A Dual-Approach towards Inhibitors of Peptide Deformylases: Scope and Limitations of Bioinorganic Models.

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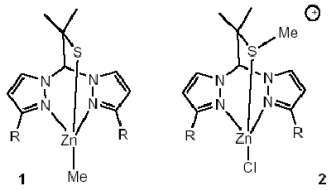
Peptide Deformylases (PDFs) are metalloenzymes involved in the removal of the *N*-terminal formyl group from newly synthesized proteins. Being essential for bacterial growth, they have been selected as an attractive target for developing novel antibacterial drugs.[1] Amongst the best inhibitors, discovered so far, are hydroxamic acids and thiols.

Our approach to design new inhibitors of PDFs is to combine biomimic studies with molecular models of the active site and enzymatic inhibition assays with the enzyme. We used **1** and **2** as small molecular models of the active site of the zinc-containing enzyme and we studied their interaction with hydroxamic acids and ketothiols, while testing similar molecules as inhibitors of PDFs.



This dual-approach highlights the limitation of models used as a unique tool to elucidate the binding mode of inhibitors in proteins. Such a reduced system disregards the amino acid residues located in the second coordination sphere of the metal in the enzymes (typically Glu133 in PDFs) which play a key role in the control of the interaction between the inhibitors and the metalloprotein.

[1] A. Boularot, C. Giglione, I. Artaud and T. Meinnel, *Curr. Opin. Invest. Drugs* 2004, **5**, 809