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# Structural basis of inhibition of nrf2-keap1 interaction and design of novel cancer chemo-preventive drug candidates

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Protein-protein interactions (PPIs) involved in cellular signalling pathways are often considered as targets for the development of new drug candidates. Inhibition of the Nrf2-Keap1 interaction leads to the release of transcription factor Nrf2, which plays an important role in controlling xenobiotic and oxidative stress. Direct inhibitors of the Nrf2-Keap1 PPI could therefore act as new cancer chemo preventive drug candidates. A series of peptides with known binding activities to Keap1 have been reported, and the conformations that these peptides can adopt were studied to develop a structural basis for the design of novel peptidomimetic chemo preventive drug candidates. For this purpose the conformations of peptides within the binding pocket of crystal structure of Keap1 were explored using different approaches, such as conformational search, molecular docking, simulated annealing and molecular dynamics.

These molecular modeling studies of peptides inhibiting the Keap1-Nrf2 PPI indicated that the different conformations and positions of the ligands in the binding pocket lead to equally favourable intermolecular interactions. This is supported also by simulated annealing studies, which suggest that heating up to 1000 K is needed to displace the ligands from their various binding positions. This led to the use of alternative experimental approaches to validate the structural basis of the peptide-Keap1 interaction. To obtain the 3D structure of the peptides in the binding pocket, nuclear magnetic resonance (NMR) is used to facilitate the design of new peptidomimetic agents with an improved binding affinity and potentially better inhibitory activity.

## Biography

Mire Zloh was awarded a B.Sc. and an M.Sc. in Physical Chemistry by University of Belgrade and was awarded a Ph.D. in Chemistry by University of London in 1998. He is working as a Professor of Medicinal Chemistry and a Head of Pharmaceutical Chemistry at the University of Hertfordshire. His research interests include computer aided drug design, structural chemistry and chemometrics. Currently, he is working on rational design of bioactive dendrimers, modeling of PEGylated proteins and developing strategies to utilize small molecule-small molecule interactions for enhancing activities of therapeutics.

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