13. Wrapping mimicking in drug-like small molecules disruptive of protein–protein interfaces

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The discovery of small-molecule drugs aimed at disrupting protein–protein associations is expected to lead to promising therapeutic strategies. The small molecule binds to the target protein thus replacing its natural protein partner. Noteworthy, structural analysis of complexes between successful disruptive small molecules and their target proteins has suggested the possibility that such ligands might somehow mimic the binding behavior of the protein they replace. In these cases, the molecules show a spatial and "chemical" (i.e., hydrophobicity) similarity with the residues of the partner protein involved in the protein–protein complex interface. However, other disruptive small molecules do not seem to show such spatial and chemical correspondence with the replaced protein. In turn, recent progress in the understanding of protein–protein interactions and binding hot spots has revealed the main role of intermolecular wrapping interactions: three-body cooperative correlations in which nonpolar groups in the partner protein promote dehydration of a two-body electrostatic interaction of the other protein. Hence, in the present work, we study some successful complexes between already discovered small disruptive drug-like molecules and their target proteins already reported in the literature and we compare them with the complexes between such proteins and their natural protein partners. Our results show that the small molecules do in fact mimic to a great extent the wrapping behavior of the protein they replace. Thus, by revealing the replacement the small molecule performs of relevant wrapping interactions, we convey precise physical meaning to the mimicking concept, a knowledge that might be exploited in future drug-design endeavors.