[P10] Protein family customised structural chemogenomics databases to investigate biomolecular interaction space

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A systematic analysis is presented of all structural protein-ligand interactions in kinase and phosphodiesterase (PDE) crystal structures present in the Protein Data Bank (PDB). The consistent structural alignment of ligand binding site residues enables the systematic analysis of protein−ligand interaction fingerprints (IFPs) within kinases and PDE protein families, the identification of subtype-specific protein−ligand interaction features, and the classification of ligands according to their binding modes. We illustrate how systematic mining of the constructed kinase (KLIFS[1-3]) and PDE (PDEStrIAn[4-5]) structure and ligand interaction annotated databases gives new insights into how conserved and protein selective interaction hot spots can accommodate the large diversity of chemical scaffolds in ligands for different protein targets.

The combination of protein-ligand interaction fingerprint analyses, ligand SAR, and protein-ligand selectivity profiles via integrated chemoinformatics workflows provide three-dimensional interaction maps to predict protein-ligand complexes for which no experimental structures are available. A substructure analyses of the cocrystallized ligands in combination with those in bioactivity databases provides a toolbox for scaffold hopping and ligand design. The structural chemogenomics analysis lead to an improved understanding of the structural requirements of selective interactions with kinases and PDEs that is useful in structure-based ligand selectivity and polypharmacology prediction and drug discovery studies.

Bibliography :

[1] O.P.J. van Linden; A.J. Kooistra; R. Leurs; I.J.P. de Esch; C. de Graaf J. Med. Chem. 57 (2014) 249-277
[2] A.J. Kooistra; G.K. Kanev; O.P.J. van Linden ; R. Leurs, I.J.P. de Esch and C. de Graaf Nucleic Acids Res. 44 (2016) 365-371
[3] http://klifs.vu-compmedchem.nl
[4] C. Jansen; A.J. Kooistra; G.K. Kanev; R. Leurs, I.J.P. de Esch, C. de Graaf J. Med. Chem. (2016)
[5] http://pdestrian.vu-compmedchem.nl