STRUCTURE-BASED PHARMACOPHORE MODELLING WITH LIGANDSCOUT

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Virtual screening together with computer assisted drug design have emerged as one answer to increasing economic pressure that forces the pharmaceutical industry to develop new drugs in a faster and more efficient way [1]. Structure-based drug design is usually tightly associated with docking, which bears the lack of computational efficiency for high-throughput virtual screening. We propose the creation of chemical feature based pharmacophore models suitable for virtual screening from experimentally determined 3D ligand-complex data.

The LigandScout program [2] provides an automated method for creating three-dimensional, chemical feature based pharmacophore models from structure data, as e.g. publicly available from the Protein Databank (PDB). In a first step, small molecule ligands are extracted and automatically analyzed in terms of chemical functionality and hybridization states including the assignment of hybridization states and bond orders. Second, from the interactions of the interpreted ligands with relevant surrounding amino acids, pharmacophore models reflecting functional and steric interactions are created, which can interactively be reviewed, modified and visualized.

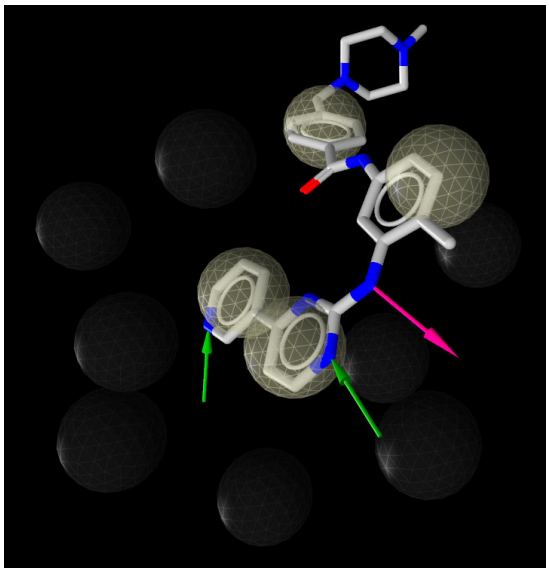

Fig. 1: Chemical function based 3D pharmacophore model automatically derived using LigandScout from PDB entry 1T46 with ligand STI-571 (Gleevec) and its alignment with the bio-active ligand conformation.

[1] H. Kubinyi. In Search for New Leads, EFMC - Yearbook 2003, 14-28.
[2] G. Wolber, T. Langer. LigandScout: 3-D Pharmacophores Derived from Protein-Bound Ligands and Their Use as Virtual Screening Filters *J. Chem. Inf. Model.,* **2005,** *45,* 160-169