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Expert Opinion

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Monthly Focus: Anti-infectives

Purine analogues as antiparasitic agents

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As parasites cannot synthesise purines *de novo* and must salvage them from their hosts, purine salvage pathways have long been considered an attractive chemotherapeutic target. Recently, the discovery of specific transition-state inhibitors, the interest in antiviral nucleoside analogues due to AIDS and their potential in lymphoproliferative diseases gave a new impulse to this research field. Among the patents disclosed recently, only iminoribitol derivatives have documented antiparasitic activities, especially against nucleoside N-hydrolases (NH), purine nucleoside phosphorylase (PNP) and also against 5'-deoxy-5'-methylthioadenosine phosphorylase (MTAP), an enzyme at the border of polyamine biosynthesis and purine salvage. Disclosed compounds with modifications of the pentose ring aimed to mimic ATP, are only expected to have an antiparasitic activity. The last group of patents consists of carboxamidines and inhibitors of nucleoside transporters with potential antiparasitic effect. Antiparasite chemotherapy should benefit from the ongoing research in this field, if these promising molecules are effectively tested on parasite models.

Keywords: antiparasitic chemotherapy, immucillin, MTAP, nucleoside hydrolase, PNP, purine analogue, purine salvage

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1. Introduction

Parasites are the causative agents of many of the major human and animal diseases. Unlike bacteria, they are also eukaryotes and their relationships with their hosts are intricate and complex. They share many metabolisms and as they do not use their host as a simple substrate, chemotherapy must rely on specific targets. Furthermore, resistance against chemotherapy has been spreading for many years and it is increasingly difficult to find new drugs effective against such important diseases as malaria, sleeping sickness and schistosomiasis. Immunocompromised patients also suffer from lethal opportunistic infections caused by protozoans such as *Toxoplasma gondii* and *Cryptosporidium parvum*. In the latter case, the urge for an efficient chemotherapy is justified by the lack of efficiency of the available drugs (Table 1). Fortunately, both protozoan and metazoan parasites seem to share a specificity relative to purine metabolism; their inability to synthesise the purine ring *de novo*. The possibility that phylogenetic divergence between parasites and their hosts in the molecules involved could be used to design inhibitors gave rise to much research on purine analogues. The availability of nucleoside analogues for the treatment of viral infections and the recent apparition of PNP inhibitors in the treatment of diseases caused by T cell proliferation gave a new impulse to this research field.

2. Purine salvage in parasites

Nearly all the parasites studied to date are obligate purine auxotrophs, they must salvage purines from their host and they have developed systems to transport,

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Table 1. The main human parasitic diseases and their expected purine salvage targets.

Parasite	Location in the host	Disease	Available chemotherapy	Resistance	Potential targets
Protozoans					
<i>Plasmodium falciparum</i>	Intracellular: hepatocytes, erythrocytes	Malaria	+	++	APRT, HGXPRT, MTAP, PNP, transporters
<i>Toxoplasma gondii</i>	Intracellular, tissue cysts	Toxoplasmosis	+	–	AK, APRT, HGXPRT, transporters
<i>Trypanosoma</i> sp.	Blood, free	Sleeping sickness, Chagas disease	+	+	HGPRT, NH, transporters
<i>Leishmania</i> sp.	Intracellular: phagocytic cells	Leishmaniasis	+	±	APRT, HGPRT, NH, MTAP, transporters
<i>Giardia lamblia</i>	Intestine, free	Giardiasis	+	–	APRT, HGXPRT, transporters
<i>Trichomonas vaginalis</i>	Vagina, free	Trichomoniasis	+	–	AK, transporters
<i>Cryptosporidium parvum</i>	Intracellular, intestine	Cryptosporidiosis	–	NA	AK, HGXPRT, IMPDH
Helminths					
<i>Schistosoma mansoni</i>	Blood vessels	Schistosomiasis	+	±	AK, APRT, HGPRT, MTAP, transporters
<i>Echinococcus multilocularis</i>	Liver	Alveolar echinococcosis	±	NA	HGPRT, PNP

