1′-HOMONUCLEOSIDES WITH TWO AND THREE HETEROATOMS IN THE FIVE-MEMBERED RINGS – A REVIEW

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Abstract. *Synthetic strategies to 1′-homonucleosides with two and three heteroatoms in the 5-membered rings (e.g. isoxazolidines, 1,3-dioxolanes, 1,3-oxathiolanes and 1,2,3-triazoles) were summarized and evaluated. Where possible, their biological activity, mostly antiviral and antitumor but sometimes as inhibitors of specific enzymes, was presented and discussed to identify structural features responsible for the particular mode of action. The further progress in this area will depend on exploration of more complex structural scaffolds as sugar replacers and expansion the set of nucleobase mimetics.*

Contents

1. Introduction

Nucleoside/nucleotide analogues belong to an important class of antiviral and antitumor drugs and the interest in this area was stimulated by earlier discoveries of naturally occurring aristeromycin **1**,[1] neplanocin A **2**[2] and oxetanocin **3**[3] (Figure 1). Antiviral nucleoside analogues contain canonical nucleobases (substituted canonical nucleobases or their close structural analogues) as natural nucleosides **4**, but the furanose ring either has a different substitution pattern or it has been replaced by a different heterocyclic ring. A list of a ribofuranoside moiety replacements includes 2′,3′-dideoxyfuranose, cyclopentane, cyclopentene, 1,3-dioxolane, 1,3-oxathiolane rings and also acyclic systems to point out the most frequently observed.

Another common structural feature of natural nucleosides and their analogues is the presence of the hydroxymethyl group to allow sequential phosphorylation to active triphosphates. In cyclic sugar ring mimics this group is usually positioned cis to nucleobases to resemble the HO-C5′ functionality of the natural nucleosides. When sugar ring replacers in the analogues lack a HO-C3′ function, after incorporation of these compounds into oligonucleotides they may serve as chain terminators. Important structural modification of natural nucleosides relied on installation of the phosphonate function at C5′ to replace the hydrolytically labile P-O bond but still allowing further phosphorylation under cellular conditions.

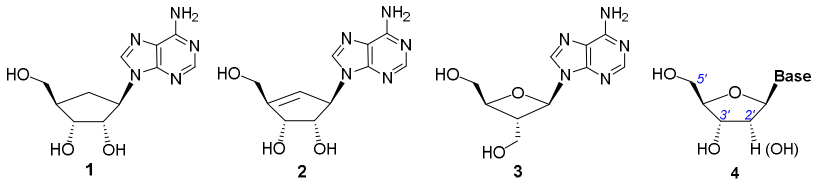


Figure 1. (–)-Aristeromycin **1**, (–)-neplanocin A **2** and (–)-oxetanocin **3** and a general structure of nucleoside **4** (B=canonical nucleobases).

A few decades of studies brought about several very active molecules within the class of modified nucleosides. Some of them have been approved as antiviral drugs, e.g. vidarabine,[4] brivudine,[5] telbivudine,[6] zidovudine,[7] didanosine,[8] carbovir,[9] entecavir,[10] amdoxovir,[11] lamivudine[12] and emtricitabine[13] which all contain cyclic sugar replacers as well as acyclovir,[14] ganciclovir[15] and penciclovir[16] bearing acyclic sugar mimics and acyclic nucleoside phosphonates-adefovir,[17] tenofovir,[18] (*S*)-HPMPA[19] and cidofovir.[20] Structures of amdoxovir **5**, lamivudine **6** and emtricitabine **7** (Figure 2) are of special interest since they contain 1,3-dioxolane and 1,3-oxathiolane rings.

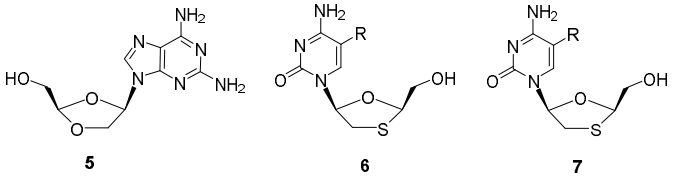


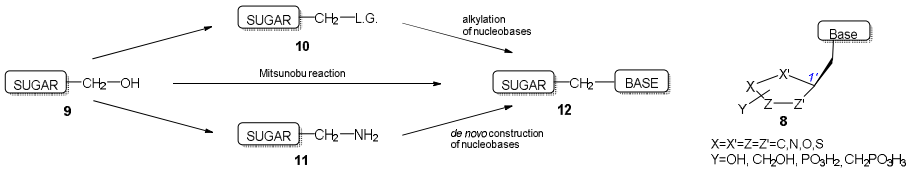
Figure 2. Amdoxovir **5**, lamivudine **6** and emtricitabine **7**.

Based on the these achievements interest in synthesis of homologues seems to be a justified extension of search for new active compounds and the 1′-homonucleoside framework formed by insertion of a methylene group between nucleobases and sugar or pseudosugar moieties looks very attractive. This new structural motive has potentially multifold influence on biological activity of homologues due to different structural and electronic features in comparison with natural nucleosides, e.g. lack of the anomeric effect, greater conformational flexibility, slightly improved lipophilicity and increased separation of HO-C5′ and nitrogen (N1 or N9) atoms of nucleobases.

Inspired by the clinical success of nucleoside analogues **5-7** which contain 1,3-dioxolane and 1,3-oxathiolane rings we wish to review accomplishments in syntheses and studies on biological activity of 1′-

homonucleosides of general formula **8**. A vast literature was limited to cover analogues characterized by the presence of five-membered rings bearing two or three heteroatoms (N, S, O) as pseudosugars and in addition these sugar mimetics have to be decorated with the hydroxyl, preferably hydroxymethyl groups to be able to undergo cellular phosphorylation. The respective phosphonates will also be discussed. The biological (antiviral, anticancer) activity of all new compounds will be emphasized to feature a therapeutic potential.

Since 1′-homonucleosides **12** lack the anomeric carbon their syntheses rely on the formation of a CH_2-Base bond via the Mitsunobu reaction[21] employing **9** or alkylation of **10**[22] with sodium or potassium salts of nucleobases (Scheme 1). These methods are supplemented by the de novo construction of pyrimidine[23-25] or purine[26-28] skeletons from the intermediate amine **11** according to the known methods. Thus, the synthetic approaches to the starting sugar/pseudosugars will be detailed to highlight the impact of the studies on 1′-homonucleosides on the synthetic organic chemistry in general.

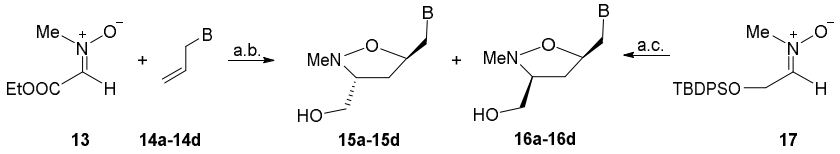


Scheme 1. Synthetic approaches to 1′-homonucleosides **12** and target 1′-homonucleosides/homonucleotides **8**.

