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Molecular mechanisms of action of selected steroids in breast cancer cells

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Oestrogen receptors (ERs) represent key biomarker for breast cancer, and their status significantly influences disease prognosis and treatment regimens. Unique library consisting of approximately 8000 steroids derived from natural compounds, e.g. brassinosteroids, with described synthetic pathways was used to find potential ligands for ERs in order to predict compounds that may block their activity.

Two compounds, MU-5562 and MU-5611 showing similar structure motives to estrone have been selected as the most promising candidates showing ER inhibitory activity comparable to routinely used ER inhibitors tamoxifen and fulvestrant. These compounds stabilize ERs similarly to tamoxifen. Determination of luciferase activity showed reduced signals comparable to commercial inhibitors. However, immunochemical analysis revealed decreased AGR2 expression indicating different mechanism of action compared to tamoxifen.

Inhibitory effect of these compounds on ER is probably caused by presence of double bond in their D ring, which protects activation of ERs by decreasing of electron density on keto group. This configuration blocks development of hydrogen bonds network, which is responsible for conformational changes of α-helix H12.

Selected combination of computational and experimental methods represents rational and fast way to determine the activity of given compounds towards ERs. We believe that these data would be used not only in research field, but also in clinical practice.

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