Repurposing of known kinase inhibitors for inhibition of trypanothione synthetase

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Trypanothione synthetase (TryS) catalyzes the two-step biosynthesis of trypanothione, which is a key intermediate in trypanosomatid parasites of the species Trypanosoma and Leishmania. Thus, TryS is an attractive drug target to cope with diseases like Chagas disease, leishmaniasis, or African trypanosomiasis that affect approximately 15 to 20 million people worldwide. Interestingly, paullones, a chemical class of potent kinase (GSK-3) inhibitors, were shown to inhibit TryS. [1] Based on a comparison of available X-ray structures, the binding of paullones to TryS seems to be in accordance with the principle of 'ligand-sensing cores'. [2] The spatial arrangement of secondary structure elements around the ATP binding sites of TryS and kinases is quite similar, independent of the overall fold, which indicates binding of similar ligands.

Unfortunately, the available Leishmania major TryS X-ray structure (pdb-id 2vps) was solved without substrates and an important loop region of the ATP grasp fold is missing. Preliminary modeling and molecular dynamics (MD) simulation studies revealed possible binding modes of ATP, GSH and glutathionylspermidine (GSP). However, the bound state of the loop region remained unexplained. [3] A more detailed analysis that utilizes X-ray structure information of a related GSP synthetase from E. coli (pdb‑id 2io7) led to a complete model of LmTryS, containing all substrates and the closed ATP grasp fold loop. Exhaustive MD simulations have confirmed this model as reasonable and revealed that the presence of ATP leads to a partial closure of an associated β-sheet over the bound triphosphate. Furthermore, this validated model gave us the possibility to model the structures of TryS from other pathogenic species of Trypanosoma and Leishmania and to compare their ATP binding sites with respect to rational drug design.

Here we present the results of different MD simulations and show how the obtained models can be used to identify further (kinase) inhibitors that own a similar molecular scaffold. These inhibitors can then be diversified to obtain selective TryS inhibitors. The approach includes a detailed comparison of the full ATP binding pocket of TryS to known kinase X-ray structures as well as docking studies of kinase inhibitors received from different kinase databases. Biochemical testing of newly identified kinase inhibitors for inhibition of TryS will be carried out.

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