Title: Structure-based Virtual Screening, Molecular Docking, Molecular Dynamics Simulation, and Metabolic Reactivity Studies of Quinazoline Derivatives for their Anti-EGFR Activity Against Tumor Angiogenesis.

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Abstract: Background: Epidermal growth factor receptor (EGFR/HER-1) and its role in tumor development and progression through the mechanism of tumor angiogenesis is prevalent in non-small lung cancer, head and neck cancer, cholangiocarcinoma & glioblastoma. Previous treatments targeting the oncogenic activity of EGFR's kinase domain have been hindered by acquired mutational resistance and side effects from existing drugs like erlotinib, highlighting the need for new EGFR inhibitors through structure- based drug designing.

Objective: The research aims to develop novel quinazoline derivatives through structure-based virtual screening, molecular docking, and molecular dynamics simulation to potentially interact with EGFR's kinase domain and impede tumor angiogenic phenomenon.

Methods: Quinazoline derivatives were retrieved and filtered from the PubChem database using structure- based virtual screening and the Lipinski rule of five drug-likeness studies. Molecular docking-based virtual screening methods and molecular dynamics simulation were then carried out to identify top leads.

Results: A total of 1000 quinazoline derivatives were retrieved, with 671 compounds possessing druglike properties after applying Lipinski filters. Further filtration using ADME and toxicity filters yielded 28 compounds with good pharmacokinetic profiles. Docking-based virtual screening identified seven compounds with better binding scores than the control drug, dacomitinib. After cross-checking binding scores, three top compounds QU524, QU571, and QU297 were selected for molecular dynamics simulation study of 100 ns interval using Desmond module of Schrodinger maestro to understand their conformational stability.

Conclusion: The research results showed that the selected quinazoline leads exhibited better binding affinity and conformational stability than the control drug, erlotinib. These compounds also had good pharmacokinetic and pharmacodynamic profiles and did not violate Lipinski's rule of five limits. The findings suggest that these leads have the potential to target EGFR's kinase domain and inhibit the EGFR-associated phenomenon of tumor angiogenesis.

Keyword: C797S Mutation, T790M Mutation, Tumour Angiogenesis, Drug Resistance, Herg Inhibition, Metabolic Reactivity.

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