AK: Adenosine kinase; IMPDH: ; MTAP: ; NA: Not applicable; NH: N-hydrolase; PNP: Purine nucleoside phosphorylase.

internalise and metabolise the required substrates, which are the ubiquitous components of the nucleic acids DNA and RNA, as well as important energy metabolism effectors such as ATP. The key molecules are usually the nucleosides adenosine, inosine and the nucleobase hypoxanthine (Figure 1), but there are marked differences in the salvage pathways and in the preferred substrates according to the parasites [1]. Because of intricate pathways and the multiplicity of enzymes and substrates, the study of purine metabolism is difficult and time-consuming. When it comes to parasites, the research is complicated by their often complex life cycles, their intra- or extracellular location and their availability in *in vitro* and/or *in vivo* suitable systems. The advent of gene technology and the increasing availability of sequenced parasite genomes will provide more information, based on a comparative strategy from gene homology as was recently the case for *C. parvum* [2] and *T. gondii* [3].

2.1 Enzymes of the purine salvage pathway

Despite a large number of enzymes involved in purine salvage, only a few of them appear to be potential targets for antiparasitic chemotherapy.

2.1.1 Purine phosphoribosyltransferases (E.C. 2.4.2.-)

These enzymes catalyse the transfer of a phosphoribosyl moiety on the nucleobases adenine (APRT), hypoxanthine, guanine or xanthine (HG(X)PRT). They are pivotal in the salvage pathway and differ according to their substrates,

APRT usually being different from HG(X)PRT. They have been studied in trypanosomatids [4], in *T. gondii* [5], in *Giardia lamblia* [6] and in the larval cestode *Echinococcus multilocularis* [7]. Even if a high HGXPRT activity was reported in *C. parvum* [8], no gene for this enzyme was found in its genome [2]. On the contrary, *Trichomonas vaginalis* lacks purine phosphoribosyltransferases and relies solely on adenosine and guanosine uptake [9]. Subversive substrates of these enzymes were the first proposed chemotherapeutic targets [10].

2.1.2 Adenosine kinase (AK; E.C. 2.7.1.20)

This enzyme phosphorylates adenosine to its 5'-monophosphate, AMP. Its activity is very high in *T. gondii* [3], and it is thought to be the main route of adenosine metabolism in *C. parvum* [11]. Various 6-substituted-9-β-D-ribofuranosyl-purines showed good selective efficacy against *T. gondii* AK, but were only parasitostatic [12].

2.1.3 Purine nucleoside phosphorylase (PNP; E.C. 2.4.2.1.)

PNP catalyses the phosphorolytic cleavage of purine ribosides to release the corresponding nucleobase and ribose-1 phosphate. Only a few studies had been performed on parasites, until the discovery of its importance in human T cell proliferation and hence, in such pathologies as psoriasis or leukaemia [13]. A high PNP activity was reported in *Plasmodium falciparum*, *T. gondii* tachyzoites [14] and in the helminth *Schistosoma mansoni* [15].

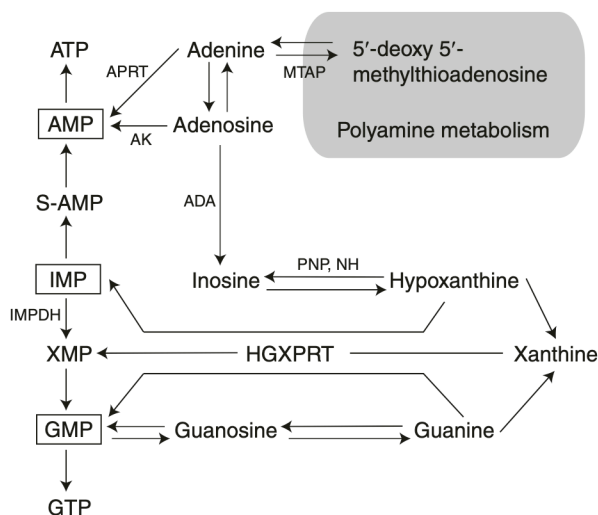


Figure 1. The purine salvage pathways of parasites. Only the relevant enzymes are indicated.

ADA; ; AK: Adenosine kinase; APRT; ; IMPDH; ; NH: N-hydrolase; PNP: Purine nucleoside phosphorylase.

