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Mini-Review

Novel nucleoside strategies for anti-HIV and anti-HSV therapy

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Summary

This mini-review describes the structure-activity relationships of several series of new nucleoside analogues. It also points to the possibilities of finding new molecular modifications which could lead to antivirals with activity both against human immunodeficiency viruses (HIV) and herpesviruses.

Nucleoside antiviral; Targeting antiviral; Herpes simplex virus; Human immunodeficiency virus

Introduction

Since the publication in 1986 on the 'in vitro' anti-human immunodeficiency viruses (HIV) activity of 3′-azido-3′-deoxythymidine (AZT) (Mitsuya et al., 1985), about 40 new nucleoside analogues were described with an anti-HIV activity that is high enough to consider these compounds 'worthwhile for further studies'. As could be expected, this initial overwhelming supply of new active compounds was followed by a decline during the last two years. In parallel with the discovery of new lead structures, considerable effort has been devoted in the research on combination chemotherapy (with the aim of obtaining synergistic antiviral effects and to overcome problems of drug resistance and toxicity) and in the research on prodrugs (to better the pharmacokinetic profile of a drug or with the purpose of drug targeting). Prodrugs are not considered here as new lead structures.

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Another major topic in antiviral research is the development of a broad spectrum antiviral agent. An important driving force for this development is based on the difficulties encountered in a fast and accurate diagnosis of a viral disease. This topic has become acute again during the last several years; e.g., AIDS patients are commonly infected with other viruses, among them herpesviruses. Although the specific role of these viruses in the pathogenesis of AIDS is not very well understood, it points to the importance of the availability of a broad spectrum antiviral. That this approach may be viable can be demonstrated by the many examples of nucleoside analogues with activity both against HIV and against herpes simplex virus (HSV). It is not surprising that compounds showing an activity against HIV could also be active against HSV. Activation by HSV viral kinase may not be needed when the nucleoside analogue is accepted as substrate for human kinases (which is a prerequisite for HIV activity). The triphosphate of these nucleoside analogues could then interact in a different way with reverse transcriptase and DNA polymerases. A broad spectrum of activity can also be obtained by interaction with cellular targets, although this approach is in principle less attractive.

Another important evolution is the discovery of more compounds with a non-nucleoside structure. This evolution is certainly important but the chance of finding a broad-spectrum antiviral agent in the non-nucleoside field is lower than in the nucleoside field.

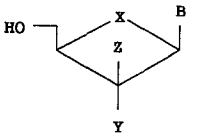
This article describes the structure–activity relationship of 8 classes of nucleoside analogues. These compounds are subdivided according to their chemical structure. The HSV-1 and HIV-1 activity of the compounds is discussed.

It is not the intention of the author to give a complete survey of the recent developments in antiviral chemotherapy. This mini-review is restricted to nucleoside analogues and not every potential nucleoside antiviral is included here. The aim of this article is merely to direct the attention of the reader to some new classes of antiviral nucleosides, which could be exploited for further drug design. In most cases, full particulars concerning the compounds discussed in this review may be obtained by consulting the original literature.

Structure–activity relationship

Nucleosides with a 4-membered ring structure

The lead compound in this series of nucleoside analogues, oxetanocin A (**1**), is a naturally occurring compound (Shimada et al., 1986). Its activity against HIV-1 is rather modest (Hoshino et al., 1987), and many analogues of this compound were synthesized during the past few years. An unexpected observation in this series of compounds is that noroxetanocin A (**2**) is inactive against HIV-1 (Wang et al., 1990), while epinoroxetanocin A (**3**) shows activity comparable to oxetanocin A (Nishiyama et al., 1990) itself. Also the significant antiviral activity of the azido analogue (**4**) (Wang et al., 1991) and the inactivity of the fluoro analogue (**5**) cannot be explained in a logical way.



