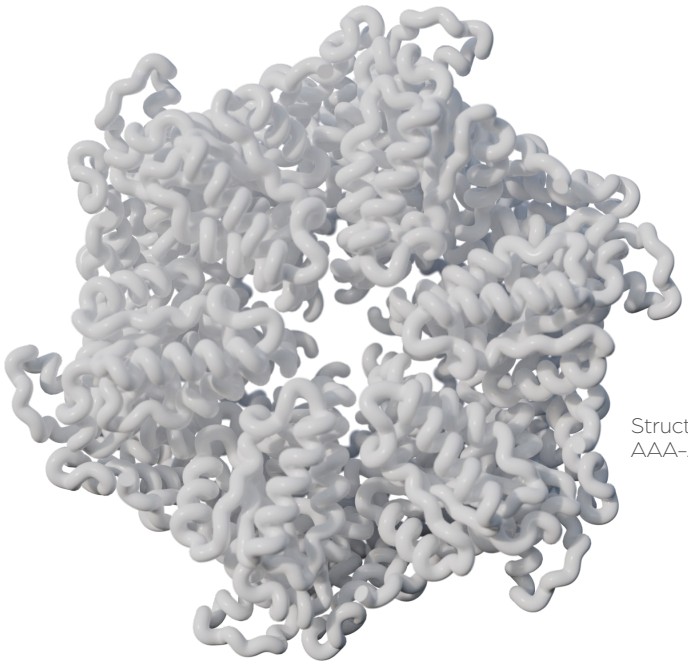
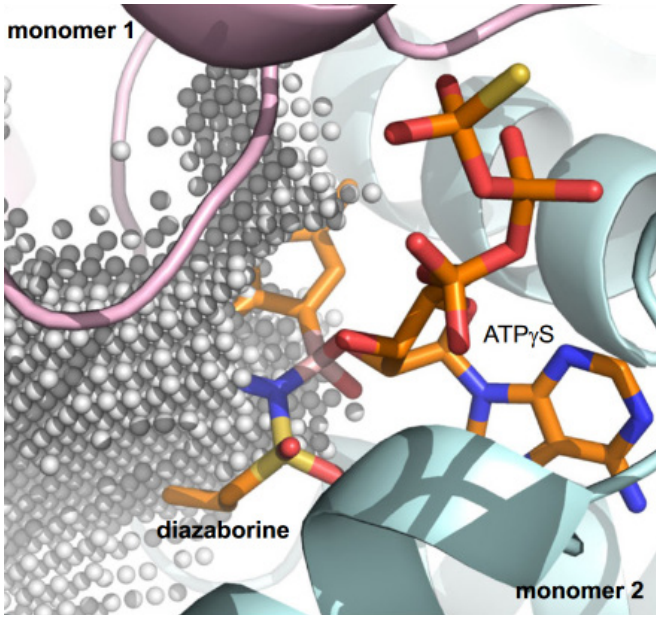


Structure of hexameric AAA-ATPase Drg1 (AFG2).

CASE STUDY | PROTEIN-LIGAND INTERACTIONS & DRUG DESIGN

Drug **Resistance**

The hexameric AAA-ATPase Drg1 plays a crucial role in eukaryotic ribosome biogenesis *via* the release of the shuttling maturation factor Rlp24. Diazaborine is a know inhibitor responsible for blocking the release of Rlp24. The mechanism of inhibition was yet to be elucidated to shed light on the formation of the diazaborine resistance, the cryo-EM structure of the Drg1 hexamer (cryo-EM) in complex with its inhibitor diazaborine was resolved. Next, a detailed cavity analysis using our Catalophore™ CavMan platform to determine the available space for the inhibitor cavities in the vicinity of ADP molecules present in the homology model was performed.
Resistance-causing mutations were identified near the D2 nucleotide-binding pocket, demonstrating the spatial incompatibility of diazaborine with the binding pocket.



Cavity analysis of the binding pocket of the model. The cavity near ADP is represented as light gray spheres. Larger parts of the diazaborine molecule not covered by the point cloud indicate that the inhibitor is incompatible with the available space in the active siteof Drg1.

M. Prattes, I. Grishkovskaya, V.V. Hodirnau, I. Rossler, I. Klein, C. Hetzmannseder, G. Zisser, C.C. Gruber, K. Gruber, D. Haselbach, H. Bergler *Nat Commun* 2021, **12**: 3483-3483.