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Computer-Aided Drug Repurposing for Mycobacterium Tuberculosis by Targeting Tryptophanyl-tRNA Synthetase

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Abstract : Mycobacterium tuberculosis is still a worldwide disease-causing agent that, according to WHO, led to the death of 1.5 million people from tuberculosis (TB) in 2020. The bacteria reside in macrophages located specifically in the lung. There is a known quadruple drug therapy regimen for TB consisting of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Over the past 60 years, there have been great contributions to treatment options, such as recently approved delamanid (OPC67683) and bedaquiline (TMC207/R207910), targeting mycolic acid and ATP synthesis, respectively. Also, there are natural compounds that can block the tryptophanyl-tRNA synthetase (TrpRS) enzyme, chuangxinmycin, and indolmycin. Yet, already the drug resistance is reported for those agents. In this study, the newly released TrpRS enzyme structure is investigated for potential inhibitor drugs from already synthesized molecules to help the treatment of resistant cases and to propose an alternative drug for the quadruple drug therapy of tuberculosis. Maestro, Schrodinger is used for docking and molecular dynamic simulations. In-house library containing ~8000 compounds among FDA-approved indole-containing compounds, a total of 57 obtained from the ChemBL were used for both ATP and tryptophan binding pocket docking. Best of indole-containing 57 compounds were subjected to hit expansion and compared later with virtual screening workflow (VSW) results. After docking, VSW was done. Glide-XP docking algorithm was chosen. When compared, VSW alone performed better than the hit expansion module. Best scored compounds were kept for ten ns molecular dynamic simulations by Desmond. Further, 100 ns molecular dynamic simulation was performed for elected molecules according to Z-score. The top three MMGBSA-scored compounds were subjected to steered molecular dynamic (SMD) simulations by Gromacs. While SMD simulations are still being conducted, ponesimod (for multiple sclerosis), vilanterol (β_2 adrenoreceptor agonist), and silodosin (for benign prostatic hyperplasia) were found to have a significant affinity for tuberculosis TrpRS, which is the propulsive force for the urge to expand the research with in vitro studies. Interestingly, top-scored ponesimod has been reported to have a side effect that makes the patient prone to upper respiratory tract infections.

Keywords : drug repurposing, molecular dynamics, tryptophanyl-tRNA synthetase, tuberculosis
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