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Barnettlysin-I: A Brief *in Silico* Analysis of a Biotechnological Tool from Snake Venom

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Abstract

Molecular modeling includes the use of *in silico* tools for structural analysis of potential molecules in order to understand their structure-activity relationship and explore their pharmacological properties. Barnettlysin-I (Bar-I) is a non-hemorrhagic fibrinolytic metalloproteinase from the snake venom *Bothrops barnetti* with an anti-platelet profile. Considering its high biotechnological potential and that cardiovascular diseases are among the top three leading causes of death worldwide, the understanding of Barnettlysin-I structure may help on planning new fibrinolytic agents with antithrombotic profile. Thus, our purpose is to study the structure-activity relationship of Bar-I and analysis its potential for biotechnological application on treating cardiovascular diseases such as myocardial infarct or stroke. In order to perform a sequence analysis, we used Clustal Omega. For a homology modeling template-based construction, the best templates were identified using the Swiss-model program. The most similar templates were 1bsw (67.42%) and 3dsl chain A (66.85%) respectively. Final construction, optimization and energy minimization were made in Deep view/Swiss-PDB Viewer 4.0. Validation of Bar-I model was performed in Procheck using the PDBSum server. In this work, we constructed the 3D-model of Bar-I by homology modeling using as template the crystal structure of acutolysin A, a three-disulfide hemorrhagic zinc metalloproteinase from *Agkistrodon acutus* (Identity = 67.42%). Overall the model revealed a conserved tertiary structure with six of the seven Cys paired (C117-C197, C157-C181, and C159-C164) and the substrate binding cleft localized between two domains. The calcium ion is in contact with E9, D75, C179 and N182 whereas Zinc interacts with H124, H128 and H134. The preference for Leu at P1' subsite is due to the small binding region whereas the comparison with other SVMP family members (e.g. mutalysin, atroxlysin and leucurolysin-B) revealed important features that characterize its interesting biotechnology profile [1-5].

Keywords: Snake venom; protein; Biotechnology; Bioinformatic

Introduction

Molecular modeling includes the use of *in silico* environment for analysis of molecules and their properties, in order to understand and/or change their Structure-Sctivity relationship (SAR), including pharmacological activity Barnettlysin-I is a non-hemorrhagic fibrinolytic metalloproteinase from the snake venom *Bothrops barnetti* with an anti-platelet profile. Considering its high biotechnological potential and that cardiovascular diseases are among the top three leading causes of death worldwide, the understanding of Barnettlysin-I structure may help on planning new fibrinolytic agents with antithrombotic profile. Our purpose is to study the Structure-Activity Relationship (SAR) of Bar-I, as the understanding of Barnettlysin-I structure may assist the biotechnological application on treating cardiovascular diseases such as myocardial infarct or stroke [6-10].

Material and Methods

In order to perform sequence analysis, we used Clustal Omega whereas we identified the best templates in Swiss model by score. The crystal structures were from Protein Data Bank (RCSB-PDB) website. Final construction, optimization and energy minimization were made in Deep view/Swiss-PDB Viewer 4.0. All molecules were minimized energy in the program. Minimization was performed in the GROMOS96 43B1 program present in the Swiss-Pdb Viewer program, using the default value of the program.

Validation of Bar-I model were made in Procheck using the PDB-Sum server. For the analysis of the 3D structure of enzymes, the program Swiss-Pdb Viewer 3.7. After energy minimization, each structure was superimposed and aligned, once at a time, with each enzyme studied and the RMS values were calculated using the Swiss-Pdb Viewer program, using only the α (Cα) carbons of the structure for a given enzyme. protein chain. Director [11-14] (Figure 1).

