# AKR1C3 as a therapeutic target in the treatment of aggressive tumors, with poor prognosis and/or resistant to traditional therapies

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Aldoketo reductase 1C3 (AKR1C3) is a metabolic enzyme that performs oxidoreduction reactions on a variety of substrates, such as endogenous steroids, prostaglandins and exogenous compounds. It is mainly expressed in prostatic tissue, but more generally it shows endocrine organ expression in adrenals, breast and uterus too. Its principal function consists in regulating the steroids' availability for the respective receptors. From a pathological perspective, AKR1C3 overexpression is involved in the development of several malignant diseases, e.g. breast cancer, castration resistant prostate cancer (CRPC), endometrial cancer, acute myeloid leukemia (AML), some of whom have currently poor prognosis. It is also involved in mechanisms of some anticancer drugs resistance, as anthracyclines and nitrogen mustards. Since its key role in resistance occurrence for different aggressive tumors with poor prognosis, AKR1C3 is here studied on one hand as a target of inhibitors that could be co-administered with drugs currently used in therapy, towards which resistance arises (e.g. abiraterone, a CYP17A1 inhibitor, or enzalutamide, an Androgen Receptor (AR) inhibitor, both used to treat CRPC), and on the other hand as a target of dual inhibitors that could bond both AKR1C3 and other target, such as CYP17A1 or AR. Starting from our potent and selective AKR1C3 inhibitors previously developed (previously published in: Pippione A.C. et al. (2018) Eur J Med Chem, 150, 930-945; Pippione A.C. et al. (2022) Eur J Med Chem, 237, 114366) and from the pharmacophore scaffold of either CYP or AR, new compounds were synthetized and tested for their ability to inhibit AKR1C3 as well as the other targets. In vitro enzymatic assays on purified proteins and cell-based assays were performed. The results obtained highlight the potential usefulness of targeting AKR1C3 and either CYP or AR to treat AKR1C3-overexpressing cancers.