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Novel nucleoside-based antimalarial compounds

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ABSTRACT

The malaria-causing parasite *Plasmodium falciparum* employs a salvage pathway for the biosynthesis of nucleotides, in contrast to *de novo* biosynthesis that is utilized by the human host. A series of twenty-two 2-, 6- and 5′-modified adenosine ribonucleosides was synthesized, with the expectation that these compounds would generate toxic metabolites instead of active nucleotides by the pathogen, while remaining inert in host cells. Bioassays with *P. falciparum* (K1 strain) indicated IC_{50} values as low as 110 nM and a selectivity index with respect to cytotoxicity toward an L6 rat myoblast cell line of >1000 for the most potent analogue.

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Protozoan pathogens impose a considerable burden on human health, especially in developing countries. *Plasmodium falciparum* is of particular concern as it is the causative agent of the most severe form of human malaria. The World Health Organization estimates that malaria affected an estimated 200 million people in 2013, resulting in ca. 600,000 deaths.[1] Moreover, infections caused by *P. falciparum*, along with other *Plasmodium* strains, have proven increasingly difficult to treat because of widespread drug resistance. Thus the effectiveness of chloroquine as both a prophylactic and therapeutic drug has been severely compromised, leading to reliance on less efficacious drugs associated with more severe side effects.[2] There are even calls[1] for the withdrawal of chloroquine from the market with the frequency of resistant haplotypes at 80% with continued use in parts of Africa.[3,4] More recent drug therapies, such as those based on artemisinin, are also beginning to encounter resistance.[5] The rapid spread of artemisinin resistance in *Plasmodium falciparum* malaria in Southeast Asia threatens the efficacy of artemisinin combination therapies.[6,7] An urgent need therefore persists for the development of novel drugs that could selectively target *P. falciparum* without causing harm to the human host.

Pathogenic protozoa are universally deficient in their capability to synthesize purines via a *de novo* pathway,[8–10] resulting in their dependence upon the salvage and reutilization of preformed purines for development and proliferation. They have several unique enzymes not present in mammals, which are exploitable targets for drug design. We report here the design, synthesis and in vitro assay of several purine ribonucleoside prodrug analogues which are intended to be activated by the parasite enzymes, but remain comparatively inert in the mammalian host. As these activation pathways are essential for the proliferation of protozoa, this approach may be more refractory to mutation and the rapid onset of resistance than with conventional drugs.

Our strategy for this new antimalarial therapy is based on adenine ribonucleoside analogues that were designed to exploit the ability of *P. falciparum* to deaminate 6-amino purine ribonucleoside analogues to the corresponding 6-oxo purine ribonucleosides for subsequent phosphorolysis to the purine base analogue (Scheme 1). The only route for adenosine metabolism in *P. falciparum* is deamination, as the inosine–adenosine–guanosine nucleoside hydrolase (IAG-NH) present in other protozoa[11,12] is absent in *P. falciparum*[13] and adenosine is not a substrate for either *P. falciparum*[14,15] or mammalian[16,17] purine nucleoside phosphorylase (PNP). Nor is there genomic evidence for an adenine phosphoribosyltransferase (APRT) activity capable of converting adenine to AMP.[18,19] Neither is there evidence for a *Pf* adenosine kinase.[18,19] However, this parasite has a unique adenosine deaminase,[20] which converts both adenosine and 5′-methylthioadenosine, the product of polyamine catabolism, to inosine and 5′-methylthioinosine respectively. The *Pf* PNP subsequently accepts both of these nucleosides and converts them to hypoxanthine,[15,20] which can in turn be utilized for nucleotide biosynthesis via a process catalyzed by *Pf*HGXPRT. By

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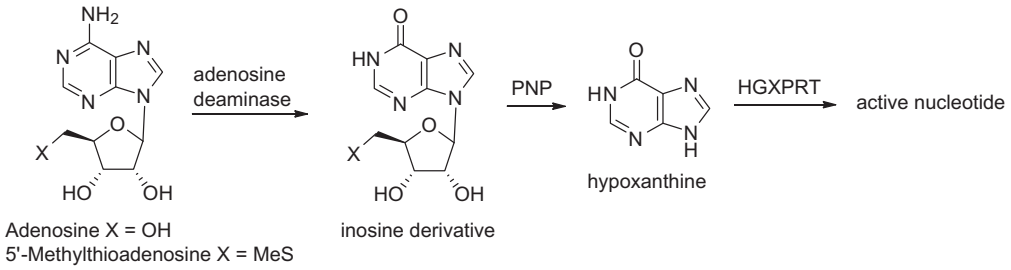


Scheme 1. Nucleoside activation by *P. falciparum*.

these means, adenosine and 5′-methylthioadenosine analogues may be converted to toxic nucleotides in *P. falciparum*, via deamination by *Pf* ADA, followed by phosphorolytic cleavage to the base analogue by *Pf* PNP and subsequent conversion to an active nucleotide analogue by *Pf* HGXPRT. Nucleosides other than the 6-amino analogs may be cleaved directly to their base counterpart via *Pf* PNP and then activated by *Pf* HGXPRT.

