A Priori Descriptors in QSAR: a Case of Gram-Negative Bacterial Multidrug Resistance to b-Lactam Antibiotics

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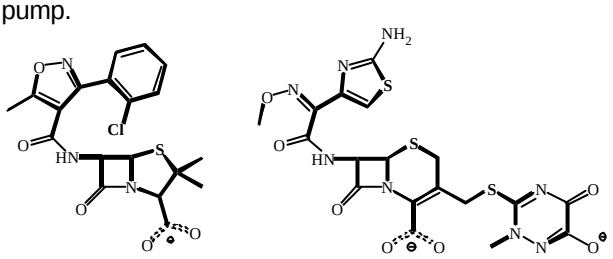
Introdução

QSAR/QSPR, LFER and related studies are based on global and local molecular descriptors. Descriptors can be measured, estimated and calculated in various ways, ranging from simple hand-made counts to complicated calculations that require expensive hardware and software. Understanding the meaning of molecular descriptors and the results obtained from regression and exploratory analysis is another aspect that may distinguish various computational approaches in QSAR-like studies. *A priori* or known-before-computer-assistance molecular descriptors [1] can be generated by hand or pocket calculator using 1D and 2D molecular formula and certain atomic/molecular constants. *A priori* global and local molecular descriptors of different nature (steric, topological, electronic, hydrogen bonding and complex) were generated for sixteen β-lactams studied previously [2]. Partial least squares (PLS) models were built and validated in the same way as previously, in order to calculate efflux rates of the β-lactams as substrates of AcrAB-TolC efflux pump in Gram-negative bacteria. Exploratory analysis (Principal Compponent Analysis PCA and Hierarchical Cluster Analysis HCA) was performed on the same data set that had been used in PLS.

Resultados e Discussão

PLS modeling. Two sets of negative logarithms of minimal inhibitor concentration of studied β-lactams excreted by two strains of *S. typhimurium* were biological activities. Hundred and five new *a priori* descriptors were generated in this study. Seven *a priori* molecular descriptors were selected and parsimonius PLS models ($Q > 0.90$, $R > 0.95$, SEV < 0.50) were built and validated. These models were comparable with previously obtained models [2] based on computed and some *a priori* descriptors. The models may provide complete explanation of the used data set as well as of the β-lactam efflux.

Exploratory analysis. Both PCA and HCA show that the molecular descriptors make groups of steric, structural/topological, hydrogen bonding and complex descriptors. The data set is at most four-dimensional in PCA (95.1% of the total variance). The third and fourth principal components (PCs) are originated mainly from hydrogen bonding, topological and some electronic (average valence electron content) descriptors. The samples are clustered with respect to their biological activities, but are primarily distinguished as penicillins and cephalosporins. The PCA scores plots show that the samples tend to form groups based on various properties like charge (anions, dianions, zwitterions, anion-zwitterions), overall hydrophobicity, and the number/type of rings in the side chains. The general PC1 accounts for hydrophobicity and hydrogen bonding potency and is quantitatively related to the biological activity. PC2 and PC3 are related to the distribution of hydrogen bonding and hydrophobic groups in the side chains, respectively. PC4 is related to molecular amphiphilicity expressed as the degree of molecular mosaic character, where elementary domains are hydrophobic or polar (Figure 1). Good β-lactam substrates of AcrAB-TolC have a few large well-defined domains. Introduction of various polar groups in the side chains increases mosaic character and makes the molecule to be more resistant to the efflux pump.



Cloxacillin (6 domains) Ceftriaxone (13 domains)

Figure 1. Distribution of hydrophobic/polar domains in a good (left) and bad (right) β-lactam substrates.

Conclusões

A priori QSAR analysis showed that the efflux rates of β-lactams from Gram-negative bacteria depend on molecular/side chain hydrophobicity/hydrogen bonding potency and molecular amphiphilicity.

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[2] Ferreira, M. M. C.; Kiralj, R., *J. Chemometr.* **2004**, *18*, 242.