ABSTRACT

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The anthracycline antibiotics are a significant group of drugs for treatment of various types of cancer. Difficulties related to their usage are cardiotoxicity and multiple drug resistance. Many factors are involved in the development of resistance; one of them is inactivation of anthracyclines by the activity of enzymes, human reductases, which are involved in biotransformation of anthracyclines by reducing their carbonyl group. Daunorubicin was selected from the group of anthracycline antibiotics, in which the potential involvement of selected carbonyl reducing enzymes in its metabolism (AKR1A1, AKR1B1, AKR1B10, AKR1C1, AKR1C2, AKR1C3, AKR1C4, CBR1 and CBR3) was subject of verification. The specific activity of selected reductases was determined by UHPLC analysis of the major metabolite, daunorubicinol. The most active reductases were AKR1B10, AKR1C3, AKR1A1 and CBR1.

There is a great potential use of cyclin-dependent kinase inhibitors (CDKi) in cancer therapy. Expected effect is primarily influencing of cell cycle and blocking of some transporters that eliminate anthracyclines from cells. It is expected, that cyclin-dependent kinase inhibitors could potentially reduce the activity of carbonyl reducing enzymes. This would cause prolongation of their activity in cells as well as increasing efficiency of cytostatics. In my research I focused on influence of CDKi on activity of two selected human reductases from AKR superfamily (AKR1A1, AKR1B10). Inhibitory effect was determined for following CDKi: AT-7519, AZD5438, dinaciclib, flavopiridol, LEE-011, palbociclib, purvalanol A, R547 and SNS-032. Whereas the inhibitory effect of tested CDKi on AKR1A1 was negligible, AKR1B10 is a suitable target for CDKi, where the greatest inhibitory potential was detected mainly in AZD5438 and dinaciclib.