2.1.4 Nucleoside N-hydrolases (NH; E.C. 3.2.2.1)

These enzymes are involved in the same reaction as PNP, except that they do not require inorganic phosphate for the nucleosidic bond cleavage. Their interest relies on their complete absence in higher eukaryotes. They were mainly described, crystallised and cloned in *Trypanosoma* and *Leishmania*. The reaction mechanism has been described and was the basis for the synthesis of transition state inhibitors, among which are the immucillins [16,17].

2.1.5 5'-deoxy-5'-methylthioadenosine phosphorylase (MTAP; E.C. 2.4.2.28)

This enzyme and its bacterial equivalent (MTAN) are at the crossroads of polyamine biosynthesis and of purine salvage, converting 5'-deoxy-5'-methylthioadenosine (MTA) to adenine. These enzymes share some characteristics with their mammalian counterparts but accept 2',3'-dideoxynucleoside analogues as substrate toxic substrates (see [1]). MTAP inhibitors could then be active against malaria, as *P. falciparum* has recently been reported to possess a MTAP pathway [18].

2.1.7 IMPDH (E.C. 1.1.1.205)

The enzyme from *C. parvum* appears to be a good candidate and inhibitors such as ribavirin and mycophenolic acid are active [19].

2.2 Nucleoside transporters

The first step in purine salvage is the transport of the hydrophilic nucleotides and nucleosides across the parasite membranes. When compared to their mammalian hosts, in which two types of equilibrative transporters (*ei* and *es*) and six kinds of proton-driven sodium concentrative transporters

(N1 – N6) have been described [20], little attention was paid to the transporters of parasites until recently. These studies were made possible by the use of specific inhibitors such as NBMPR and the permeants tubercidin and formycin B (Figure 2). There is usually an adenosine and an inosine transporter in many parasites [1,21,22].

2.3 Purine analogues as potential antiparasitic agents

Despite the availability of many purine analogues, only a few have been studied as antiparasitic agents. The antiviral inosine analogue, 2',3'-dideoxyinosine (ddI), was shown to be active against *T. gondii* *in vitro* and in a toxoplasmic encephalitis model in mice [23,24]. It was also active against *C. parvum* *in vitro*, as well as formycin B [25]. Perhaps the best example of a successful analogue is the use of allopurinol in clinical use against leishmaniasis [26], alone or in combination with classical chemotherapy.

3. Patents

Most of the recently disclosed patents on purine analogues are related to antiviral and/or anticancer activity; only a few claim effects primarily on parasitic diseases, the others cite parasites essentially by analogy.

3.1 Transition-state inhibitors:

Furneaux *et al.* [101] disclosed various immucillin derivatives that inhibit PNP, nucleoside N-hydrolase (NH) or PPR. The compounds are transition-state inhibitors in which the iminoribitol moiety is linked to a 9-deazapurine with the possibility of an 8-methyl or 8-fluoryl (1) substituent. However, only the determination of the inhibition constants of the compounds for bovine PNP is provided. The same authors [102] disclosed other inhibitors of nucleoside phosphorylases and nucleosidases with the purpose of adding another target to the patented PNP inhibitors, MTAP. The disclosed compounds are derivatives of immucillin-A: 5'-thio-immucillin-A and 8-aza-5'-thio-immucillin-A derivatives, 5'-O-substituted immucillin-A derivatives and 5'-deoxy-substituted immucillin-A derivatives. The authors provide the inhibition constants against MTAP and MTAN for the preferred analogues. These analogues are specific inhibitors either of MTAP or of the bacterial enzyme MTAN, a very interesting result because immucillin-A itself does not inhibit MTAP. Data on inhibition of mouse liver MTAP by 5'-methylthio-immucillin-A (2) are provided, but no antiparasitic effects are given. Inhibitors with broader specificities against nucleoside phosphorylases and nucleosidases, including MTAP and MTAN, were reported by Evans *et al.* [103]. Particularly, the authors stress that the location of the nitrogen atom in the ribitol ring may be critical for the inhibitory properties and that the disclosed compounds have a link at the C-1-position of the sugar moiety. The authors provide data on the inhibition constants of the compounds against human PNP, human MTAP, bacterial MTAP and MTAN. Of interest are the data about inhibition of the *P. falciparum* PNP by compound 8 (3), which displays a

