Mycobacterium tuberculosis methionine aminopeptidase a new target for the development of novel antitubercular compounds.

ShT-04.4-2

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Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis, is a major global health challenge in particular due to Multi-Drug Resistant (MDR) strains, and eXtensively Drug Resistant (XDR) strains. Methionine aminopeptidase (MetAP) is essential for the N-terminal methionine excision of peptides during protein synthesis hence regulates proteins activity by determining and enabling additional modifications, including acetylation and others. This enzyme is indispensable for all life forms, including eukaryotes and prokaryotes and is particularly vital for bacterial replication. As such, MetAP represents a potential target for the development of antibacterial and anti-tuberculosis therapies. In Mtb, the mapB gene encodes the MetAP1c isoform that is of major significance. To this purpose, the enzyme was produced in recombinant form and purified. The enzyme activity assay was set up, using a synthetic fluorescent substrate, allowing the investigation of its steady-state kinetic properties, and divalent metal ions dependence. The enzyme was then proved to be suitable for inhibition studies, thus was used for the *in silico* and *in vitro* screening of compounds library, to identify scaffolds suitable to be developed as significant inhibitors. The identification and validation of inhibitors could pave the way for novel drugs to fight tuberculosis, particularly against drug-resistant Mtb strains. Our findings contribute valuable knowledge to the ongoing efforts to address the global tuberculosis burden and underscore MetAP1c as a promising target for future anti-tuberculosis drug development, this will be supported by a study in Mtb cells to further confirm the anti-mycobacterial activity of the developed compound.