EXPLORING PROTEIN FLEXIBILITY IN 4D-QSAR: APPLICATION TO A SET OF TRYPANOTHIONE REDUCTASE INHIBITORS

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In 3D-QSAR analysis, the interactions between ligands and chemical probes are mapped onto a surface or grid surrounding a set of compounds, which are superimposed in 3D space. This surface or grid represents a hypothetical binding site of some biological target. The quality of the QSAR model depends critically on the correct superimposition of the ligands. However, the absence of structural information from the target makes the correct ligands' superimposition almost impossible. The accommodation of ligands in a binding site employing methodologies such as automated docking is one way to handle such situations. But, the docking approaches does not take into account the protein flexibility,[1] which can be considered the major drawback. Nowadays, flexible docking methods and/or molecular dynamics simulations of complexes having docked conformations[2] have been used to overcome these issues.

In this study the advantages of docking method followed by the ligand-receptor molecular dynamics simulations were considered to test such 4D-QSAR approach. The conformational ensemble profile (CEP) of each ligand was aligned based upon both the common structural features from the investigated set of ligands and the relevant amino acid residues in the binding site (see fig. 1a). A preliminary set of 33 phenothiazine derivatives acting as inhibitors of trypanothione reductase (TR) from *Trypanosoma cruzi* was selected from ref. 3. TR enzyme is considered a potential target for the rational design of new selective anti-T. cruzi agents due to the trypanothione redox-defense system, which is a fundamental metabolic difference between the mammalian host and trypanosomal parasite.

LQTAQSAR[4] models were built employing the ordered predictor selection[5] algorithm for variable selection and partial least squares method for regression. The y–randomization and leave–N–out cross-validation procedures were carried out in addition to the external validation. PLS models provided the following statistics: $Q^2 = 0.84$, $R^2 = 0.91$ for 8 variables selected and 3 latent variables. The selected descriptors presented in fig. 1b provided information regarding both intrinsic ligand structural information as well as key interaction sites within TR binding pocket. The results are promising and reinforce the importance of induced fit for building grid based QSAR models.

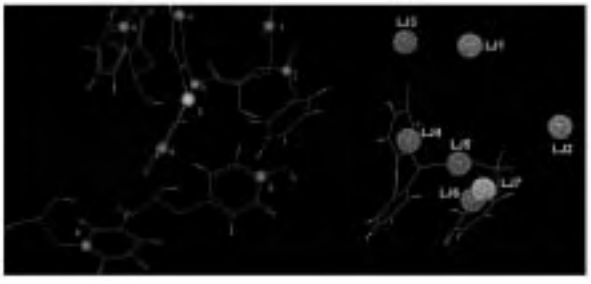

Figure 1. (a) Atoms selected to align the CEP of each ligand of the investigated set. (b) Visualization of the 3D interaction descriptors of the best QSAR model.

References:

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