2. Five-membered heterocycles containing two heteroatoms-1,2-isomers

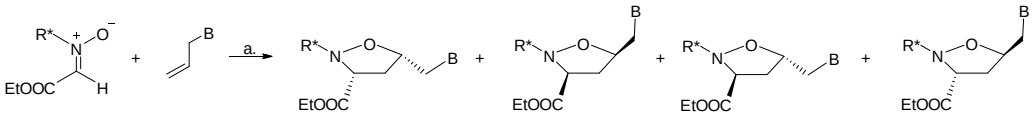
2.1. Isoxazolidine-based 1′-homonucleosides

To synthesize isoxazolidine 1′-homonucleosides containing the hydroxymethyl group at C3 1,3-dipolar cycloadditions of *N*-allyl nucleobases and appropriate nitrones seem to be the best approach. When *C*-ethoxycarbonyl-*N*-methylnitrone **13** was reacted with N^1-allylthymine **14a**, N^1-allyl-5-fluorouracil **14b**, N^4-acetyl-N^1-allylcytosine **14c** or N^9-allyladenine **14d** the 2:1 mixtures of the respective trans and cis diastereoisomeric isoxazolidines were obtained which after chromatographic separation and reduction provided homonucleosides **15a-15d** and **16a-16d** (Scheme 2).[29] However, from a nitrone **17** and allyl pyrimidine nucleobases **14a-14c** 7:1 mixtures of the respective trans and cis cycloadducts were produced giving homonucleosides **15a-15c** after chromatographic purification and deprotection. This was not the case for N^9-allyladenine **14d** since a 2:1 mixture of diastereoisomeric trans and cis cycloadducts was formed from the nitrone **17** allowing to isolate both products **15d** and **16d**.



Scheme 2. Synthesis of 1′-homonucleosides **15** and **16** (**a** B=thymin-1-yl; **b** B=5-fluorouracil-1-yl; **c** B=N^4-acetylcytosin-1-yl; **d** B=adenin-9-yl); reagents: a. 80°C; b. $LiAlH_4$; c. TBAF.

Enantiomerically pure isoxazolidine 1′-homonucleosides were synthesized from *N*-chiral nitrones **18** and **19** tagged with protected D-ribosyl and D-mannosyl residues, respectively.[30] The reaction of **18** with N^1-allylthymine **14a** was highly diastereoselective (a cis:trans ratio 86:14) while that with N^1-allyl-5-fluorouracil **14b** was almost diastereospecific (a cis:trans ratio 99.7:0.3) and led to the formation of the cycloadducts (3*S*,5*R*)-**21a** and (3*S*,5*R*)-**21b** as major products with high enantioselectivity (Scheme 3). Application of the nitrone **19** did not influence the cis:trans diastereoselectivity significantly (92:8 for N^1-allylthymine and 87:13 for N^1-allyl-5-fluorouracil) and major cis (3*R*,5*S*)-**24** and (3*S*,5*R*)-**25** isomers were formed in comparable amounts.[30]



18
19

14a
14b

(3*R*,5*S*)-**20a**
(3*R*,5*S*)-**20b**
(3*R*,5*S*)-**24a**
(3*R*,5*S*)-**24b**

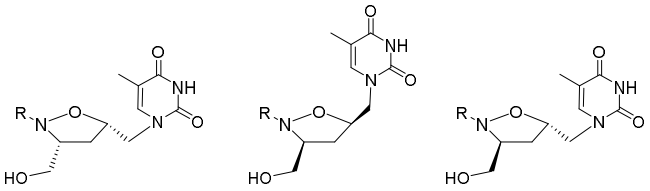
(3*S*,5*R*)-**21a**
(3*S*,5*R*)-**21b**
(3*S*,5*R*)-**25a**
(3*S*,5*R*)-**25b**

(3*S*,5*S*)-**22a**
(3*S*,5*S*)-**22b**
(3*S*,5*S*)-**26a**
(3*S*,5*S*)-**26b**

(3*R*,5*R*)-**23a**
(3*R*,5*R*)-**23b**

Scheme 3. Asymmetric synthesis of precursors to isoxazolidine 1′-homonucleosides **20**-**23** (R*=5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl) and **24**-**26** (R*=2,3;5,6-di-*O*-cyclohexylidene-α-D-mannofuranosyl); (**a** B=thymin-1-yl; **b** R=5-fluorouracil-1-yl); reagents: a. 80°C.

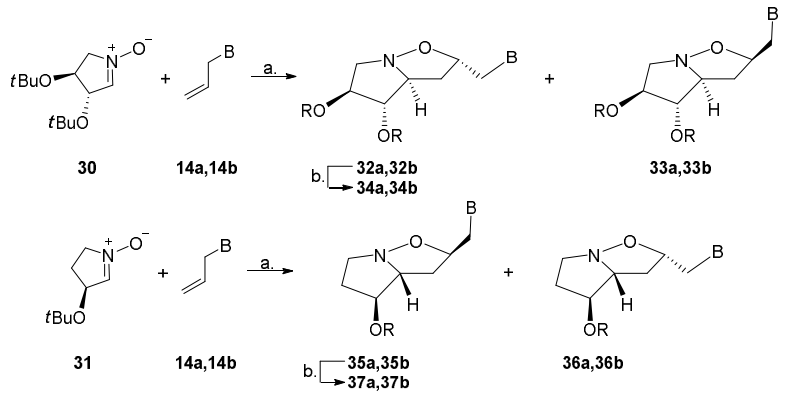
Selected isoxazolidine 1′-homonucleosides carrying hydroxymethyl groups **27**, **28** and **29** (Figure 3) were screened to establish their activity against a broad panel of viruses but all appeared inactive at concentrations up to 400 μM.[30]



27a,27b **28a,28b** **29**

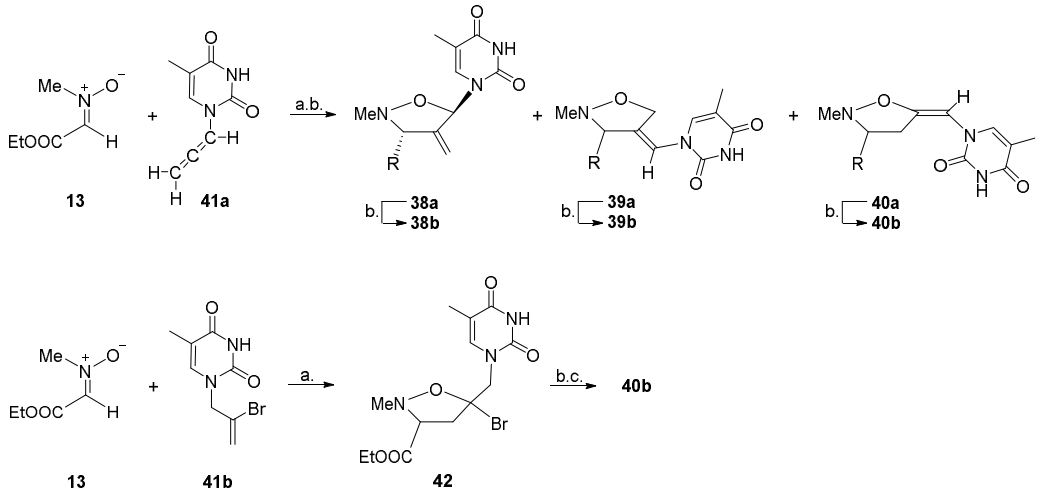
Figure 3. Isoxazolidine 1′-homonucleosides **27a** (R=H), **27b** (R=2,3;5,6-di-*O*-cyclohexylidene-α-D-mannofuranosyl), **28a** (R=H), **28b** (R=2,3;5,6-di-*O*-cyclohexylidene-α-D-mannofuranosyl) and **29** (R=2,3;5,6-di-*O*-cyclohexylidene-α-D-mannofuranosyl).

