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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  $\geq$  -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.



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