Molecular Cloning, Overexpression, Biophysical studies, and Structure-based inhibitor design for the Raetz pathway peripheral membrane protein UDP-diacylglucosamine pyrophosphohydrolase (LpxH) from Salmonella typhi

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Antimicrobial resistance (AMR) is a crucial public health problem throughout the world. While all types of AMR are concerning, resistance caused by bacteria is currently seen as the most life-threatening, especially in Asian sub-continents. This increasing problem of AMR (especially in Gram-negative bacterial pathogens) and MDR necessitates the characterization of new antibiotic targets and potent drugs as the “antibiotic pipeline” is muted [1]. The Raetz pathway of lipid A synthesis is essential for the survival and fitness of most Gram-negative bacteria. In these bacteria, lipid A forms the membrane anchor of lipopolysaccharide (LPS), which forms the outer leaflet of the outer membrane protecting the bacteria from various stressors. LpxH (UDP-diacylglucosamine pyrophosphohydrolase) which has less sequence conservation with other bacterial species [2] and lacks a mammalian homolog promises to be an excellent drug target for the development of novel antibiotics. Typhoid fever, caused due to bacterium Salmonella Typhi, is a deadly infection that is generally spread through infected food or water. Increasing antimicrobial resistance in S. Typhi is a serious public health concern, especially in industrializing countries. Molecular cloning, expression, and biophysical studies of LpxH have been done from S. Typhi. Pharmacophore-based screening using Protein−Ligand Interaction Fingerprint (PLIF) from MOE software was used to obtain a potent natural product inhibitor (compound 1615) which showed a good binding affinity of -11.375 kcal/mol and also interact with catalytic residues Asn79, Arg80, Leu83, Phe141, Ile152, Met156, Arg157, and His195 of LpxH. Currently, crystallization attempts and the determination of LpxH three-dimensional structures are underway.

References

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