Supramolecular landscape of bio-complex: versatility of peptide-based synthons

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Short peptides as pre-proteins carrying primary information on life are at the heart of nearly every aspect of bio-systems. They form basic structural elements in cells and interfere with protein-protein interactions, essential in bio-processes. Ligand-protein systems form complex supramolecular architecture via non-covalent interactions [1]. On the other hand, short peptides are much simpler but provide sufficient bio-structural information. Supermolecules of peptide-derived compounds reveal interactions with either themselves or neighboring moieties. The concept of supramolecular synthons, recurring patterns of non-covalent interactions between functional groups, is a useful approach for the interpretation of ligand-protein binding. Notably, the same synthon patterns of peptides are observed in the protein environment, as a natural synergy, which is disregarded. Thus, a deep insight into the supramolecular nature of peptide crystal structures, which cannot be mimicked by any other molecules, is of prime importance. Knowledge can be systematized in the synthons collection, which can be of tremendous value in the context of combining small-molecular crystal data with macromolecular supermolecules. It yields key complementary information needed in the design of suitable molecules for use in bio-context, including not only drugs but also vaccines or biomaterials. We should „understand and exploit what small molecules tell us; it is just a matter of listening" [2-4].

This work will present examples of how peptide-based synthon H-bonding patterns can be applied to the study of ligand-protein complexes, to address challenges such as binding affinity, target specificity, and selectivity. A comparison of classical and non-classical interactions in which synthons are involved will be discussed in detail. A deeper understanding of supramolecular mapping of bio-complexes opens new prospects and can be helpful in the rational design of next-generation peptide-based bio-systems with controlled hierarchic assemblies, effective target binding, and high responsivity to diverse stimuli, and completely new bio-functions.

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