# ABSTRACT

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Title of diploma thesis: Syntesis of dexrazoxane analogues as potential cardioprotectants II

Doxorubicin, daunorubicin and other anthracycline antineoplastic antibiotics are very important anticancer agents. Due to their high toxicity in the heart muscle, these highly effective drugs are often associated with acute cardiotoxicity and dose-dependent cardiomyopathy. This cardiomyopathy is characterized by enlargement of the left ventricle and complete systolic dysfunction. It is assumed that this side effect is mainly caused by reactive oxygen species, whose formation is catalysed by complex of anthracyclines and iron ions. The only clinically used drug that significantly reduce anthracycline cardiotoxicity is dexrazoxane (DEX). DEX is *in vivo* metabolised to a substance ADR-925, which chelates the iron ions. DEX is also a catalytic inhibitor of topoisomerase II (TOP2). Interestingly, the cardioprotective effects of DEX were discovered accidentally and only few structure-cardioprotective activity relationships studies were published. The aim of this work was to develop a method for the preparation of DEX analogue 4,4'-(propane-1,2-diyl)bis(piperazin-2-one) (MK-15) bearing piperazin-2-one cycles instead of original piperazin-2,6-dione cycles, and to prepare the sufficient amount of MK-15 for *in vitro* and *in vivo* studies. First, we developed a large-scale synthesis of piperazin-2-one. Then we optimized the synthesis of MK-15 via the reaction of piperazine-2-one with the appropriate alkylating agents. Finally, we prepared sufficient quantities of MK-15 in several batches. Cardioprotective effects were studied *in vitro* on isolated rat neonatal cardiomyocytes and *in vivo* on rabbit model of chronic anthracycline cardiotoxicity. These results will help us to understand the mechanism of action of DEX and potentially elucidate the role of iron chelation in the cardioprotective effect of DEX.