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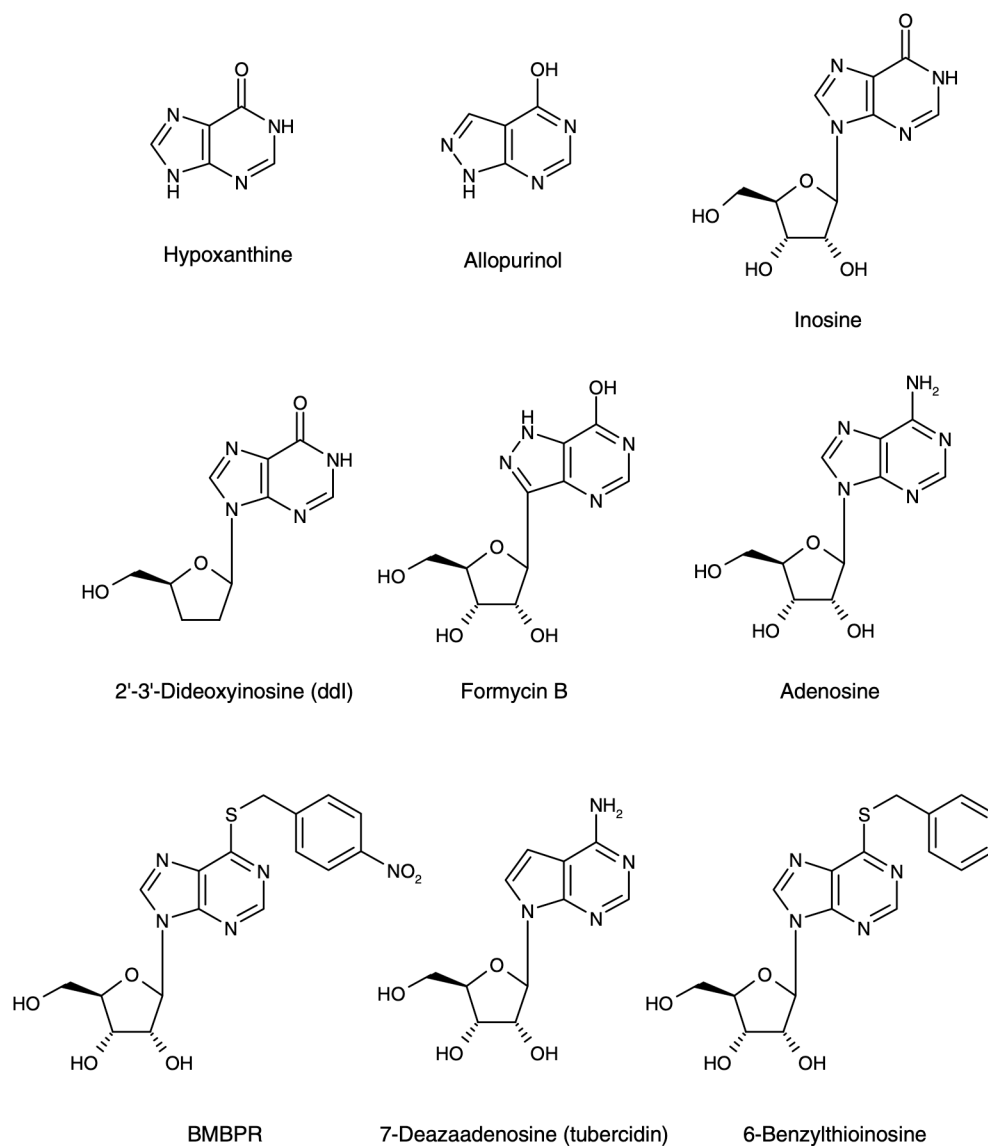


Figure 2. Natural purines, common analogues and permeants.

