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In silico designing of imidazo [4, 5-b] pyridine as a probable lead for potent decaprenyl phosphoryl-β-D-ribose 2′-epimerase (DprE1) inhibitors as antitubercular agents

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Tuberculosis (TB) is a major worldwide concern whose control has been exacerbated by HIV, the rise of multidrug-resistance (MDR-TB) and extensively drug resistance (XDR-TB) strains of *Mycobacterium tuberculosis*. The interest for newer and faster acting antitubercular drugs is more remarkable than any time. As per figures of WHO, burden of TB has increased drastically in past couple of years. To search potent compounds is need and challenge for researchers. In the previous decade rigorous actions have been made to find new leads for antitubercular drug development using both target-based and structure-based methodologies. Here, we tried to design lead for inhibition of decaprenyl phosphoryl-β-D-ribose 2α-epimerase (DprE1) enzyme. DprE1 that catalyzes the 2-step epimerization of decaprenyl-phospho-ribose (DPR) to decaprenyl-phospho-arabinose (DPA), a key precursor that serves as the arabinose donor required for the synthesis of cell-wall arabinans. DprE1 catalyzes the first step of epimerization, namely FAD-dependent oxidation of the C2' hydroxyl of DPR to yield the keto intermediate decaprenyl-phospho-2'-keto-D-arabinose (DPX). We had a selection of 23 compounds from azaindole series for computational study and they were drawn using Marvin Sketch. Ligands were prepared using Maestro molecular modeling interface, Schrodinger, v10.5. A common pharmacophore hypothesis was developed by applying dataset thresholds to yield active and inactive set of compounds. There were 326 hypotheses were developed. On the basis of survival score ADRRR (Survival Score: 5.453) was selected. Selected pharmacophore hypotheses were subjected to virtual screening results into 1000 hits. Hits were prepared and docked with protein 4KW5 (oxydoreductase inhibitor) was downloaded in .pdb format from RCSB Protein Data Bank. Protein was prepared using protein preparation wizard. Protein was preprocessed, workspace was analyzed using force field OPLS 2005. Glide grid was generated by picking single atom in molecule. Prepared ligands were docked with prepared protein 4KW5 using glide docking. After docking, on the basis of glide score top five compounds were selected, (5223, 5812, 0661, 0662 and 2945) and the glide docking score (-8.928, -8.534, -8.412, -8.411, -8.351) respectively. There were interactions of ligand and protein, specifically, HIS 132, LYS 418, TRY 230, ASN 385. Pi-pi stacking was observed in few compounds with basic imidazo [4, 5-b] pyridine ring. We had basic azaindole ring in parent compounds but after glide docking, we received compounds with imidazo [4, 5-b] pyridine as a basic ring. That might be the new lead in process of drug discovery.

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