[P20] An exploration of the 3D chemical space has highlighted a shape profile for the compounds intended to orthosterically inhibit protein-protein interactions.

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The vital role of Protein-Protein Interactions (PPI) for Life makes them the subject of a growing number of drug discovery projects. Yet, the specific properties of PPI (often described as flat, large and hydrophobic) require a dramatic paradigm shift in our way to design the small compounds meant to modulate them with therapeutic perspectives. To this end, successful inhibitors of PPI targets (iPPI) may be used to discover what singular properties make this type of inhibitors capable of binding to such intricate surfaces. Among the properties from which lessons could be learnt, the 3D characteristics of iPPI have been pinpointed as essential. Understanding the putative shape profile of iPPI could therefore help the design of a new generation of inhibitors with improved ligand efficiencies.

In an attempt to identify such putative 3D characteristics, we have collected the bioactive conformations of 58 orthosteric iPPI and compared them to those of 1623 inhibitors of conventional targets (e.g enzymes) collectively from different databases (2P2I, PDBind, PDB). Because the known heavier and more hydrophobic character of iPPI could conceal other characteristics, we have imposed that none of the identified descriptors correlate with the hydrophobicity or the size of the compound. The newly identified properties were further confirmed as characteristic to iPPI using the data of much larger datasets including our iPPI-DB, eDrugs3D and a representative subset of the bindingDB. Most noticeably, the essential property revealed by this study illustrates how iPPI manage to bind to the hydrophobic patches of PPI. Interestingly, the absence of correlation of such property with the hydrophobicity and the size of the compounds, that can be a liability for drug developments, opens new ways to design potent iPPI with a better balance for some of the pharmacokinetic features.