MS5-P7 Crystal structures of *Trypanosoma brucei* hypoxanthine-guanine-xanthine phosphoribosyltransferase

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Human African Trypanosomiasis (HAT) is a deadly infectious disease caused by the protozoan parasite *Trypanosoma brucei*. Due to the debilitating side-effects and emerging resistance to the current drugs available for this disease, new therapeutic targets and medications urgently need to be found. One potential new target is 6-oxopurine phosphoribosyltransferase (PRTase) an enzyme in the purine salvage pathway, whose activity appears to be essential for the production of nucleoside monophosphates required for incorporation into DNA and RNA in protozoan parasites. To begin evaluation of this enzyme as a potential drug target we have shown it can utilize the three naturally occurring 6-oxopurine bases, guanine, hypoxanthine and xanthine as substrates. Hence, we classify the enzyme as a HGXPRTase. Acyclic nucleoside phosphonates (ANPs) have previously been identified as a class of compounds that inhibit human and *Plasmodium* HG[X]PRTases. We have demonstrated that several acyclic nucleoside phosphonates (ANPs) are good inhibitors of this enzyme with K_i values as low as 2 μM. Five crystal structures of *Tbr*HGXPRT (1.5-2.9 Å resolution) have been determined. These are in complex with products of reaction, GMP and IMP and with three ANPs. Two of the ANPs that bind to the enzyme induce an unusual conformational change at the location where pyrophosphate, a product of the reaction, would be expected to bind to the enzyme. Such a change has not been observed in structures of the human enzyme suggesting a possible route to selective inhibition.

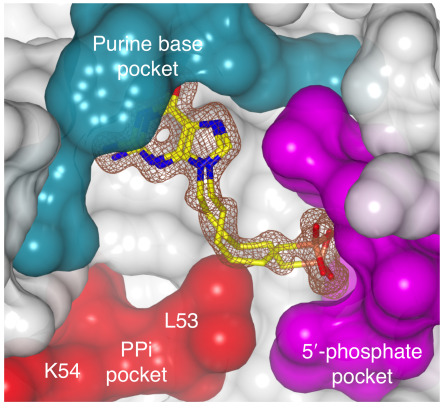

Figure 1. Surface structure representation of the *Tbr*HGXPRT.MIC-612 complex. F_o-F_c "omit" electron density for MIC-612 is overlayed.

Keywords: Trypanosoma brucei, purine salvage, acyclic nucleoside phosphonates