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$2P2I_{3D}$: An Academic Diverse Chemical Library Dedicated to PPIs

We have recently developed $2P2I_{DB}$, a hand-curated structural database dedicated to PPI with known orthosteric inhibitors ([1,2], http://2p2idb.cnrs-mrs.fr). Analysis of the small molecule inhibitors present in $2P2I_{DB}$ led us to propose the 'rule-of-four' as a guideline to characterize PPI inhibitors [3]. Using dedicated support vector machine approaches, we have developed $2P2I_{HUNTER}$, a tool for filtering potential orthosteric PPI modulators from large collection of compounds [4]. This innovative tool has been applied to a set of 8.3 million compounds from the "big vendors" to design several in silico PPI focused chemical libraries [5]. Compounds corresponding to medicinally important privileged structures identified as core structures in numerous therapeutics were prioritized in a medicinal oriented version of the library. The library was filtered with carbon bond saturation index (Fsp3) to escape from flatland, which resulted in a structurally diverse chemical library, $2P2I_{3D}$, of 1,683 compounds [5]. The molecules have been purchased from the providers, stored in 384-well plates and evaluated using homogeneous time-resolved fluorescence spectroscopy (HTRF) on the AD2P Platform (part of the National Network of the French Screening Platform, Marseille) and in collaboration with several Biotech and Pharmaceutical companies against a standard set of PPI targets (P53/MDM2; TCF/βcatenin; BRD4 Bromodomain; PDZ domains and SH3 domains) to evaluate their ability to enhance hit rates in general screening campaigns ($2P2I_{HTS}$ Program). The design and molecular properties of the different in silico chemical libraries and the HTS results will be discussed during this presentation.

References

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[3] Morelli, X., Bourgeas, R., Roche, P. **2011**. Chemical and structural lessons from recent successes in protein-protein interaction inhibition (2P2I). ***Curr Opin Chem Biol***. 15, 1-7.

[4] Hamon V., *et al.* **2013**. $2P2I_{HUNTER}$: A Tool for Filtering Orthosteric Protein-Protein Interaction Modulators via a Dedicated Support Vector Machine. ***Journal of the Royal Society, Interface*** Nov 6;11(90):20130860. doi: 10.1098/rsif.2013.0860.

[5] Hamon V., et al. **2013**. $2P2I_{CHEM}$: focused chemical libraries dedicated to orthosteric modulation of protein–protein interactions **Med. Chem. Commun.,4, 797-809**