A pyrrolo[1,2-*b*]isoxazolidine scaffold as a replacer of a pentofuranose system in 1′-homonucleosides was constructed in a 1,3-dipolar cycloaddition of pyrrolidine nitrones **30** or **31** and N^1-allylthymine **14a** or N^1-allyl-5-fluorouracil **14b** (Scheme 4).[31] Thus, from the former nitrone bicyclic cycloadducts **32a** and **33a** as well as **32b** and **33b** were obtained in a 7:1 or 10:1 ratio, respectively. After separation major isomers were deprotected to give 1′-homonucleoside mimetics **34a** or **34b**. In a similar way from the latter nitrone compounds **35a** and **36a** as well as **35b** and **36b** were formed in ca. 4:1 ratios. Again, major isomers were deprotected to afford bicyclic 1′-homonucleosides **37a** or **37b**.



Scheme 4. Synthesis of 1′-homonucleosides **34a** (R=H, B=thymin-1-yl), **34b** (R=H, B=5-fluorouracil-1-yl), **37a** (R=H, B=thymin-1-yl), **37b** (R=H, B=5-fluorouracil-1-yl) and their precursors **32/33** (R=*t*-Bu, B=thymin-1-yl/5-fluorouracil-1-yl) and **35/36** (R=*t*-Bu, B=thymin-1-yl/5-fluorouracil-1-yl); reagents: a. 80°C; b. TFA.

When N^1-allenylthymine **41a** was reacted with *C*-ethoxycarbonyl-*N*-methylnitrone **13** a mixture of **38a** and **39a** and an exomethylene 1′-homonucleoside precursor **40a** containing a nucleobase positioned within a rigid framework was obtained in a 2.6:7:1 ratio, respectively (Scheme 5).[32]

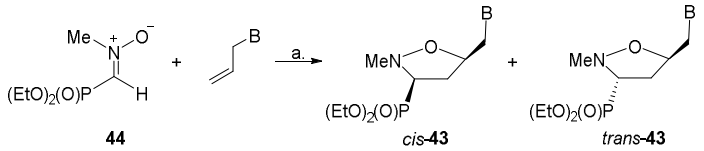


Scheme 5. Synthesis of exomethylene 1′-homonucleosides **40a** (R=COOEt), **40b** (R=CH_2OH) and related compounds **38a** (R=COOEt), **38b** (R=CH_2OH), **39a** (R=COOEt) and **39b** (R=CH_2OH); reagents: a. MW, 80 °C; b. $NaBH_4$; c. TEA.

A borohydride reduction provided nucleoside mimetics **38b**, **39b** and **40b**. However, the minor exomethylene 1′-homonucleoside **40b** could be obtained as a single isomer after cycloaddition of (2-bromo-

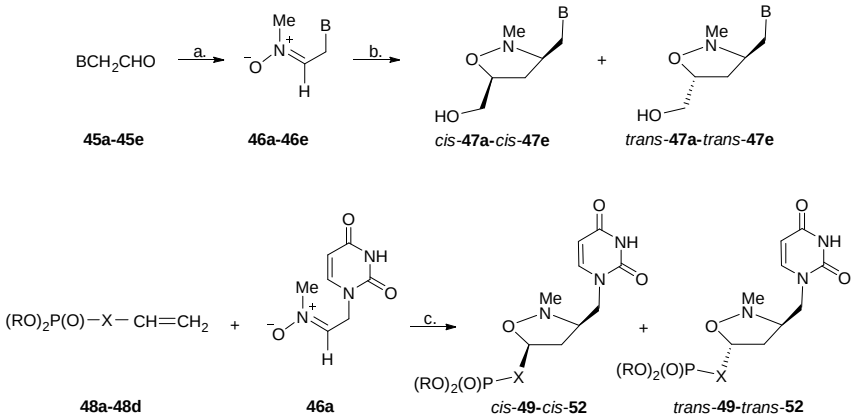
2-propen-1-yl)thymine **41b** and the nitrone **13** followed by a borohydride reduction and dehydrobromination of a mixture of diastereoisomeric cycloadducts **42**.[32]

A library of 1′-homonucleotide analogues *cis*- and *trans*-**43** having the isoxazolidine ring as a pentofuranose moiety replacer was synthesized from a phosphonylnitrone **44** and 19 structurally diversified allyl nucleobases or their mimetics (Scheme 6).[33] In all cases trans isomers were formed as major products but trans to cis diastereoselectivities (2-62%) were low to moderate. Unfortunately, compounds **43** appeared inactive against a broad panel of viruses at concentrations up to 250 μM. They were also not very efficient in inhibition of a tumor cell proliferation except for murine leukemia L1210 cell line with the IC_{50} values observed in the 33-100 μM range for 3-phosphonoisoxazolidines decorated with 3-acetylindol-1-yl, 5,6-dimethylbenzimidazol-1-yl and N-morpholinyl substituents.



Scheme 6. Synthesis of 1′-homonucleotides **43** (B listed in ref. 33); reagents: a. 60 °C.

As an alternative to the already discussed isoxazolidine 1′-homonucleosides in which the nitrogen atom replaces C4′ in the pentofuranose moiety the reversed arrangement of the oxygen and nitrogen atoms in isoxazolidine analogues of 1′-homonucleosides could be achieved when nucleobase-derived nitrones **46** would have been applied. It was readily accomplished starting from N^1-pyrimidine- or N^9-purine-acetaldehydes **45a**-**45e** (Scheme 7).[34]

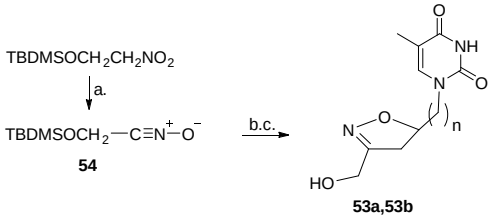


Scheme 7. Synthesis of isoxazolidine 1′-homonucleosides **47a** (B=uracil-1-yl), **47b** (B=5-fluorouracil-1-yl), **47c** (B=5-bromouracil-1-yl), **47d** (B=thymin-1-yl), **47e** (B=adenin-9-yl) and isoxazolidine 1′-homonucleotides **49** (R=Et, X=none), **50** (R=Et, X=CH_2), **51** (R=*i*-Pr, X=CH_2O) and **52** (R=Et, X=CH_2OCH_2); reagents: a. MeNHOH, Na_2CO_3, water; b. $H_2C{=}CHCH_2OH$, 60 °C; c. **48a** (R=Et, X=none) or **48b** (R=Et, X=CH_2) or **48c** (R=*i*-Pr, X=CH_2O) or **48d** (R=Et, X=CH_2OCH_2), MW, 65-80 °C.

1,3-Dipolar cycloadditions of nitrones **46a**-**46e** with allyl alcohol led to the formation of 1′-homonucleosides *cis*- and *trans*-**47a**-**47e**, with moderate to good (28-82%) diastereoselectivities. The nitrone **46a** was also subjected to cycloadditions with vinylphosphonates **48a**-**48d** providing isoxazolidine 1′-homonucleotide analogues *cis*- and *trans*-**49**-**52**, again with moderate to good (28-78%) diastereoselectivities.

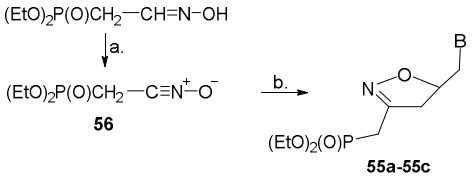
2.2. Isoxazoline-based 1′-homonucleosides

Synthesis of 1′-homonucleosides possessing less conformationally flexible isoxazoline ring **53a** was reached again by the 1,3-dipolar cycloaddition but employing a nitrile oxide **54** prepared in situ from the protected 2-nitroethanol and N^1-allylthymine **14a** (Scheme 8).[35] Neither 1′-homonucleoside **53a** (n=1) nor the nucleoside analogue **53b** (n=0) were found active against HIV-1.[35]



Scheme 8. Synthesis of 1,2-oxazoline-based 1′-homonucleoside **53a** (n=1); reagents: a. PhCNO, TEA; b. N^1-allylthymine; c. HF, CH_3CN.

