PPI Inhibitors Libraries: Docking search against PDZ domain-containing proteins

Receptor-based approach

- PDZ proteins are key to cell life
- Therapeutic potential includes neurology, cancer and immunology drug discovery
- Highly conserved binding site
- Pathway event coordinators

The PAINS and in-house developed structure filters aimed at discarding compounds with toxic and other unfavorable groups were applied to the Life Chemicals' Stock Collection. Lipinski's rule of five & Veber rule filters were also applied to the Collection before screening. Thereafter, diversity set of 50,000 compounds was created and proceeded to virtual screening with Unity Model (SYBYL-X) against corresponding protein structure.

1) First PDZ domain of Magi1(d1)

The Unity Query Model based on 2I04 PDB entry [1] was created as superposition of features of the ligand structure (human papillomavirus (HPV) E6) and corresponding residues from the substrate binding groove of PDZ domain of Magi1. Therefore, the final Unity model contained structural elements both from PDZ binding site residues and HPV E6 peptide pharmacophore (Fig. 1). The screening model included: nine hydrogen bond donor features (donor site), six hydrogen bond acceptor features (acceptor site) and two hydrophobic features (hydrophobic sites). Partial match constraints for a hit compounds include at least one feature to donor and acceptor sites and two hydrophobic features (Fig. 2).

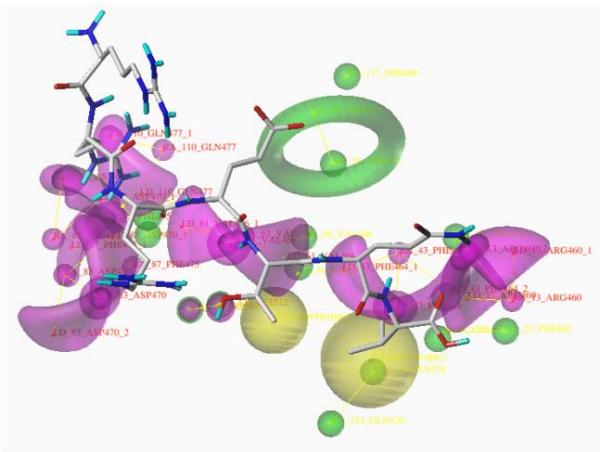

Fig. 1. Unity search query for potential inhibitors of PDZ d1 Magi1 with HPV E6 binding pose. The query was prepared with comparison of pharmacophore model of HPV E6 and features created from the binding pocket residues of Magi1 PDZ1. Donor sites are colored in green, Acceptor sites are colored in violet and Hydrophobic feature is brown.

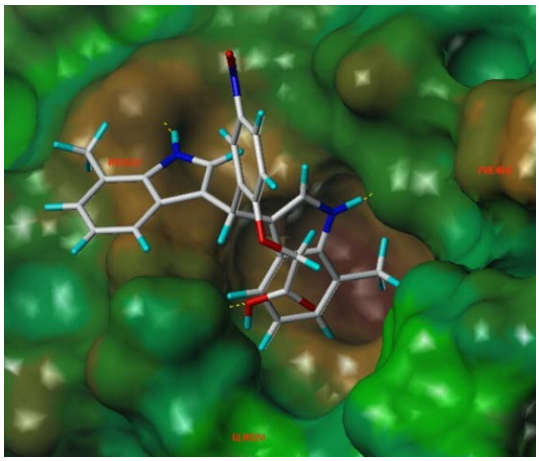

Fig. 2. Docking pose of a hit molecule F2196-0085 that is characterized by three intermolecular hydrogen bonds with substrate binding groove of PDZ (His512, Phe464 and Glu520). Hydrophobic interactions are observed in hydrophobic pocket P0 and hydrophobic pocket P1.
QFit = 47.98

2) Second PDZ domain of PSD-95 (2 screening models)

The first docking model created was based on 2KA9 PDB entry (Fig.3) [2].

The query features were identified from the key residues of the PDZ domain responsible for ligand binding (Fig.4).

Unity query included (Fig. 5):

8H-bond donor features, minimum 2 features match;
4H-bond acceptor features, minimum 2 match;
1 hydrophobic feature match (tolerance is 2.2 Å);
Totally at least 5 feature constraints are set to meet hit compound.
MOLCAD Surface (solvent-accessible surface) was created using Fast Connolly function with VdW ratio 1Å.

1,100 compounds were identified as hits.

The second screening model was based on 1QLC PDB entry [3]. There are some differences in the binding groove conformation of PDZ domain observed in 2KA9 pdb (comparison of the surface shapes colored by hydrophobicity in both .pdbs is shown on Fig. 6).

