

Identification of potential riboflavin synthase inhibitors by virtual screening and molecular dynamics simulation studies

ABSTRACT

Riboflavin synthase is an important enzyme catalyzing the last step of riboflavin biosynthesis in microorganisms. Due to the absolute dependency of the microbes to this biosynthetic pathway coupled with its nonexistence in humans, riboflavin synthase (RiS) is considered as a prospective drug target. The riboflavin synthase for this study was derived from *Leptospira kmetyi*, a pathogenic bacterium locally isolated in Malaysia. Leptospirosis, an infectious disease caused by pathogenic *Leptospira*, is a serious growing public health issue. Treatment of leptospirosis with antibiotics over time resulted in the evolution of antibiotic resistance strains, thus requiring the development of newer but safe antimicrobial agents. In this study, a computational approach involving virtual screening followed by molecular dynamics (MD) simulation was implemented in order to identify possible inhibitors against riboflavin synthase. The model of *Leptospira kmetyi* riboflavin synthase predicted from *E. coli* riboflavin synthase (1I8D) was used as the drug target to screen for potential compounds from the ZINC database through virtual screening. The potential compound with the highest Glide score (-10.987 Kcal/mol) was identified to be ZINC21883831. Chemically it is 2-[(2-chloro-4-fluoro-phenyl)methylsulfanyl]-7-phenyl-3,5-dihydropyrrolo[2,3-e]pyrimidin-4-one. The top three docked complexes from the virtual screening and apo-structures were subjected to molecular dynamics simulation to predict the stabilities of the *Leptospira kmetyi* riboflavin synthase-ligand complexes. Stability parameters including RMSD, RMSF, SASA and Rg of the complexes were evaluated from 60 ns of the MD simulation trajectories. Insights from this study provide promising starting points for the rational designs of new effective and safe anti-leptospirosis drugs.

Keyword: Riboflavin synthase; Virtual screening; Molecular dynamics simulation; Leptospirosis