SUMMARY

Title: New possibilities of cardioprotection in anthracycline cardiotoxicity

This PhD thesis is a commented collection of 3 published original papers describing experimental research into protective effects of bisdioxopiperazine derivatives, including clinically used drug dexrazoxane (DEX), against chronic anthracycline (ANT) cardiotoxicity.

In the first part, selected derivatives of DEX with chemical structure modified on dioxopiperazine cycles were studied. *In vitro* experiments suggested a loss of cardioprotective potential in all derivatives tested including those with the smallest change in the ring structure. This assumption was later confirmed in head-to-head comparison with DEX *in vivo* on a chronic ANT cardiotoxicity model in rabbits. The loss of cardioprotective effect did not correlate with iron chelating properties of the derivatives´ metabolites, but it showed good association with ability of parent compounds to interact with topoisomerase IIβ (TOP2B). These experiments also confirmed that the *in vitro* assays used in this study are suitable for prediction of cardioprotective effects of these substances against chronic ANT cardiotoxicity *in vivo*.

The other part focused on compound ICRF-193 which differs to DEX by a single methyl attached to the aliphatic linker. This compound showed higher potency in both TOP2B and cytoprotective assay against ANT toxicity in primary cardiomyocytes *in vitro*, but its poor water-solubility precluded *in vivo* study. This was overcome by design of water-soluble prodrugs of ICRF-193 in which the release of the active metabolite and cytoprotective potential were characterized *in vitro* in primary cardiomyocytes. A selected prodrug (compound GK-667) was than administered intravenously to rabbits and plasma pharmacokinetics of the parent prodrug, active and inactive metabolite were investigated. Plasma concentrations of active ICRF-193 suggested that GK-667 deserves examination for its cardioprotective effects against chronic ANT cardiotoxicity *in vivo*.

Finally, it was revealed that the prodrug GK-667 can provide dose-dependent cardioprotective effects against chronic ANT cardiotoxicity on the rabbit model with almost complete protection against most of cardiotoxicity parameters at higher studied dose (5 mg/kg). Thus, based on a dose ratio to ANT it seems to be the most potent bisdioxopiperazine cardioprotectant reported so far. It was revealed that it acts as cardioprotectant through its active metabolite ICRF-193 which inhibits TOP2B and thus prevent ANT-induced DNA damage and following signalling in the heart. The agent did not affect either ANT pharmacokinetics *in vivo* or ANT anticancer effect *in vitro*, thus it seems to be an interesting drug candidate for further advanced study and development as cardioprotective agent against chronic ANT cardiotoxicity.