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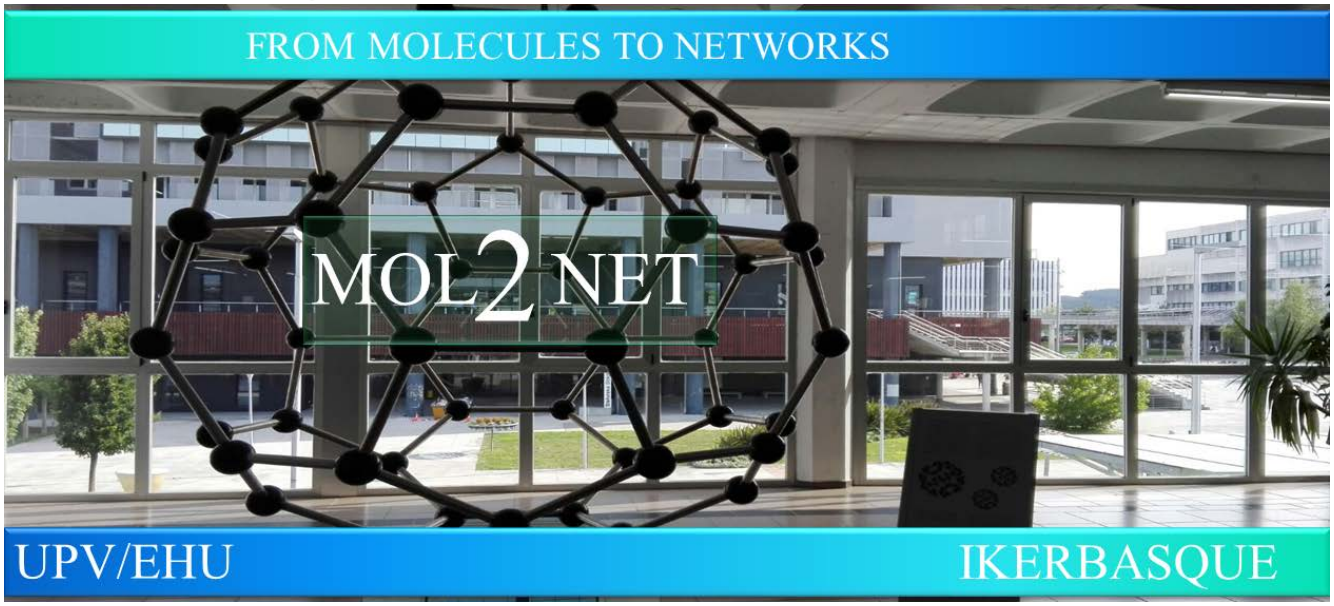

Protein ligand complexation: a computational and experimental approach

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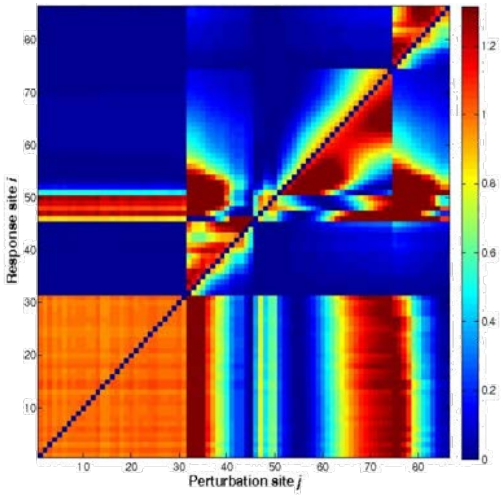
Graphical Abstract



Abstract.

Herein, we present an integrated computational and experimental study to tackle the interactions between proteins and ligands. As an example of a protein we have chosen fibrinogen, a blood serum protein related to coagulation processes. While as a ligand we have chosen a penicillin: cloxacillin. With respect to computational tools molecular docking simulation with elastic network based on collective low-frequency normal modes and perturbation response

	scanning maps were proposed to evaluate the conformational binding mechanism. With respect to the experimental part, the tools chosen were calorimetric (ITC and DSC) and spectroscopic (Raman and fluorescence). The combination of all these techniques will give us a broad and concise view of the bonding process between the two species.

Introduction *(optional)*

Despite the enormous attention that for so many years have enjoyed by the scientific community protein-ligand interactions, far from diminishing, has increased the interest and fascination that this topic exercise upon researchers. For this purpose, molecular docking and ITC experiments were performed to evaluate the conformational binding mechanism of fibrinogen under the unbound and bound states with cloxacillin [1-5].

