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In Silico Exploration of Quinazoline Derivatives as EGFR Inhibitors for Lung Cancer: A Multi-Modal Approach Integrating QSAR-3D, ADMET, Molecular Docking, and Molecular Dynamics Analyses

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Abstract : A series of thirty-one potential inhibitors targeting the epidermal growth factor receptor kinase (EGFR), derived from quinazoline, underwent 3D-QSAR analysis using CoMFA and CoMSIA methodologies. The training and test sets of quinazoline derivatives were utilized to construct and validate the QSAR models, respectively, with dataset alignment performed using the lowest energy conformer of the most active compound. The best-performing CoMFA and CoMSIA models demonstrated impressive determination coefficients, with R^2 values of 0.981 and 0.978, respectively, and Leave One Out cross-validation determination coefficients, Q^2, of 0.645 and 0.729, respectively. Furthermore, external validation using a test set of five compounds yielded predicted determination coefficients, R^2 test, of 0.929 and 0.909 for CoMFA and CoMSIA, respectively. Building upon these promising results, eighteen new compounds were designed and assessed for drug likeness and ADMET properties through in silico methods. Additionally, molecular docking studies were conducted to elucidate the binding interactions between the selected compounds and the enzyme. Detailed molecular dynamics simulations were performed to analyze the stability, conformational changes, and binding interactions of the quinazoline derivatives with the EGFR kinase. These simulations provided deeper insights into the dynamic behavior of the compounds within the active site. This comprehensive analysis enhances the understanding of quinazoline derivatives as potential anti-cancer agents and provides valuable insights for lead optimization in the early stages of drug discovery, particularly for developing highly potent anticancer therapeutics

Keywords : 3D-QSAR, CoMFA, CoMSIA, ADMET, molecular docking, quinazoline, molecular dynamic, egfr inhibitors, lung cancer, anticancer
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