# Chemometric and QSAR prediction of the multidrug resistance of VmrA efflux pump from *Vibrio parahaemolyticus*

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## Introduction

Multidrug resistance (MDR) of microbes and parasites as well as of cancer cells to currently used drugs is becoming one of the major problems in combating infectious and parasitic diseases and cancer, respectively. Among major mechanisms of multidrug resistance in cellular microbes and cancer cells are efflux pumps, macromolecular systems that extrude drugs and a large variety of structurally dissimilar substances from cell into the outside medium. MDR efflux pump VmrA exists in *V. parahaemolyticus*, a marine bacteria that causes seafood poisoning, wound and soft tissue infections, septicemia and other infections worldwide. VmrA is being effective against several structurally unrelated drugs, organic dyes, detergents and xenobiotics. It is a Na+/drug antiporter that extrudes substrates from the cytoplasm to the periplasmic space in a Gram-negative bacterial cell. Its functional form consists of a protomer placed in the inner membrane, with 448 residues in strain AQ3334 [1]. 3D structure of VmrA is not known yet. Substrates of this pump, although structurally very diverse, share some common properties that are responsible for their efflux from *V. parahaemolyticus*. This fact is the basis to construct (Quantitative) Structure-Activity Relationship ((Q)SAR) models for diverse drugs (i.e. of different classes) and to predict the multidrug resistance of the VmrA with respect to other diverse drugs.

## Results and Discussion

**Biological activities.** The efflux powers of two *E. coli* strains KAM32 and KAM32/pVCJ6, with and without incorporated VmrA, respectively, were expressed as minimal inhibitory concentration (MIC) in the form pMIC=-log(MIC) for twelve drugs [1]: a phenylindole derivative, tetraphenylphosphonium, acriflavine, ethidium, chloramphenicol, norfloxacin, rhodamine 6G, tetracycline, erythromycin, streptomycin, deoxycholate, and dodecyl sulfate. The MDR character of the VmrA was defined as pMIC$\Delta$=abs[pMIC(KAM32)-pMIC(KAM32/pVCJ6)] for this training set of agents.

**Molecular descriptors.** The structures of the agents from training and prediction set (19 agents: tetracyclines, β-lactams and analogues, hydroxyanisoles, sorbic acid, DNA intercalators, organic dyes and a modified amino-acid) were modeled according to available crystal structure data and geometry-optimized at PM3 semi-empirical level. Total of 120 molecular descriptors was obtained using software (Titan, MOPAC, Chem3D) for optimized 3D structures, and also from 2D chemical formula: steric, electronic, hydrophobic, hydrogen bonding, topological, compositional and complex descriptors.

**Regression models (QSAR).** Satisfactory Partial Least Squares (PLS) and Principal Component Regression (PCR) models were constructed for the two pMICs with software Pirouette, using five descriptors and one principal component: $Q > 0.76$, $R > 0.84$, $SEP < 0.57$, $SEV < 0.73$. Predicted pMICs for the training and prediction sets were in agreement with experimental data and chemical knowledge. The MDR parameter pMIC$\Delta$ was predicted well for 9 and 10 agents from the training and prediction sets, respectively.

**SAR models related to QSAR.** Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) were performed for the training and training+prediction sets related to the two pMICs. The scores plots and corresponding dendograms showed similarities between the training and training +prediction sets in terms of clustering. This aided in satisfactory predicting to which agent the VmrA would be resistant.

**SAR models with discriminatory descriptors.** Eight descriptors that described well experimental pMIC$\Delta$, were used in PCA-HCA analysis of the training and training+prediction sets. Like previous SAR analysis, this one also aided in clear predicting the MDR character of the VmrA efflux pump.

## Conclusions

The presented QSAR and chemometric (SAR) methodologies are able, in complementary sense, to predict the MDR character of the VmrA pump with respect to diverse agents.

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[1] Chen, J.; Morita, Y.; Huda, M. N.; Kuroda, T.; Mizushima, T. and Tsuchiya, T., *J. Bacteriol.* **2002**, *184*, 572.