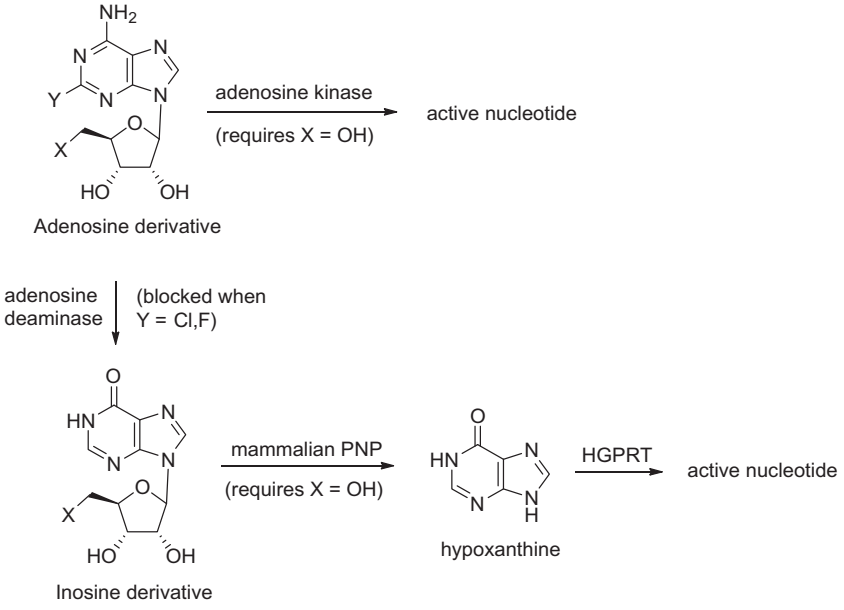
Finally, we endeavoured to enhance the specificity of the adenosine analogues by protecting them from direct activation to a toxic form by the host. Thus, in order to block 5′-phosphorylation via human adenosine kinase, we modified the 5′-hydroxyl group by reduction to the corresponding 5′-deoxy analogue, or by replacement with a methylthio group. An alternative potential activation pathway in the host would be through deamination to the inosine analogue, followed by the action of human PNP to produce the hypoxanthine base analogue and the further conversion of the resulting base to an active nucleotide by hypoxanthine phosphoribosyltransferase (HGPRT) (Scheme 2). Substitution of the 2-position of the purine moiety with chlorine or fluorine is known to block deamination via mammalian adenosine deaminase.[21,22] Adenosine is also not converted to adenine by human PNP,[16,17] thereby sparing the possibility of adenine base analogues from being converted to the nucleotides by human APRT. Thus, our nucleoside-based antimalarial strategy was designed to afford toxic drugs through their conversion to 2-halopurines, while remaining refractory to phosphorylation and deamination in the host cells, in order to prevent the formation of toxic metabolites.

During the course of this work, compounds **1**–**22** (Table 1) were synthesized and assayed for their activity against *P. falciparum*. Compounds **1**,[23] **2**,[24] **3**,[23,25] **4**,[26] **6**,[27] **7**,[23] **9**,[27] **11**[24]and **15**[28] have been reported previously and the syntheses of new compounds **5**, **8**, **10**, **12**–**14** and **16**–**22** are outlined in Schemes 3–6 and described in Supplementary data.

2-Amino-6-chloropurine (**23**) was condensed with 5′-modified ribose triacetate derivatives **24**[29] and **25**[30–32] by a variation of the Vorbruggen method[33] to afford **26** and **27**, respectively. Diazotization in the presence of iodine then afforded the 2-iodo derivatives **28** and **29**, respectively. Nucleophilic aromatic substitution of the 6-chloro substituent with methanolic ammonia or methylamine, with concomitant deacetylation, provided the products **5**, **6**, **16** and **17**, as shown in Scheme 3. Palladium-catalyzed cyanation of the 2-iodo substituents of the latter compounds afforded the 2-cyano analogues **12**, **13**, **18** and **19**, respectively.

Nucleophilic aromatic substitution of the 2-chloro-5′-deoxyadenosine derivative **1**[23] with hydrazine hydrate produced **8** and its subsequent selective diazotization afforded the corresponding azide **10a** as a mixture with its tetrazole tautomer **10b** (Scheme 4).[34,35] The known 5′-methylthio analogue **11a**[24] was prepared similarly, again as a mixture with its tautomer **11b**.

Product **14** was obtained from the condensation of 6-chloropurine (**30**) with ribose derivative **24**,[29] via the intermediacy of **31**, which was directly subjected to treatment with methylamine in methanol without prior isolation (Scheme 5).



Scheme 2. Nucleoside activation by mammals.

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