VolkswagenStiftung

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

Initiative: Konformationelle Kontrolle biomolekularer Funktionen (beendet)

Bewilligung: 12.04.2007

Laufzeit: 3 Jahre

Vacuolar type ATPases (V-ATPases) are heteromultimeric, proton translocating membrane proteins which energize many different transport processes. As their functionality is correlated with various diseases such as renal acidosis or cancer, the development and molecular understanding of selective and synthetically accessible inhibitors present highly desirable research goals. The polyketide natural products archazolid A and B constitute novel types of particularly efficient and specific inhibitors of V-ATPases, both in vitro and in vivo. Based on the results of the pilot project detailed analyses of the bioactive conformation, the energetic and structural correlation to the solution structure and the interplay between conformation, configuration and activity are envisaged. Likewise, it is planned to study selected archazolid analogues in order to influence the bioactivity and to attain synthetically simplified derivatives with similar or improved biological profiles. Based on an innovative modular approach, the first synthesis of the natural products will be completed, and novel derived compounds will be prepared and their biological profile studied in full detail. Finally, investigations of the binding domain will be initiated to understand the conformational properties of the inhibitors on a molecular level.

Projektbeteiligte

Dr. Dirk Menche
Helmholtz-Zentrum für
Infektionsforschung GmbH
Abt. Medizinische Chemie
Braunschweig

Dr. Florenz Sasse
Helmholtz-Zentrum für
Infektionsforschung GmbH
Abt. Chemische Biologie
Braunschweig

Prof. Dr. Helmut Wieczorek
Universität Osnabrück
Fachbereich Biologie/Chemie
Tierphysiologie
Osnabrück

Dr. Markus Huss
Universität Osnabrück
Fachbereich Biologie/Chemie
Tierphysiologie
Osnabrück