COMPUTATIONAL ANALYSIS OF PHTHALAZINE BASED VEGFR-2 INHIBITORS: A STRATEGY TO OVERCOME SUNITINIB INDUCED SIDE EFFECTS

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ABSTRACT

The present study focuses on the rational design and evaluation of novel phthalazine derivatives as potential inhibitors of vascular endothelial growth factor receptor-2 (VEGFR-2), a critical target in anti-angiogenic cancer therapy. VEGFR-2 plays a pivotal role in tumor progression by promoting neovascularization, essential for tumor growth and metastasis. In this investigation, eighteen phthalazine derivatives were structurally designed using ChemDraw Ultra and subsequently evaluated through comprehensive *in silico* methods. Molecular docking studies against VEGFR-2 (PDB ID: 3VHK) revealed that compounds 4 and 8 demonstrated remarkable binding affinities, with docking scores of –10.3 and –10.0 kcal mol^{-1}, respectively, outperforming the standard drug sunitinib (–8.4 kcal mol^{-1}). ADME-Tox profiling further confirmed favorable pharmacokinetic properties, including good gastrointestinal absorption and drug-likeness. To assess the dynamic stability of the protein–ligand complexes, 200 ns molecular dynamics (MD) simulations were performed using the Desmond module of the Schrödinger Suite. The RMSD and RMSF analyses affirmed stable and consistent interactions over the simulation period. Collectively, these findings highlight the promising potential of phthalazine derivatives, particularly compounds 4 and 8, as potent VEGFR-2 inhibitors warranting further preclinical investigation.