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Multi-target molecular docking analysis of tetrazolo[1,5-*c*]quinazoline derivatives against essential bacterial enzymes

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Introduction. The development of antibacterial agents targeting essential bacterial enzymes represents a critical approach to address antimicrobial resistance. This computational study evaluated synthetic compounds against four bacterial enzyme targets involved in DNA replication, fatty acid synthesis, cell wall biosynthesis, and lipopolysaccharide assembly.
Materials and methods. The compound library consisted of ethanoic, propanoic and butanoic acid derivatives, benzothiazole-substituted acetamides, and fluorinated benzyl derivatives of the tetrazolo[1,5-*c*]quinazoline scaffold (compounds KB-56, 60, 63, 65, 96-104, 106-112). Molecular docking simulations were performed using CB-Dock2 web server against DNA gyrase subunit B (RCSB PDB ID: 1AJ6), FabI enoyl-ACP reductase (1NHG), UDP-*N*-acetylglucosamine enolpyruvyl transferase (3VCY), and LpxC deacetylase (4FWR). Binding affinities were calculated using AutoDock Vina scoring function and compared with reference inhibitors novobiocin, triclosan, fosfomycin, and CHIR_090. Binding cavity volumes and key residue interactions were analyzed for each target-ligand complex.
Results and discussion. Molecular docking analysis revealed target-dependent binding profiles for tetrazolo[1,5-*c*]quinazoline derivatives. FabI (1NHG) demonstrated highest affinities (-8.6 to -12.0 kcal/mol), with compound 97 achieving -12.0 kcal/mol, exceeding triclosan (-8.4 kcal/mol) by 3.6 kcal/mol. Benzothiazole derivatives (96, 97, 112) consistently outperformed references, with 86% surpassing triclosan. MurA (3VCY) exhibited favorable binding (-7.5 to -10.5 kcal/mol), where compound 109 achieved -10.5 kcal/mol versus fosfomycin (-4.4 kcal/mol). DNA gyrase (1AJ6) presented competitive results (-6.8 to -8.9 kcal/mol), with compounds 96 (-8.9 kcal/mol) and 108 (-8.8 kcal/mol) slightly exceeding novobiocin (-8.6 kcal/mol). LpxC (4FW6) analysis showed reference CHIR_090 (-10.3 kcal/mol) outperforming synthetic compounds, though compounds 101 and 109 approached this benchmark (-10.0 and -9.9 kcal/mol). Structure-activity analysis indicated benzothiazole substitution enhanced multi-target binding, while fluorinated benzyl derivatives showed target-specific selectivity. Four compounds (96, 97, 109, 112) demonstrated multi-target potential (average ≥ -9.7 kcal/mol), suggesting broad-spectrum antibacterial feasibility. Computational predictions require experimental validation through enzymatic assays and cellular testing.
Conclusions. The computational results suggest potential of tetrazolo[1,5-*c*]quinazoline derivatives for developing inhibitors targeting fatty acid synthesis, cell wall biosynthesis, DNA replication, and lipopolysaccharide assembly. The benzothiazole-substituted and fluorinated benzyl derivatives demonstrated particularly favorable binding interactions. The path forward involves systematic experimental validation of computational predictions, structure-based optimization of lead compounds, and strategic development of both single-agent and combination therapies targeting the most promising mechanisms identified in this analysis.
References: doi: 10.1093/nar/gkac394, 10.1002/jcc.21334, 10.1021/bi970294+, 10.1074/jbc.M112000200, 10.1107/S1744309112006720, and 10.1073/pnas.0709412104.

Зміст