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Results and Discussion *(optional)*

A clustered docking analysis involving different fibrinogen regions was performed. The results showed corroborates that the antibiotic binding interactions occur with a higher binding probability in the fibrinogen E-region compared with the two D-regions (see Figure 1, left)[6]. To explore conformational changes of regulatory chains (N and Q) under the presence of cloxacillin inducing local perturbations we perform the LPRS maps in collective low-frequency modes (Figure 1, right)[7-9]

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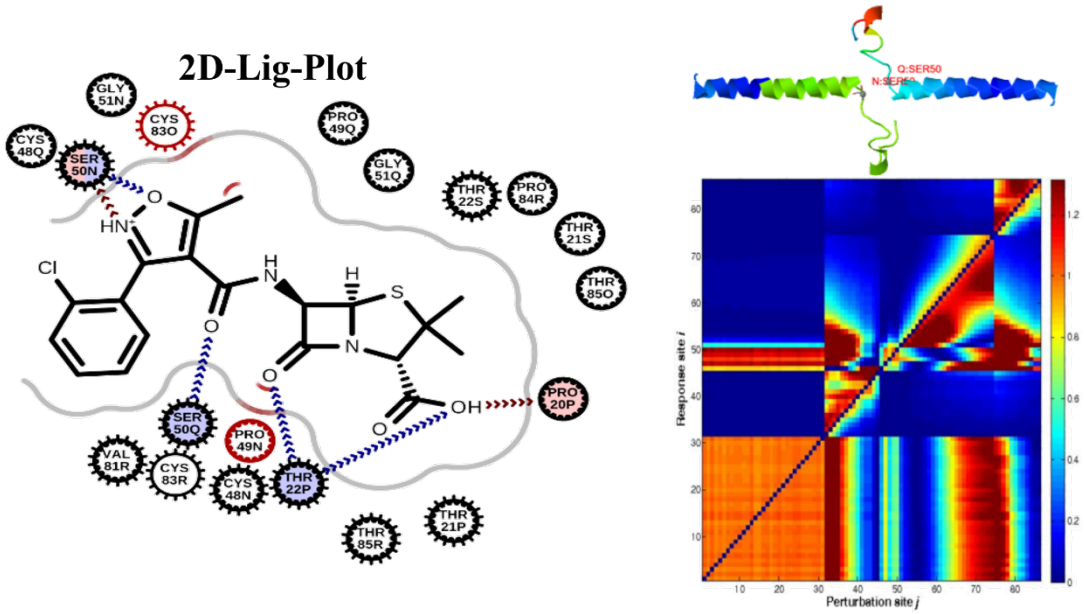

Figure 1. Left: lig-plot diagram. Right: graphical representations of the generated local perturbation response (LPRS maps) showing the relationship between (i-j)-pairs of residues as i-sensor residues (x-axis) to j-effector residues

The experimental analysis was performed by using isothermal titration calorimetry (ITC) and differential scanning calorimetry. Results can be observed in Figure 2.

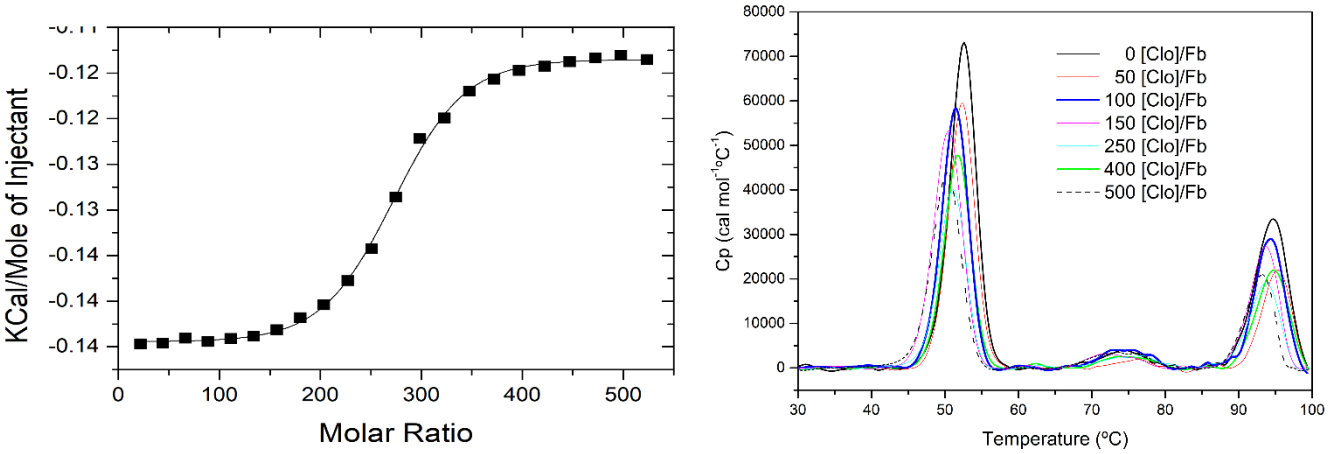

Figure 2. Left: Experimental points obtained from ITC measurements. Right: Experimental thermograms obtained from DSC.

Conclusions

In the present study we combined computational and experimental approaches to evaluates the conformational binding mechanisms of fibrinogen with cloxacillin. The performed 2D-lig-plot diagrams revealed that the most relevant antibiotic interactions with the E-region (pocket 1) are mainly based on hydrophobic (C···C)-backbone-side-chain non-covalent and acceptor/donor interactions with critical regulatory. LPRS maps revealed the subtle differences in the conformational dynamics of relevant E-region chains under unbound and bound state with the cloxacillin. The experimental results excellently corroborated the computational predictions and the relevant role that the penicillin molecular structure play in the binding process was confirmed by quantitative calorimetric data on ITC and DSC.

References

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