

## **ABSTRACT**

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Title of diploma thesis: New inhibitors of topoisomerase II - study of antiproliferative effects and influence on antitumor activity of anthracyclines

Despite the dose-limiting cardiotoxicity, anthracyclines (ANT) are among the most effective and widely used antitumor drugs. The only registered drug to prevent this adverse effect is dexrazoxane, whose cardioprotective activity is currently attributed to interaction with topoisomerase 2 (TOP2) beta. This relatively new hypothesis provides an opportunity for the discovery and study of new TOP2 inhibitors, that could be more beneficial cardioprotective drugs. An essential condition for the use of a potential cardioprotective agent is, however, the absence of a negative influence on anticancer efficacy.

In this work, we studied the antiproliferative activity of new substances derived from the molecule BNS-22, which is a catalytic inhibitor of TOP2 and manifested cardioprotective activity. We also studied the activity against the antiproliferative effect of daunorubicin (DAU), to clarify the compatibility in case of combined use. These experiments were performed on the leukocytic cell line HL-60 using the MTT assay of cytotoxicity. Furthermore, we tested the inhibitory activity against the TOP2 alpha isoform using a decatenation assay. This enzyme is considered a key target for the activity of TOP2 poisons, so it was necessary to refute the possibility of interference with ANT and the risk of suppressing their antitumor activity.

The outcome of this work was that all investigated inhibitors have antiproliferative activity and they significantly inhibit TOP2 alpha. Nevertheless, they did not suppress the antitumor activity of DAU. Thus, these studied substances have the potential for cardioprotective use and are suitable for consequent research in this area.