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De novo design of novel *Mycobacterium tuberculosis* pantothenate synthetase inhibitors

Taylane da Silva Araújo[1], Manoelito Coelho S. Junior[1], Raquel G. Benevides[1].
[1]Programa de Pós-Graduação em Biotecnologia, Universidade Estadual de Feira de Santana. *Laboratório de Modelagem Molecular, Av. Transnordestina, s/n - Novo Horizonte, Feira de Santana - Bahia, 44036-900.*
araujotaylane@gmail.com

Tuberculosis is infectious disease with 10.4 millions new cases reported per year [1]. The major concern of this disease are the multidrug resistant (MDR) and extensively resistant (XDR) strains, modifying the treatment, last up to 20 months and have 60-75% efficacy [2]. Therefore there is a need to identify new drugs for the tuberculosis treatment [3], in this scenario the enzyme pantothenate synthetase (PS) is an excellent therapeutic target for *Mycobacterium tuberculosis*, since the importance of the enzyme (which is related to the virulence and persistence of the pathogen) has already been proven by the knockout of the panC gene [4]. In order to identify possible inhibitors for PS, an in silico ligand- structure-based *de novo* design. The theoretical molecules was design by two different methods using the web serve E-Lead3D [5] and LigBuilder2.0 software [6] (Figure1). For the E-Lead3D, besides information related to structure, 11 inhibitors were extracted for the CHEMBL and used as template molecule (Tanimoto Coefficient > 0.8). With this method 550 molecules were design. LigBuilder2.0 uses the active site cavity properties (hydrophobic access, HBond donor and HBond acceptors, surface and volume) for the design of the molecules. This method generated 6,282 molecules. Then, all the theoretical molecules created were together submitted to alignment in the screening using pharmacophore model, using the model constructed on other assay of our working group [7]. This model has 9 pharmacophore features, a hydrogen donor center, three acceptor centers and five hydrophobic centers. 458 molecules filtered by pharmacophore model (4.49 < QFIT > 40.4) were submitted to molecular docking using DOCK 6.8 software. The protein (PDB ID 4MUH) was prepared in the CHIMERA 10.1, the docking parameters was analyzed by redocking (RMSD value) from the crystallographic ligand. The RMSD = 1,63 Å indicates docking success in repositioning the ligand in protein active site. The molecules were order by number according to Grid Score function. The top ranked molecule is show in Figure 2A, similarity analysis in ZINC15 database (TC<0.9) showed no correspondence match. This molecule forms hydrogen bond observed between carbonyl groups of the ligand and residues Gln69, Gln161 and Ser193. In addition, another hydrogen interaction occurs between the ether group of the molecule and the N-terminal portion of Met37; Hydrophobic interactions between the aliphatic portions of the ligand and the side chains of the residues Pro35, Val139, Phe70 and Leu143, and between the aryl ring of the molecule and the Lys57 side chain; Two salt bridges are observed with one of the carbonyls of the ligand and residues Arg195 and Lys157; π-stacking T-shaped

interaction at the His41 also between the ring aryl. The techniques *de novo* design used in this study show promising because this molecule has inhibitory properties against PS and no similar results have been found in the ZINC15 database, suggesting to be an unpublished molecule.

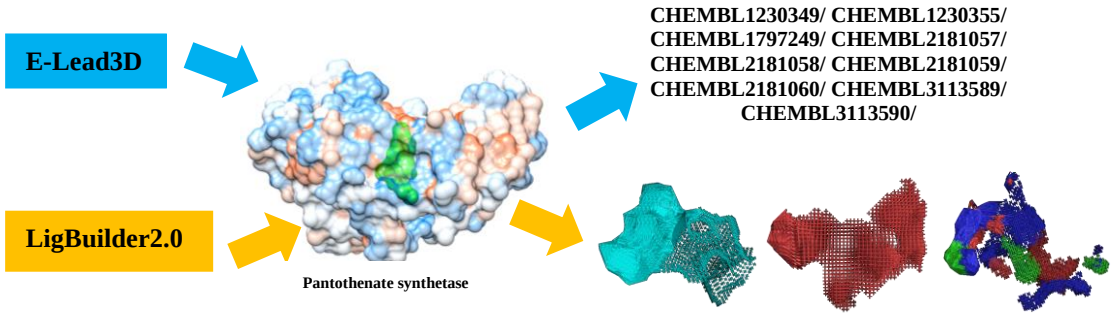

Figure 1: Construction strategy of E-Lead3D tools, using 11 inhibitors (CHEMBL code) as template and LigBuilder2.0 using surface (blue), volume (red) and donor centers HBond (blue), HBond acceptor (red) and hydrophobic (green) of the active site.

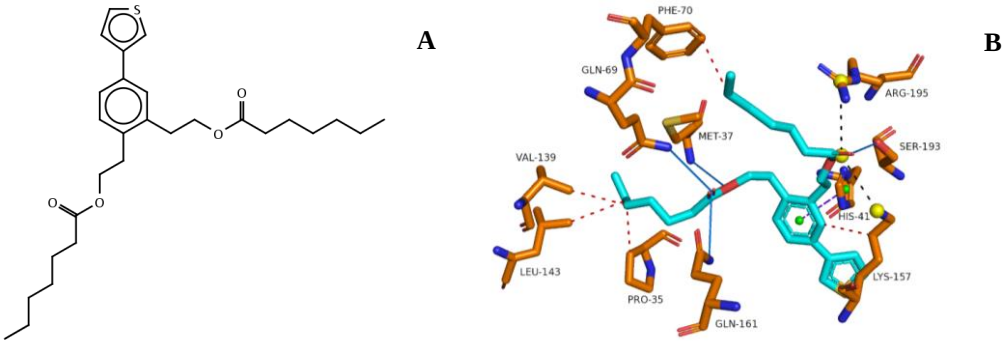

Figure 2: (A) Top ranked molecule by molecular docking. (B) Map of the intermolecular interactions between the top ranked molecule (cyan) and the active site residues of the enzyme (orange). Blue lines - hydrogen bond; Pink dashed lines - hydrophobic interactions; Black dashed lines - salt bridge and Lilac dashed line – π-stacking T-shaped interactions.

Key-words: Tuberculosis, pantothenate synthetase, *de novo* design, pharmacophoric modeling, docking.
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