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SAR, SITE-DIRECTED MUTAGENESIS AND CELL PROLIFERATION STUDIES ON NEW STEROID AROMATASE INHIBITORS

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Aromatase is a cytochrome P-450 enzyme that catalyses the aromatization of androgens, the final step in the biosynthesis of estrogens. Aromatase inhibitors reduçe the synthesis of estrogens and offer a therapeutic alternative for the treatment of estrogen-dependent cancers such as breast cancer.[1]

In this work we are presenting our recent studies on the design, synthesis and biological evaluation of hit compounds (Fig. 1) that allowed the establishment of new SAR on aromatase inhibitors.[2,3] Additionally, site-directed mutagenesis studies combined with computer-assisted protein-ligand docking experiments were performed in the selected lead compounds suggesting that the binding geometry of steroid aromatase inhibitors to the enzyme active site is dissimilar.[4] These findings strong contribute to the elucidation of the aromatase active site and may help in the development of new aromatase inhibitors. Furthermore, the effects of lead compounds on MCF-7aro cell proliferation and induction of cell death were investigated. Our results showed that apoptosis and autophagic processes are involved as mechanisms of cell death.[5]

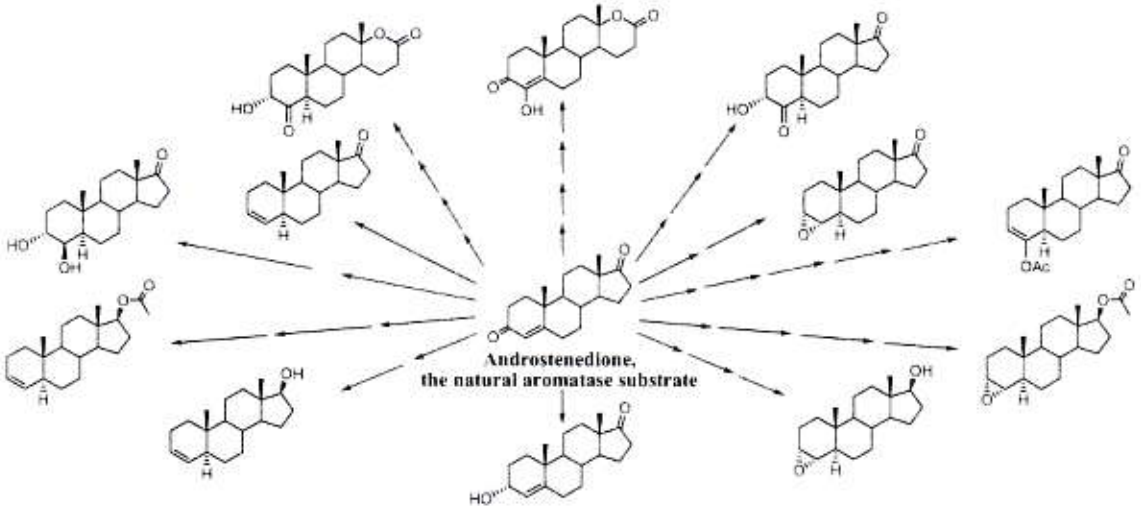

Figure 1. Substrate-based aromatase inhibitors designed, synthesized and evaluated

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