INHIBITION OF PROTEIN TYROSINE PHOSPHATASE B (PTPB) FROM MYCOBACTERIUM TUBERCULOSIS: AN INITIAL SCREENING OF NEW SYNTHETIC COMPOUNDS

Lückmann, L. H.¹; Mascarello A¹,²; Terenzi, H.¹
¹Centro de Biologia Molecular Estrutural – BQA/UFSC, Santa Catarina, Brasil; ²Dipartimento di Chimica e Tecnologie del Farmaco, Università di Roma La Sapienza, Roma, Italia.

*Mycobacterium tuberculosis* expresses two protein tyrosine phosphatases, PtpB, and PtpA, associated with virulence by contributing to intracellular pathogen survival. These enzymes are secreted by the bacteria and are responsible for modulating host signal transduction pathways. Due to the emergence of antibiotic resistance, the search for new drugs against *M. tuberculosis* is an urgent need. As PtpB, and PtpA are important virulence factors, they are considered promising targets for new anti-tuberculosis drug development. The objective of this work is search for novel PtpB inhibitors. *Escherichia coli* BL21(DE3) was used to express recombinant PtpB, and its purification was performed by metal affinity chromatography. The catalytic activity of PtpB was determined spectrophotometrically at 405 nm using p-nitrophenyl phosphate as substrate. We screened a structurally diverse, pharmacophore-rich, drug-like small molecule library of more than 5 million compounds from ZINC database against PtpB active site. After this extensive evaluation, we selected six compounds to enzymatic assays with PtpB. From initial screening, two compounds showed PtpB inhibition superior to 50 % at final concentration of 25 µM. IC₅₀ values, using eleven different inhibitor concentrations, indicated significant inhibition of PtpB with IC₅₀ < 35 µM for these two compounds. To assess the inhibitors selectivity we performed a screening against PtpA, and human phosphatases LYP, PEST, and PTP1B. Our data shows that the compounds are quite selective for PtpB, PtpA, and PTP1B, showing similar IC₅₀. These compounds might help as a starting point for further optimization aimed at the development of anti-TB agents.

Keywords: phosphatase; recombinant protein; PtpB; *Mycobacterium tuberculosis*

Acknowledgments: CNPq, FAPESC, CAPES, MCTI, FINEP.