# 4. CONCLUSIONS

Iron chelators and the flavonoids have been studied in order to elucidate the molecular mechanisms that eventually lead to their cardioprotective effects against anthracycline cardiotoxicity. The investigations described in this thesis allowed us to conclude that:

a. The oxidative toxicity of the anthracyclines might not be due to hydroxyl radicals but rather some other reactive oxygen species (e.g. superoxide radicals) and thus, chelation of redox-active iron is not the sole determinant of an effective protector. Iron, however, might still play role in some oxidative stress-independent mechanisms of anthracycline toxicity.

b. Dexrazoxane and the flavonoid monoHER significantly reduced the initiation of apoptosis in A549 cells suggesting a kind of antagonism between these compounds and doxorubicin. Although most clinical studies have not found decreased antitumour response to doxorubicin in dexrazoxane-treated patients, the risk/benefit ratio of dexrazoxane should be carefully considered before its administration to each individual patient.

c. Neither PIH or SIH exert undesirable interactions with the main anthracycline biotransformation enzymes i.e. cytochrome P450 and cytosolic reductases. On the contrary, these compound were able to prevent anthracycline-induced loss of P450 activity.

d. carbonyl reductase (EC 1.1.1.184) as the most important daunorubicin-C13-reductase i.e. superior to the members of AKR class, whose contribution to C13-dihydrometabolite formation is only minor. These findings have implications for the design of new cardioprotectors as pharmacological inhibitors of carbonyl reductases.

e. The cardioprotective effects of the flavonoids cannot be associated with a single physico-chemical or biochemical property of the flavonoid. However, we found that the degree of carbonyl reductase inhibition is not critical for the cardioprotective action of the flavonoids. From 10 flavonoids studied, monoHER and the 7-trimethylammonium derivate of quercetin were the best protectors against doxorubicin toxicity in neonatal rat ventricular cardiomyocytes.