LUNATIN 2 AS POTENT YERSINIA PROTEIN TYROSINE PHOSPHATASE INHIBITOR

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Introduction and Objectives: The pathogenic bacteria Yersinia are causative agents in human diseases ranging from gastrointestinal syndromes to bubonic plague. There is an increasing risk on misusing infectious agents, such as Yersinia pestis, as bioterrorism weapons and instruments of warfare for mass destruction. The pathogenicity of Yersinia is absolutely dependent on the activity of a bacterial virulence factor called YopH, a protein tyrosine phosphatase (PTP). YopH disrupts host signal transduction processes by dephosphorylating a variety of proteins associated with the focal adhesion. This interferes with the immune response of the host, including phagocytosis. Because of its potential use for bioterrorism, YopH has recently emerged as an important target for antiplague therapeutics. In this study, Lunatins peptides and its analogues were synthesized and tested for their ability to inhibit enzymatic activity Yersinia enterocolitica PTP YopH.

Material and Methods: Lunatin 2 synthesis was accomplished by using Rink amide resin under standard Fmoc-based solid-phase protocols and peptides purification was performed by reverse phase chromatography on C18 column. The inhibitory activity was evaluated in vitro against recombinant YopH from Y. enterocolitica, using p-nitrophenyl-phosphate as substrate. On the basis of the collected IC50 values, we investigated the mechanism of YopH inhibition of the most potent peptide. Results and Conclusion: We have identified a new class of YopH potent inhibitor, Lunatin 2, which exhibits a IC50 value of 1.37 µM for YopH and displays a 12-fold selectivity in favor of YopH against PTP-PEST, LYP and PTP1B human PTPs. Lunatin 2 was identified as mixed inhibitor of YopH, with Ki value of 1.41 µM and Ki of 6.16 µM. These results suggest the discovery of a new class of potent inhibitors with kDa molecular mass, which can potentially provide a starting point for further development of new inhibitors for this class of enzymes.

Keywords: Lunatin, Yersinia, YopH

Financial support: CNPq, FAPEMIG, CAPES and INCTTOX