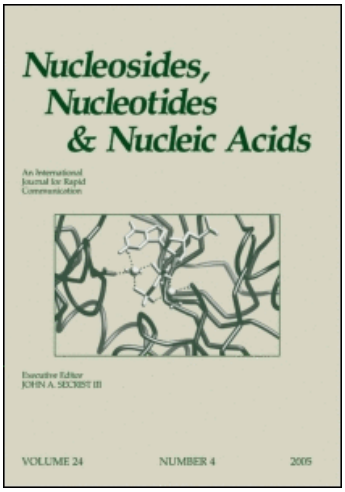

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Targets for the Antiviral Activity of Pyrimidine and Purine Nucleoside Analogues

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To cite this Article De Clercq, Erik(1987) 'Targets for the Antiviral Activity of Pyrimidine and Purine Nucleoside Analogues', Nucleosides, Nucleotides and Nucleic Acids, 6: 1, 197 — 207
To link to this Article: DOI: 10.1080/07328318708056192
URL: http://dx.doi.org/10.1080/07328318708056192

NUCLEOSIDES & NUCLEOTIDES, 6(1&2), 197-207 (1987)

TARGETS FOR THE ANTIVIRAL ACTIVITY OF PYRIMIDINE AND PURINE NUCLEOSIDE ANALOGUES*

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Abstract. In our attempts to develop nucleoside analogues with selective antiviral activity we have envisaged the following targets : viral DNA polymerase (whether or not via viral dThd kinase), reverse transcriptase, AdoHcy hydrolase, dTMP synthetase, OMP decarboxylase and CTP synthetase.

Relatively minor structural modifications suffice to obtain analogues of the natural nucleosides that are specifically targeted at key enzymes in the virus replicative cycle. For the pyrimidine nucleosides, these modifications involve substitutions at the 5-position of the pyrimidine ring, whether or not combined with 2',3'-dideoxygenation and 2',3'-didehydrogenation of the ribose moiety, or replacement of the latter by a cyclopentyl or cyclopentenyl ring. From the purine nucleosides selective antiviral agents can, again, be obtained by transformation of the sugar moiety to a cyclopentyl or cyclopentenyl ring. Furthermore, the "sugar" part of the molecule does not have to be cyclic, as testified by the marked antiviral activity of such acyclic nucleoside analogues as 9-(2-hydroxyethoxymethyl)guanine (acyclovir)[1], 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG)[2] and (S)-9-(2,3-dihydroxypropyl)adenine [(S)-DHPA][3].

Thymidylate synthetase

5-Substituted 2'-deoxyuridines (dUrd) with a rather small and electronegative C-5 substituent such as fluorine (1), trifluoromethyl (2), nitro (3), formyl (4), or other electron-withdrawing groups, have been

