DERIVATION OF STRUCTURAL FEATURES THAT AFFECT DRUG METABOLISM BY CYP2C9

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Understanding the cytochrome metabolism-affecting structural features of ligands is an important and challenging task in drug discovery as it can help develop safe and effective therapeutic agents [1]. In this work, we report virtual ligand screening of a large dataset of 4.2 millions of available compounds from Enamine and Chemrar companies. As target structures for parallel docking we obtained five crystal structures from Protein Data Bank (PDB) of different conformations (4NZ2, 5A5I, 5W0C, 5XXI, 6VLT) chosen by the difference in root mean square deviation from alignments (Figure 1). We ran high-throughput (HTVS) and standard (SP) precision mode docking setups in Schrödinger 2018 software, consequently decreasing the dataset to highly scored 5000 compounds. We clustered the docked ligands by their structural features by applying UPGMA algorithm to distance matrices of molecular fingerprint vectors. We filtered out few representative compounds from each cluster to run activity assays. In the course of this work we are planning to filter out and to study experimentally the binding of the ligands by their distance to the heme and azole-containing compounds from the database.

Fig. 1. Structural comparison of available crystal structures of CYP2C9 in PDB.

References

[1] S.C. Gay, A.G. Roberts, and J.R. Halpert, Future Med Chem. 2010, 2(9): 1451-1468