Kinase Targeted Docking Library

Kinases are an extensive class of enzymes catalyzing phosphorylation, hence, affecting reactivity and binding properties of the substrates and regulating the energy balance. Therefore, kinases are crucial to many phases of cell life. Modulators of protein kinase activity are firmly established as a major class of drug targets for the pharmaceutical industry. Consistently high interest in this class of targets reflects both advances in identifying selective protein kinase inhibitors and a growing perception of the fact that these drugs offer a novel, well-tolerated oral therapy for some of the most untreatable cancers and immune disorders.

Life Chemicals offers a Kinase Docking Library, designed using receptor-based approach. We have developed a docking and scoring strategy to identify potentially active and selective inhibitors on the base of crystal 3D structures of protein-ligand complexes of five kinases from different families:

- CDK2 (cyclin dependent kinase 2)
- GSK3 (glycogen synthase kinase 3)
- PKB (protein kinase B)
- SRC kinases (2 protein structures)
- EGFR (epidermal growth factor receptor)

Initially, Life Chemicals Stock Compounds Collection was filtered according to the Lipinski rule, and toxicophore and undesired functionalities were removed. 3D structures were generated in SYBYL-X and further the ligands dataset was prepared within LigPrep program (Schrödinger software package). The protein-ligand structures recorded in the corresponding PDB entries [1-6] were analyzed and optimized in SYBYL-X. Thereafter, the identification of key residues and features of the ligands, responsible for the binding, was performed with the following grid maps generation of the binding sites. The docking process was carried out with Glide docking tool, which provides exhaustive and tunable search based on constraints in electrostatic grid maps and hydrophobic regions. Validation of the protein binding site models and docking procedure was performed using a reference sets of inhibitors with known bioactivity data. Finally, the compounds have been selected according to score values related to the results of docking validation experiment. As a result, over **13,000** compounds were obtained to be included into the Life Chemicals Kinase Docking Library.

References

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