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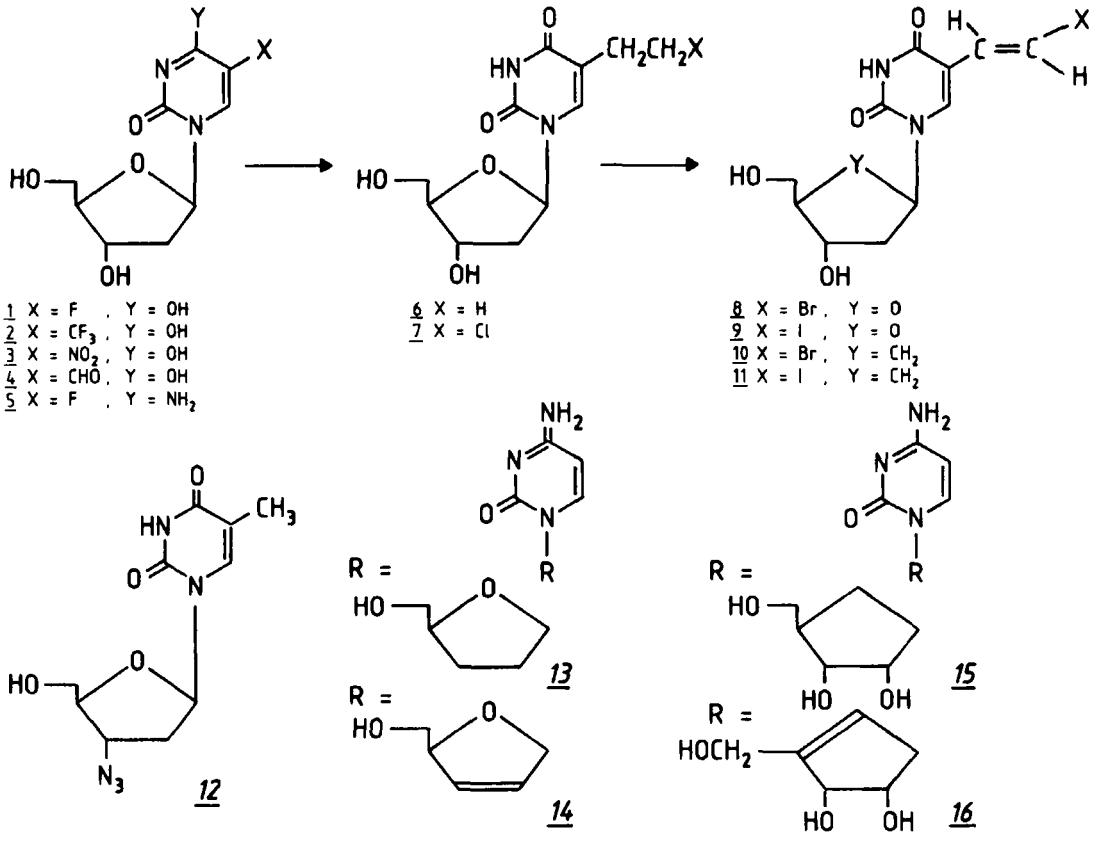
This paper is dedicated to Professor Morio Ikehara at the occasion of his retirement from Osaka University in March 1986.



recognized as potent inhibitors of dTMP synthetase.[4-6] This enzyme may act as the principal, if not the sole, intracellular target for the inhibitory activity of these compounds on tumor cell growth[5]. Also, the activity of 3 against vaccinia virus has been attributed to an inhibition of dTMP synthetase[7]. While dTMP synthetase is essential for the growth of tumor cells and replication of vaccinia virus, it does not appear to play an important role in the replication of herpes simplex virus (HSV)[8], probably because HSV meets its dTTP requirements via the dThd salvage pathway. HSV has no difficulties in securing the salvage of dThd, as it is able to induce its own dThd kinase (TK) in infected cells. At least, wild-type (TK^+) HSV strains do so. TK^-HSV mutants, which are deficient in dThd kinase activity, do not.

We[9] have recently found that TK^-HSV mutants are much more susceptible than TK^+HSV strains to the inhibitory effects of 1, 2, 3, 4, 5, and

the 5'-monophosphates and 3',5'-cyclic monophosphates thereof,[10-12] and as the anti-TK$^-$HSV activity of these compounds was readily reversed by dThd, but not dUrd, dTMP synthetase could be identified as the target for their antiviral activity. Apparently, TK$^-$HSV mutants are much more dependent on de novo biosynthetic pathways, including the synthesis of dTMP from dUMP catalyzed by thymidylate synthetase, than are the TK$^+$HSV strains, and, this makes them more vulnerable to inhibitors acting at the dTMP synthetase level. To act as dTMP synthetase inhibitors, 5-fluoro-dUrd (1) and its congeners should be converted intracellularly to the corresponding 5'-monophosphates. This phosphorylation is readly accomplished by cellular dThd kinase(s).

Viral DNA synthesis, via phosphorylation by viral dThd kinase

In contrast with 5-fluoro-dUrd (1) and its congeners (2-5), dUrd derivatives[4,13,14] containing an ethyl (6, 7) or ethenyl (8-11) group at C-5 are preferentially phosphorylated by the virus-encoded dThd kinase. These compounds are not active against TK$^-$HSV mutants[15]. However, they are strongly inhibitory to TK$^+$HSV strains and other herpesviruses [i.e. VZV (varicella-zoster virus), SHV-1 (suid herpesvirus type 1), BHV-1 (bovid herpesvirus type 1)] which encode a virus-specific dThd kinase recognizing the compound as substrate. It is remarkable that the carbocyclic analogues 10 and 11 are as efficient substrates for the HSV-1-encoded dThd kinase as their parent compounds[16,17].

