The crystal structure of AMP deaminase as starting point for the design of new herbicides

Jörg Freigang[1]

[1]Bayer AG, Crop Science Division, Monheim, joerg.freigang@bayer.com, Germany

Adenosine monophosphate deaminase (AMPD; EC 3.5.4.6) is the molecular target of the herbicidally active natural product coformycin [1], which undergoes phosphorylation in planta to give the corresponding phosphate. A published low resolution crystal structure of AMPD from *Arabidopsis thaliana* in complex with coformycin phosphate [2] could not conclusively explain the efficient binding of the ligand to the active site. In an attempt to better understand the molecular mechanism of AMPD inhibition at atomic level, we were able to obtain the structure of the complex at significantly improved resolution. Surprisingly, a comparison of our data with the published structure revealed important differences in the protein conformation, leading to a substantially altered binding mode for the ligand. Our new structure allowed a detailed view into the enzyme's catalytic mechanism and explains how coformycin phosphate can act as a transition state analogue. In addition, we solved the crystal structure of the unligated protein, which more closely resembles the conformation of the published structure and implies large conformational changes of the protein during ligand binding and catalysis. The detailed knowledge of the catalytic mechanism and the structural information allowed the design of novel mechanism-based inhibitors with improved herbicidal properties [3]. To further simplify their chemical structures, the crystal structure was used as a starting point for a virtual screening approach to identify new non-ribosyl AMPD inhibitors. After further optimization, the best compound exhibited herbicidal activity, but at lower levels than observed for nucleoside AMPD inhibitors.

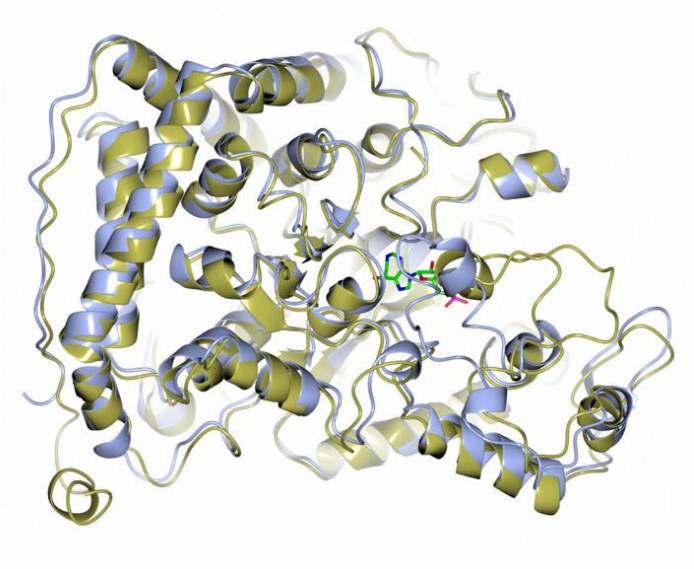

Fig. 1 Superposition of AMPD from *Arabidopsis thaliana* in ligated (blue) and unligated (gold) form

[1] Isaac BG, Ayer SW, Letendre LJ, Stonard RJJ. Herbicidal nucleosides from microbial sources. J. Antibiot (Tokyo), 44, 729–732 (1991)

[2] Han BW, Bingman CA, Mahnke DK, Bannen RM, Bednarek SY, Sabina RL, Phillips GN Jr. Membrane association, mechanism of action, and structure of Arabidopsis embryonic factor 1 (FAC1). J. Biol. Chem. 281, 14939-47 (2006)

[3] Lindell SD, Maechling S, Klein R, Freigang J, Laber B, Blanazs L, Leonhardt M, Haupt S, Petry T, Sabina RL. Mechanism and structure based design of inhibitors of AMP and adenosine deaminase. Biorg. Med. Chem. 43, 116272-83 (2021)