The Unity query contained:

8 H-bond donor features, minimum 1 feature must be matched;
4H-bond acceptor features, minimum 2 must be matched;
1 hydrophobic feature which must be matched (tolerance is 2.5 A);
at least 4 features must be matched by a hit compound.
MOLCAD Surface (solvent-accessible surface) was created by Fast Connolly type with VdW ratio of 1 Å.

1,800 hits were found.

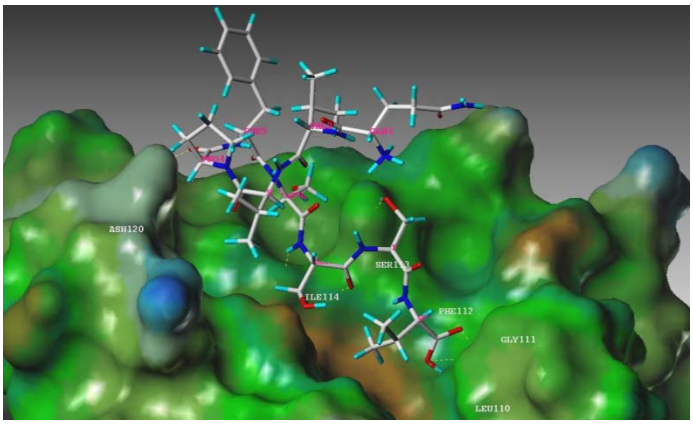

Fig. 3. Cypin peptide bound to PSD95 PDZ2 (2KA9.pdb). PDZ domain surface is colored by hydrophobicity from brown (hydrophobic) to blue (hydrophilic).

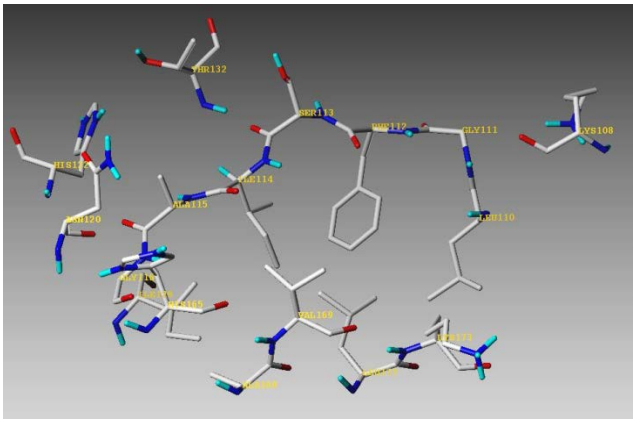

Fig. 4. Amino acid residues that are critical for the PDZ domain-ligand interaction.

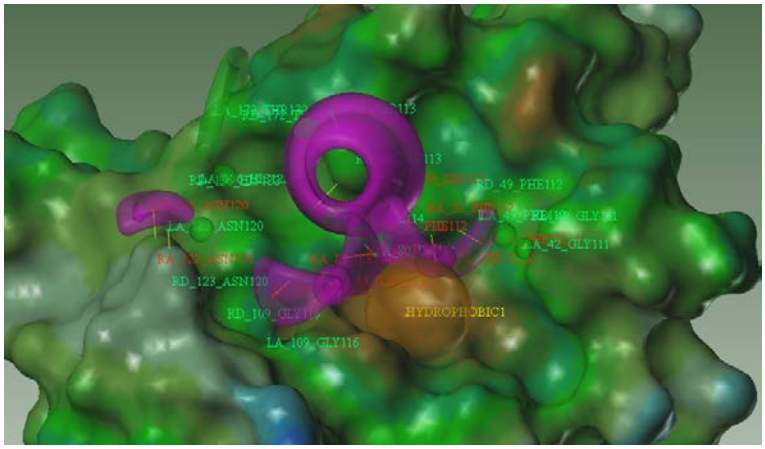

Fig. 5. Unity search query with surface volume of the PSD95 PDZ2. Donor sites colored in green, Acceptor sites colored in violet and Hydrophobic feature is brown.

