ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Biochemical Sciences

Candidate: Bc. Kateřina Grofková

Supervisor: Mgr. Lenka Laštovičková, Ph.D.

Title of diploma thesis: The use of selected inhibitors to overcome anthracycline resistance in breast cancer therapy

The breast cancer is a heterogenic disease and a worldwide problem mainly for women. It has been treated with anthracycline antibiotic doxorubicine for decades. The greatest problem of this treatment is a cardiotoxicity usually associated with a metabolite of doxorubicine – doxorubicinole. This metabolite is produced in an enzymatic reaction catalysed by carbonyl reductases. A multidrug anthracycline resistance, caused by induced expression of carbonyl reductases and efflux ABC transporters, is another serious problem. Therefore, new inhibitors of carbonyl reductases and efflux ABC transporters have been searched for, to overcome multidrug resistance and reduce doxorubicine cardiotoxicity.

The inhibitory effect of several proteinkinase inhibitors (afatinib, erlotinib hydrochloride, dacomitinib and tipifarnib) on carbonyl reductase activity (AKR1A1, 1B1, 1B10, 1C3 and CBR1) was investigated in the thesis. The greatest inhibitory potential was found for inhibitor tipifarnib and enzyme AKR1C3. The inhibition of 10μM tipifarnib was 91.32 % and 96.36 % was observed for 50μM tipifarnib. The value of IC_{50} was experimentally determined to 1.03 ± 0.03 μM and inhibitory constant Ki^{app} to 0.07 μM. A noncompetitive type of inhibition was defined from the Lineweaver-Burk plot. Comparing the intensity of binding (inhibitor to enzyme) it was suggested that tipifarnib is a tight-binding inhibitor. Based on these results it can be assumed that combination of doxorubicine and tipifarnib could improve therapeutic effect by inhibition of AKR1C3.