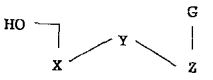
1	X = O	; Y = CH_2OH	; Z = H	; B = adenine
2	X = O	; Y = OH	; Z = H	; B = adenine
3	X = O	; Y = H	; Z = OH	; B = adenine
4	X = O	; Y = N_3	; Z = H	; B = adenine
5	X = O	; Y = F	; Z = H	; B = adenine
6	X = CH_2	; Y = CH_2OH	; Z = H	; B = adenine
7	X = CH_2	; Y = CH_2OH	; Z = H	; B = guanine
8	X = CH_2	; Y = H	; Z = H	; B = guanine
9	X = O	; Y = H	; Z = H	; B = adenine
10	X = CH_2	; Y = OH	; Z = H	; B = guanine

The most important progress, however, was made with the synthesis of the carbocyclic analogues. Compounds with a purine base moiety and especially those with an adenine (**6**) and guanine (**7**) base demonstrate significant anti-HIV activity (Norbeck et al., 1990). The adenine analogue gives 63% protection at 2.4 μg/ml (ATH 8 cells) while the guanine analogue gives 100% protection at 0.25 μg/ml (Norbeck et al., 1990). The activity is due to the isomer which corresponds best with the structure of the naturally occurring nucleoside: 2′-deoxyguanosine (Bisacchi et al., 1991). Both compounds (**6** and **7**), however, do show cytotoxicity. It is also worthwhile to mention that the carbocyclic analogue without a 2′-hydroxymethyl substituent (**8**) is able to protect ATH 8 cells against the cytopathic effect of HIV-1 (Maruyama et al., 1990). Also the oxetanocin A analogue lacking the 2′-hydroxymethyl substituent (**9**) demonstrates anti-HIV activity (Kitagawa et al., 1991). Although it is very difficult, if not impossible, to extrapolate in vitro data to an in vivo situation, it seems that the safety margin of most of these compounds is rather narrow.

The carbocyclic guanine analogue with the 2′-hydroxymethyl group substituted by an hydroxyl group (**10**) was reported independently by two groups as having antiviral activity against herpes simplex virus types 1 and 2, human cytomegalovirus and varicella zoster virus (Nishiyama et al., 1989; Jacobs et al., 1989). Nucleoside analogues with a cyclobutyl moiety are interesting lead structures for further drug design because of the broader spectrum of activity of some of their congeners. Besides its activity against HIV, Cyclobut-G (**7**) (Norbeck et al., 1990) is as potent as acyclovir against HSV-1 and HSV-2. It is more potent than acyclovir against VZV (varicella-zoster virus) and EBV (Epstein-Barr virus) and also shows excellent activity against HCMV (human cytomegalovirus).

Acyclic nucleoside analogues

Acyclovir (**11**), ganciclovir (**12**) and penciclovir (**13**), which has an activity spectrum similar to that of acyclovir, are the lead structures for the design of new acyclic nucleosides. The progress in this field is rather slow. Some more



11	$X=CH_2$	; Y = O	; $Z=CH_2$
12	$X=CH\text{-}CH_2OH$	; Y = O	; $Z=CH_2$
13	$X=CH\text{-}CH_2OH$	; $Y=CH_2$	; $Z=CH_2$
14	$X=CH_2$	; $Y=CH_2$	; Z = O
15	$X=CH\text{-}CH_2OH$	; $Y=CH_2$	; Z = O
16	X = CHOH	; $Y=CH_2$	; Z = O
17	$X=CH_2$	; $Y=CH\text{-}CH_2OH$	; Z = O

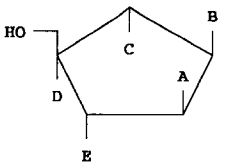
$HO\text{-}CH_2\text{-}CH{=}C{=}CH\text{-}B$