1′-Homonucleotides containing a phosphonomethyl group attached to an isoxazoline ring **55** were constructed via 1,3-dipolar cycloaddition of a nitrile oxide **56** obtained from the oxime of diethyl phosphonoacetaldehyde and allyl nucleobases **14a**-**14c** (Scheme 9).[36]



Scheme 9. Synthesis of 1′-homonucleotides **55a** (B=thymin-1-yl), **55b** (B=5-fluorouracil-1-yl), **55c** (B=N^4-acetylcytosin-1-yl); reagents: a. NBS, TEA; b. N^1-allyl nucleobases: **14a** or **14b** or **14c**, 60 °C.

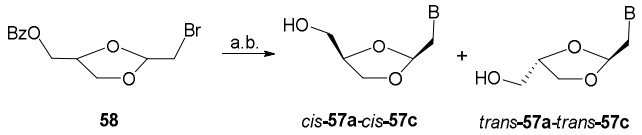
Compounds **55a** and **55b** were inactive (EC_{50}>400 μM) against HSV-1 and HSV-2 and did not show any appreciable cytotoxicity on VERO and MOLT-3 cells (CC_{20}>400 μM). Although **55a** inhibited reverse transcriptase (RT) of avian myeloblastosis retrovirus with EC_{100}=10 μM, AZT used as a reference compound was much more powerful (EC_{100}=10 nM).[36]

3. Five-membered heterocycles containing two heteroatoms-1,3-isomers

3.1. 1,3-Dioxolane-based 1′-homonucleosides

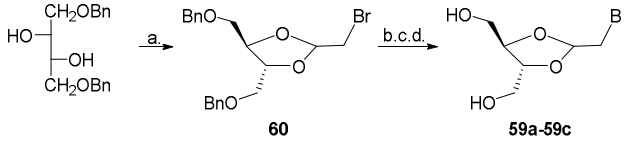
The 1,3-dioxolane ring may serve as a pentofuranose mimic in two ways since when its first oxygen atom is superimposed with the furanose one, the second oxygen atom can replace C2′ or C3′ and both versions have been explored.

Synthesis of 1′-homonucleosides **57a**-**57c** with the 1,3-dioxolane ring in which the oxygen atom replaces C2′ commenced with the preparation of a 3:2 mixture of *cis*- and *trans*-4-(benzoyloxymethyl)-2-(bromomethyl)-1,3-dioxolanes **58** from bromoacetaldehyde diethyl acetal and 1-*O*-benzoylglycerol (Scheme 10).[37] A mixture of dioxolanes **58** was reacted with sodium salts of uracil, thymine or adenine to give cis and trans mixtures of the protected 1′-homonucleosides which were separated chromatographically and later deprotected to give the analogues containing uracil *cis*- and *trans*-**57a**,[37] thymine *cis*- and *trans*-**57b**[38] and adenine *cis*- and *trans*-**57c**.[37] Monophosphates of *cis*- and *trans*-**57b** as well as triphosphate of *trans*-**57b** were also prepared.[38]



Scheme 10. Synthesis of 1,3-dioxolane 1′-homonucleosides **57a** (B=uracil-1-yl), **57b** (B=thymin-1-yl) and **57c** (B=adenin-9-yl); reagents: a. uracil or thymine or adenine, NaH; b. NH_3, MeOH.

1′-Homonucleosides containing the 2,4,5-trisubstituted 1,3-dioxolane ring **59** were synthesized from D-tartaric acid via 1,4-di-*O*-benzyl-D-threitol which was transformed into the acetal **60** when reacted with bromoacetaldehyde diethyl acetal (Scheme 11).[39] Alkylation of sodium salts of uracil and adenine with **60** followed by deprotection gave 1′-homonucleosides **59a** and **59b**. To get the respective 1′-homonucleoside having guanine **59c** the acetal **60** was reacted with N^2-palmitoylguanine in the presence of potassium carbonate. Neither compounds **59** proved active against HIV-1, HSV-1, HSV-2, HCMV and VZV at concentrations lower than 100 μM nor they were toxic in CEM and HFF host cells.

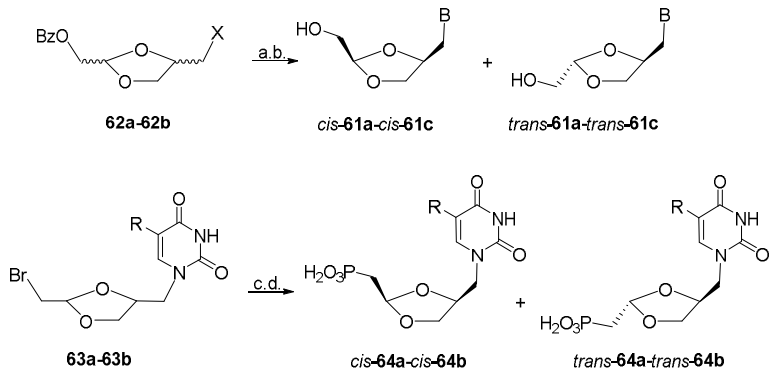


Scheme 11. Synthesis of 1,3-dioxolane 1′-homonucleosides **59a** (B=thymin-1-yl), **59b** (B=adenin-9-yl) and **59c** (B=guanin-9-yl); reagents: a. $BrCH_2CH(OEt)_2$, H^+; b. thymine or adenine, NaH or N^2-palmitoylguanine, K_2CO_3; c. $HCOONH_4$, Pd-C; d. NH_3, MeOH.

1′-Homonucleosides having a 1,3-dioxolane ring in which the second oxygen atom replaces C3′ can be easily obtained taking advantage of the cyclic acetal formation from a substituted diol and the appropriate aldehyde or acetal. From benzoyloxyacetaldehyde and 1-*O*-tosylglycerol an approximately equimolar mixture of *cis*- and *trans*-2,4-disubstituted 1,3-dioxolanes **62a** was produced and it was further transformed into 1′-homonucleosides *cis*- and *trans*-**61a** as well as *cis*- and *trans*-**61b** by alkylation of thymine and

adenine, respectively (Scheme 12).[40,41] In analogous manner a cis/trans mixture of 1′-homonucleosides containing cytosine **61c** was obtained from the bromide **62b** (Scheme 12).[42] Dioxolanes **61a-c** were inactive against HIV-1 in CEM cells and HSV-1, HSV-2, HCMV and VZV in HFF cells at concentrations lower than 100 μM nor they were toxic in CEM and HFF host cells as well.[43] On the other hand compound **61c** and its phosphate appeared weak inhibitors of α-2,3-sialyltransferase (5 and 16%) at concentration 100 μM.[44] Nevertheless, 1′-homonucleoside **61c**, its *O*-phenylphosphate as well as the respective *O*-phenyl-*N*-(methoxy-L-alaninyl)phosphate used as cis/trans mixtures were found to inhibit cytopathogenicity of HIV-1 in MT4 cells with IC_{50}=0.24-1.12 μg/ml, approximately 10 times less efficiently when compared to AZT.[42]

Phosphonate analogues of 1′-homonucleosides *cis*- and *trans*-**61** were synthesized when N^1-(2,3-dihydroxypropyl)uracil or thymine were first reacted with bromoacetaldehyde diethyl acetal and then the respective 2-bromomethyl-1,3-dioxolanes **63a** and **63b** were treated with triisopropyl phosphite followed by hydrolysis to give 1′-homonucleotide analogues *cis*- and *trans*-**64a** as well as *cis*- and *trans*-**64b** containing uracil or thymine, respectively (Scheme 12).[40,41]

