ABSTRACT

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Title of the thesis: Synthesis of dexrazoxane analogs

Anthracycline antibiotics (ANT), such as daunorubicin, doxorubicin or epirubicin, belong amongst the most effective antineoplastic drugs. They are being used to treat leukemias as well as solid tumors. One of the limiting factors of these highly active substances is their cardiotoxicity. Supposedly, cardiotoxicity can originate in the following basis; either by the interaction with Fe ions which form reactive oxygen species (ROS) or directly caused by the inhibition of topoisomerase IIβ by ANTs in cardiomyocytes. Irreversible damage to heart muscle cells can lead to heart failure. Dexrazoxane (DEX) is the only drug clinically used for ANT-inducted cardiotoxicity prevention. DEX is a bisdioxopiperazine derivative, and its mechanism of action is not fully clear. There are two main hypotheses: 1. chelation of intracellular iron ions and reduction of ROS formation, 2. catalytic inhibition of topoisomerase IIβ.

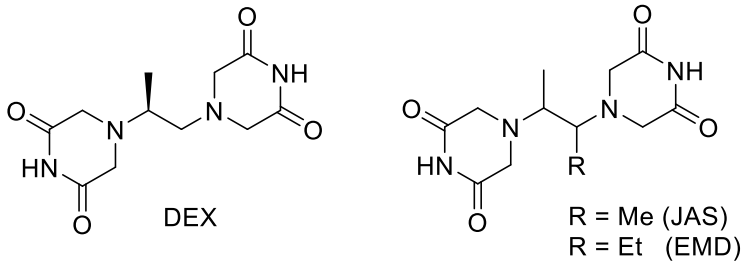

Figure 1: Structure of dexrazoxane and dexrazoxane analogues prepared in this thesis.

The thesis aimed to prepare DEX analogues with a modified linker. Namely, the butane-2,3-diyl analogue (JAS) and pentane-2,3-diyl analogue (EMD). The first key point in the synthesis of the desired analogues was the preparation of the corresponding diamines. The initial compounds were butane-2,3-diol and pentane-2,3-dione, reduced to pentane-2,3-diol. It was necessary to separate the diastereomers during the synthesis to obtain pure products and/or pure racemic mixtures. In the EMD synthesis, the separation of diastereomers took place during the purification of tetra(*tert*-butyl) ester of 2,3-diaminopentane-*N*,*N*,*N*',*N*'-tetracetic acid through

the column chromatography. The JAS synthesis enabled the separation of racemate from *meso*-form of butane-2,3-diamine dihydrochloride due to their different ability to crystallize from the reaction mixture. The critical point of the synthesis was the cyclization of bisdioxopiperazine cycles. Two alternative approaches were utilized. The first method was the cyclization of *N*,*N*,*N*',*N*'-tetraacetic acid in formamide at a high temperature. The second method used tetramethyl ester, which cyclized in dioxane using formamide and sodium hydride. Both cyclization reactions resulted in the final products in the yield 11–66 %.

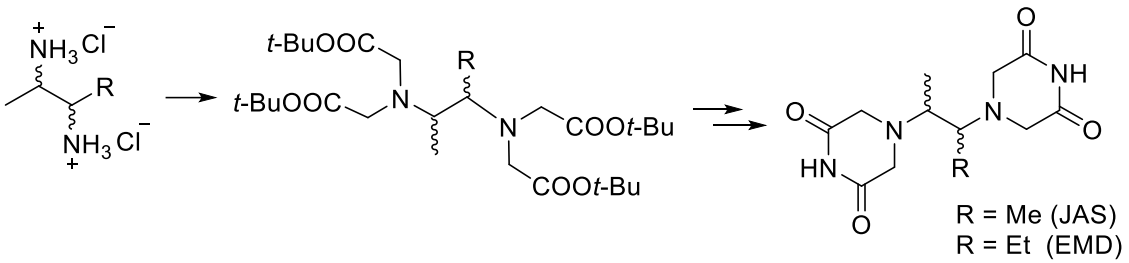

Figure 2: Scheme of synthesis bisdioxopiperavine derivatives

The final compounds were tested for cardioprotective potential and their inhibitory activity to topoisomerase IIβ *in vitro* was examined. The results showed that the position of the substituents on the linker has an impact on their effectiveness. Furthermore, both substances proved to have cardioprotective activity, but it depended on the configuration on the chiral carbons.