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Binding mechanism of histone deacetylase inhibitors

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Performing kinetic studies on protein ligand interactions provides important information on complex formation and dissociation. Beside kinetic parameters such as association rates and residence times, kinetic experiments also reveal insights into reaction mechanisms. We developed several types of homogeneous fluorescence-based assays to elucidate the binding mechanism of inhibitors to human and bacterial members of the histone deacetylase protein family. A global fit procedure will be presented which integrates equilibrium titration and kinetic data to analyze the underlying mechanism of interaction. Independently determined equilibrium parameters and the apparent dissociation rate of the tracer are employed to set constraints on the flexible parameters (e.g. rate constants) during the fitting process of the kinetic time courses. Two different modes of action, simple one-step binding and a two-step mechanism comprising initial binding and induced fit, are verified. In contrast to the bacterial HDAH, all compounds bind to human *HDAC1, HDAC6* and *HDAC8* through a two-step induced fit mechanism. Arguments will be provided for the thesis that the relationship between quantitative kinetic and mechanistic information and chemical structures of active substances will serve as a valuable tool for drug optimization.

Biography

Franz-Josef Meyer-Almes has completed his PhD from University of Goettingen. He has 10 years experiences in biotech and pharma companies. He is a Professor for Physical Biochemistry and has published more than 40 papers in reputed journals and holds more than 10 patents and patent applications.

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