Structure-activity relationships, ligand efficiency and lipophilic efficiency profiles of benzophenone-type inhibitors of the multidrug transporter P-glycoprotein

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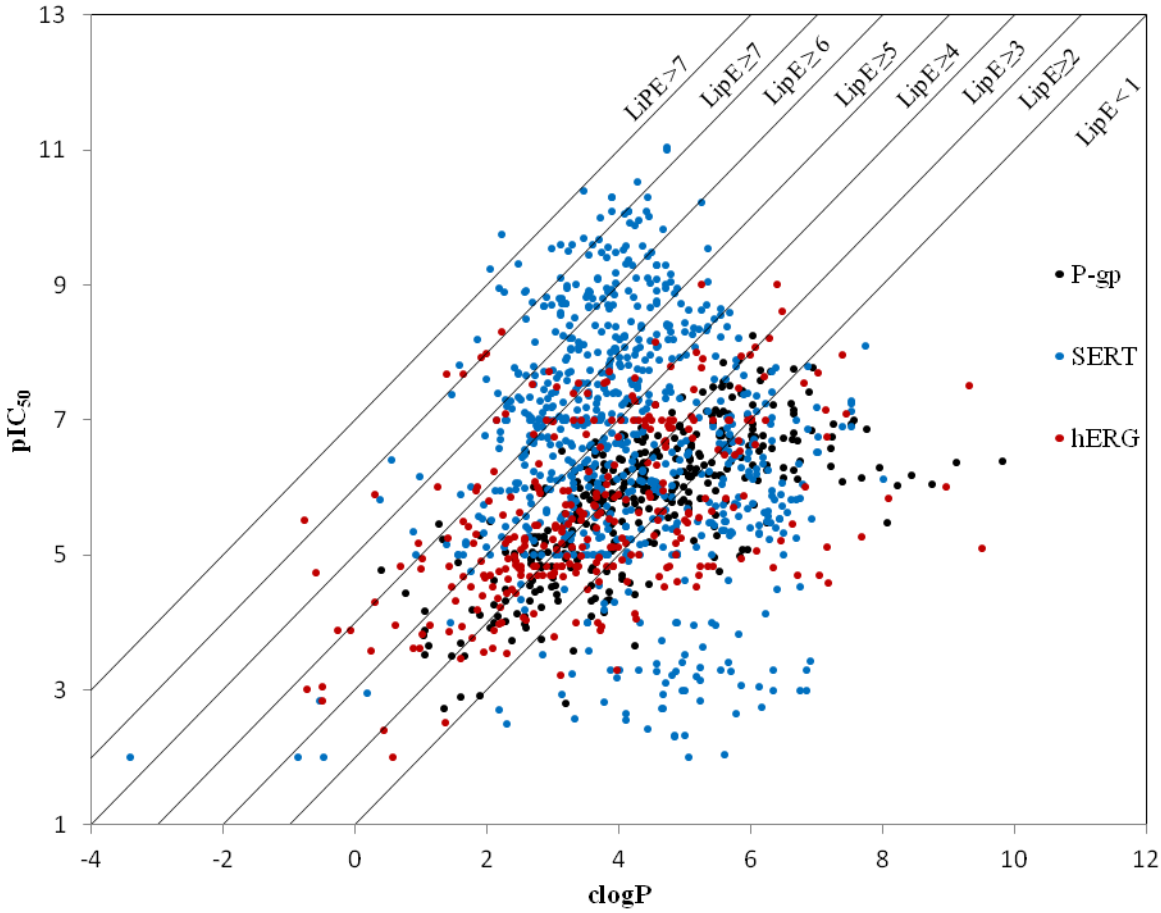
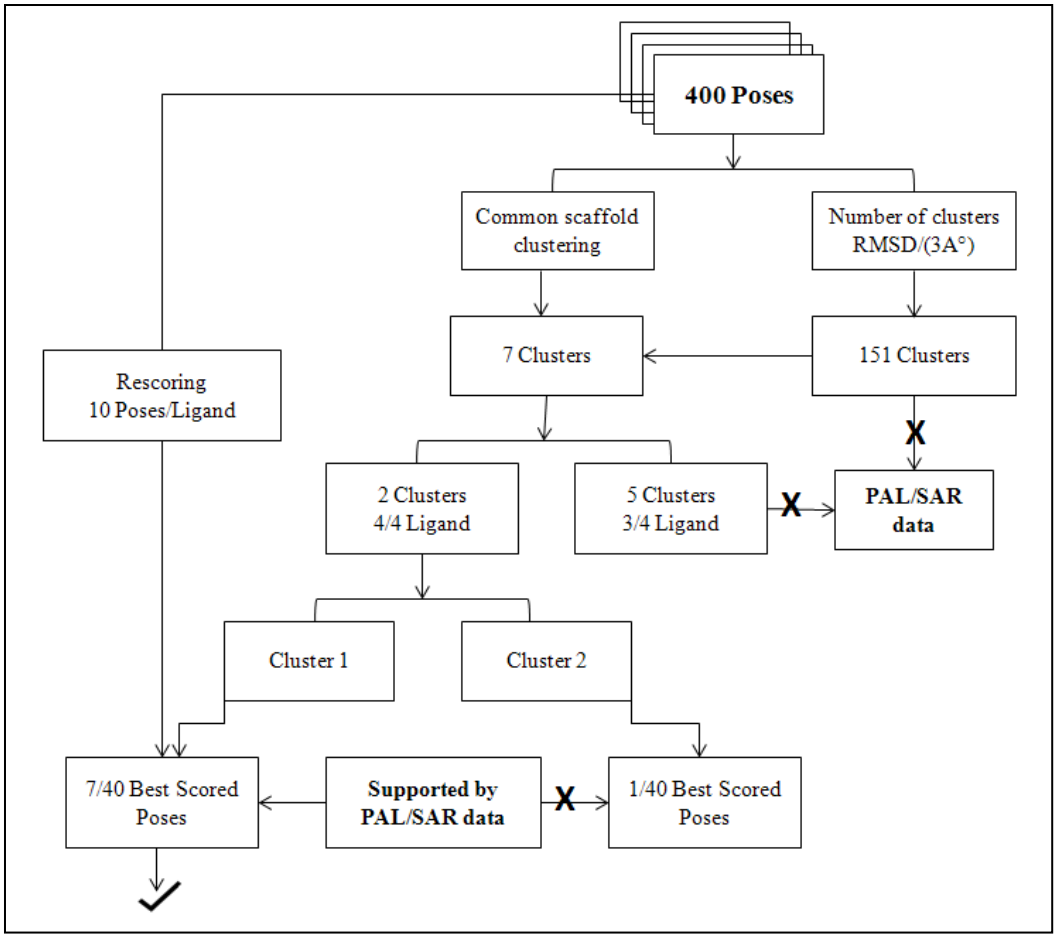
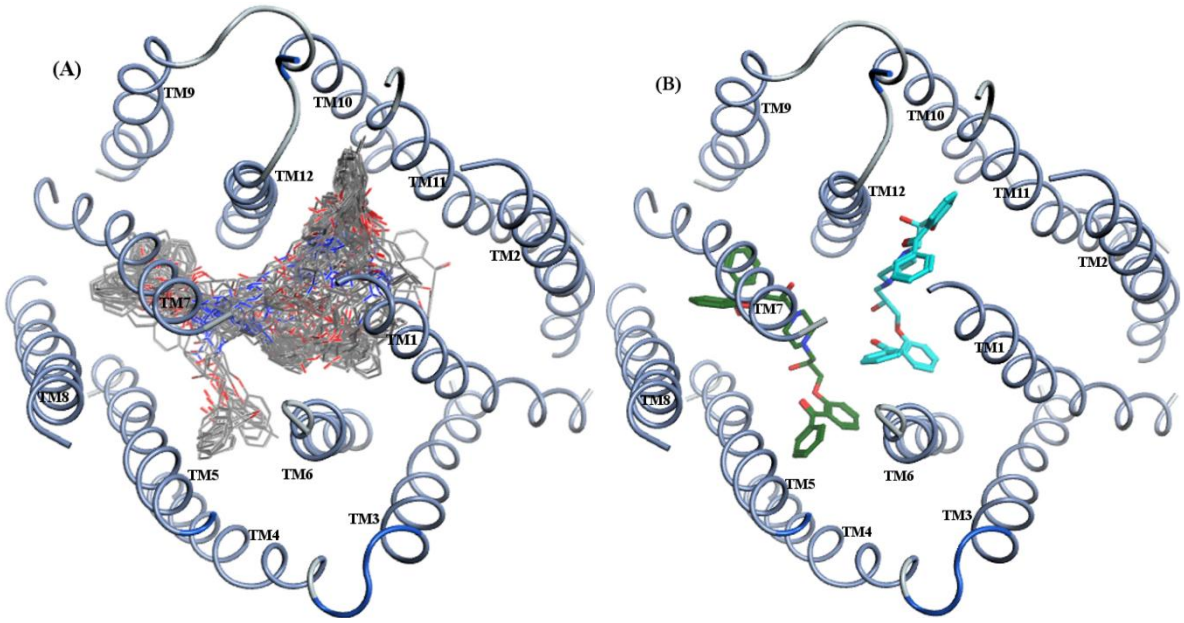
Supporting Information