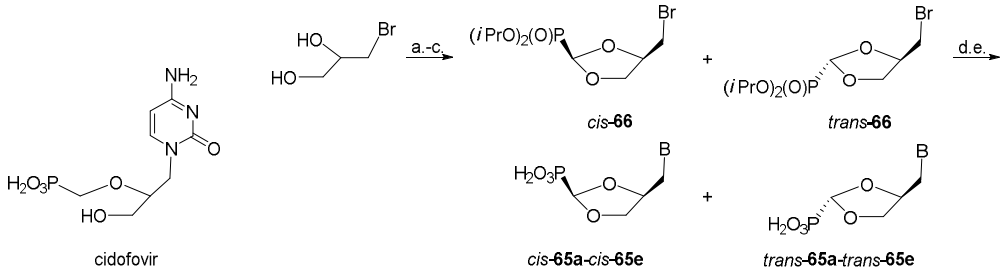


Scheme 12. Synthesis of 1,3-dioxolane 1′-homonucleosides **61a** (B=thymin-1-yl), **61b** (B=adenin-9-yl), **61c** (B=cytosin-1-yl) from precursors **62a** (X=OTs) and **62b** (X=Br) and phosphonates **64a** (R=H) and **64b** (R=Me); reagents: a. thymine or adenine, NaH or cytosine, K_2CO_3; b. NH_3, MeOH or NaOH, MeOH; c. (*i*-PrO)$_3$P; d. TMSBr.

Clinical usefulness of cidofovir prompted interest in studies on biological activity of its cyclic analogues e.g. **65** which could be viewed as 1,3-dioxolane 1′-homonucleotides. Their syntheses utilize racemic 3-bromo-1,2-propanediol or both (*R*) and (*S*) enantiomers to convert them first into cyclic ortoesters and then into a 2:5 mixture of *cis*- and *trans*-phosphonates **66** which could be separated (Scheme 13).[45] In a final step uracil, thymine, cytosine, adenine and guanine were introduced by nucleophilic substitution of the bromide.

Only racemic *cis*-**65e** was found active (IC_{50}=20 μg/mL) against HCMV, although its potency was 200 times lower than that of ganciclovir, while others appeared inactive (IC_{50}>100 μg/mL). All racemic phosphonates showed no cytotoxicity to F2002 cell lines (CD_{50}>100 μg/mL). When enantiomers of 1′-homonucleotide analogue **65e** were obtained it was discovered that the antiviral activity is attributed to (2*S*,4*R*)-**65e** (IC_{50}=45 μg/mL) while its mirror image (2*R*,4*S*)-**65e** was inactive (IC_{50}>100 μg/mL).

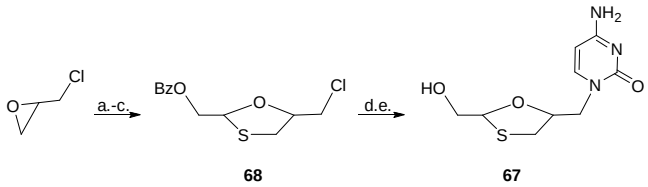
Furthermore, although (2*S*,4*S*)-**65e** exhibited noticeable anti-HCMV activity (IC_{50}>30 μg/mL) this compound was also cytotoxic (CD_{50}>30 μg/mL).[45]



Scheme 13. Synthesis of 1,3-dioxolane 1′-homonucleotide analogues **65a** (B=uracil-1-yl), **65b** (B=thymin-1-yl), **65c** (B=cytosin-1-yl), **65d** (B=adenin-9-yl) and **65e** (B=guanin-9-yl); reagents: a. $HC(OMe)_3$, H^+; b. *i*-PrOH, H^+; c $(i\text{-}PrO)_3P$, $ZnCl_2$; d. uracil or thymine, NaH or cytosine, Cs_2CO_3 or 6-chloropurine, Cs_2CO_3 or 2-amino-6-chloropurine, Cs_2CO_3; e. TMSI.

3.2. 1,3-Oxathiolane-based 1′-homonucleosides

Synthesis of the 1′-homonucleoside having the 1,3-oxathiolane ring **67** began with an epoxide ring opening in epichlorohydrin using thioacetic acid to give 1-chloro-3-mercaptopropan-2-ol which served as a precursor to the 2,5-disubstituted-1,3-oxathiolane **68** (Scheme 14).[42]



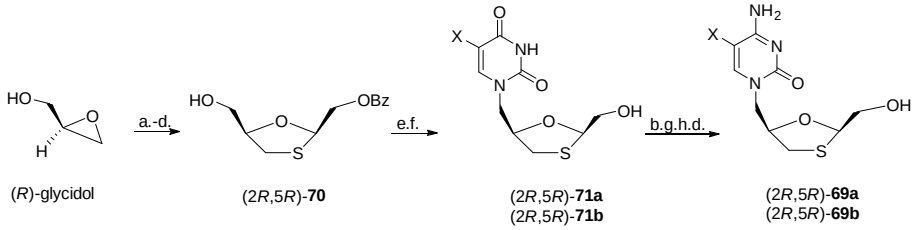
Scheme 14. Synthesis of the 1,3-oxathiolane-based 1′-homonucleoside **67**; reagents: a. $CH_3C(O)SH$; b. MeOH, HCl; c. $BzOCH_2CHO$, H^+; d. cytosine, K_2CO_3; e. NH_3, MeOH or NaOH, MeOH.

1′-Homonucleoside **67** containing the 1,3-oxathiolane ring, its *O*-phenylphosphate and the respective *O*-phenyl-*N*-(methoxy-L-alaninyl)phosphates proved to inhibit cytopathogenicity of HIV-1 in MT4 cells with IC_{50}=0.31-1.26 μg/ml but they were less effective than AZT and of almost equal potency when compared with counterparts having the 1,3-dioxolane rings.[42]

Syntheses of enantiomerically pure 1′-homolamivudine (2*R*,5*R*)-**69a** and 1′-homoemtricitabine (2*R*,5*R*)-**69b** were efficiently accomplished from (*R*)-glycidol and involved the oxirane ring opening with hydrogen sulphide and protection of the primary hydroxyl group (Scheme 15).[46]

The intermediate substituted 2-mercaptoethanol was condensed with benzoyloxyacetaldehyde to give a 5.7:1 mixture of 1,3-oxathiolanes (2*R*,5*R*)- and (2*S*,5*R*)-**70**. Uracil and 5-fluorouracil fragments were introduced into the major cis isomer (2*R*,5*R*)-**70** by the Mitsunobu reaction to provide 1′-homonucleosides

(2*R*,5*R*)-**71a** and (2*R*,5*R*)-**71b**, respectively, after deprotection. The uracil to cytosine conversion was achieved via formation of an 1,2,4-triazole derivative at C4 of the pyrimidine ring followed by ammonolysis.

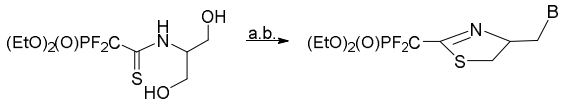


(*R*)-glycidol (2*R*,5*R*)-**70** (2*R*,5*R*)-**71a** (2*R*,5*R*)-**71b** (2*R*,5*R*)-**69a** (2*R*,5*R*)-**69b**

Scheme 15. Synthesis of 1′-homolamividine **69a** (X=H) and 1′-homoemtricitabine **69b** (X=F); reagents: a. H_2S; b. TBDPSCl; c. $BzOCH_2CHO$; d. TBAF; e. N^3-benzoyluracil or N^3-benzoyl-5-fluorouracil, PPh_3, DEAD; f. NH_3, MeOH; g. *p*-$ClC_6H_4OP(O)Cl_2$, 1,2,4-triazole, pyridine; h. NH_4OH.

