Structural Interaction Fingerprints as a tool for assessing ligand selectivity between two targets

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SIFTs (Structural Interaction Fingerprints) are precise and rapid tool for binding site description. In this research, SIFt describing physical ligand-protein interactions consists of 9-bit fragments providing information with residues and type of interaction (hydrophobic, aromatic, charge, polar, sidechain, backbone). A collection of such fingerprints is then merged into an averaged string, a profile, showing frequencies of occurrence of each interaction.

In this research, two varying protein families were designated as targets: G-protein coupled receptors (GPCRs) class A, and protein kinases. From each group protein pairs were selected with experimentally solved crystal structures, and known set of selective ligands modulating their activity. Active (Ki < 10 nM) and inactive (Ki > 1000 nM) ligands were selected from ChEMBL database, separately for each protein. Afterwards, they were docked to their target structures in order to generate averaged interaction profiles for active and inactive compounds.

Having those profiles, the comparison with singular SIFt fingerprints is produced for compounds selective to target/antitarget protein pairs. Basing on complementarity between those two, one can select compounds with high affinity to target and low affinity to antitarget.

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