In vitro and in silico analysis of novel steroidal oxime and azine derivatives: binding affinity for estrogen, androgen, and glucocorticoid receptors and inhibition of aldo-keto reductases

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Steroid hormones regulate various biological processes and their structurally modified analogs have found extensive use in medicine as anti-inflammatory and anticancer agents by targeting steroid receptors. Steroid derivatives were proven to be efficient drugs against several types of cancer, particularly hormone-dependent. Recently, enzymes from the aldo-keto reductase (AKR) superfamily have also gained attention as important targets in anticancer drug discovery. These enzymes play a crucial role in the metabolism of xenobiotics, steroids, and carbohydrates and in the development of cancer and drug resistance, making their inhibition a focus for therapeutic research. This study aimed to evaluate the biological activity of newly synthesized steroidal oxime and azine derivatives including *in vitro* screening of their binding affinity for estrogen (ER), androgen (AR), and glucocorticoid receptors (GR) and inhibition of AKR1C3, as well as *in silico* prediction of molecular interactions between targets and ligands identified in the preliminary screening. Methods applied included a fluorescent assay in yeast for identifying and quantifying steroid receptor-ligand binding, fluorescence spectroscopy to identify AKR1C3 inhibitors, and molecular docking to explain the molecular basis of protein-ligand interactions. Among tested compounds, one compound showed a high selective binding affinity for the ligand-binding domain of ERβ. Several compounds were identified as potent GR ligands, with binding affinities higher than prednisolone, while no ligands were detected for ERα and AR. In the enzymatic assay, all tested steroidal oxime derivatives and two azine derivatives exhibited potent inhibitory effects against AKR1C3, higher than ibuprofen. These results encourage future studies to discover mechanisms behind the action of these steroid derivatives and may serve as a starting point for the design of new anticancer drugs or adjuvants.