Acyclic Nucleoside Phosphonates Containing A Second Phosphonate Group As Potent Inhibitors Of 6-Oxopurine Phosphoribosyltransferases With Antimalarial Activity

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Hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT) is a key enzyme of the purine salvage pathway. This enzyme is a validated target for anti-malarial chemotherapy because parasites of the genus *Plasmodium* are unable to synthesise purine bases *de novo* and depend on the transport of preformed bases from the host cell. HG(X)PRT then catalyses the conversion of these 6-oxopurine bases to the corresponding nucleoside monophosphates which are required for DNA/RNA production. Specific structural analogues of nucleotides - acyclic nucleoside phosphonates (ANPs) - have been recognized as potent inhibitors of HG(X)PRT.

Crystal structures of HG(X)PRT in complex with known inhibitors suggested that attachment of an additional functional group which could occupy the pyrophosphate binding site may lead to the increased affinity of these ANP-based inhibitors. These new compounds where prepared by multistep synthesis and are referred to as acyclic nucleoside bisphosphonates (ANbPs)[1]. Their prodrugs have promising antimalarial activity in erythrocyte cultures.

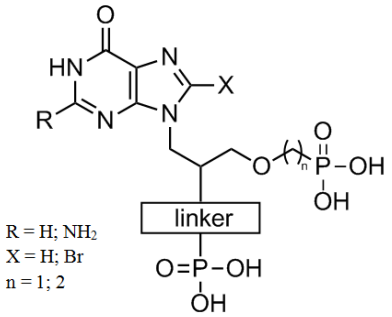

FIG. Examples of ANbPs structures.

1) Keough D.T. et al. *J. Med. Chem.* **2013**, 56, 2513.