

# Identification of *Mycobacterium tuberculosis* CtpF as a target for designing new antituberculous compounds

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The emergence of tuberculosis (TB) produced by multi-drug resistance (MDR) and extensively-drug resistance (XDR) *Mycobacterium tuberculosis* (Mtb), encourages the development of new antituberculous compounds, as well as the identification of novel drug targets. In this regard, plasma membrane P-type ATPases are interesting targets because they play a crucial role in ion homeostasis and mycobacterial survival. We focused on Mtb CtpF, a calcium P-type ATPase that responds to a broad number of intraphagosomal conditions, as a novel target. In this study, we evaluated the capacity of cyclopiazonic acid (CPA), a well-known inhibitor of the sarco-endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA), to inhibit the ATPase activity of CtpF and the Mtb growth demonstrating that CtpF is a druggable target. A homology modeling of CtpF was generated for molecular docking studies of CtpF with CPA and key pharmacophoric features were identified, which were used to perform a pharmacophore-based virtual screening of the ZINC database, and to identify CtpF inhibitor candidates. Molecular docking-based virtual screening and MM-BGSA calculations of candidates allowed identifying six compounds with the best binding energies. The compounds displayed in vitro minimum inhibitory concentrations (MIC) ranging from 50 to 100 µg/mL, growth inhibitions from 29.5 to 64.0% on Mtb, and inhibitions of Ca<sup>2+</sup>-dependent ATPase activity in Mtb membrane vesicles (IC<sub>50</sub>) ranging from 4.1 to 35.8 µM. The compound ZINC63908257 was the best candidate by displaying a MIC of 50 µg/mL and a Ca<sup>2+</sup> P-type ATPase

inhibition of 45% with  $IC_{50} = 4.4 \mu M$ . Overall, the results indicate that CtpF is a druggable target for designing new antituberculous compounds. © 2019 Elsevier Ltd

Antimycobacterial therapeutics

Cyclopiazonic acid

Molecular docking

P-type ATPases

Tuberculosis

cyclopiazonic acid

dimethyl sulfoxide

plasma membrane calcium transporting adenosine triphosphatase

rifampicin

sarcoplasmic reticulum calcium transporting adenosine triphosphatase

tuberculostatic agent

unclassified drug

zinc 09787234

zinc 12584082

zinc 14541509

zinc 45605493

zinc 55090623

zinc 63908257

animal cell

Article

bacteriostatic activity

controlled study

drug design

drug screening

drug targeting

enzyme inhibition

IC50

minimum inhibitory concentration

molecular docking

Mycobacterium tuberculosis

nonhuman

pharmacophore