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Potent aromatase inhibitors and molecular mechanism of inhibitory action

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Highlights

► Discovery of novel non-steroidal inhibitors against aromatase

► Novel compounds demonstrate higher potencies in aromatase inhibitory than letrozole

► Computational models of aromatase with different substrates are built

► Binding mode of substrates to aromatase has significant impact on pharmacological effect

Abstract

Estrogen is a significant factor in the maintenance and progression of hormone-dependent breast cancer. As well known, aromatase mediates the production of estrogen. Thus, reduction of aromatase with chemical molecules has been considered to be an effective treatment for estrogen receptor-positive (ER+) breast cancer. In this work, we designed and synthesized a series of novel non-steroidal molecules containing 2-phenylindole scaffold and moiety of either imidazole or 1,2,4-triazole to enhance their binding capacity with the aromatase. Among these molecules, a compound named as **8o** was confirmed experimentally to have the highest inhibitory activity to aromatase. Further cell activity assay proved that compound **8o** has low cytotoxicity and is a promising lead for