Para-(benzoyl)-phenylalanine as a potential inhibitor against leptospirosis

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Key points

- Leptospirosis is a zoonotic disease with more than 500,000 severe cases annually in the world. Human leptospirosis is mainly caused by pathogenic *Leptospira interrogans*. Symptoms of infection include fever, chills, headache, and severe myalgia. In 5-15% cases, multiple organ damage is reported and the mortality rate has been shown to be 5-40%. People exposed to recreational activities, farming, and post-flood conditions are at major risk of getting infected through contaminated water, rodents, or pet animals. As number of animals act as hosts, the acquiring of infection can have considerable economic implications in developing countries like India.
- Lipid A is one of the three components of LPS that contains multiple hydrophobic fatty acid chains which anchor the LPS into the leptospiral membrane. Designing inhibitory drug molecules targeting Lipid A biosynthesis would dissolve the structural integrity of membrane structure leading to cell lysis and death of *Leptospira*.
- LpxC being the first enzyme among the three drug targets of Lipid A (lpxC, lpxD and lpxB) biosynthesis pathway; blocking the enzyme with suitable inhibitor would stop synthesizing substrates for lpxD and lpxB. Also, there is no alternative mechanism in *Leptospira* to replace the catalytic activity rendered by lpxC; hence, the drug target was selected herein for rational drug design and proposed para-(benzoyl)-phenylalanine as a potential inhibitor against leptospirosis.

Material and Methods

SGI FUEL Workstation

Active site prediction and virtual screening

Results and Discussion

PROQ LG score 4.712,

CαRMSD: 0.25Å and overall RMSD 0.72Å

Conclusion

- Common drug targets from the unique pathways of pathogen are of significant interest towards designing drugs against leptospirosis. LpxC participates in unique LPS biosynthesis pathway and is common among all sequenced pathogenic *Leptospira* without any alternative mechanism to replace its catalytic activity. Thus, targeting lpxC for novel inhibitor discovery is worth mentioning.
- The highly reliable lpxC 3D model with predicted active site residues paved the way for proposing 12 potential inhibitors and Para-(benzoyl)-phenylalanine as the best one to start with experimental validation towards designing anti-leptospirosis drug.

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