18	B = adenine
19	B = cytosine

rigid analogues with antiviral activity have been synthesized (Ashton et al., 1988; Phadtare and Zemlicka, 1989). Adenallene (**18**) and cytallene (**19**) are excellent inhibitors of HIV replication (Phadtare and Zemlicka, 1989), while 9[[(2)-2-(hydroxymethyl)cyclopropyl]methyl]guanine shows modest antiherpes activity (Ashton et al., 1988). The major progress comes from the SmithKline Beecham Laboratories. They discovered a series of acyclic nucleoside analogues with a 9-alkoxypurine structure (**14–17**) (Harnden et al., 1990; Bailey et al., 1991). The movement of the oxygen function from the 2′-position to the 1′-position changes the electronic configuration of the molecule. This N-O bond is stable to a wide variety of acidic and basic conditions and also against metabolic degradation. The most active compound in this series is the acyclovir analogue **14** which is more potent than acyclovir [IC_{50} 0.44 μg/ml (HSV-1), 0.15 μg/ml (HSV-2), 0.93 μg/ml (VZV)]. The ganciclovir analogue (**15**) (Harnden et al., 1990) shows an activity spectrum comparable to penciclovir [IC_{50} 1.4 μg/ml (HSV-1), 1.4 μg/ml (HSV-2), 2.6 μg/ml (VZV)]. Compound **17** (Bailey et al., 1991) is only active against VZV in tissue culture. All compounds lack activity against CMV.

Carbocyclic fluorinated nucleosides

Several arabinofuranosyl nucleosides with a 2′-fluoro atom and a pyrimidine base moiety show strong antiherpetic activity (Watanabe et al., 1979). Most of them, however, are too toxic for systemic use. Carbocyclic versions of antiviral nucleosides are mostly less toxic than the nucleoside itself. Moreover, some carbocyclic analogues of natural nucleosides do show antiherpetic activity on their own, i.e. carbocyclic 2′-deoxyguanosine (Bennett et al., 1990). These considerations encouraged chemists of the Glaxo group to synthesize the carbocyclic analogues of 2′-deoxy-2′-fluoro-β-D-arabinofuranosyl nucleosides. Surprisingly the analogues with a pyrimidine base moiety (**20,21**) show rather modest activity as antiherpes agents (Borthwick et al., 1990). The guanine analogue (**22**) (Borthwick et al., 1988), on the other hand, shows extremely high



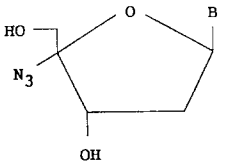
20	A = F	; C = D = H	; E = OH	; B = thymine
21	A = F	; C = D = H	; E = OH	; B = 5-iodouracil
22	A = F	; C = D = H	; E = OH	; B = guanine
23	A = F	; C = D = H	; E = OH	; B = adenine
24	A = H	; C = F ; D = H	; E = OH	; B = guanine
25	A = H	; C = F ; D = H	; E = OH	; B = 5-iodouracil
26	A = F	; C and D : C = C	; E = OH	; B = guanine
27	A and E : C = C		; C = D = H	; B = guanine
28	A = C = D = E = H			; B = guanine
29	A = D = E = H		; C = F	; B = guanine
30	A = F	; C = H	; D = E = OH	; B = guanine
31	A = F	; C = H ; D = F	; E = OH	; B = guanine

activity against both HSV-1 (ID_{50} 0.006 μg/ml) and HSV-2 (ID_{50}, 0.05 μg/ml) (Borthwick et al., 1991). In vivo, it is 100 times more active than acyclovir (Borthwick et al., 1991). Even more surprising is that the carbocyclic guanine analogue (**22**) is 1000 times more active than the ribonucleoside analogue: 2′-deoxy-2′-fluoro-araG (Borthwick et al., 1991). This compound (**22**), however, is not unique in the group of fluorinated carbocyclic nucleosides. 2′-Deoxy-2′-fluoro-ara-aristeromycin (**23**) (Biggadike et al., 1988) and the 6′-α-fluoro analogues of carbocyclic 2′-deoxyguanosine (**24**) (Borthwick et al., 1991) and carbocyclic 5-iodo-2′-deoxyuridine (**25**) (Biggadike et al., 1987) are also endowed with potent antiherpes virus activity. However, the activity of the latter (**25**) was not confirmed in a later publication (Borthwick et al., 1990). The 4′,6′-unsaturated compound bearing a 2′-fluoro substituent (**26**) is also equipotent to acyclovir (Biggadike et al., 1990).