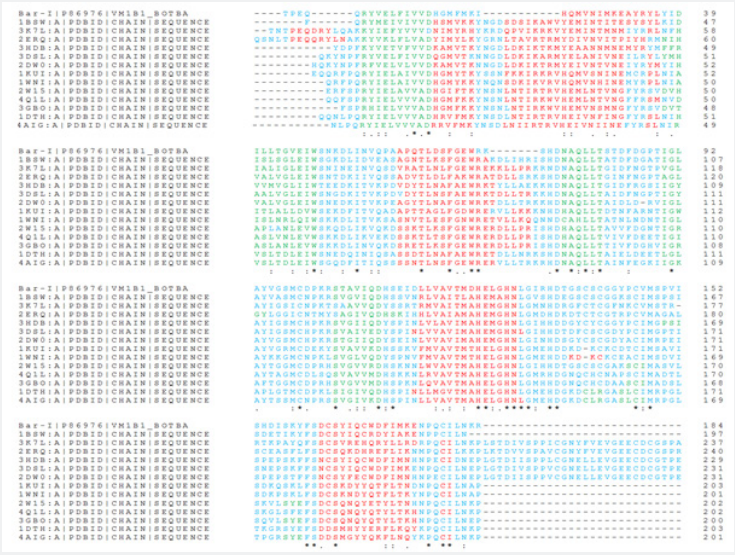
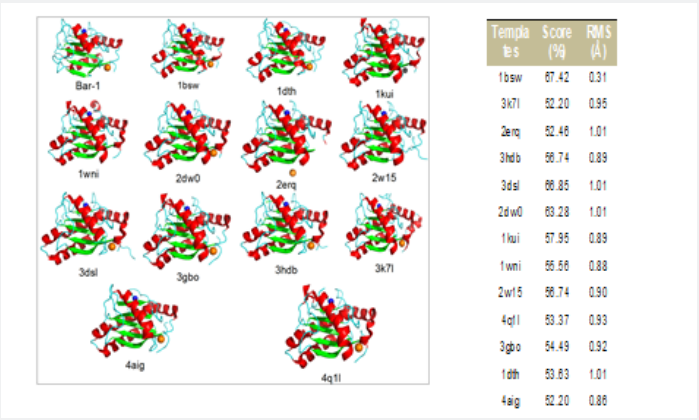


Figure 1: Clustal Omega align of Bar-I sequence with the sequence of the best identity score templates, colored by secondary structure (alpha helixes – red; beta sheets – green; coils – light blue).



Templates	Score (%)	RMS (Å)
1bsw	67.42	0.31
3k7l	62.20	0.95
2erq	62.46	1.01
3hdb	66.74	0.89
3dsl	66.85	1.01
2dw0	63.28	1.01
1kui	57.95	0.89
1wni	65.56	0.88
2w15	66.74	0.90
4q1l	63.37	0.93
3gbo	64.49	0.92
1dth	63.83	1.01
4aig	62.20	0.86

Figure 2: Comparation of secondary structure (left) and highest similarity of Bar-I with other proteins. Left - β-sheet – green, α-helix – red), coil – light blue, Ca2+ – orange, Zn+ – dark blue, Cd+ – dark gray, Right - the highest identity score templates, found by using Swiss-Model program. The Root Mean Square (RMS) values were calculated for Bar-I model and similar proteins.

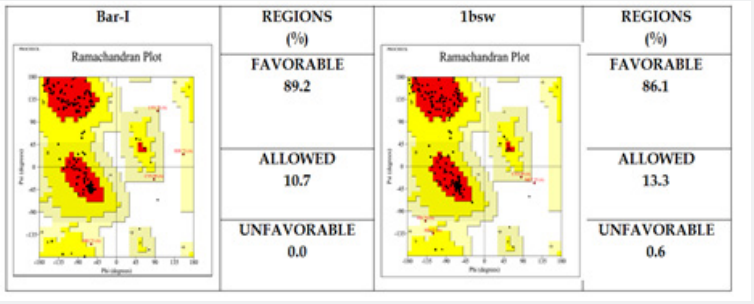


Figure 3: Comparation between Ramachandran plots of Bar-I and Acutolysin (1bswA), to validate it structural model stereochemistry stability.

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Results and Discussion

The most similar templates were 1bsw (67.42%) and 3dsl chain A (66.85%) respectively. Thus, in this work we constructed the 3D-model of Barnettlysin-I by homology modeling by using as template the crystal structure of acutolysin A, a three-disulfide hemorrhagic zinc metalloproteinase from *Agkistrodon acutus* (Identity = 67.42%). Overall the model revealed a conserved tertiary structure with six of the seven Cys paired (C117-C197, C157-C181, and C159-C164) and the substrate binding cleft localized between two domains. The calcium ion is in contact with E9, D75, C179 and N182 whereas Zinc interacts with H124, H128 and H134. The preference for Leu at P1' subsite is justified by the small binding region whereas the comparison with other SVMP family members (e.g. mutalysin, atroxlysin and leucurolysin-B) revealed important features that characterize its interesting profile (Figures 2 & 3).

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