Rational design of covalent inhibitors

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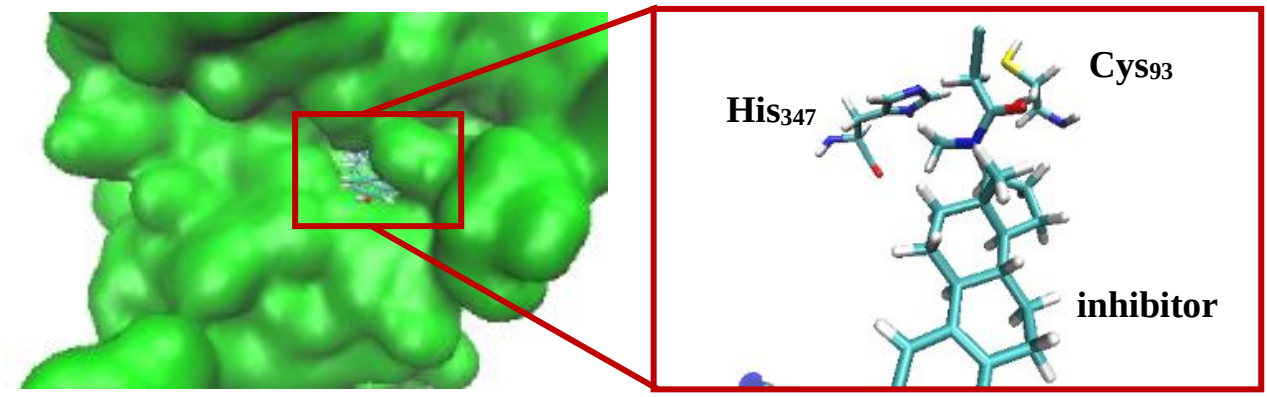

Most drugs consist of ligands which interact with their target non-covalently. They have the advantage that they are so unreactive that unintended reactions with DNA or proteins do not take place. However, they have the drawback that generally their free energy of binding does not exceed 15 kcal/mol. Higher binding affinities can only be achieved with ligands which form a covalent bond with their target. Despite famous examples as Penicillin or Aspirin in the past the industry hesitated to develop new covalent drugs because they fear unintended side reactions resulting from the reactivity of ligands. [1] Since about 2005 covalent ligands undergo an intensive renaissance in academia and industry, because various very selective drugs were detected in the last few years. [2][3] This work presents a protocol for the rational design of covalent inhibitors starting from a non-covalent ligand.
The system investigated was FadA5 a thiolase of Mycobacterium tuberculosis. [4] Several synthesizable inhibitors have been designed and investigated in respect of their stability in protein via docking and molecular dynamic simulations. QM methods were used to investigate thermodynamic and kinetics of the inhibition reaction.

[1] J. Singh et al., *Nat. Reviews*, **2011**, *10*, 307-317.
[2] V. Hirsch, *BioDrugs*, **2015**, *29*, 167-183.
[3] T. Schirmeister et al, *JACS*, **2016**, *138*, 8332-8335.
[4] Schaefer et al., *Structure*, **2015**, *23*, 21-33