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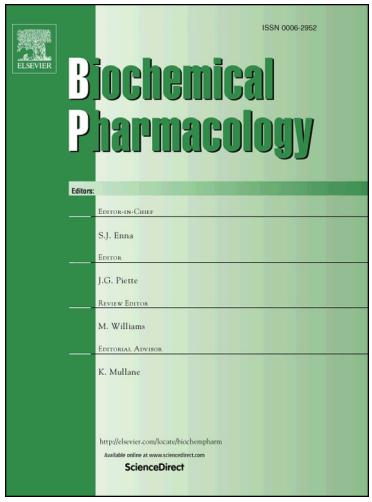

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Roscovitine and purvalanol A effectively reverse anthracycline resistance mediated by the activity of aldo-keto reductase 1C3 (AKR1C3): A promising therapeutic target for cancer treatment

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Abstract

Members of the short-chain dehydrogenase/reductase (SDR) and aldo-keto reductase (AKR) superfamilies mediate the reduction of anthracyclines to their less potent C-13 alcohol metabolites. This reductive metabolism has been recognized as one of the most important factors that trigger anthracycline resistance in cancer cells. In our study, two purine analogues, purvalanol A and roscovitine, were identified as effective inhibitors of aldo-keto reductase 1C3 (AKR1C3), an enzyme that is overexpressed in many cancer types and is also a key player in tumour cell resistance to anthracyclines. Purvalanol A and roscovitine potently inhibited human recombinant AKR1C3 (Ki = 5.5 μM and 1.4 μM, respectively) and displayed similar activity in experiments with intact cells. Ligand-protein docking calculations suggested that both inhibitors occupied a part of the cofactor-binding site. Furthermore, we demonstrated that the combination of daunorubicin with purvalanol A or roscovitine exhibited a synergistic effect in AKR1C3 overexpressing cells. Based on these findings, it is possible to presume that purvalanol A and roscovitine may have the potential to enhance the therapeutic effectiveness and safety of anthracyclines via inhibition of AKR1C3.

Keywords: Anthracyclines; AKR1C3; Cyclin-Dependent Kinase; Drug Resistance; Inhibition

Abbreviations: AKR, aldo-keto reductase; FBS, foetal bovine serum; CDK, cyclin-dependent kinase; CI, combination index; Dau, daunorubicin; Dau-ol, daunorubicinol; DOX, doxorubicin; DMSO, dimethyl sulfoxide; Fa, fraction affected; HCT116-AKR1C3, cells transfected with pCI_AKR1C3; HCT116-EV, cells transfected with empty vector pCI; MTT, 3-(4,5-dimethylthiazoyl-2-yl)2,5-diphenyl tetrazolium bromide; NADPH, nicotinamide