Protein-protein interactions are involved in many biological events and the development of molecules targeting PPIs is one of the main goals of contemporary medicinal chemistry. Recently, much attention has been paid to the design of peptides containing non-natural amino acids (nnAAs) able to stabilize a certain secondary structure, often the right-handed helical one, in order to combine the high selectivity and specificity and low toxicity of well-designed peptides with the stability toward peptidases and proteases provided by the nnAAs. One of the most exploited classes of nnAAs is that of chiral Ca-tetrasubstituted amino acids (cCTAAs), which stabilize the helical secondary structure by limiting the backbone conformational freedom and induce a preferential helical screw sense in otherwise achiral peptidesthanks to their side chains. In this framework, after a protocol optimization,1 the mechanisms responsible of the helical screw sense inversion have been studied through PNEB simulations. It has been found that two complementary mechanisms are responsible of the helical stabilization and screw senseselectivity: the first depends on the steri hindrance exerted by the cCTAA in an area parallel to the peptide helix axis, whereas the second consists in the strengthening of the helical H-bond network thanks to peculiar C-H···O=C interactions.2,3 Furthermore, it has been observed that the helical screw sense inversion requires the formation of γ-turns, although a preferential screw sense inversion direction was not found.

At the same time, computational methods for the estimation of binding energies, suchas MMGBSA, usually applied for classic ligand-receptor complexes have to be tested and optimized on PPIs, because of their peculiar structural features. Therefore, an MMGBSA based method, called Nwat-MMGBSA, aimed to improve the correlation between predicted binding energies of PPI complexes and experimental data, has been developed. This approach consists in the inclusion, as part of the receptor, of hydration shells around the ligand during the MMGBSA calculations,4 and it proved to be robust and reproducible, giving equivalent results by using different setups. Finally, anon-negligible advantage of Nwat-MMGBSA is represented by the possibility to automatize it, making it applicable for drug design/discovery purposes.