Pharmacophores: Well Suited Tools for Accurate Virtual Screening

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In silico or virtual screening has gained considerable impact for the efficient discovery of novel bioactive compounds in modern pharmaceutical research. The concept of chemical feature-based pharmacophore models has been established as state-of-the-art technique for characterizing the interactions between a macromolecule and a ligand. The results of numerous case studies have been published, clearly indicating the merits of this approach for efficient hit discovery [1].

While in ligand-based drug design, feature-based pharmacophore creation from a set of bioactive molecules is a frequently chosen approach; structure-based pharmacophores are still lacking the reputation to be an alternative or at least a supplement to docking techniques. Nevertheless, screening using 3D pharmacophores as filters bears the advantage of being faster than docking. Additionally, it transparently provides the user with relevant information that is used by the screening algorithms to characterize the ligand-macromolecule interaction.

Inte:Ligand Gmbh has developed rapid and efficient tools for automatic interpretation of ligand-protein interactions and subsequent transformation of this information into 3D chemical feature-based pharmacophore models. As an extension of this approach, parallel pharmacophore-based screening has been introduced as an innovative in silico method to predict the potential biological activities of compounds by screening them with a multitude of pharmacophore models. Using LigandScout [2], the entire Protein Databank has been processed, and a database of structure-based pharmacophore models for all targets of potential interest for drug development has been generated.

We present an overview of this technology together with the results of an application example employing a set of antiviral compounds that were submitted to in silico activity profiling using a subset of the Inte:Ligand pharmacophore database. The results of the screening experiments show a clear trend towards correct prediction of activity profiles [3]. In addition, using our approach one is able to obtain information about binding of the ligands under investigation also to 'anti'-targets, such as enzymes of the cytochrome P450 family, or to the hERG channel. Thus, off-target activity can be determined easily, giving support to the medicinal chemists in their hit-to-lead and lead optimization studies.

References