Small molecule protein-protein interaction modulators: challenges and opportunities for drug discovery

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Fundamental processes in living cells are largely controlled by macromolecular interactions and among them, protein-protein interactions (PPIs) have a critical role while their dysregulations can contribute to the pathogenesis of numerous diseases. Although PPIs were considered as attractive pharmaceutical targets already some years ago, they have been thus far largely unexploited for therapeutic interventions with low molecular weight compounds. Several limiting factors, from technological hurdles to conceptual barriers, are known, which, taken together, explain why research in this area has been relatively slow. However, this last decade, the scientific community has challenged the dogma and became more enthusiastic about the modulation of PPIs with small drug-like molecules. In fact, several success stories were reported both, at the preclinical and clinical stages. In this review article, written for the 2014 International Summer School in Chemoinformatics (Strasbourg, France), we discuss *in silico* tools (essentially post 2012) and databases that can assist the design of low molecular weight PPI modulators (these tools can be found at www.vls3d.com). We first introduce the field of protein-protein interaction research, discuss key challenges and comment recently reported *in silico* packages, protocols and databases dedicated to PPIs. Then, we illustrate how *in silico* methods can be used and combined with experimental work to identify PPI modulators.