K_i value of 500 pM, but human PNP and *Mycobacterium tuberculosis* PNP are also inhibited with values of 1100 and 1300 pM, respectively. Data are also given for *in vivo* inhibition of the mouse MTAP. Evans and Tyler recently reported a method for preparing methylene-linked cyclic amine deazapurines as inhibitors for the same enzymes [104]. This patent claims an easier route based on the Mannich reaction for the synthesis of these analogues, but no biological test is provided. Of the 28 compounds described, the 4-chlorophenylthiomethyl derivative is shown in compound 4.

3.2 ATP analogues

Prokop *et al.* recently disclosed a wide variety of nucleoside analogues with use against proliferating cells [105]. Among the

many compounds reported, only compounds 95e (5) and 155d (6) are purine analogues with silyl substituents on the cyclopentene ring. The authors give data about assays on the BJAB tumour cell line and on apoptosis. As far as human therapy is concerned, solid tumours and acute lymphoblastic leukaemia are the targets of choice. However, diseases caused by protozoan and helminths are cited, without any data provided. Bottaro *et al.* disclosed nucleoside pyrophosphate and triphosphate analogues that are stable or uncleavable functionally equivalent analogues [106]. Their claim is for isosterically and electronically equivalent functional groups. The examples shown are pyrimidine analogues (7), but any purine may be linked. The compounds are claimed to be useful against infectious diseases caused by protozoans, such as

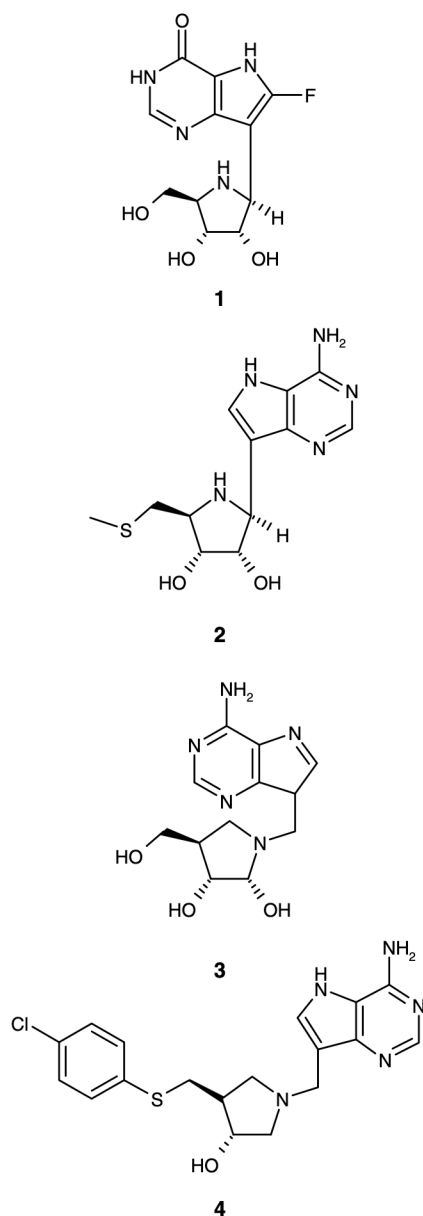


Figure 3. Transition state inhibitors.

amoebiasis, leishmaniasis, Chagas disease, malaria and toxoplasmosis. Interestingly, they are also reported to be able to treat parasitic diseases caused by nematode worms, such as toxocarosis and trichinosis, but no evidence is given.

3.3 Carboxamidines and inhibitors of nucleoside transport:

Tam *et al.* reported the synthesis of nucleoside analogues with a carboxamidine-modified bicyclic base that are claimed to be useful in T cell disorders, such as autoimmune diseases [107]. The disclosed compounds are also aimed to act as prodrugs, such as acylated derivatives, pyridine esters or salts, activated

in the patient's body by chemical cleavage. The example chosen is the inosine analogue ICN-10776 (8) either in L- or D-configuration. The authors cite a potential activity against protozoal and helminth infections, but the only results provided deal essentially with the modulation of Type 1 or 2 lymphocyte responses *in vitro*. Even if they are not specifically directed against parasites, novel ribavirin analogues were disclosed by Wang *et al.* [108]. This IMPDH inhibitor also interacts with human *es* nucleoside transporters and hence is haematotoxic in long-term treatments. The disclosed compounds possess a heterocyclic base moiety (diazole [9] or triazole [10]) and are claimed to be useful in the treatment of a wide variety of conditions, especially viral diseases and cancer. A great number of combinations are described and deal with various modifications of either the pentose or the heterocyclic moieties.