3.3. 1,3-Thiazoline-based 1′-homonucleosides

1′-Homonucleotide analogues containing a thiazoline ring **72** were obtained employing the Mitsunobu protocol which executed both a thiazoline ring closure in the difluorophosphonate **73** and alkylation of N^3-benzoylthymine or 6-chloropurine to provide compounds **72a** or **72b**, respectively (Scheme 16).[47]



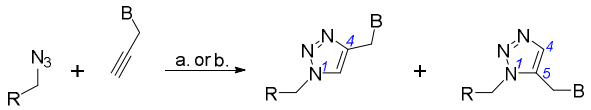
73 **72a,72b**

Scheme 16. Synthesis of 1′-homonucleotide analogues **72a** (B=thymin-1-yl) and **72b** (B=6-chloropurin-9-yl); reagents: a. N^3-benzoylthymine or 6-chloropurine, PPh_3, DEAD; b. NH_3, MeOH.

4. Five-membered heterocycles containing three heteroatoms

4.1. 1,2,3-Triazole-based 1′-homonucleosides

The 1,3-dipolar cycloaddition of organic azides **74** and alkynes is very easy to perform and this reaction has found numerous applications in the synthesis of 1′-homonucleoside analogues when N^1- or N^9-propargyl nucleobases **75** were employed (Scheme 17). Whether or not the 1,2,3-triazole ring may mimic the ribofuranose moieties, the interest in the field was tremendous and will be discussed in this chapter.



74 **75** **76** **77**

Scheme 17. A general approach to 1′-homonucleosides **76** and **77**; reagents: a. heating; b. Cu(I)-catalysts.

Early syntheses of 1,2,3-triazolonucleosides relied on thermal cycloadditions and they usually resulted in the formation of 1,4- and 1,5-cycloadducts, **76** and **77**, respectively, with 1,4-disubstituted products

predominating. A series of 1′-homonucleoside analogues **78a-h** containing the (2-hydroxyethoxy)methyl group characteristic of acyclovir was prepared[48] (Figure 4) but they appeared inactive against HIV-1 and HIV-2 at concentrations up to 100 μg/mL.[49] Cycloadditions of 3′-azido-3′-deoxythymidine (AZT) and *N*-propargyl nucleobases afforded a series of "double head" analogues **79** (Figure 4) but their antiviral activities were not disclosed so far.[50] The same idea justified the synthesis of a compound **80** from a theophylline-derived azide and N^1-propargyl thymine.[51]

Since the discovery catalytic properties of copper(I) salts the 1,3-dipolar cycloadditions of azides to alkynes were carried out in a regiospecific manner to efficiently provide 1,4-disubstituted isomers only ("click chemistry").[52] Under these conditions acyclovir-like compounds **78a**, **78b**, **78e**, **78g** and **78h** were synthesized by the click-approach in standard and MW-accelerated ways.[53]

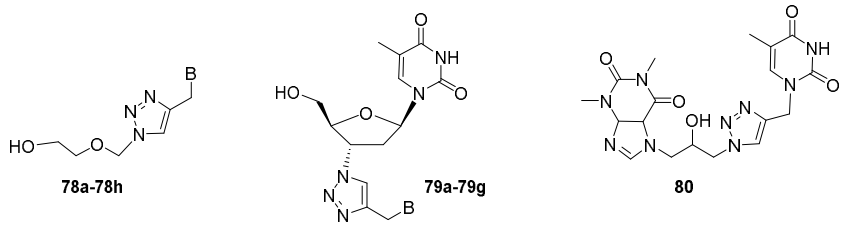


Figure 4. 1′-Homonucleoside analogues containing the (2-hydroxyethoxy)methyl group **78** (**a** B=thymin-1-yl; **b** B=uracil-1-yl; **c** B=5-chlorouracil-1-yl; **d** B=5-bromouracil-1-yl; **e** B=5-iodouracil-1-yl; **f** B=5-fluorouracil-1-yl; **g** B=adenin-9-yl; **h** B=N^2-acetylguanin-9-yl), "double head" 1′-homonucleoside analogues **79** (**a** B=thymin-1-yl; **b** B=uracil-1-yl; **c** B=adenin-9-yl; **d** B=5-chlorouracil-1-yl; **e** B=5-bromouracil-1-yl; **f** B=5-iodouracil-1-yl; **g** B=5-fluorouracil-1-yl) and **80**.

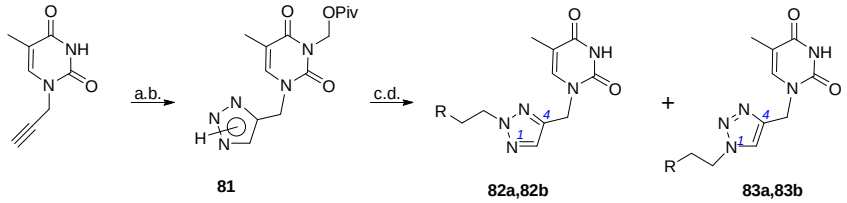
In a similar fashion 1′-homonucleoside analogues **76** (Scheme 17) containing hydroxyalkyl chains (R=$HOCH_2$,[54,55] $HOCH_2CH_2$,[54] $HOCH_2CH(OH)$[56,57] and $HOCH_2CH_2CH_2$[58]) were obtained. In the latter case compounds **76** (R=$HOCH_2CH_2CH_2$; B=uracil-1-yl, thymin-1-yl, 6-azauracil-1-yl and adenin-9-yl) were found inactive in inhibition of human rhinovirus (HRV) in HeLa cells and hepatitis C virus (HCV) in human hepatocarcinoma cells as well as they did not show noticeable antibacterial activity (MIC>64 μg/mL) for several Gram-positive and Gram-negative bacteria.[58]

To synthesize 2,4- and 4,5-disubstituted 1,2,3-triazoles more sophisticated approaches were employed. Thus, N^3-protected thymine 1,2,3-triazole **81** (Scheme18) was efficiently alkylated with a variety of reagents to produce mixtures of isomers including, among others, 1′-homonucleoside analogues which after separation and deprotection gave **82a** and **83a** (R=OH).[55] The alkylation site in **83a** was proven by identity with the product of the Cu(I)-catalyzed cycloaddition.[55]

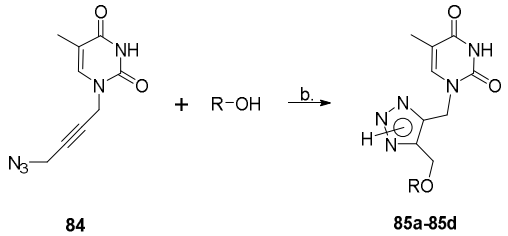
The 4,5-disubstituted 1,2,3-triazolo-1′-homonucleosides **85a-d** were easily obtained by the Banert cascade reaction starting from the azide **84** (Scheme 19). The general applicability of this protocol provided several derivatives containing the hydroxymethyl residue of interest in studies of antiviral activity though the relevant data has not been yet disclosed.[59]

A search for biologically active 1′-homonucleosides included also syntheses of compounds in which the 1,2,3-triazole ring can be regarded as a linker between furanoside or pyranoside fragments and

nucleobases (Figure 5). A series of compounds containing 2-deoxyribofuranoside moiety **86** was prepared in the Cu(I)-catalysed cycloaddition but they did not show any appreciable antiviral activity towards HCV and three selected flaviviruses (YFY, DENG, WNV).[60] Furthermore, the observed inhibition of viral replication was associated with cytotoxicity to the host cells.



