Efficient inhibition of SmNACE by coordination complexes is abolished by S. mansoni sequestration of metallic ions

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Résumé

The blood fluke *S. mansoni* is the causative agent of the intestinal form of the neglected tropical disease Schistosomiasis. In their adult form parasites express on the outer tegument a NAD catabolizing enzyme called *Sm*NACE. Using virtual screening, we recently identified aroylhydrazone derivatives capable of inhibiting the recombinant enzyme at nM concentration [1].The most potent inhibitor however showed no activity on the native enzyme when tested on live parasites.

Mass spectroscopy and spectrophotometry experiments, combined with activity assays in different experimental conditions have revealed that the high potency against recombinant *Sm*NACE by this class of compounds is dependent on the formation of a coordination complex with metal cations, such as Ni(II), Zn(II) and Fe(II), that are loaded on the protein surface. We have also demonstrated that the live parasites effectively sequesters the metal from the coordination complex, thereby abolishing inhibition. Importantly, the modeling of the transition complex enabled the discovery of a new metal-free analogue, which is now the most potent and selective inhibitor of native *Sm*NACE known.

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