The available nucleoside transport inhibitors are often toxic, mutagenic, ineffective *in vivo* or non-specific. Assuming that their combination with nucleoside analogues should enhance their biodisponibility, Buolamwini reported novel nucleoside transporters inhibitors [109]. The claim is for conformationally restrained NBMPR analogues lacking the *in vivo* lability of the S⁶-nitrobenzyl substituent. The nitro-tetrahydroisoquinoline moiety of the preferred compound (11) is supposedly not easily cleaved *in vivo*. The disclosed compounds are thus susceptible to prevent metabolic inactivation and formation of toxic metabolites. Although primarily aimed at cancer, heart disease and strokes, and bacterial infections, the compounds are said to be suitable for treating malaria, giardiasis and toxoplasmosis. Although inhibition of [³H]-uridine uptake in JB6 cells is described, no data are provided about an antiparasitic effect.

4. Expert opinion

The purine salvage pathway has been an attractive target against parasites for almost 30 years [10]. Many studies have pointed out that, in fact, only a few enzymes were of interest as chemotherapeutic targets: PPRT, AK, and more recently, NH, PNP and MTAP, the latter being rather related to polyamine metabolism. However, despite a fair amount of information about these promising antiparasitic metabolic targets, only allopurinol has reached preclinical and clinical use. There are many reasons for this situation:

- The host's enzymes and transporters are able to bind to and to be inhibited by the analogues, even if they are different. This is the cause of the reported toxicity of many analogues [27]. There is also often a lack of availability of adequate animal models to test the compounds pharmacologically [1].
- Due to the numerous pathways in which the purines are involved, many analogues are ineffective or non-specific *in vivo*, not to mention their inability to cross biological barriers. Conversely, an unexpected target may be discovered: the antiviral acyclic analogue S-HPMPA is

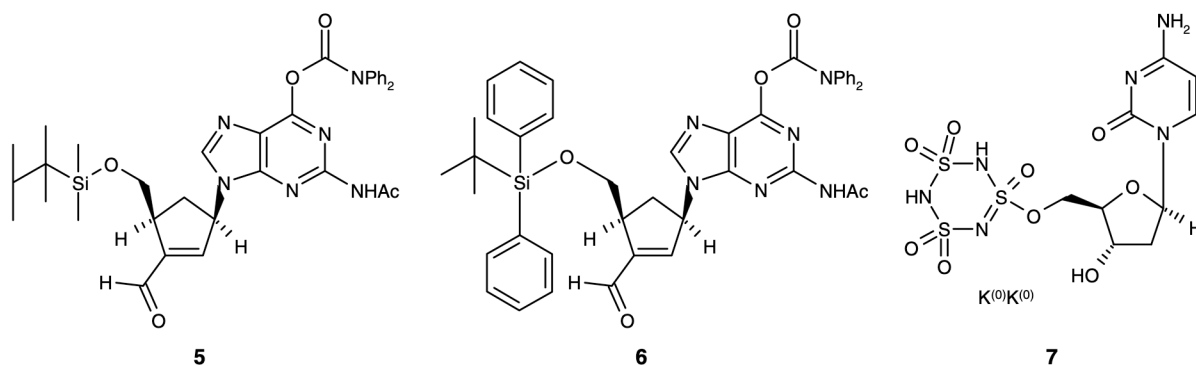


Figure 4. ATP analogues.

