Virtual screening of novel inhibitors for mono-ADP-ribosylating toxins

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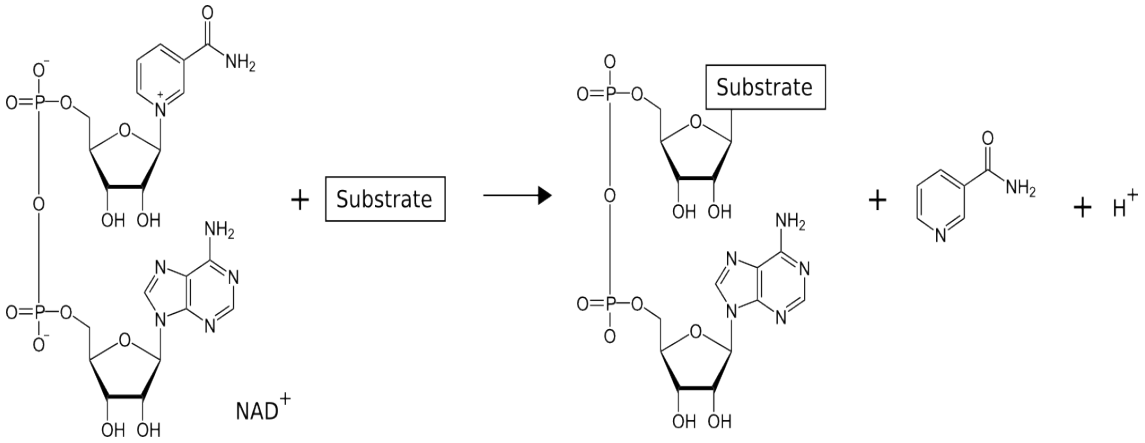
ADP-ribosyltransferases (ADP-RTs) are a family of enzymes secreted by pathogenic bacteria. They catalyse the hydrolysis of NAD^+ and the transfer of the ADP-ribosyl group onto specific target proteins [1,2].



Although ADP-RTs are important drug targets, only few inhibitors are known so far. The high selectivity of these inhibitors suggest different mechanism of binding to the ADP-RTs active sites. To explain the structural differences, we started a systematic program towards the development of new ADP-RT inhibitors. This is based on multiple virtual screening experiments (e.g. docking, pharmacophore searching and binding free-energy calculations) and the development of an *in vitro* assay for ADP-RTs. Active compounds identified in the first screening round are the basis for further *in silico* studies and optimisation steps. The aim of the current work is the discovery of novel drug-leads and the formulation of structure-function relationships which can explain the selectivity of ligand binding to the NAD^+ pocket. This is interesting from a drug discovery perspective, as many enzymes utilizing NAD^+ are valid or potential drug targets.

[1] Krueger, K.M. And Barbieri, J.T., Clin. Microbiol. Rev. 8, 1995, 34-47.

[2] Holbourn, K.P. Et al., FEBS J. 273, 2006, 4579-4593.