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3D Molecular Shape Similarity, an Efficient Tool for Virtual Screening

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Structure-based virtual screening approaches fall into two main classes: those based on protein coordinates and those based on ligand coordinates. When a protein-ligand cocrystal is available in an industrial project setting, virtual screening using docking has become the method of choice. In recent years, shape-based virtual screening methods have become increasingly popular in the field of computer aided drug discovery and are established as important tools for virtual screening. The method were used, among others, to find ZipA-FtsZ protein- protein interaction inhibitors, for the identification of a novel class of cannabinoid receptor 1 antagonists, for screening on cruzain inhibitors, aiming at improved selectivity over cathepsin L., for investigations on 30 selective G-protein coupled receptor agonists, screening of HIV entry inhibitors for the CXCR4 (a CXC chemokine receptor) and CCR5 (chemokine (C- C motif) receptors, and so forth. The increasing popularity of the method underscores the necessity to systematically investigate the efficiency of method compared to other methods, and also to find out the limitations and optimal usage for shape-based virtual screening. The presentation is an overview of some representative papers on this growing field.

Reference:

1. Comparison of shape-matching and docking as virtual screening tools. Hawkins, P. C. D.; Skillman, A. G.; Nicholls, A. *J. Med. Chem.* **2007**, *50*, 74–82.
2. How To Optimize Shape-Based Virtual Screening: Choosing the Right Query and Including Chemical Information. J. Kirchmair, S. Distinto, P. Markt, D. Schuster, G. M. Spitzer, K. R. Liedl, G. Wolber *J. Chem. Inf. Model.*, **2009**, *49*, 678-692.
3. ShaEP: Molecular Overlay Based on Shape and Electrostatic Potential. M. J. Vainio, J. S. Puranen, and M. S. Johnson *J. Chem. Inf. Model.*, **2009**, *49, 492-502.*

Summary:

The evaluation of efficiency of 3D molecular shape-based virtual screening methods were presented in the articles. It was shown, that the method, even though it uses only the molecular structure of an active ligand as the sole information, can detect pharmacologically active molecules. The software called ROCS was the subject of the most investigations, and it has been shown to compare favorably with various docking tools. It was concluded by various studies that the method has a more consistent performance regarding protein targets. The software is surprisingly only slightly sensitive to the conformation of the query molecule, and artificially generated minimal structures can also give comparable results instead of the bio-active conformer (which is not always available). The biggest limitation of the method, the larger number of false negatives (compared to docking) can be successfully eliminated by using a set of active ligands as queries.