[P7] Exploring the binding modes of fragments and their drug-like superstructures

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Fragment-based drug design (FBDD) is based on the assumption that a fragment binding mode will be conserved when the fragment is part of a larger, drug-like ligand. Although case studies demonstrate the applicability of the FBDD hypothesis [1,2] and more than 15 FBDD-derived compounds have reached clinical trials [3], examples where the fragment binding mode is not preserved in the ligand have also been found [4]. Up-to-date, no systematic analysis of the extent of conservation between fragment and ligand binding modes has been performed.

To derive general rules for the success or failure of FBDD, we explored the binding modes of fragments and their drug-like superstructures crystallized with the same protein targets. Based on an investigation of all 3D structures in the Protein Data Bank, we identified more than 13,000 unique fragment-ligand pairs bound to the same protein. The pairs were examined for binding mode conservation using shape overlap and interaction pattern similarity [5]. Here, we present the analysis focused on four drug targets which exhibit the largest number of 3D structures of fragment-ligand pairs. Interestingly, in the majority of cases (as exemplified in Figure 1) the fragment overlaps well with the respective ligand. Trends observed for the four drug targets will help to define the characteristics of the minimal fragment structure retaining the ligand binding mode.

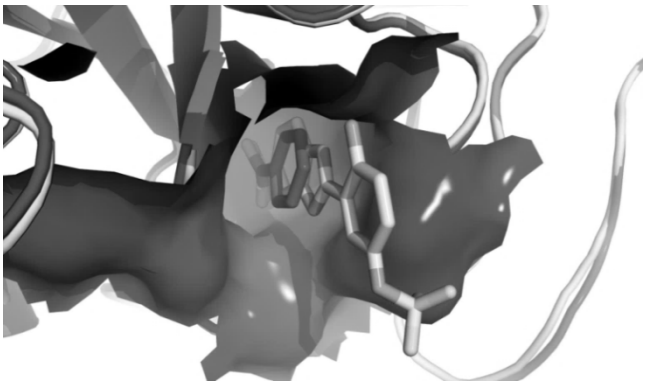

Figure 1: Example of conserved fragment-ligand binding mode.

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