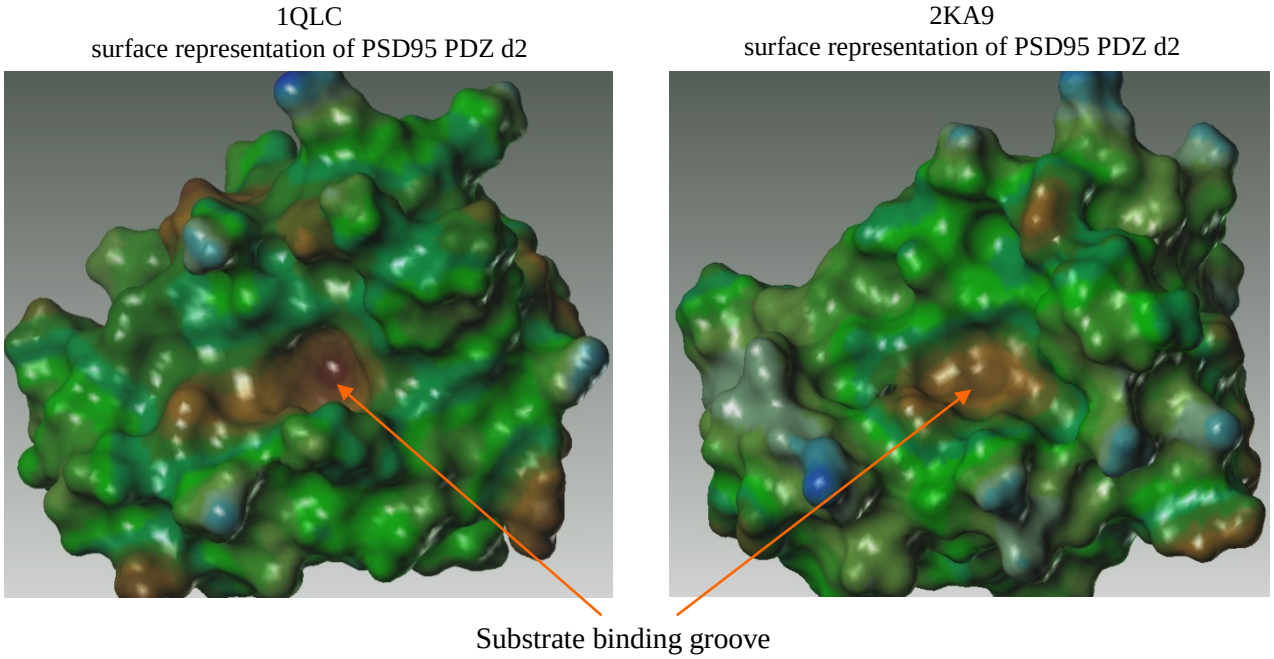

Fig. 6. The structure of PSD95 PDZ d2 have some conformational differences if compare 1QLC and 2KA9 PDB entries.

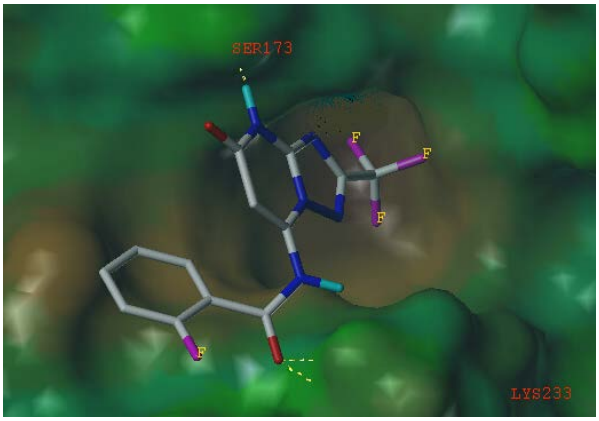

Fig. 7. Example of a hit compound F3225-8235 binding conformation. QFIT = 65.03. The compound forms two hydrogen bonds with Ile114 and Asn120 from the PSD95 PDZ2 substrate binding site.

References

1. Zhang Y., Dasgupta J., Ma R.Z., Banks L., Thomas M., Chen, X.S. Structures of a human papillomavirus (HPV) E6 polypeptide bound to MAGUK proteins: mechanisms of targeting tumor suppressors by a high-risk HPV oncoprotein. J. Virol. 2007, 81, pp. 3618–3626.

2. Wang W.N., Weng J.W., Zhang X., Liu M.L., Zhang M.J. Creating conformational entropy by increasing interdomain mobility in ligand binding regulation: a revisit to N-terminal tandem PDZ domains of PSD-95. *J. Am. Chem. Soc.*, **2009**, 131, pp. 787–796.

3. Tochio H., Hung F., Li M., Bredt D.S., Zhang M. Solution structure of the second pdz domain of postsynaptic density-95. *J. Mol. Biol.*, **2000**, 295 (2), pp. 225–237.

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