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Virtual Screening and in Silico Toxicity Property Prediction of Compounds against Mycobacterium tuberculosis Lipoate Protein Ligase B (LipB)

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Abstract : The drug discovery and development process is generally known to be a very lengthy and labor-intensive process. Therefore, in order to be able to deliver prompt and effective responses to cure certain diseases, there is an urgent need to reduce the time and resources needed to design, develop, and optimize potential drugs. Computer-aided drug design (CADD) is able to alleviate this issue by applying computational power in order to streamline the whole drug discovery process, starting from target identification to lead optimization. This drug design approach can be predominantly applied to diseases that cause major public health concerns, such as tuberculosis. Hitherto, there has been no concrete cure for this disease, especially with the continuing emergence of drug resistant strains. In this study, CADD is employed for tuberculosis by first identifying a key enzyme in the mycobacterium's metabolic pathway that would make a good drug target. One such potential target is the lipoate protein ligase B enzyme (LipB), which is a key enzyme in the M. tuberculosis metabolic pathway involved in the biosynthesis of the lipoic acid cofactor. Its expression is considerably up-regulated in patients with multi-drug resistant tuberculosis (MDR-TB) and it has no known back-up mechanism that can take over its function when inhibited, making it an extremely attractive target. Using cutting-edge computational methods, compounds from AnalytiCon Discovery Natural Derivatives database were screened and docked against the LipB enzyme in order to rank them based on their binding affinities. Compounds which have better binding affinities than LipB's known inhibitor, decanoic acid, were subjected to in silico toxicity evaluation using the ADMET and TOPKAT protocols. Out of the 31,692 compounds in the database, 112 of these showed better binding energies than decanoic acid. Furthermore, 12 out of the 112 compounds showed highly promising ADMET and TOPKAT properties. Future studies involving in vitro or in vivo bioassays may be done to further confirm the therapeutic efficacy of these 12 compounds, which eventually may then lead to a novel class of anti-tuberculosis drugs.

Keywords : pharmacophore, molecular docking, lipoate protein ligase B (LipB), ADMET, TOPKAT
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