Caspases: characterization of intermolecular interactions in active site

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Caspases are enzymes belonging to the family of cysteine proteases, that play crucial role in apoptosis, necrosis and inflammation. Apoptosis is a programmed cell death, failure of which can trigger a tumor development. Initiator caspases receive a signal, get activated and cleave effector caspases, which cleave other proteins leading to cell death. This chain reaction is known as "caspase cascade".

For the purpose of this project various caspases interacting with inhibitors were examined. The Protein Data Bank [1,2] was utilized to find the highest quality structures of caspases bounded up with ligands. After structure validation, all missing hydrogen atoms were added. Electron density distribution of protein complexes was reconstructed using the Transferred Aspherical Atom Model approach based on the University at Buffalo Databank [3,4]. This database contains multipolar parameters describing electron density of pseudoatoms obtained via theoretical calculations. On the basis of electron density distribution, energy of electrostatic interactions was calculated. Characterization of intermolecular interactions was possible thanks to calculations in the Mopro [5] or XD [6] program.

Investigations of energetic properties of caspases may contribute to our knowledge about protein properties in general and, more importantly, gives an opportunity to find novel ligands binding more effectively to their actives sites, what is essential for drug design.

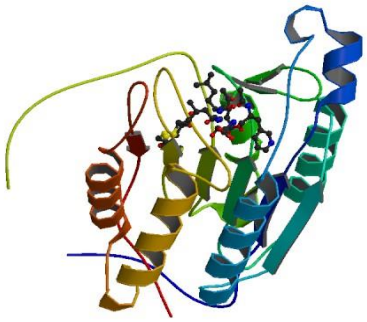

Figure 1. An example of caspase with a ligand (PDB ID: 4PS1) [7]

References:

1. RCSC PDB www.rcsb.org/pdb
2. Berman, H.M *et al.* (2000) *Nucl. Acids Res*., 28: 235-242.
3. Volkov, A., Li, X., Koritsanszky, T. S., Coppens, P. (2004) *J. Phys. Chem. A*, 108: 4283–4300.
4. Jarzembska, K. N., Dominiak, P. M. (2010) *Acta Cryst A*, 68: 139-147.
5. Guillot B., Viry L., Guillot R., Lecomte C. & Jelsch C. (2001) *J. Appl. crystallogr*., 34: 214-223.
6. Volkov, A.; Macchi, P.; Farrugia, L. J.; Gatti, C.; Mallinson, P.; Richter, T.; Koritsanszky, T. (2006) *XD2006 - a computer program package for multipole refinement, topological analysis of charge densities and evaluation of intermolecular energies from experimental and theoretical structure factors*.
7. DOI: 10.2210/pdb4ps1/pdb