The ultimate target for EDU (6), BVDU (8), IVDU (9) and their carbocyclic analogues 10 and 11 would be the viral DNA, since, once phosphorylated to their 5'-triphosphate, all these compounds can serve as alternate substrates of the viral DNA polymerase, and hence be incorporated into viral DNA. This is, again, the most remarkable for the carbocyclic analogues C-BVDUTP and C-IVDUTP, which have indeed been shown to be incorporated into DNA, in both cell culture[18] and cell-free systems[19]. However, BVDUTP and C-BVDUTP also act as inhibitors of the DNA polymerase reaction, and therefore, it must be sorted out to what extent the antiviral action of these molecules is due to a direct inhibitory effect on the viral DNA polymerase or secondary to their incorporation into viral DNA. For EDU, incorporation into viral DNA seems to be primordial for its antiviral action[20]: within the HSV-1-infected cell, it is preferentially incorporated into viral DNA, rather than cellular DNA; and this incorpo-

ration correlates closely with a reduction in viral DNA synthesis and virus progeny. The antiviral action of IVDU would also be subsequent to its incorporation, and concomitant fragmentation of viral DNA; whereas in the antiviral action of C-IVDU, which is incorporated into DNA only to a minor extent, a direct inhibitory effect on the viral DNA polymerase may play a relatively greater role (R. Bernaerts and E. De Clercq: unpublished data).

Reverse transcriptase

As it is a specifically viral gene product and closely associated with the virus replicative cycle, the retrovirus-associated reverse transcriptase (RNA-directed DNA polymerase) has been considered as an attractive target for putative anti-AIDS agents[21]. The most potent and selective inhibitors of the AIDS virus (HIV : human immunodeficiency virus) which have been reported so far, are the pyrimidine 2',3'-dideoxynucleosides 12 (AzddThd), 13 (ddCyd) and 14 (ddeCyd).[22-24] They are postulated to act as DNA chain terminators, but before they can do so they must be phosphorylated by cellular kinases to the corresponding 5'-triphosphates. The reason(s) for their selectivity remain to be established. These may be related to either a greater affinity of the 2',3'-dideoxynucleoside 5'-triphosphates for the reverse transcriptase than for the cellular DNA polymerase (α, β, γ) or a better accessibility of the reverse transcriptase, or both.