This structure–activity relationship, however, cannot be extended to compounds with anti-HIV activity. In contrast with the unsaturated compound carbovir (Vince and Hua, 1990) (**27**), carbocyclic dideoxyguanosine (**28**) is not active against HIV (Vince and Hua, 1990), and the introduction of a fluorine atom in the 6′-α-position (**29**) does not benefit the anti-HIV activity (Coe et al., 1990). The SAR of carbocyclic nucleosides is clearly distinct from the SAR of furanose nucleosides.

4′-Substituted nucleoside analogues

Despite the occurrence of a 4′-substituted nucleoside in nature (nucleocidin), modifications at this position have seldom been studied. Recently two 4′-substituted carbocyclic nucleosides were synthesized which show high antiherpetic activity (Biggadike et al., 1990). The compound with a 4′-α-hydroxyl function (**30**) is 4 times more active than acyclovir against HSV-2 in vivo while the 4′-α-fluoro compound (**31**) is 30 times more effective than acyclovir in the same test system. These 4′-substituted nucleosides were



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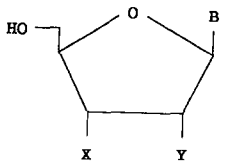
obtained from the 4′,5′-unsaturated analogues by addition reactions. This chemistry was previously developed by J.P.H. Verheyden and J.G. Moffatt on normal nucleosides (Verheyden et al., 1975). Recently, a patent from the same laboratory appeared describing the potent anti-HIV activity of 2′-deoxy-4′-azido nucleosides (**32**) (Maag et al., 1990). All compounds with natural bases (T,A,G,C,I,U), show high anti-HIV activity. The presence of a 3′-hydroxyl group is a prerequisite for anti-HIV activity. The potency of 4′-azidothymidine (**32**, B = thymine) is comparable to that of AZT. The potent activity of 4′-substituted nucleosides either against HIV or against HSV opens new perspectives for drug design.

Branched- chain nucleosides

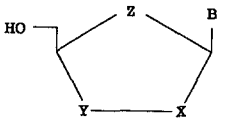
Branched-chain dideoxynucleoside analogues like **33–35** can be considered either as ring expanded oxentanocin (**1**) analogues or as analogues of dideoxynucleosides. Some molecular modelling work with these nucleoside analogues by Tseng and co-workers demonstrates acceptable fit between the structure of 3′-hydroxymethyl dideoxynucleosides and oxetanocin A. 3′-Hydroxymethyl-2′,3′-dideoxyadenosine indeed shows similar anti-HIV activity as oxetanocin A itself (Tseng et al., 1991). However, both compounds are not very potent, and neither of them was able to provide full protection against the cytopathic effect of HIV. The 2′-hydroxymethyl analogue **34** is not active. A more interesting compound, however, seems to be the cytosine analogue **35**, not only because of its higher activity against HIV-1 (Sterzycki et al., 1991; Svansson et al., 1991) but also because of its broader spectrum of activity (HIV, HSV-1, HSV-2, CMV, VZV, EBV). This compound (**35**) can be considered as a new lead for the construction of new and potent broad spectrum antivirals.

