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High throughput virtual screening to identify a novel inhibitor against Pyrazinamide resistant tuberculosis

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Abstract

In recent years multi drug resistance tuberculosis (TB) has become a serious health problem globally. The emergence of multi-drug resistant mycobacterium strains has made most of the convention drugs ineffective. Therefore development of new therapeutic strategies such as finding of novel and more efficient inhibitors against drug resistant mutant proteins are required. In this study, we have analyzed the mechanism of mutations responsible for resistance against first-line anti-tuberculosis pyrazinamide pro-drug. First, pyrazinamide (pro-drug), activated Pyrazinamide (drug) and its isoforms were analyzed for their binding affinity against mutant forms of PncA (Pyrazinamidase) at the ligand binding cavity. It was observed that due to the mutations, after conversion of pro-drug to drug, the strong binding of PncA reduces the release of activated form of Pyrazinamide to inhibit other virulent proteins. So in order to discover a novel Drug molecule against mutant PncA, high throughput virtual screening was performed at the same cavity with the 826 drugs like antituberculant compounds derived from ChEMBL database. The predicted lead molecule was found with having suitable affinity and bond interactions in both wild and mutant PncA protein. For the further confirmation, the lead compound was compared against some frequently occurring mutations individually. In all mutated forms, the lead molecule was found more efficient than the activated Pyrazinamide. Hence we believe that this molecule may act as a novel drug to improve the therapy of pyrazinamide resistant tuberculosis.

References

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