

P008 Interactions between the human sigma class glutathione transferase active site and non-glutathione ligands.

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The glutathione transferases are phase II detoxication enzymes that catalyse conjugation of glutathione (GSH) to many non-polar compounds. They are functional as dimers, with one active site per monomer that is divided into a GSH binding site, and a second ligand binding site. Crystal structures of the human sigma class GST were determined in the presence and absence of a non-GSH inhibitor providing two different active site conformations. Ethacrynic acid and nocodazole were characterised as low affinity inhibitors, and docking calculations were applied to identify the active site conformation likely to best facilitate inhibitor binding. Filtering the solutions based on Chemscore, energy, conformation (compared Cambridge Structure Database entries), and strain (energy difference between the docked and its minimised conformation, along with RMSD) was required. Nocodazole preferred the non-ligand active site, and was confirmed by crystallographic analysis. Although the correct binding mode was not predicted, the hydrophobic core was well positioned, and an H-bond correctly identified. Neither active site conformation was suited to ethacrynic acid binding.