Replacement of carbon-atoms by hetero-atoms in the carbohydrate moiety

Two basic ideas have led to the synthesis of nucleoside analogues where carbon-atoms in the sugar ring are replaced by hetero-atoms: the high anti-HIV activity of dideoxynucleoside with a strong electron withdrawing group in the 3′-position (fluorine atom) and the continuing efforts of making nucleosides stable against rapid enzymatic and/or chemical degradation. In this perspective it seems logical to exchange the carbon atom in the 3′-position by an electron attacking hetero-atom. Such a substitution also gives no supplementary steric hindrance. This approach was followed with variable success, and the results can be explained, partially, by comparing the structure of these nucleoside



33	$X=CH_2OH$	; $Y=H$	; B = adenine
34	$X=H$	; $Y=CH_2OH$	; B = adenine
35	$X=CH_2OH$	; $Y=H$	; B = cytosine

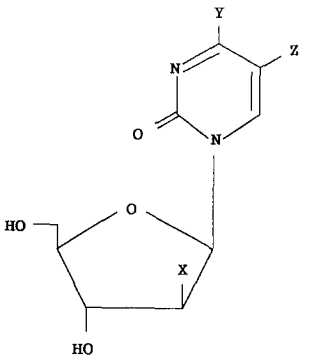


36	$X=CH_2$	; $Y=NH$	; $Z=CH_2$	
37	$X=O$	; $Y=CH_2$	; $Z=CH_2$	
38	$X=CH_2$	; $Y=O$	; $Z=CH_2$	; B = adenine
39	$X=CH_2$	; $Y=O$	; $Z=O$	; B = thymine
40	$X=CH_2$	; $Y=S$	; $Z=O$	; B = cytosine
41	$X=CH_2$	; $Y=S$	; $Z=CH_2$	

analogues with the structure of the normal dideoxynucleoside congener. No basic substituent should be present in the 3′-position (**36**) (Ng and Orgel, 1989). A 2′-substituted dideoxynucleoside analogue (**37**) (Bamford et al., 1991) gives compounds with a lower activity than a 3′-substituted analogue (**38**) (Huryn et al., 1989). The structure of dioxolane-T (**39**) (Norbeck et al., 1989) and 1,3-oxathiolane-C (**40**) (Soudeyns et al., 1991) is compatible with HIV-activity. Rather unexpected is the inactivity of the tetrahydrothiophene nucleoside **41** (Jones et al., 1991). The activity against herpesviruses of these nucleoside analogues have not yet been published.

5-Substituted pyrimidine nucleosides

Substitution of the 5-methyl group of thymidine by other groups has led to a multitude of compounds with either cytostatic or anti-viral properties, i.e., 5-fluoro-2′-deoxyuridine, 5-ethyl-2′-deoxyuridine, 5-iodo-2′-deoxyuridine. The most potent anti-HSV-1 agent among these 5-substituted-2′-deoxyuridine derivatives is 5-(E)-bromovinyl-2′-deoxyuridine (**42**) (De Clercq et al., 1979). The arabinofuranosyl analogues (**43**) shows comparable anti-HSV-1 activity (Machida et al., 1981) and superior anti-VZV activity (Busson et al., 1981; Machida et al., 1982). A structure–activity relationship study of 5-substituted 2′-deoxyuridine nucleosides revealed that for optimum anti-HSV-1 activity the 5-substituent should be unsaturated, conjugated with the pyrimidine ring, not larger than 4 carbon atoms in length, not branched and endowed with a hydrophobic, electronegative function (Goodchild et al., 1983). The same SAR can be found in a new class of pyrimidine nucleoside analogues substituted in

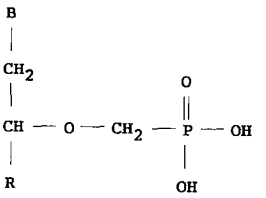


42	X = H	; Y = OH	; Z = CH = CHBr (E)
43	X = OH	; Y = OH	; Z = CH = CHBr (E)
44	X = H	; Y = OH	; Z = furan-2-yl
45	X = H	; Y = OH	; Z = thien-2-yl
46	X = OH	; Y = OH	; Z = thien-2-yl
47	X = H	; Y = NH_2	; Z-thien-2-yl
48	X = H	; Y = OH	; Z = 5-chlorothien-2-yl
49	X = H	; Y = OH	; Z-5-bromothien-2-yl

