Conformation-activity relationship of the archazolids: Development of a novel class of highly potent V-ATPase inhibitors

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Vacuolar type ATPases (V-ATPases) are heteromultimeric, proton translocating proteins which are localized in a multitude of eukaryotic membranes and energize many different transport processes. Their malfunction is correlated with various diseases such as renal acidosis or cancer. The polyketide natural products archazolid A and B constitute novel types of particularly efficient (IC50 in the low nanomolar range) and specific inhibitors of V-ATPases, both in vitro and in vivo. Their unique structures have not been synthetically attained, nor has the conformation of the archazolids been studied. This project aims to analyse in detail the interdependence of conformation and biological function of these potent natural enzyme inhibitors. Of particular interest will be the elucidation of the 3D-structure in solution and of the bioactive conformation, the energetic and structural correlation between these two states and the interplay between conformation, configuration and activity. In an initial pilot project, a proof of principle shall be obtained by which the conformation of the archazolids and the time-scale of ligand binding are resolved.

Projektbeteiligte

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