VIRTUAL SCREENING COMPUTER-AIDED TOOLS IN MODERN DRUG DESIGN

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Virtual screening approaches implementation in drug design workflows have recently become an approximate but useful alternative to laboratory-based high-throughput screening methods. Modern tendencies of in silico design strategy application for the process of novel potent biologically active compounds construction include molecular modeling and virtual screening methodologies. Typically, drug discovery strategy with the computational chemistry methods implementation is aimed on the potent lead compounds identification for a pre-selected protein target from the virtual library of drug-like chemicals using receptor-based and ligand-based virtual screening techniques. The most potent compounds are selected for chemical optimization towards the specific molecular target.

Virtual combinatorial library scaffold-based generation produces multiple scaffolds for further lead chemical optimization taking the advantage of implementing and using scaffolds as starting points particularly in the target space of the same protein family. The scaffold-based drug discovery paradigm in fact is realized *via* scaffold candidates identification using a low-affinity screening of an intermediate molecular weight compounds, their examining for the number and types of interactions made with the target, their ability for further chemical optimization validation towards the newly generated compounds examining as potent and selective inhibitors for the given protein target.

Lead compounds identification as potential drug-like candidates may be realized by performing two-dimensional (2*D*) or three-dimensional (3*D*) similarity searches, by applying diversity analysis techniques, and by computational docking against the target protein. The last two are commonly implemented as throughput ligand-based and receptor-based virtual screening techniques.

The virtual screening ligand-based strategy relies on the information about the structure of ligands and the screening process is based only on the characterization of known active compounds. It includes QSAR analyses technique with the most recent refine predictive models employing around the certain scaffold-based structures.

The structure-based (or receptor-based) approach for the combinatorial library virtual screening (molecular docking) is used when the structure of the receptor is known or can be modeled. Thus, the results of structure-based approaches can be seen to depend critically on the quality of the protein structure and docking protocol applied.

The molecular docking approach both with rigid or flexible receptor can be used to model the interaction between a ligand and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate bio-molecular mechanisms of biological nano-systems functioning. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within binding site of the receptor and assessment and scoring of the binding affinity.

Strictly speaking, structure-based methods might be expected to give better results than ligand-based approaches, because they try to model the steric, electrostatic, hydrophilic and hydrophobic features of protein-ligand interactions.

Protein-ligand interaction modeling and summarizing, pharmacophore queries generation and prediction of molecular mechanisms which ensure the affinity and inhibitory activity of novel compounds towards multiply receptors allow formulating the basic electronic and steric criteria to be met by the lead compounds structures to ensure their more effective binding to selected targets and their stronger inhibitory potency.