Quantitative Drug Structure – Complex Geometry Relationships in b-Lactam Efflux by Bacterial Multidrug Resistance Pump AcrAB-TolC

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Introdução

Multidrug Resistance (MDR) of pathogen and opportunistic bacteria to many drugs in current use is a serious problem in medicine. This phenomenon is the cause of elevated morbidity and mortality, medical costs and threats to immunocompromised people. One of the most frequent MDR mechanisms is the drug efflux from bacteria cells by overexpressed MDR pumps. A bacteria cell possesses various types of MDR pumps. Each pump type is responsible for rapid and efficient efflux of large variety of structurally unrelated compounds. However, these compounds share some common physico-chemical properties like charge, amphiphilic or lipophilic character, solubility and acid/base properties. Pump-drug intermolecular interactions are non-specific. Tricomponent pump AcrAB-TolC is the main efflux system in *E. coli*, *S. typhimurium* and several Gram-negative bacteria. Lipophilicity, hydrogen bonding and electronic properties of β-lactams are quantitatively related to their biological activities (efflux rates) [1]. Sixteen β-lactams (penicillins and cephalosporins) and four organic dyes (Figure 1) are studied in order to correlate their molecular properties with drug–AcrB geometry and give more insight into the mechanism of β-lactam efflux from Gram-negative cells [2].

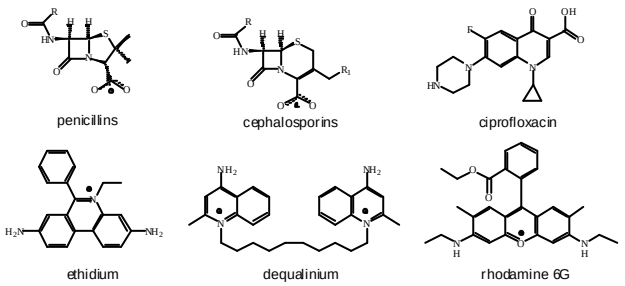

Figure 1. Structures of drugs studied in this work.

Resultados e Discussão

Molecular descriptors. Molecular structure of all drugs were optimized at semi-empirical PM3 level in package Spartan Pro. Several electronic (dipole moment and its components, polarizability and hiperpolarizabilities) and steric (principal moments, molecular box dimensions, molecular projection areas) molecular descriptors were calculated by using Spartan, MOPAC and molecular graphics plots. Many of these variables exhibit linear and non-linear intercorrelations as well as correlations with biological activities, frequently showing two or more classes of drugs. These relationships prove that the four drugs form a unique data set with the β-lactams.

Molecular graphics. Methods of molecular graphics were applied to the existing crystal structure of AcrB, TolC and AcrB complexes with the four dyes. The drug efflux pathway shows to have a complex structure, especially the vestibules, transmembrane grooves, the central cavity receptors and the pore entrance/channel. Various distance and angle parameters at the central hole were measured in the four drug-pump complexes to define the drug position with respect to AcrB.

Quantitative drug-pump relationships. The drug-pump geometry parameters were correlated with the electronic and steric descriptors of the dye molecules. These relationships were then used to predict positional and orientation parameters of the β-lactams in the central cavity of AcrB protein. Due to the small number of available crystal structures (four), rigorous correlations were considered, and the best predicted parameters were selected, and certain corrections were made in accordance with literature and chemical knowledge.

b-Lactam efflux mechanism. β-Lactam molecules as good pump substrates act like molecular dipoles oriented with their polar parts to the inner membrane and preserve this orientation along their whole pathway. The hydrophobic side chain R (Figure 1) is the head that enters the pore channel after drug binding in the central cavity.

Conclusões

Good β-lactam substrates of AcrAB-TolC efflux pump are elongated molecules with well-defined dipole characteristics. The dipole orientation is crucial for efficient drug efflux.

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[2] Ferreira, M. M. C.; Kiralj, R., *J. Mol. Graph. Mod.*, submitted.