

The impact of crystallisation conditions on Structure-based drug design

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The 3D structures of proteins with inhibitors provide the basis for structure-based drug design studies that utilize docking procedures. We performed a detailed comparison of the complexes of methylene blue (MB) and decamethonium with acetylcholinesterase (AChE) that were generated using crystals obtained using either PEG-200 or (NH₄)₂SO₄. The position of the ligands within the active-site gorge of the enzyme obtained in the presence of PEG-200 is influenced by the fact that PEG-200's are seen within the active site. Consequently, both ligands are positioned ~2.5 Å further up the gorge than in the corresponding complexes obtained using crystals precipitated with (NH₄)₂SO₄; Spectroscopic evidence supported such a difference in positioning also in solution for the ligands. These results have implications for structure-based drug design using docking procedures.

Another example is the drug studies in Phosphotriesterase (PTE). I have solved 20 PTE structures from three different constructs, 4 different crystallization conditions, 5 different space groups and 6 different compounds soaking into the PTE crystals. Our structure analysis showed the importance of 'choice of the appropriate' crystallization conditions, protein constructs and space groups for drug studies in PTE.

[1] Dym, O. et al. (2016). *Protein Science*. 25 (6) 1081–1160.

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