research groups, fully effective anticancer drugs are still unknown. One of the most widely used groups of anticancer drugs are anthracycline antibiotics, which history dates back to the 1960s, when the first compounds were isolated from bacteria. The main representatives of this group - doxorubicin (DOX) and daunorubicin (DNR) - are highly effective against several types of cancers, but their usage is limited due to the side effects caused by them. The most serious ANT side effect is cardiotoxicity, which can manifest even several years after the treatment.

There are several theories trying to explain the possible mechanism of cardiotoxicity caused by ANT. Many studies postulate that the most important factor is ANT metabolism to the secondary-alcohol compounds that do not possess anticancer activity and moreover are harmful to the heart muscle. One of the most widely described examples of these properties refers to the metabolites of DOX and DNR – doxorubicinol (DOXol) and daunorubicinol (DNRol), respectively.

In the organism, the formation of DOXol and DNRol is regulated by the enzymes belonging to two groups: carbonyl reductases (CBR) and aldo-keto reductases (AKR). Among them, CBR1 and AKR1C3 are classified as the most important in ANT metabolism. There are several research papers which evaluate potential positive effect on anticancer therapy by using CBR1 or AKR1C3 inhibitors. The results show that after application of enzyme's inhibitor, the concentration of the drug that is necessary to obtain anticancer effect decreases. Moreover, the metabolic rate of ANT is reduced and thus the benefit/risk ratio is increased. The results are promising, but the resistance of cancer cells against ANT is still not fully overcome. However, there is no research based on the simultaneous inhibition of the both mentioned enzymes. This mechanism could further increase DOX/DOXol or DNR/DNRol ratio leading to the significant improvement of their potency. A smaller amount of toxic metabolites could lead to decreased probability of cardiotoxic effect. Unfortunately, compounds with dual CBR1-AKR1C3 properties are still unknown.

The information described above was the starting point for the project objectives, which are the determination of the structural features necessary to obtain dual CBR1-AKR1C3 inhibitors; virtual screening, purchase and verification of CBR1-AKR1C3 inhibitory properties of the selected compounds; determination of the chemosensitizing and cardioprotective effects of dual CBR1-AKR1C3 inhibitors.

The project will consist of two parts: *in silico* and *in vitro.* In *in silico* part, advanced computer software will be used to optimize crystal structures of CBR1 and AKR1C3 to obtain valuable models that will reproduce the real binding mode of ligands (molecules that have affinity for a particular molecular targets such as enzymes or receptors) within enzymes' catalytic sites. For this purpose, series of docking simulations will be performed. Models of high predictive value will be selected through retrospective virtual screening and molecular dynamics simulations. Such data will be essential to develop pharmacophore models of the enzymes' ligands – three-dimensional maps showing structural features that determine whether a molecule can bind to its potential target. The pharmacophore models will be used in virtual screening of commercially-available chemical compound libraries (for example ZINC database) to select compounds that possess proper structural features to be classified as promising dual CBR1-AKR1C3 inhibitors. Then the chosen compounds will be examined due to their ADMET (Absorption-Distribution-Metabolism-Excretion-Toxicity) properties and the best ones will be purchased and tested in series of *in vitro* studies. First, the compounds will be tested on recombinant CBR1 and AKR1C3 enzymes to confirm their inhibitory properties. The most potent compounds will be used in the experiments on cancer cell lines. The research will consist of a series of experiments evaluating cell viability and proliferative properties after administration of ANT and ANT in combination with CBR1-AKR1C3 inhibitors. Additionally, it is planned to examine these combinations on rat cardiomyocytes.

The issue of ANT resistance and cardiotoxicity is so significant because of the widespread use of this group of drugs in the therapy of many types of cancer. The results of the project will expand knowledge about the role of ANT metabolism in cancer resistance and cardiotoxicity. *In silico* research will allow to describe a new class of compounds – dual CBR1-AKR1C3 inhibitors. *In vitro* study will answer the question whether this inhibitory approach would be useful in anticancer therapy by potentiating ANT activity, that would eventually lead to a reduction in their therapeutic doses. It will also indicate if dual CBR1-AKR1C3 inhibitors could be used as cardioprotectants. The application of this strategy can significantly increase the effectiveness and safety of ANT treatment, and thus improve the comfort of therapy for many patients.