ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Organic and Bioorganic Chemistry

Student: Mgr. Jan Šůs

Supervisors: Assoc. Prof. PharmDr. Jaroslav Roh, Ph. D.

Title of rigorosum thesis: Synthesis of cardioprotective ion chelators derived from diethylenetriaminepentaacetic acid

Anthracyclines (ANTs) such as doxorubicin or daunorubicin are widely used anticancer drugs. However, their administration is associated with high risk of cardiotoxicity. Chronic ANT cardiotoxicity is characterized by dilated cardiomyopathy, with subsequent development of left ventricular contractile dysfunction and congestive heart failure. It is supposed that the complexation of ANTs with intracellular iron ions leads to the formation of reactive oxygen species, which causes serious tissue damage especially in myocardium. However, recent studies showed that the mechanism of action is more complex and the inhibition of topoisomerase IIβ (TOP2β) may play a crucial role.

The only drug preventing cardiotoxicity of ANTs with established clinical efficacy is dexrazoxane (DEX). The mechanism of action of DEX is not fully elucidated, it probably involves either chelation of intracellular ions by its metabolite ADR-925 (Fig. 1) or the inhibition of TOP2β by the parent compound.

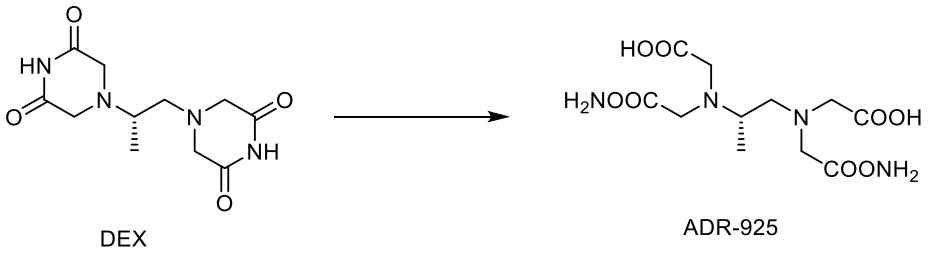

Fig. 1. Dexrazoxane and its metabolite ADR-925

This work may be divided into three parts. In the first part, we synthetized dexrazoxane´s metabolite ADR-925 in the amounts necessary for subsequent *in vitro* and *in vivo* testing in order to study mechanisms of cardioprotection of DEX.

In the second part, we designed several potential cardioprotective iron chelators derived from diethylenetriaminepentaacetic acid (DTPA, Fig. 2). The lead compound ES-5 (Fig.

2) was synthetized and evaluated *in vitro* in isolated neonatal rat cardiomyocytes and *in vivo* in rabbit model of chronic ANTs cardiotoxicity.

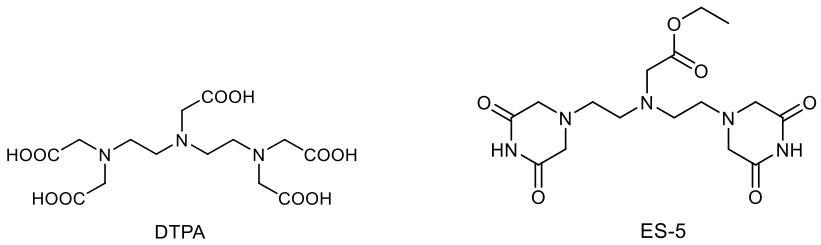

Fig. 2. Structures of diethylenetriaminepentaacetic acid (DTPA) and ES-5

In the third part, we focused on the synthesis of analogues of DEX with modified linker. The compound JS-X (Fig. 3) was synthetized and intended for subsequent *in vitro* and *in vivo* testing.

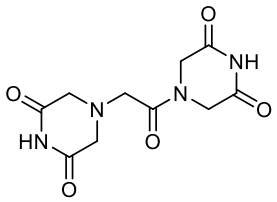

Fig. 3. Structure of JS-X