the 5-position with either a furane or thiophene ring (**44,45**) (Wigerinck et al., 1991). The compounds show a very similar spectrum of **42** (HSV-1, VZV). In addition, the anti-HSV-1 activity is retained either by modifying the carbohydrate part to an arabinofuranosyl moiety (**46**) or by changing the 5-substituted uracil into a 5-substituted cytosine base (**47**) (Wigerinck et al., 1991). Also in this series introduction of an halogeno substituent (chlorine **48**, bromine **49**), increases the antiviral activity (Wigerinck et al., 1991). In this context it should be remembered that the modification of the 5-position of dideoxynucleoside with a pyrimidine base moiety could also benefit the anti-HIV selectivity as was demonstrated by the synthesis of 5-chloro-3′-fluoro-2′,3′-dideoxyuridine (Van Aerschot et al., 1989).

Nucleoside phosphonates

An important step in the development of antivirals with a broad spectrum of activity is the discovery of acyclic nucleoside analogues bearing a phosphonate function (Holy et al., 1991). The phosphorous-carbon bond of phosphonates is stable against enzymatic hydrolysis. These compounds were designed to overcome problems of inefficient intracellular phosphorylation. The main advantages of these phosphonates can be summarized as follows: greater activity than normal nucleoside analogues against TK^- strains, greater activity in vivo than expected from the in vitro antiviral data, prolonged antiviral activity following administration of a single dose and a broad antiviral spectrum (HSV, CMV, EBV, HBV, HIV). Both, the activity against TK^- strains and the broad antiviral spectrum may be the result of the lack of dependence on phosphorylation by viral encoded thymidine kinase, leading to



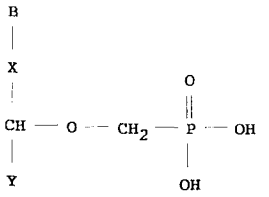
	R	B	EC_{50} (μM) HIV-1 (1)	HSV-1 (2)	HSV-2 (2)
50	CH_2OH	adenine (3)	>20	6.6	13
51	CH_2OH	guanine	>100	22	62
52	CH_2OH	diaminopurine	>40	31	62
53	H	adenine	5.9	26	26
54	H	guanine	2.7	15	26
55	H	diaminopurine	1.4	7.5	2.6

(1) assays carried out in MT-4 cells;
(2) assays carried out in PRK cells;
(3) data from the S enantiomer. Other compounds as racemic mixtures.

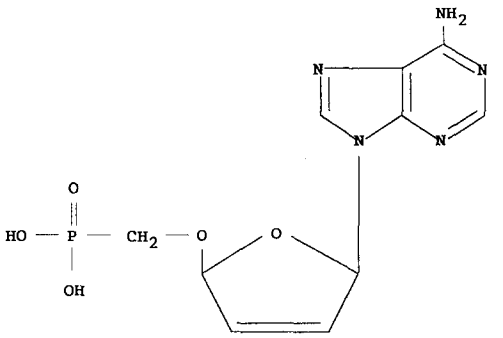
equal phosphorylation in both uninfected and virus-infected cells. The disadvantage of the acyclic nucleoside phosphonates are their generally low oral bioavailability. Based on SAR studies, the acyclic nucleoside phosphonates were first divided into two groups: those with an hydroxypropyl substituent (**50–52**) (HPMP series) showing good activity against HSV replication but poor activity against HIV, and those with an ethyl substituent (**53–55**) (PME series) showing activity against herpesviruses as well as against HIV. Some variations in the base part seem to be acceptable.