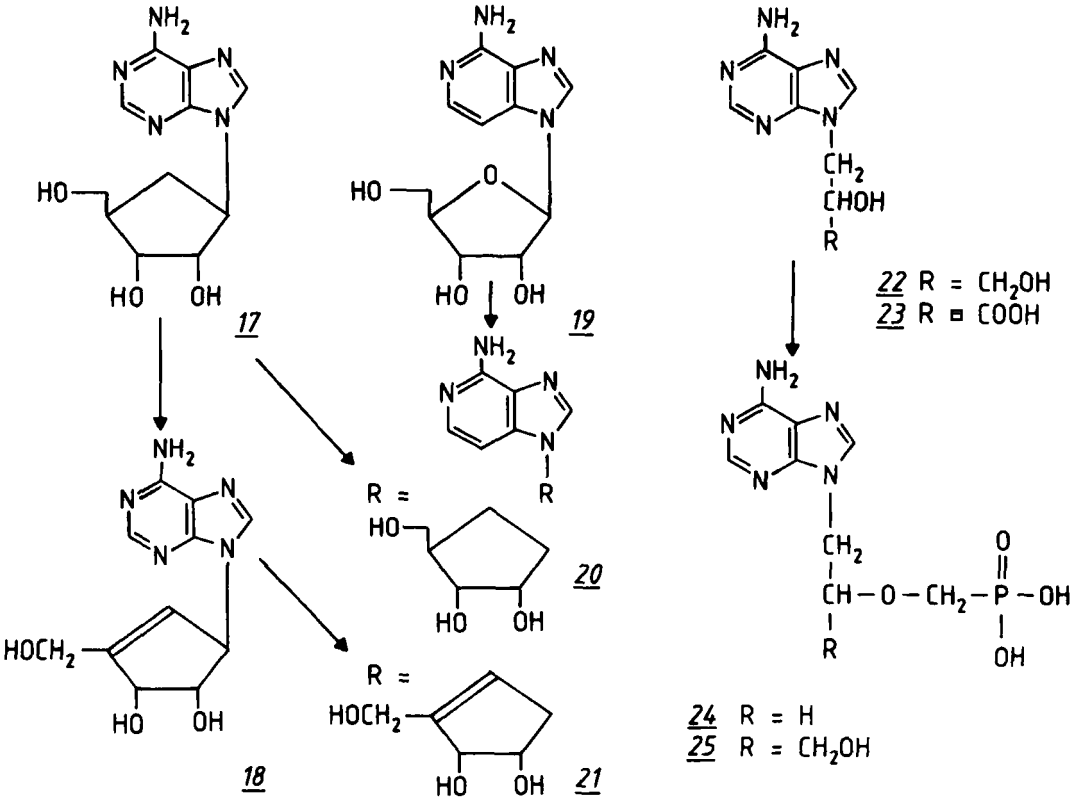
Cytidine 5'-triphosphate synthetase

The enzyme CTP synthetase that catalyzes the conversion of UTP to CTP has since long been recognized as a target for the antitumor action of 3-deazauridine[25]. More recently, the carbocyclic [cyclopentyl (15) and cyclopentenyl (16)] analogues of cytidine have also been assumed to interfere with CTP synthetase[26,27]. C-Cyd (15) and Ce-Cyd (16) are endowed with a unique antiviral activity spectrum, including DNA viruses [pox (vaccinia)], (-)RNA viruses [rhabdo (vesicular stomatitis), paramyxo (parainfluenza)], (+)RNA viruses [toga (Sindbis, Semliki forest)] and double-stranded RNA viruses (reo) (E. De Clercq: unpublished data). C-Cyd and Ce-Cyd also proved much more inhibitory to TK^-HSV than TK^+HSV strains[9].

The antiviral activity of C-Cyd and, in particular, Ce-Cyd is readily reversed by Cyd, but not dThd or dCyd, which seems compatible with an antiviral action targeted at CTP synthetase. Urd proved equally efficient as Cyd in reversing the antiviral effects of C-Cyd, although it was much less efficient than Cyd in reversing the antiviral effects of Ce-Cyd. This indicates that, while CTP synthetase may be the main target for the antiviral action of Ce-Cyd, C-Cyd may also interfere with other steps (i.e., OMP decarboxylase) in the de novo biosynthesis of pyrimidine nucleotides.

S-adenosylhomocysteine hydrolase

AdoHcy hydrolase, a key enzyme in AdoMet-dependent transmethylation reactions, has been identified as an important target in the broad-spectrum antiviral activity of both carbocyclic and acyclic adenosine analogues. Carbocyclic adenosine [aristeromycin, C-Ado (17)] is active against a broad spectrum of RNA and DNA viruses, but only at concentrations which are equal or close to those that are toxic for the host cells[28]. Upon



conversion of its cyclopentyl to a cyclopentenyl ring, C-Ado, now designated neplanocin A [Ce-Ado (18)], gains a marked increase in antiviral potency and specificity[29]. 3-deazaadenosine [c^3Ado (19)] akin to C-Ado is not very selective in its antiviral activity, but, upon conversion to its cyclopentyl derivative C-c^3Ado (20), it becomes both more potent and more selective as a broad-spectrum antiviral agent[30].

Independently from the carbocyclic adenosine analogues, acyclic adenosine analogues, i.e. (S)-DHPA (22) and 3-adenin-9-yl-2-hydroxypropanoic acid [(RS)-AHPA (23)] alkyl esters have been developed as broad-spectrum antiviral agents[3,31]; and all these compounds share a remarkably similar activity spectrum, in that they are specifically active against poxviruses (vaccinia), (-)RNA viruses [rhabdo (rabies, vesicular stomatitis), paramyxo (parainfluenza, measles)] and double-stranded RNA viruses [reo (rota)]. A close correlation has been found between the antiviral potency of 18, 20, 22 and 23 and their inhibitory effects (Ki/Km) on AdoHcy hydrolase[32], which point to the latter as the target enzyme for the antiviral activity of these compounds. If this correlation holds up for Ce-c^3Ado (21), also termed 3-deazaneplanocin[33], then Ce-c^3Ado should be the most active antiviral agent of the whole series, as it has been claimed to be more potent than any previously known compound in inhibiting AdoHcy hydrolase activity[33].

