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Type	Poster
Session	Protein structure and function
Title	Design and computational analysis of a new bifunctional cephalosporin
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Motivation

Cephalosporins are a class of beta lactam antibiotics that are very popular for their bactericidal activity, low toxicity, and low costs of production. From the discovery of the first representative, cephalosporin C, hundreds of semisynthetic compounds have been created in order to widen their spectrum of action and tune their pharmacological properties [1]. However, the insurgence of antimicrobial resistance against these compounds has prompted the researchers to modify these molecules in order to counteract defense mechanisms developed by bacteria. Among the different strategies, an opportunity is offered by the creation of bifunctional compounds in which two or more azetidinone rings are associated in a single molecule [2].
During the last years we have designed, synthesized and tested several compounds belonging to an innovative class of bifunctional cephalosporins, bearing an additional isolated beta lactam ring with different substituents joined to the scaffold of the 7-aminocephalosporanic acid moiety via an amide bond. These compounds have proven to be effective against Gram+ organisms, in particular against S. aureus, one of the most important genus of multi-resistant pathogens. Unfortunately, they are not effective against Gram- organisms, although they were predicted to bind favorably to the penicillin-binding proteins (PBP, the natural targets for this class of antibiotics) belonging to several Gram- bacteria [3- 5]. We hypothesize that this could be due to the fact that the cell wall of Gram- bacteria is much less permeable to external molecules, in particular if these molecules are relatively big, like these compounds. To encompass this issue, we have designed a new derivative bearing a moiety that could improve the penetration of the bacterial cell wall, and we have analyzed its interactions with its natural target proteins by using a computational approach.

Methods

The structure of the new compound has been designed and saved in 3D. pdb format by using ChemDraw and Chem3D Pro 12.0 (Perkin Elmer). Several structures of PBPs and of beta lactamases were selected on the basis of their structural class and quality criteria [3-5]. To study the interactions, a covalent docking approach has been applied by using the flexible side chain approach implemented in AutoDock 4.2 [6]. The parameters used to setup simulations for this compound are the same used in our previous studies [3-5]. The conformations corresponding to the best energetic and to the most populated cluster of poses obtained from covalent docking, have been analysed with Discovery Studio (DassaultSystèmes, 2015).

Results

The computational analysis showed no significant difference between the binding energies predicted for the enzymes belonging to Gram+ bacteria and those predicted for Gram- bacteria, nor between the two diastereoisomers obtainable from the synthesis of the compound, in agreement with data obtained previously [3-5]. The compound interacts with the residues of the active site of the PBPs especially with H-bonds, but the aromatic moieties bound to the isolated ring can modulate the affinity. The presence of the new moiety does not perturb the binding to PBPs, but it interacts differently with beta lactamases, allowing to suppose that this new moiety might improve the resistance of this compound to hydrolysis. These data suggest that this molecule is a promising starting point for the development of new bifunctional cephalosporins with improved antimicrobial activity.

Info

References:
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Figure	
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Availability	-

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