Comparing the structure of both series, the question arises if the hydroxyl function is responsible for the drop in activity against HIV-1 or if the whole hydroxymethyl group represents too much steric hindrance. A first answer to this question was provided by J. Bronson et al. who reported on the HIV-activity of the R isomer of the 2′-methyl analogue **56** (Bronson et al., 1990). It seems indeed that the presence of the hydroxyl group is responsible for the poor anti-HIV activity which could be explained by the necessity of the nucleoside analogue to function as chain terminator. These data were confirmed by the synthesis of the fluorinated analogues of **50**, (**57**), **51**, (**58**) and **52** (**59**) by A. Holy (Balzarini et al., 1991). These compounds, however, are no longer active against herpesviruses.

Recently a phosphonate isostere of acyclovir monophosphate (**60**) was synthesized (Kim et al., 1991b). This compound inhibits the replication of HSV-1 (2.6 μg/ml), HSV-2 (11 μg/ml) and HCMV (5.0 μg/ml). It demonstrates that the spacer between the phosphonate function and the base moiety can be modified without losing completely the antiviral activity. However, the presence of the β-oxygen atom, plays a critical role for antiherpes virus activity. The structural requirement seems not to be so stringent at that



56	$X = CH_2$	; $Y = CH_3$	; B = guanine
57	$X = CH_2$	; $Y = CH_2F$	; B = adenine
58	$X = CH_2$	; $Y = CH_2F$	; B = guanine
59	$X = CH_2$	; $Y = CH_2F$	; B = diaminopurine
60	$X = CH_2O$	; Y = H	; B = guanine
61	$X = OCH_2$	; Y = H	; B = guanine
62	$X = OCH_2$	; Y = H	; B = diaminopurine
63	$X = OCH_2$	; $Y = CH_2OH$	; B = guanine
64	$X = OCH_2$	; $Y = CH_2OH$	; B = diaminopurine.



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position as is also demonstrated by a series of compounds synthesized by the SmithKline Beecham group (Duckworth et al., 1990) (**61–64**). Here the N-CH_2 functionality is replaced by the N-O-CH_2 group. This series of compounds do not show the same SAR as Holy's series. In contrast with the latter, the hydroxypropyl derivatives retain retrovirus activity (visna virus) and demonstrate significant lower activity against herpesviruses than the ethyl series. Therefore, the questions can be asked if the different acyclic phosphonate nucleosides have the same mode of action and if their activity has to be explained by interference with viral or cellular processes.

All the previously mentioned compounds are acyclic nucleoside analogues. The replacement of the 5′-$(HO)_2P(O)OCH_2$-functionality of normal nucleoside analogues by a 5′-$(HO)_2P(O)CH_2CH_2$-group or a 5′-$(HO)_2P(O)CH_2OCH_2$-group has led to compounds with low activity. Only when the replacement is both isosteric and isoelectronic, has improved antiviral selectivity against HIV been demonstrated (Kim et al., 1991a). In this regard, the results with the D4A

analogue **65** are noteworthy. This biologically active isostere of D4A monophosphate is effective in animals both after peroral and after intraperitoneal applications (Yang et al., 1991).

Conclusions

Three types of broad spectrum antiviral agents are known: those which interact with cellular targets (i.e., SAH hydrolase), those with multiple interaction places (i.e., ribavirin), and those which interact more specifically with all kinds of polymerases after intracellular phosphorylation (i.e., DNA polymerase and reverse transcriptase). The many examples of new nucleoside analogues, described in this review, which show 'in vitro' antiviral activity against both herpesviruses and human immunodeficiency viruses, are a clear proof that the discovery of an antiviral agent with broad spectrum activity, belonging to the third group, could be a realistic objective for the future. As is mentioned in the Introduction, the chance of finding a broad-spectrum antiviral agent in the non-nucleoside field is lower than in the nucleoside field. Indeed, viruses are very diverse and non-nucleosides are expected to interact with very specific targets, hence a narrow spectrum could be expected from these compounds.

Although the mode of action of most of these compounds has not yet been proven, phosphonate analogues and nucleosides with a 4-membered 'carbohydrate' moiety appear to be the most promising candidates to attain this goal, i.e., activity against both DNA viruses and retroviruses.

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