TITLE: *Mycobacterium tuberculosis* Ino1 AS A DRUG TARGET?

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ABSTRACT:
Tuberculosis remains the leading cause of death by infectious disease worldwide. Despite the modern therapeutic regimen efficacy, the strategies have been suffering from the emergency of multidrug resistant *Mycobacterium tuberculosis* lineages over the last years. Even using drug combination, drug activity is impaired by major limitations such as the slowly killing of the bacillus, increasing the risk for developing tolerant or drug-resistant phenotypes. Inositol-1-phosphate synthase - Ino1 (Rv0046c), plays a key role in *M. tuberculosis* metabolism, since it is able to *de novo* biosynthesis of inositol. Inositol is a product from glucose-6-phosphate conversion, mediated by Ino1. Additionally, inositol attends multiple cellular functions such as forming the backbone of lipoarabinomannan and lipomannan in the first steps of the mycobacterial cell envelope constructruction. Glycoconjugates such as phosphatidylinositol, phosphatidylinositol mannosides, lipomannan and lipoarabinomannan, are anchored in membrane by inositol. The mycobacterial Ino1 presents a distinct structuctural arrangement from that known in eukaryotic organisms, and the lack of inositol, usually is associated with bacillary growth and virulence inhibition. In this sense, Ino1 inhibition could be suggested as a potential drug target. We aim to report the virtual screening of putative Ino1 inhibitors. The crystal structure of myo-inositol 1-phosphate synthase from *M. tuberculosis* in complex with NAD, zinc (PDB entry 1GR0) and the reference ligand 2-deoxy-D-glucitol 6-(E)-vinylhomophosphonate was used in simulations. A library of 222 molecules from Zinc database was screened, considering analogs of inhibitors previously described on BRENDA database. The virtual screening was performed using softwares Autodock version 4.0 and Molegro version 5.5. We determined two anticonvulsants, valrocemide and carbamazepine, which showed high ligation scores with Ino1. Some data in literature with valproate and carbamazepine came to corroborate our findings in decreasing the *M. tuberculosis* virulence. In this case, further work is required to establish the potential of this anticonvulsants as adjunctive drug for tuberculosis therapy.

Keywords: tuberculosis, virtual screening, drug development.

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