Scheme 18. 1′-Homonucleos(t)ides **82** and **83** [**a** R=OH; **b** R=$CH_2P(O)(OEt)_2$] *via* alkylation of the 1,2,3-triazole **81**; reagents: a. $ClCH_2OPiv$, K_2CO_3; b. TMS-N_3; c. RCH_2CH_2Br, DBU; d. NH_4OH, MeOH.



Scheme 19. The Banert cascade reaction in the synthesis of 4,5-disubstituted 1,2,3-triazolo-1′-homonucleos(t)ides **85** [**a** R=H; **b** R=CH_2CH_2OH; **c** R=$CH_2CH(OH)CH_2OH$; **d** R=$CH(CH_2OH)_2$; **e** R=$CH_2P(O)(OEt)(OH)$]; reagents: a. deprotective steps.

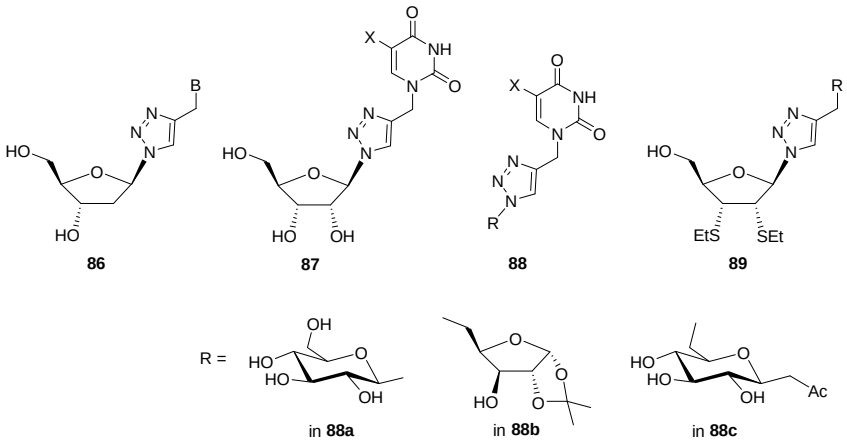


Figure 5. 1′-Homonucleoside analogues **86** (B see ref. 60), **87** (X=H, F, Cl, Br), **88** (X=H, Me) and **89** (R=cytosin-1-yl, thymin-1-yl, Ph, *p*-F–C_6H_4, *p*-MeO–C_6H_4).

After incorporation of the analogues **86** (B=uracil-1-yl, B=adenin-9-yl) into short-chain DNA oligomers it appeared that duplexes are less stable due to structural constrains in base pairing.[60]

Under "click" conditions 1′-homonucleoside analogues **87** were constructed from 1-azido-D-ribofuranose and 5-substituted N^1-propargyl pyrimidines to study the inhibition of Ribonuclease A.[61] It appeared that **87** (X=H) acted as a competitive inhibitor of RNase A (K_i=1.6 μM) significantly exceeding the potency of uridine (K_i=28.5 μM) thus proving the separation of nucleobase and sugar units has a crucial effect on the inhibitory efficacy. The introduction of the 1,2,3-triazole fragment into compounds **87** containing C5 substituted pyrimidines (X=Br, Cl, F) also resulted in increase of the inhibitory power in comparison to uridines substituted at C5 and thymidine.[61] Furthermore, the known[61,62] analogues **87** did not inhibit HCV replication.[62]

A large series of nucleoside analogues **88** containing uracil or thymine (Figure 5) was synthesized from N^1-propargyl pyrimidine nucleobases and the sugar azides under "click" conditions.[63] At 10 μM concentration they showed 3.3-47.4% inhibition of α-glucosidase with **88a** (X=H), **88b** (X=H) and **88c** (X=H) being the most active (47.4, 41.8 and 34.6%) as compared to the potency (53.4%) of acarbose, an anti-diabetic drug.[63]

Novel 1′-homonucleoside analogues **89** (R=cytosin-1-yl, thymin-1-yl) and compounds **89** (R=Ph, *p*-F-C_6H_4, *p*-MeO-C_6H_4) containing a ribofuranose ring functionalized at C2′ and C3′ with the ethanothio groups to introduce the fragment found in several compounds active as enzyme inhibitors were synthesized in the usual manner.[64] Surprisingly, the analogues having aromatic substituents were found moderately cytotoxic (EC_{50}=9.6-44.2 μM) in vitro against $HepG_2$, A549, LAC and HeLa cell lines, while those with thymine or cytosine moieties appeared inactive (EC_{50}>100 μM).[64]

4.2. 1,2,3-Triazole-based phosphonates of 1′-homonucleosides

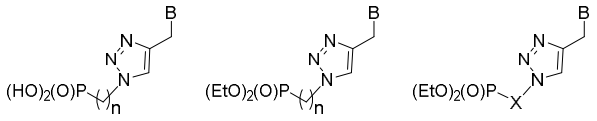
The general strategy to phosphonates flanked with 1′-homonucleoside 1,2,3-triazoles takes advantage of the 1,3-dipolar cycloaddition of the appropriate ω-azidoalkylphosphonates and N^1- or N^9-propargyl nucleobases or their close structural analogues (Scheme 17).

A short series of phosphonate nucleoside analogues **90a-f** was evaluated against HCV in Huh 5.2 cells to reveal at least four compounds worth of further interest.[65] Thus, both **90d** (B=uracil-1-yl, n=2) and **90e** (B=adenin-9-yl, n=1) inhibited HCV (IC_{50}=16 μM) while **90a** (B=thymin-1-yl, n=1) and **90b** (B=thymin-1-yl, n=2) were only slightly less active (IC_{50}=26 and 20 μM) and all of them were not cytotoxic (CC_{50}>300 μM). However, compounds **90** were inactive against HIV.[65] In other studies[55,66,67] which also included *O*,*O*-diethylphosphonates **91** and 1,3-tri- (n=3) and 1,4-tetramethylene (n=4) chains neither esters nor phosphonic acids bearing canonical nucleobases were found active against a broad panel of DNA and RNA viruses at concentrations up to 100 μM. They were also not cytotoxic (Vero, HEL, HeLa cells) as well as cytostatic (CEM cells) at concentrations up to 100 μM or 250 μM, respectively.

On the other hand, among 1′-homonucleotides containing the 1,2,3-triazole ring substituted at C4 with nine unnatural nucleobases or their mimetics several compounds with promising activity have been discovered.[67] Thus, activity against herpes simplex viruses (HSV-1, HSV-2) in HEL cells (EC_{50}=17 μM) and feline herpes virus in CRFK cells (EC_{50}=24 μM) was observed for the compound **91** (n=3; B=N^3-

benzoylbenzuracil-1-yl). Four other analogues **91** (n=1, 2, 3, 4; B=3-acetylindol-1-yl) significantly (IC_{50}=2.8-12 μM) inhibited proliferation of human T-lymphocyte CEM cells.[67]

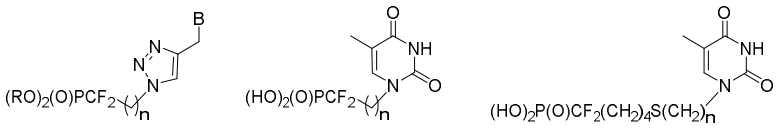
Installation of the hydroxyl group in the alkyl chain in analogues **92a-m** [X=$CH(OH)CH_2$,[66,67] $CH_2CH(OH)CH_2$,[56,66,67] $CH(OH)CH_2CH_2$[67]] (Figure 6) did not produce any compound endowed with antiviral and/or cytotoxic activity, although one could expect better binding through H-bonds.



