

## Abstract

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Title of diploma thesis: Effect of selected cytostatics for the treatment of leukemia on the activity of human carbonyl reducing enzymes

Key words: reductases, leukemia, cytostatics, inhibition

Anthracycline antibiotics, especially daunorubicin, are widely used for the treatment of acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL).

Although the efficacy of these drugs is high, treatment is still limited due to cardiotoxicity and tumor cell resistance to anthracyclines.

Mechanisms that contribute to the formation of anthracycline resistance include metabolic biotransformation (reduction) to less efficient secondary alcohols. The reduction is catalyzed by carbonyl reducing enzymes belonging to aldo-keto reductase (AKR) and short chain dehydrogenase/reductase (SDR) superfamilies.

The discovery of AKR and SDR inhibitors could help to overcome anthracycline resistance and also reduce cardiotoxicity caused by these drugs.

The aim of the diploma thesis was to find out whether all-*trans*-retinoic acid, cyclophosphamide, cytarabine, cladribine and prednisolone are able to inhibit anthracycline reductases AKR1A1, AKR1B10, AKR1C3, AKR7A2 and CBR1.

The methodology of the diploma thesis includes *in vitro* incubation of the enzymes with daunorubicin as substrate in sodiumphosphate buffer, isolation of daunorubicinol from the reaction mixture and measurement of its amount by high performance liquid chromatography (UHPLC). The amount of daunorubicinol determined by UHPLC is then used to calculate the specific activity.

The most active inhibitors were all-*trans*-retinoic acid that decreased the activity of AKR1B10 ( $IC_{50} = 74,5 \mu M$ ) and AKR1C3 ( $IC_{50} = 1,2 \mu M$ ) and prednisolone that decreased activity of AKR1C3 ( $IC_{50} = 57,6 \mu M$ ).