Design and characterisation of inhibitory peptides against Bleg1_2478, an evolutionary divergent B3 metallo-β-lactamase

ABSTRACT

Previously, a hypothetical protein (HP) termed Bleg1_2437 (currently named Bleg1_2478) from Bacillus lehensis G1 was discovered to be an evolutionary divergent B3 subclass metallo-β-lactamase (MBL). Due to the scarcity of clinical inhibitors for B3 MBLs and the divergent nature of Bleg1_2478, this study aimed to design and characterise peptides as inhibitors against Bleg1_2478. Through in silico docking, RSWPWH and SSWWDR peptides with comparable binding energy to ampicillin were obtained. In vitro assay results showed RSWPWH and SSWWDR inhibited the activity of Bleg1_2478 by 50% at concentrations as low as 0.90 µM and 0.50 µM, respectively. At 10 µM of RSWPWH and 20 µM of SSWWDR, the activity of Bleg1_2478 was almost completely inhibited. Isothermal titration calorimetry (ITC) analyses showed slightly improved binding properties of the peptides compared to ampicillin. Docked peptide-protein complexes revealed that RSWPWH bound near the vicinity of the Bleg1_2478 active site while SSWWDR bound at the center of the active site itself. We postulate that the peptides caused the inhibition of Bleg1_2478 by reducing or blocking the accessibility of its active site from ampicillin, thus hampering its catalytic function.]

Keyword: Inhibitory peptide; Bleg1_2478; B3 subclass metallo-β lactamase; Docking; Inhibition; Active site