Quantitative relationships between β-lactam molecular properties and β-lactam/AcrAB-ToIC complex geometry as determinants of MDR efflux

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THE OBJECTIVES OF THIS WORK

1) To predict the position and orientation of 16 β-lactam antibiotics in the central cavity of the multidrug efflux pump AcrB (a component of AcrB-ToIC membrane transporter) that exists in several Gram-negative bacteria by using only known molecular structures and calculated properties of drugs (β-lactams and four organic dyes: dequalinium, ethidium, ciprofloxacin, rhodamine 6G) and protein-drug (AcrB-organic dyes) complexes to predict AcrB-organic dye complexes to protein-drug complex geometry optimizations nor molecular dynamics simulations were performed;

2) To show that the β-lactams and the organic dyes, although structurally diverse, have properties in common that are responsible for their active efflux;

3) To use this similarity and the AcrB-organic dye complexes to predict AcrB-β-lactam geometry and to rationalize it with Quantitative Drug Structure – Complex Geometry Relationships + Exploratory Analysis.

THE AcrAB-ToIC PUMP, ITS MULTIDRUG RESISTANCE (MDR) EFFLUX MECHANISM, AND ITS SUBSTRATES

1. A schematic representation of the AcrAB-ToIC pump in E. coli. The two main drug efflux mechanisms are predicted to be involved: (A) the two main drug efflux mechanisms are predicted to be involved: (A) a drug pore, which is located in the cytoplasmic membrane, and (B) a 70-kDa protein named AcrB that transports the effluxed drug to the periplasmic region where it can be exported out of the cell.

2. A 3D representation of the 3D structure of trimers TolC (PDB: 1EK9, space group P21, S. tiphymurium) and AcrB (PDB: 3F01, space group P212121, S. tiphymurium). The two main drug efflux mechanisms are predicted to be involved: (a) a drug pore, which is located in the cytoplasmic membrane, and (B) a 70-kDa protein named AcrB that transports the effluxed drug to the periplasmic region where it can be exported out of the cell.

3. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

4. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

5. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

6. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

7. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

8. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

9. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

10. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

11. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

12. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

13. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

14. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

15. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

16. A schematic representation of the AcrB-TolC complex with the organic dye dequalinium (DEQ) bound at the vestibule entrance. The position of the vestibule, the transmembrane groove (TMG), the β-loops, and the polypeptide chain (green) are visible. Conserved motifs, salt bridges, and hydrogen bonds are indicated.

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