The selectively of AdoHcy hydrolase inhibitors as antiviral agents may reside in either quantitative or qualitative differences in methylation requirements between virus-infected and uninfected cells[34]. The ultimate target of these inhibitors would be the 5'-capping of viral mRNA. This corresponds to one of the targets ribavirin[35] is supposed to interact with[36]. The antiviral activity of AdoHcy hydrolase inhibitors is markedly enhanced in the presence of exogenously added L-homocysteine, probably because of a shift in the equilibrium AdoHcy $\rightleftarrows$ Ado + Hcy towards the formation of AdoHcy, and, hence, inhibition of the AdoMet-dependent methyltransferase reactions[34] (E. De Clercq: unpublished data).

To act as inhibitors of AdoHcy hydrolase adenosine analogues do not have to, and should not, be phosphorylated to their 5'-mono-, di- or triphosphate form. In fact, such phosphorylation may make them reactive at other targets. To distinguish those adenosine analogues that specifically act at AdoHcy hydrolase from those adenosine analogues that act at later stages in the biosynthesis of nucleic acid precursors, thus requiring

phosphorylation, i.e. by adenosine kinase (AK), a paired AK^+/AK^- cell system has been proposed[37]. Those adenosine analogues that require phosphorylation to exert their antimetabolic effects should be much less active in AK^- than in AK^+ cells, whereas those adenosine analogues that function at the AdoHcy hydrolase level should not be markedly affected by the absence of AK activity. This premise has been borne out[37].

Viral DNA synthesis, not via phosphorylation by viral dThd kinase

Starting from (S)-DHPA (22), phosphonate derivatives (24, 25) have been prepared which are endowed with an antiviral activity spectrum that is fundamentally different from that of the parent compound. Hence, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine [(S)-HPMPA (25)] is active against a broad variety of DNA viruses, including HSV, VZV (and TK^- mutants of both HSV and VZV), human cytomegalovirus (CMV), Epstein-Barr virus (EBV), SHV-1, BHV-1, equid herpesvirus type 1, phocid herpesvirus type 1 (seal herpesvirus), African swine fever virus, vaccinia virus and human adenoviruses[38]. (S)-HPMPA (25) is also inhibitory to retroviruses, i.e. Moloney murine sarcoma virus, and so is the closely related 9-(2-phosphonylmethoxyethyl)adenine [PMEA (24)]. However, other RNA viruses are not affected by these compounds.

There are some similarities in the activity spectrum of (S)-HPMPA and that of other phosphorylated or phosphonylated compounds which have recently been described, i.e. DHPG cyclic phosphate[39,40] and DHPG phosphonate[40,41]. It is postulated that (S)-HPMPA is as such taken up by the cells and phosphorylated intracellularly by host cell-encoded kinases to its diphosphoryl derivative. The target enzyme of (S)-HPMPA may well be the viral DNA polymerase. In HSV-1-infected cells, (S)-HPMPA inhibits viral DNA synthesis at a concentration which is by 3 to 4 orders of magnitude lower than the concentration required to inhibit cellular DNA synthesis (within infected or uninfected cells) (E. De Clercq, T. Sakuma and R. Bernaerts: unpublished data). Thus, the compound seems to be endowed with a remarkable specificity towards viral DNA synthesis.