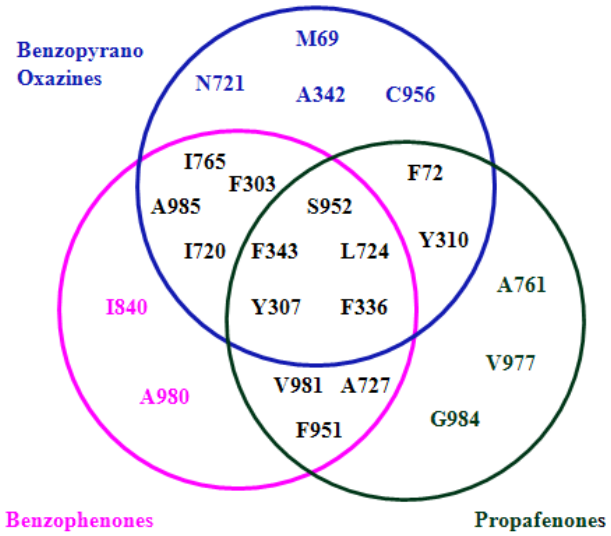
SM Figure 1. LipE distribution profiles of inhibitors of P-gp, SERT and hERG. A LipE value of greater than 5, clog ~2.5 and potency of ~10nM are considered to be standard threshold of most promising ligands by Leeson *et al.*[1]



