Alpha-Mannosyltransferase (pimA) from Mycobacterium tuberculosis H37Rv: molecular modeling, virtual screening and molecular dynamic studies

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Background
The consumption has been a scourge of mankind since ancient times. This illness have been charged a high price in human lives, so many efforts have been made in order to defeat the Mycobacterium tuberculosis (Mtb). Nowadays the tuberculosis is responsible for two million of deaths/year and is a global emergency which needs to be urgently repressed. The complete structural genomics sequence of Mycobacterium tuberculosis open a new era and had a major impact of our understanding of this pathogen and also in research of microbial drugs. However, the accumulation of biochemical and structural data has not been sufficient for development an effective vaccine or anti-tubercular drug. The cell wall biosynthesis is a potential pathway to discovery new inhibitors against Mtb. Alpha-mannosyltransferase (AM), which is involved in the transfer reaction of the mannose from GDP-mannose to the carrier lipid phosphatidyl-mylo-inositol [1], has been propose as a potential target to virtual screening (VS) initiatives, seeing that this enzyme is absent in humans. The present work has the ambition to find new inhibitors to AM, based on molecular modeling, VS and molecular dynamics (MD) simulation.

Materials and Methods
The molecular modeling simulation was performed with MODELLER 9v7 [2]. The flexible docking simulations were carried out by the program MolDock 3.2.0 [3]. The MD simulations were performed using GROMACS 4.0.5 [4].

Results and Conclusions
The homology model of the MtAM present good stereochemical quality, according to Ramachandran \( \phi - \psi \) plot. The process of the VS was carried out with a commercial database (Sigma Aldrich) that is composed by 15,186 molecules. From the total number of molecules in the database, only 40 compounds were selected as promising inhibitors for MtAM, based on three filters, the docking algorithm, Lipinski rule and ADMETox. MD simulations were applied to the three best ligands, which were ZINC12958622, ZINC12958628 and ZINC03202703. The root mean square deviation (RMSD) showed that all ligands are stable in the active-site during 20ns of the simulation. The computational study could help in the drug discovery process however, in vitro assays are require to correlate our obtained results.

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