Orotidylate decarboxylase, other targets and multiple targets

Among the antiviral agents, ribavirin and pyrazofurin have since long been known for their broad-spectrum activity, but only recently has ribavirin been pursued for (aerosol) treatment of respiratory tract virus

infection and (systemic) treatment of Lassa fever[42]. Pyrazofurin, which inhibits the replication of several viruses (vesicular stomatitis, measles, polio, Sindbis) at concentrations which are about 1000-fold lower than those at which ribavirin inhibits these viruses[43], has, nevertheless, received little, if any, attention as an antiviral agent. Pyrazofurin has been pursued primarily as an antitumor agent. Its main target of action is assumed to be OMP decarboxylase[44,45], and this enzyme has also been proposed as the target for 6-azauridine, another antimetabolite with broad-spectrum antiviral properties[46]. In addition, pyrazofurin may also act at AICAR formyltransferase[47] and thus interfere with the de novo biosynthesis of both purine and pyrimidine nucleotides. Both actions require a previous phosphorylation of the compound to its 5'-monophosphate by adenosine kinase.

The broader the activity spectrum, the greater the likelihood that multiple targets are involved. This is best illustrated by ribavirin, one of the antiviral agents with the broadest activity spectrum known. Its mechanism of action is clearly multipronged, involving (i) inhibition of IMP dehydrogenase, resulting in a depletion of the intracellular GTP pools, (ii) inhibition of 5'-cap formation of mRNA and (iii) inhibition of the initiation of transcription and elongation of viral mRNA[36,42].

Conclusion

The prime requirement for an antiviral drug is selectivity, and one may wonder therefore whether and how an action targeted at any of the enzymes listed in Table 1 may afford such selectivity. The viral dThd kinase, viral DNA polymerase and reverse transcriptase are specific virus-encoded products, and since these enzymes differ from their cellular counterparts in a number of aspects including substrate affinity, it does not seem too difficult to envisage how compounds that specifically interact with these enzymes, acquire selectivity towards virus replication.
Even an action targeted at AdoHcy hydrolase may be regarded as a virus-specific event, not because AdoHcy hydrolase is encoded by the virus genome but because it is functionally associated with specific virus-encoded methyltransferases. Other putative target enzymes, viz. dTMP synthetase, CTP synthetase and OMP decarboxylase are of purely cellular origin; and antiviral compounds interacting at these levels may acquire selectivity only commensurately with the quantitatively greater demands imposed

TABLE 1. Targets for antiviral activity of nucleoside analogues

Targets	Compounds
- Thymidylate synthetase	5-fluoro-dUrd (1), 5-trifluoromethyl-dUrd (2), 5-nitro-dUrd (3), 5-formyl-dUrd (4), 5-fluoro-dCyd (5)

- Viral DNA synthesis
  - incorporation into viral DNA
  - via phosphorylation by viral dThd kinase
	5-ethyl-dUrd (6), 5-(2-chloroethyl)-dUrd (7), (E)-5-(2-bromovinyl)-dUrd (8), (E)-5-(2-iodovinyl)-dUrd (9), and carbocyclic (cyclopentyl) analogues thereof (10, 11)

- Reverse transcriptase - DNA chain termination	3'-azido-2',3'-ddThd (12), 2',3'-ddCyd (13), 2',3'-didehydro-2',3'-ddCyd (14)
- Cytidine 5'-triphosphate synthetase	cyclopentyl and cyclopentenyl analogues of cytidine (15, 16)
- AdoHcy hydrolase - AdoMet-dependent methyltransferase	C-Ado (17), Ce-Ado (18), $_3c^3$Ado (19), C-c Ado (20), Ce-c^3Ado (21), (S)-DHPA (22), (RS)-AHPA (23)
- Viral DNA synthesis (viral DNA polymerase ?) - not via phosphorylation by viral dThd kinase	PMEA (24), (S)-HPMPA (25)
- Orotidylate decarboxylase	Pyrazofurin, 6-azauridine

by virus-infected cells on these enzymes. Only to the extent that the virus infection increases the cell's dependence on de novo biosynthetic pathways, selectivity may be expected from drugs interfering with the enzymes involved in these pathways.

Acknowledgments

I should like to acknowledge the outstanding contributions made by my co-workers, whose names appear as co-authors on the original articles cited in the references below. I should also like to thank Christiane Callebaut for her dedicated editorial help, and the Belgian F.G.W.O. (Fonds voor Geneeskundig Wetenschappelijk Onderzoek, project 3.0040.83) and the Belgian G.O.A. (Geconcerteerde Onderzoeksacties, project 85/90-79) for financial support of our investigations.

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