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Structure-Based Drug Design of ER-ALPHA ANTAGONISTS for Breast Cancer Treatment

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Abstract: *Breast cancer remains one of the most significant global health challenges, accounting for over two million new cases annually. Despite the widespread use of endocrine therapies such as tamoxifen and aromatase inhibitors, treatment efficacy is often limited by resistance, reduced specificity, and adverse effects. In this study, molecular docking approaches were employed to explore novel ligand interactions with estrogen receptor alpha (ERα), a key driver of hormone-dependent breast cancer progression. The 3D structure of ERα (PDB ID: 3ERT) was retrieved from the Protein Data Bank and optimized using* ***pdb2pqr.py*** *to ensure proper protonation and structural refinement. Structural modifications were introduced in rings A and B of the ligand scaffold, and both* ***E- and Z-oxime isomers*** *were evaluated to assess their binding affinity and conformational stability within the ERα ligand-binding domain. Tamoxifen was included as a reference selective estrogen receptor modulator (SERM) to benchmark the docking results. The computational findings highlight the potential of structurally modified ligands to exhibit improved receptor binding compared to standard therapies, providing promising candidates for further exploration alongside current aromatase inhibitors. This study underscores the importance of integrating in silico docking strategies for the rational design of next-generation endocrine therapies targeting hormone-dependent breast cancer*

Keywords*:* Breast cancer, Estrogen receptor alpha (ERα), Molecular docking, Tamoxifen

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