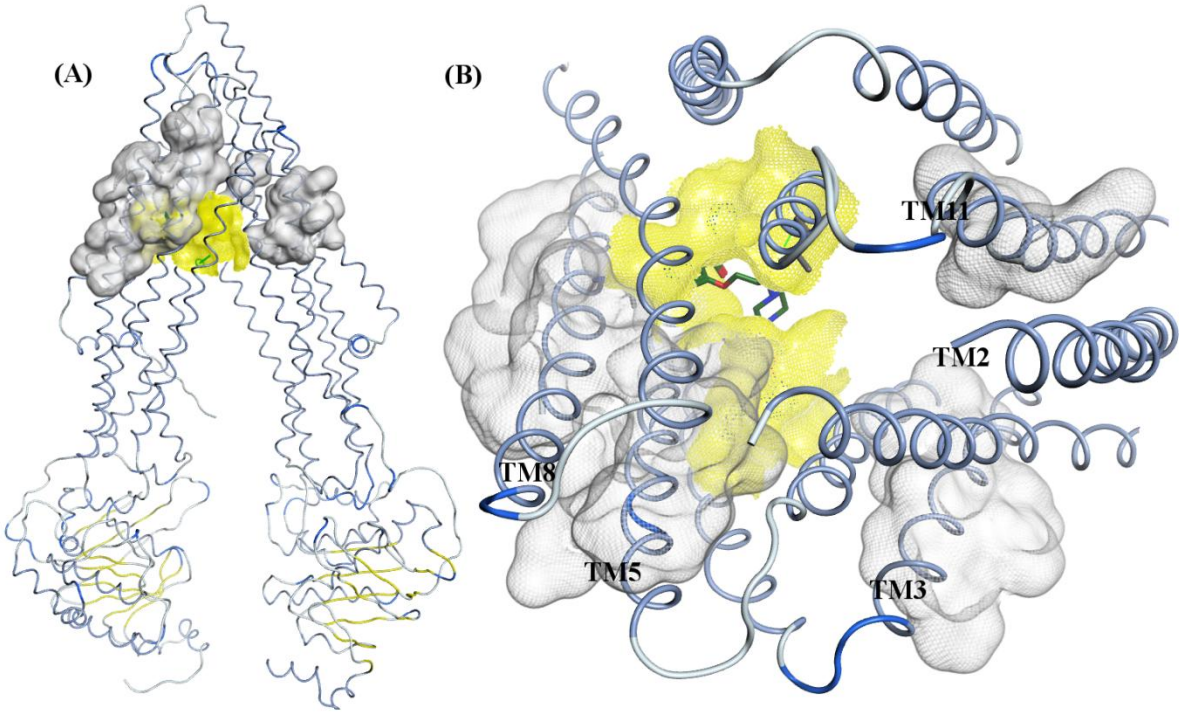
Workflow 1. Selection of preferred binding mode of benzophenone derivatives **6**, **19**, **20** and **23.**



SM Figure 2. (A) Showing docking poses in 7 clusters based on common scaffold of ligands. (B) Docking poses of **23** in two different clusters containing all four ligands, poses with green and blue color are representatives of cluster 1 and 2 respectively.



SM Figure 3. Overlap of interacting amino acid residues of propafenone type inhibitors of P-gp.



SM Figure 4. Photolabeled drug binding domains of propafenone analogs (TM3, 5, 8 and 11) represented by gray color.[2,3] Yellow regions represent TM5, 6, 7, 8, 9 and 12 as proposed interaction positions of benzophenoness. Both regions are represented in (A) front view and (B) top view.

References

1. Leeson, P. D.; Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. Nat Rev Drug Discov 2007, 6, 881-890.

2. Parveen, Z.; Stockner, T.; Bentele, C.; Pferschy, S.; Kraupp, M.; Freissmuth, M.; Ecker, G. F.; Chiba, P. Molecular Dissection of Dual Pseudosymmetric Solute Translocation Pathways in Human P-Glycoprotein. Mol Pharmacol 2011.

3. Pleban, K.; Kopp, S.; Csaszar, E.; Peer, M.; Hrebicek, T.; Rizzi, A.; Ecker, G. F.; Chiba, P. P-glycoprotein substrate binding domains are located at the transmembrane

domain/transmembrane domain interfaces: a combined photoaffinity labeling-protein homology modeling approach. Mol Pharmacol 2005, 67, 365-374.