STRUCTURAL INSIGHT INTO SELECTIVE INHIBITION OF SCHISTOSOMA MANSONI PURINE NUCLEOSIDE PHOSPHORYLASE (SMPNP)

Castilho M.S. ,[a] Postigo, M. P.[b] Pereira, H. M. [b] Andricopulo, A. D.[b]

[a] Faculdade de Farmácia, Universidade Federal da Bahia, Campus Universitário de Ondina, CEP 40170-115,Salvador, Brazil. Fax: 55 7132372255; Tel: 55 7132836930; E-mail: castilho@ufba.br. [b]CBME, Instituto de Física de São Carlos, USP, São Paulo, Brazil

Purine nucleoside phosphorylase (PNP) is a key enzyme in the purine salvage pathway which selective inhibition has been claimed as an important strategy for Schistosomiasis treatment. Aiming at developing selective inhibitors of *Sm*PNP, kinetic studies of 12 ground-state inhibitors were carried through a standard spectrophotometric assay, employing 10 µM of inosine (substrate) for *Sm*PNP and 64 µM for *Homo sapiens* PNP (*Hs*PNP), at pH 7.4, and 50 mM of phosphate buffer. Readouts, performed at 293 nm, show that deazaguanine derivatives with aromatic moieties at position 9 have no selectivity towards *Sm*PNP in comparison to *Hs*PNP. On the other hand, 9-ribose substituted compounds show 3-6 fold selectivity ratio towards *Sm*PNP. In order to shed some light over the structural features that are responsible for this, the crystallographic structure of *Sm*PNP in complex with guanosine (*Sm*PNP-GUA) was crystallized and its X-ray crystallographic structure refined to 2.05Å resolution using CCP4 software (R=0.18, R_{free}=0.25). The interaction profile of guanosine in the *Sm*PNP active site shows that purine moiety binds exactly as in *Hs*PNP, however the ribose is H-bonded to Tyr^{202}, what can not be possible in the human counterpart that shows a Phe in the equivalent position. 9-ribose substituted compounds have high similarity to guanosine and thus should bind equally. Therefore, it is reasonable to assume that ribose containing inhibitors also H-bond to Tyr^{202}, thus selectively inhibiting *Sm*PNP.
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