

ORAL PRESENTATION

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3D-QSAR reloaded: Open3DALIGN meets COSMOsar3D

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A novel set of 3D descriptors, based on local grid-based COSMO σ -profiles (LSPs), has been recently proposed as a promising alternative to force-field based MIFs in 3D-QSAR [1]. These descriptors are grounded in the quantum chemistry-based COSMO-RS theory, which has become one of the methods of choice for the prediction of fluid

phase equilibrium constants (e.g., partition coefficients, solubilities, vapor pressures) in pharmaceutical chemistry and chemical engineering.

Herein we present two applications of COSMOsar3D to ligand-based and structure-based modeling. In the first case, we formulated a binding mode hypothesis for a

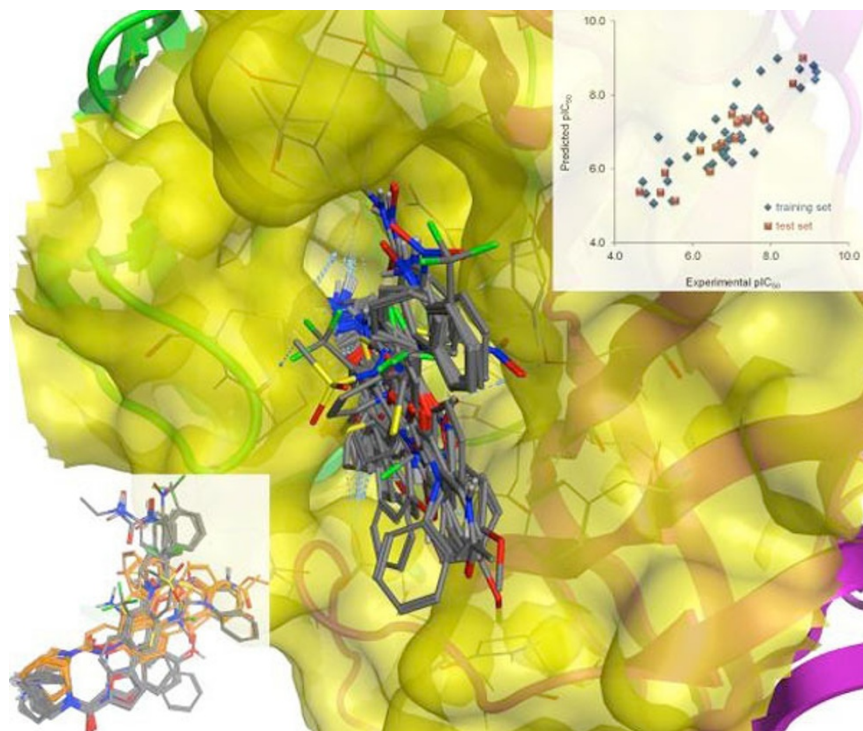


Figure 1 α_7 ligand binding mode hypothesis (left); experimental vs predicted pIC₅₀ plot (top).

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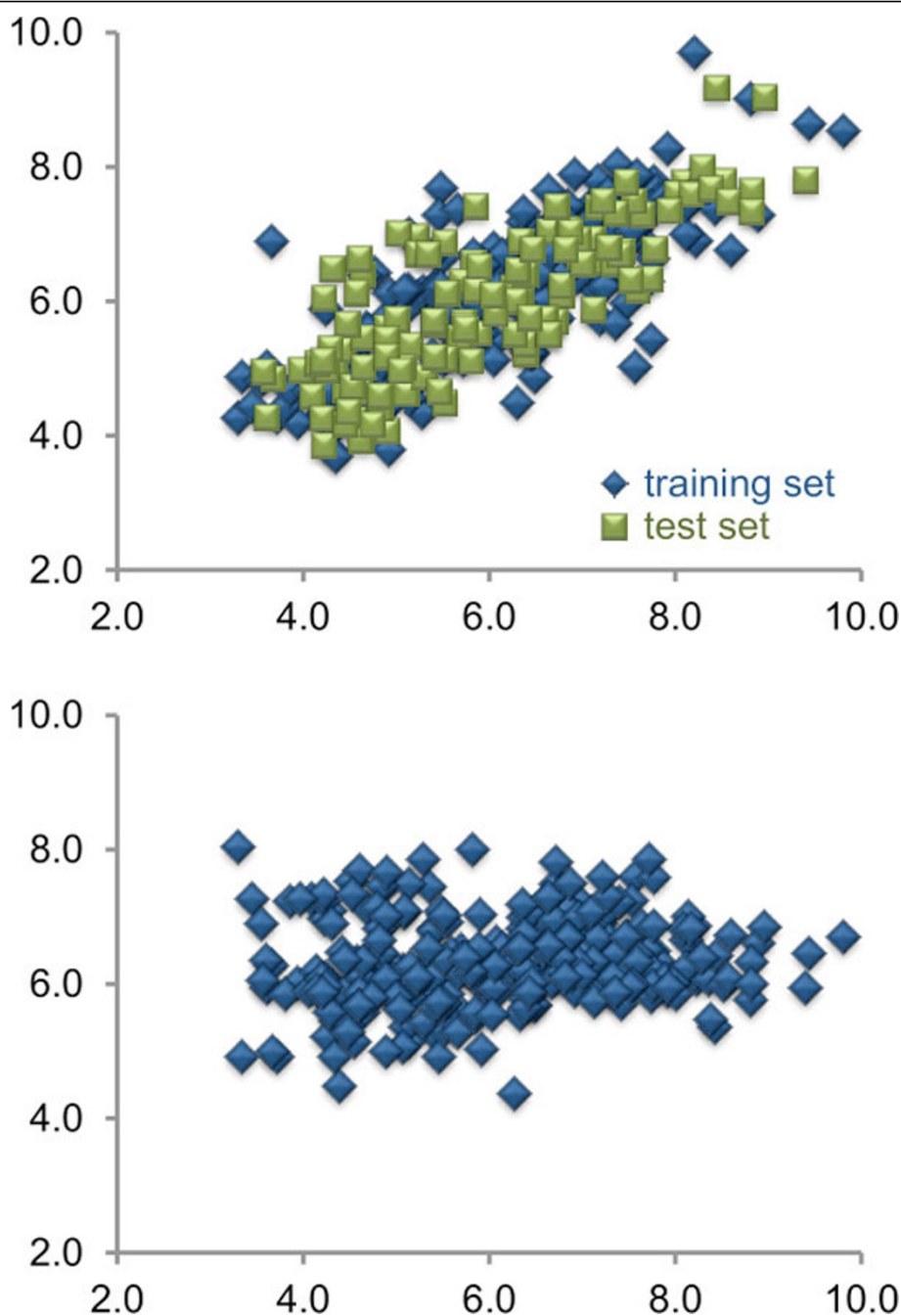


Figure 2 Comparison between the accuracy of pIC50 predictions made by COSMOsar3D (top) and AutoDock VINA (bottom).

series of 59 partial agonists at the human α_7 nicotinic receptor using an iterative unsupervised alignment procedure implemented in Open3DALIGN [2]. Our hypothesis is compatible with site-directed mutagenesis data and fits an independent α_7 receptor homology model; the associated COSMOsar3D model has excellent predictive power (Figure 1).

In the second case we used the Sutherland datasets to compare the accuracy of pIC50 predictions based on

AutoDock VINA scores to those based on COSMOsar3D models Open3DALIGN'ed on co-crystallized templates; in this context, COSMOsar3D predictions proved to be far more effective in ranking ligand potencies (Figure 2).

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