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Structure– and ligand–guided screening of Lpt A inhibitors: An initial study for developing novel Neisserial antibacterials

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Pathogenic gram-negative bacteria such as *Neisseria meningitidis* and *Neisseria gonorrhoeae* have developed resistance against antibiotics due to their ability in creating an envelope on the outer layer of lipooligosaccharides (LOS). The cationic phosphoethanolamine (PEA) decoration of LOS lipid A is regulated by lipid A–PEA transferase (LptA) which may serve as a prominent target for developing new antibiotics. The discovery of neisserial LptA has provided a structural aspect to its catalytic mechanisms and ligand recognition that are crucial for inhibitor development. A combination of structure– and ligand–based approach has been employed to explore novel potent LptA inhibitors among millions of commercially-available compounds and approved drugs. A total of 4000 hit molecules obtained from LIDAEUS structure–based screening and PubMed ligand similarity search were further examined through a semi-flexible docking simulation performed in MOE and Schrödinger's Glide. Best hits were therefore carefully selected based on their docking score, drug likeness and pharmacological properties. Free energy of binding calculation and ligand interaction analysis suggest that the selected 20 hit compounds have a stronger binding affinity than LptA natural substrate and possess a more effective interaction with catalytically–essential residues. Further 5000–picosecond molecular dynamics (MD) simulation of these 20 compounds also confirms that they all maintained a stable complex conformation showing a low total root mean square deviation (RMSD), capability to maintain interactions with active site and an acceptable Ramachandran plot. Selected hits can be further analyzed *in vitro* and examined through a pre-clinical trial. This study provides an insight to drug repurposing which may serve as an initial step to develop novel potent LptA inhibitors to combat the virulence of multi-drug resistant Neisseria.

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