

Title: Identifying Potent Breast Cancer Inhibitors Against ER α Target Using Pharmacophore Model, 3D-QSAR and MD Studies

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Abstract: the current investigation, 109 known ER α inhibitors have been developed in the current research; pharmacophore modeling, Molecular docking, MM-GBSA, and MD study have been performed to investigate the binding affinity of 9-anilinoacridines with heterocyclic substitutes as selective ER α inhibitors for breast carcinoma. Pharmacophore model have been developed by Schrodinger suite 2019–2 phasemodule. To predict binding free energy of the ligands in complex with PDB and post docked energy minimization was performed by Prime, MM-GB/SA module. The Induced fit docking studies were performed on the ligand modulated dynamic behaviour of the protein molecular dynamics study. A statistical substantial 3D - QSAR design was created using the pharmacophore hypothesis. 109 known ER α inhibitors have been developed with pIC₅₀ values between 4.0 and 6.0 and were used in ligand-based pharmacophore modelling and 3D-QSAR analysis. R² (0.8294), Q² (0.7~0.8), and F value (83.5) were used to statistically validate the developed five-point hypothesis DHRRR1 employing a minimum square of four. Molecular dynamics simulations were run to comprehend the conformational changes and ligand stability at the protein active pocket. The predicted 3D-QSAR model significantly correlated with experimentally reported *in-vitro* antitumor activity. These *in-silico* discoveries will help in the future search for potent ER α inhibitors with desirable pharmacophoric properties.

Keywords: Estrogen receptor alpha (ER α) inhibitors; Breast carcinoma; Pharmacophore modeling; Molecular docking; MM-GBSA binding free energy; Induced fit docking; Molecular dynamics simulation; 3D-QSAR; 9-Anilinoacridine derivatives; In-silico drug design

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