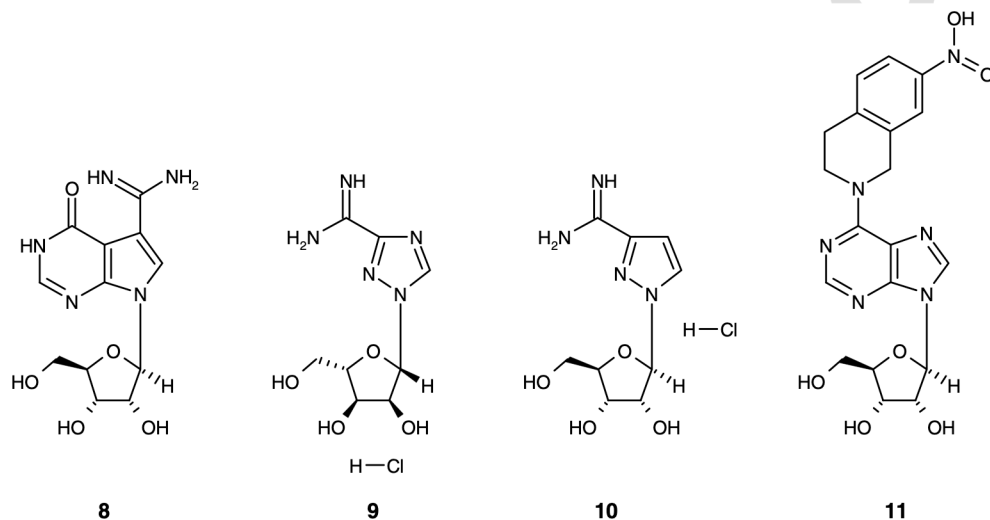


Figure 5. IMPDH and NT inhibitors.

active against *S. mansoni* [28] and the adenosine analogue tubercidin inhibits glycolysis in *T. brucei* [29].

- In addition, parasites may have many ways to escape the toxicity of the analogues, as was reported with *T. gondii* and 6-thiopurines [30].

So what has changed in recent years? The finding that the specific protozoal nucleoside N-hydrolases were pivotal in the purine metabolism of trypanosomatids triggered a remarkable series of studies that enabled the design of specific transition state inhibitors, the immucillins [31]. These subversive substrates were in turn used to design inhibitors of PNP, an enzyme involved in many human pathologies, such as lymphoproliferative diseases and cancer [13,32]. On the other hand, the AIDS pandemic prompted the research on purine and pyrimidine acyclic analogues aimed to block viral DNA polymerases. In addition, AIDS patients often suffer from opportunistic parasitic diseases and the purine

analogues used against HIV could be useful against these parasites [33].

The recently disclosed patents reviewed here can be divided into three main categories:

- Compounds directly based upon the original antinucleoside N-hydrolase inhibitors, where substantial evidence exists of their antiparasitic activity. These patents not only deal with iminoribitol inhibitors effective against NH and PNP, but also PPRT and MTAP, an enzyme of polyamine biosynthesis. The transition state inhibitor immucillin-H has antimalarial properties [34] and MTAP has been recently noted as an attractive target against *P. falciparum* [35].
- nucleoside analogues with other modifications of the pentose moiety. The use of a cyclopentene ring leads to compounds supposedly inhibitors of rapidly proliferating cells. In addition, silyl substituents are claimed to also be anti-

parasitic. Their mode of action could be much more diverse than the purine salvage in itself, as these compounds are intended to mimic ATP.

- The third group may be considered to more specifically target the parasitic nucleoside and nucleobase transporters that could be used to bypass the toxicity of most of the available purine analogues. The carboxamidines disclosed here were not intended to interfere with the purine salvage pathway, but to disrupt the synthesis of the viral nucleic acids. Their pharmacological side effect, haematotoxicity, is due to their binding to the human equilibrative nucleoside transporters. Even if only a possible antiparasitic activity is suggested, the chemical structure of the

ribavirin analogue ICN-10776 could also interfere with the parasitic salvage purine pathways.

Some patents not reviewed here, albeit specifically designed against lymphoproliferative diseases, deserve careful attention. This is the case for dioxolane derivatives, a class of antivirals and antitumour purine analogues [36]. Generally, most of the patents reviewed claim only putative antiparasitic activity and thus should be tested for antiparasitic activity. Parasites, especially protozoans, multiply rapidly, as do cancer cells and viruses, and the antiparasitic field should benefit from antiviral and immunosuppressive drugs research.

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