90a-90f **91a-91m** **92a-92m**

Figure 6. Phosphonate nucleoside analogues **90** (B=uracil-1-yl, thymin-1-yl, adenin-9-yl; n=1, 2), **91** (B see ref. 67, n=1-4) and **92** [B see ref. 67, X=$CH(OH)CH_2$, $CH_2CH(OH)CH_2$, $CH(OH)CH_2CH_2$].

Powerful thymidine phosphorylase (TPase) inhibitors were identified among 1′-homonucleotide analogues **93** (Figure 7) having a difluorophosphonate moiety to better mimic acidity of natural phosphates.[68,69] For the most active compound **93** (R=H; n=4; B=thymin-1-yl) 90% inhibition of TPase was observed at 1 mM concentration and 68% at 100 μM. These data compare favourably with those found for 6-amino-5-bromouracil (100% and 77%, respectively), a reference TPase inhibitor. It is worth mentioning the linear 1′-homonucleotide analogues **94** and **95** (Figure 7) are also capable of inhibiting TPase although less efficiently.[69] In search for SAR it appeared that the distance between phosphorus and nitrogen atoms has a major impact on inhibition but it is not a decisive factor.



93 **94** **95**

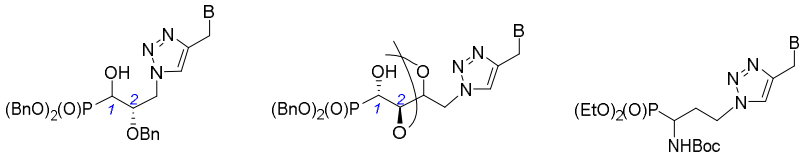
Figure 7. Phosphonate nucleoside analogues **93** (R=H, *i*-Pr; n=1, 3, 4; B=uracil-1-yl, thymin-1-yl, 6-chloropurin-9-yl, hypoxanthin-9-yl, 2-amino-6-chloropurin-9-yl, guanin-9-yl), **94** (n=8, 9, 11) and **95** (n=3, 4, 6).

Two series of 1′-homonucleotide analogues **96a-l** and **97a-g** (Figure 8) were efficiently synthesized under microwave irradiation from the respective ω-azidoalkylphosphonates and the selected N^1- or N^9-propargyl natural nucleobases (uracil, thymine, N^4-acetylcytosine, adenine) or their structural analogues and some of them exhibited promising antiviral activity.[70]

Thus, (1*S*,2*S*)-**96** (B=N^3-benzoyluracil) was found active against vesicular stomatitis virus (EC_{50}=9 μM) and respiratory syncytial virus (EC_{50}=12 μM) in HeLa cells, while (1*R*,2*S*)-**96** (B=N^3-benzoylbenzuracil) showed potency against both herpes simplex viruses (HSV-1, HSV-2) in HEL cell cultures (EC_{50}=2.9 and 4 μM, respectively) and feline herpes virus in CRFK cells (EC_{50}=4 μM).

Furthermore, in preliminary assays of cytostatic activity on murine leukemia (L1210), human T-lymphocyte (CEM) and human cervix carcinoma (HeLa) cells (1*S*,2*S*)- and (1*R*,2*S*)-**96** (B=N^3-benzoylbenzuracil) were the most potent (EC_{50}=4-7 μM, respectively).

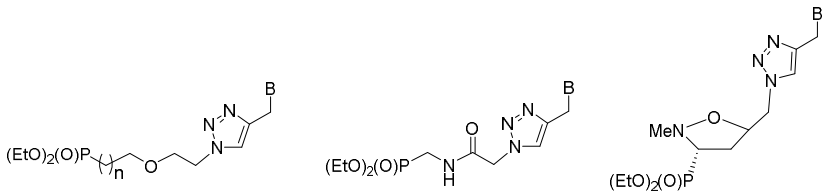
Among 1′-homonucleotide analogues (*R*)- and (*S*)-**98a-h** equipped with the 1-(*N*-Boc-amino)phosphonate residue (Figure 8) only (*R*)-**98** (B=3-acetylindol-1-yl) revealed moderate (EC_{50}=45 μM) activity against vesicular stomatitis virus in HeLa cells.[71] On the other hand, significant cytotoxicity to CRFK cells (CC_{50}=2.9 μM) was observed for (*S*)-**98** (B=adenine).[71]



(1*S*,2*S*)-**96a-96l** (1*R*,2*S*)-**96a-96l** (1*S*,2*R*,3*S*)-**97a-97g** (1*S*,2*R*,3*R*)-**97a-97g** (*R*)-**98a–h** (*S*)-**98a–h**

Figure 8. Phosphonate nucleoside analogues **96** (B see ref. 70), **97** (B see ref. 70) and **98** (B see ref. 71).

Another modification of the phosphonoalkyl chain in 1′-homonucleotide analogues **99a-l** and **100a-l** (Figure 9) resulted in identification of the compound **99** (B=3-acetylindol-1-yl) which inhibited the proliferation of human T-lymphocyte cells (IC_{50}=64 μM).[72]



99a-99l n=0 **100a-100l** n=1 **101a-101h** **102a-102d**

Figure 9. Phosphonate nucleoside analogues **99** (B see ref. 72), **100** (B see ref. 72), **101** (B=adenin-9-yl, thymin-1-yl, uracil-1-yl, N^4-acetylcytosin-1-yl, N^3-benzoylbenzuracil-1-yl, N^3-benzoyluracil-1-yl, 5,6-dimethylbenzimidazol-1-yl, 3-acetylindol-1-yl) and **102** (B=uracil-1-yl, thymin-1-yl, N^4-acetylcytosin-1-yl, adenin-9-yl).

An acyclic fragment of nucleoside analogues was modified by introducing a carbamoyl moiety and the 1,2,3-triazole ring was constructed in the usual manner to provide compounds **101a-h** prepared from N^1- or N^9-propargyl natural nucleobases as well as their *N*-propargyl mimetics (Figure 9).[73] In this series of analogues a moderate activity against the vesicular stomatitis virus (EC_{50}=45 μM) in HeLa cell cultures was noticed for the compound **101** (B=N^3-benzoylbenzuracil-1-yl).[73]

The click chemistry was also applied to the construction of 1,2,3-triazolyl-1′-homonucleotide analogues *trans*-**102a-d** and *cis*-**102a-d** containing the additional isoxazolidine ring (Figure 9) but they were

found inactive against a broad panel of RNA and DNA viruses at concentration as high as 250 mM as well as they were not cytotoxic.[74]

5. Conclusions

Since 2002 when chemistry of 1′-homonucleosides was reviewed,[75] the interest in this class of compounds has significantly increased. In the covered area syntheses of structural frameworks as a furanose moiety replacers have been based on well-established methods, e.g. isoxazolidines from nitrones and alkenes and thus the variety of 5-membered heterocyclic rings is so far rather limited. In early studies nucleoside analogues bearing mostly canonical nucleobases were explored. Later on the molecular diversity of 1′-homonucleosides was ensured by extending the set of nucleobases for their close structural analogues and on nonpolar nucleobase isosters.[76] A few active compounds were discovered including anti HIV-1 **61c** and **67** as well as potent inhibitors of α-glucosidase and thymidine phosphorylase, **88a**-**88c** and **93**, respectively. There are a wealth of options to make further progress in this area by designing structures containing less common heterocycles as pseudosugars and further exploration of new nucleobase mimetics.

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