In silico study of metallo-β-lactamases

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Since the discovery of penicillin, β-lactam antibacterial compounds have been developed and extensively used to fight infections. The broadly use of these compounds triggered resistance mechanisms on bacteria, among which we can highlight the hydrolisys of the β-lactam ring by β-lactamases. Among of β-lactamases, metallo-β-lactmases (MβL) are of the highest concern. Studies related to MβL activity rely on understanding how structural arrangement of catalytic metal ions, Zn(II), and amino acid constellation promote the activation of nucleophilic water by using Zn(II) as a Lewis acid.[1]

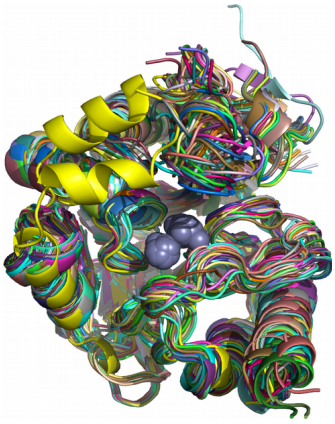

Figure 1: Alignment of 75 crystal structures obtained by Mustang algorithm

Herein, we describe an interesting structural correlation among 75 crystal structures of MβL deposited in PDB by aligning them using Mustang[3] algorithm (Figure 1). Although the results show a Root Mean Square Deviation (RMSD) lower than 2 Å, the structures share a very low sequential similarity and identity, 5.4% and 4.7% respectively. The physical-chemical parameters were analysed by Fpocket and APBS softwares.[2,3] As shown by Table 1 the parameters present high deviations demonstrating that the chemical nanoenvironments are different despite their structural similarity, which is due to the low sequence similarity of amino acid residues. Therefore, despite of differences in the residues among the structures, the catalytic function of all MβL is preserved. Our observation is in agreement with Meliá *et. al.* and Meini *et. al.* They demonstrated that despite of residues differences of MβL's subgroups B1, B2 and B3 they all share the same activation mechanism against β-lactams.[1,4]

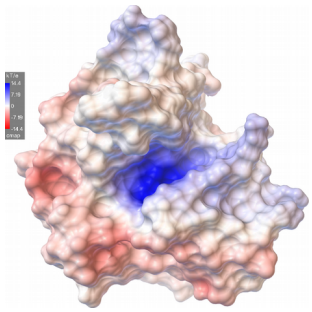

Figure 2: 4hl2 electrostatic surface calculated by APBS software

We also have observed by the solution of Poisson-Boltzmann equation that all 75 crystal structures of MβL shares a very similar electrostatic positive surface over the catalytic site at pH of 7.4 (Figure 2). In summary, our studies aim to provide information to allow the design of a selective inhibitor, which is going to tackle the difficulties of finding a drug that presents not only selectivity but more specificity over inhibition of MβL. Therefore, our study look for a parameter that could help to design a drug capable of inhibit all 75 studied structures independently of their subgroups, in order to achieve a broad spectrum activity.

Table 1: Fpocket calculated parameters

Property	Average	Std.D.
Druggability Score	0,18	0,24
Total SASA (Å²)	257,41	149,99
Polar SASA (Å²)	119,04	71,50
Apolar SASA (Å²)	138,37	94,49
Volume (Å³)	576,63	374,11
Mean aplha sphere radius (Å)	3,82	0,34
Hydrophobicity score (%)	21,77	11,72
Mean alpha sphere solvent access	0,51	0,06
Volume score	4,02	0,49
Polarity score	8,69	4,26
Charge score	1,03	0,97
Flexibility	0,26	0,15

1 Meini, M. R.; Llarrull, L. I.; Vila, A. J.; *FEBS Lett*. **2015**, 589, 3419.

2 Le Guilloux, V. ; Schmidtke, P.; Tuffery, P.; *Fpocket: An open source platform for ligand pocket detection*, *BMC Bioinformatics,* **2009**, 10:168 A

3 Dolinsky, T.J.; Nielsen, J.E.; McCammon, J.A.; Baker, N.A.; *Nucleic Acids Res*, **2004**, 32, W665-W667.

4 Meliá, C.; Ferrer, S.; Moliner, V.; Bertran, J.; *Arch. Biochem. Biophys.* **2015**, 582, 116.