Oligopeptides have been attracting an increasing interest due to their applications in anticancer therapy, drug delivery or as supramolecular biofunctional materials. Simple biomolecules in bio-systems, whose architecture is controlled by non-covalent interactions, have an input in understanding of bio-systems. Supramolecular interactions in a precise co-operation just like virtuosos play a symphony of *life*. Rational design of smart biomaterials should be based on thorough knowledge on interactions, what is still challenging. The concept of supramolecular synthons is useful in small supramolecules study and helps to understand the ligand binding in the protein-active-sites. This work focuses on introducing new bio-synthons, viewed in a holistic way at the supramolecular landscape, based on our research or from the CSD/PDB. We revealed that weak interactions (π-π, C-H-π, a lone pair-π, etc.) play a vital role in synthons creation. Interplay of them leads to cooperativity. In particular, fluorenylmethoxycarbonyl (Fmoc) participates in bio-synthons via C-H-O(π), C-Br(I)-π interactions. Peptides modified by Fmoc are used as hydrogelators or inhibitors in therapies of Alzheimer’s diseases, while presence of cyclopropyl in APIs, similar to proline, increases bio-activity. The cyclopropyl has ability (due to C-C bonds character) to formation of π-cyclopropyl-H-C synthon. We highlight relevance of proline-based synthons and synthon methodology in study of APIs/biomaterials polymorphism. The results will contribute to the development of supramolecular chemistry of biomolecules, which has a bright future ahead in interpretation of bio-phenomena, advanced therapeutic approaches.

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