One-step protein labeling with the tubulin tyrosine ligase - Substrate scope explained by computational studies

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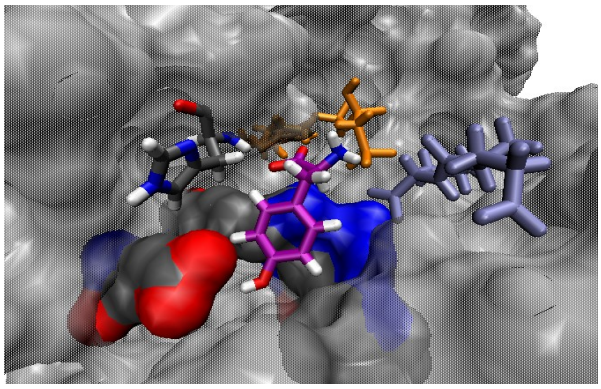

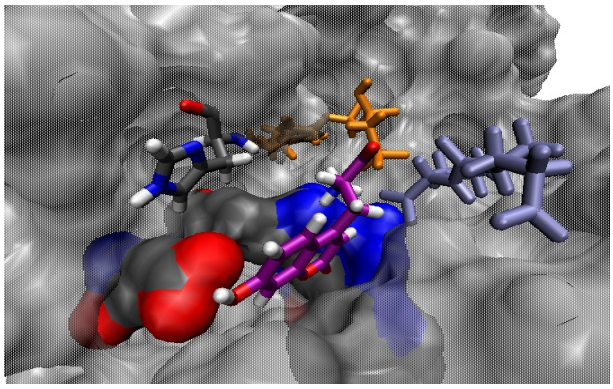

Enzymatic catalysis provides a powerful tool for chemical synthesis. One example is the enzyme tubulin tyrosine ligase (TTL), which enables chemoenzymatic protein functionalization using tyrosine-derivatives [1]. Recent studies show that, the wild type TTL also accepts and ligates other unnatural amino acids, which can differ in size and structure, such as a coumarin-derivative, enabling one-step-fluorescence labeling.

To get insight into the broad substrate scope of TTL docking studies were performed. In these studies the binding behavior of the natural substrate tyrosine as well as other canonical and unnatural amino acids were investigated. Based on these information the important features of the binding pocket such as π-stacking interactions and hydrogen bond formation can be pointed out. Furthermore, molecular dynamic simulations were performed to predict the stability and flexibility of the substrates within the pocket [2].

[1] D. Schumacher, J. Helma, F.A. Mann, G. Pichler, F. Natale, E. Krause, M.C. Cardoso, C.P.R. Hackenberger, H. Leonhardt: Versatile and Efficient Site-Specific Protein Functionalization by Tubulin Tyrosine Ligase; *Angew. Chem. Int. Ed.*; **2015**; *54*, 1-6

[2] D. Schumacher, O. Lemke, J. Helma, L. Gerszonowicz, V. Waller, T. Stochek, P.A. Durkin, N. Budisa, H. Leonhardt, B.G. Keller, C.P.R. Hackenberger: Broad substrate tolerance of tubulin tyrosine ligase enables one step chemoenzymatic protein labeling, *submitted*