Chemistry Central Journal

Poster presentation

Open Access

Selectivity of new caspase 3 and 8 tetrapeptide substrates can be explained by automated docking analysis

R Schulz*, P Reszka and PJ Bednarski

Address: Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, University of Greifswald, Friedrich-Ludwig-Jahn-Straße 17, 17487 Greifswald, Germany

* Corresponding author

from 4th German Conference on Chemoinformatics
Goslar, Germany. 9–11 November 2008

Published: 5 June 2009

Chemistry Central Journal 2009, **3**(Suppl 1):P76 doi:10.1186/1752-153X-3-S1-P76

This abstract is available from: http://www.journal.chemistrycentral.com/content/3/S1/P76

Caspases are cysteine proteases and are considered key-mediators in apoptotic cell death. Selective quantification of the various caspase activities in cancer cells is important for detecting cell death caused by cancer therapy. We have designed and synthesized a series of novel fluorogenic tetrapeptide substrates for caspase 8 and investigated the substrates for selective cleavage by either caspases 3 or 8 in enzyme assays. At the same time we have used the automated docking program AutoDock (ver 3, [1,2]) to dock the new substrates into the active sites of X-ray crystal structures of human caspases 3 and 8, respectively. AutoDock was confirmed to be an appropriate tool for substrate binding prediction because substrate docking results are comparable with documented X-ray crystal structure of caspase 3 and 8 bounded with analogous tetrapeptide inhibitors [3,4]. Enzyme-substrate conformations with changes in free energy of binding (ΔG) were calculated with AutoDock and compared to the experimental determined Michaelis-Menten constant Km. A significant correlation between the experimental Km and theoretical ΔG was found. Enzyme kinetics showed the substrates to have 100-fold lower Km-values for caspase 8 compared to caspase 3. This selectivity was reflected in the significantly larger negative ΔG-values between the substrates docked to caspase 8 as opposed to caspase 3. These results will help in the design of even more selective caspase substrates.

References

1. Morris GM, *et al.*: **Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function.** *J Comp Chem* 1998, **19:**1639-1662.
2. Goodsell DS, *et al.*: **Automated Docking of Flexible Ligands:Applications of AutoDock.** *J Mol Recognition* 1996, **9:**1-5.
3. Becker JW, *et al.*: **Reducing the Peptidyl Features of Caspase-3 Inhibitors: A Structural Analysis.** *J Med Chem* 2004, **47:**2466-2474.
4. Watt W, *et al.*: **The atomic-resolution structure of human caspase-8, a key activator of apoptosis.** *Structure Fold Des* 1999, **7:**1135-1143.