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Novel 1'-homo-*N*-2'-deoxy- α -nucleosides: synthesis, characterization and biological activity†

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For the first time, a series of novel 1'-homo-*N*-2'-deoxy- α -nucleosides containing natural nucleobases as well as 5-fluoro and 5-iodopyrimidine analogs have been synthesized in an efficient manner. Additionally, a high yield protocol for the assembly of a dimeric scaffold containing two sugar moieties linked to the *N*-1 and *N*-3 positions of a single pyrimidine base has been accomplished. The structures of the novel homonucleosides were established by a single crystal X-ray structure of 1'-homo-*N*-2'-deoxy- α -adenosine and NMR studies. The biological activity of these 1'-homo-*N*-2'-deoxy- α -nucleosides as antiviral (HIV-1 and HBV) and cytotoxic studies was measured in multiple cell systems. The unique structure and easy accessibility of these compounds may allow their use in the design of new nucleoside analogs with potential biological activity and as a scaffold for combinatorial chemistry.

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1. Introduction

Nucleosides are building-blocks of nucleic acids, where these molecules play a key role in the genetic process of all living organisms. Natural nucleosides offer a unique framework for the design of novel therapeutic drugs due to their central function in biological processes. As a result, over thirty chemically modified nucleosides and their analogs are on the market for the treatment of cancer and viral infections.¹ Undoubtedly nucleoside scaffolds have been an excellent starting point for introducing chemical modifications leading to the discovery of biologically functional molecules. In nature, nucleosides appear mainly as β -anomers and rarely as the α -anomers. More recently the syntheses of α -anomeric nucleosides have attracted wide attention due to their unique properties and potential applications.² Additionally, the position of the glycosidic bond could be altered by inserting another carbon atom to create 1'-homo-*N*-nucleoside structures. This structural motif imparts several unique features such as the absence of an anomeric effect, enzymatic and chemical stability of the glycosidic bond, conformational flexibility, extra lipophilicity and increased distance between the 5'-hydroxyl group and the base.³ In our ongoing quest for the design and synthesis of novel nucleoside

analog, we embarked on the synthesis of less common modification 1'-homo-*N*-2'-deoxy- α -nucleosides where two features are incorporated in a single molecule. To the best of our knowledge, this is the first report on the synthesis of 1'-homo-*N*-2'-deoxy- α -nucleosides containing all four natural bases in an efficient manner. Additionally, herein we describe the synthesis of a bifunctional scaffold where two sugar units were linked to a single pyrimidine base.

Considering the importance of nucleoside analogs as bioactive motif, we reasoned that new methods for the synthesis of 1'-homo-*N*-2'-deoxy- α -nucleosides are warranted. Hitherto, two major methods were used to prepare 1'-homo-*N*-nucleosides: (i) introduction of the nucleobase by nucleophilic displacement of a leaving group at *C*-1' exocyclic methyl group of the pentofuranose ring; and (ii) *de novo* construction of the nucleobase by condensation reactions from methylamino derivatives at *C*-1'.⁴

Following these routes, 1'-homo-*N*-bicyclic carbonucleosides **1** (Fig. 1),⁵ 1'-homo-*N*-bicyclico-[2.2.1]heptane nucleosides **2**,⁶ emissive 1'-homo-*N*-nucleosides **3**,⁷ and 1'-homo-*N*-locked nucleoside **4**⁸ were synthesized. Also, α -nucleosides analogs such as arabinonucleosides **5** or 2'-deoxy- α -nucleosides **6** are easily formed due to reduced steric hindrance compared with β -ribonucleosides.^{2,9} Additionally, α -nucleosides are used to prepare α -oligonucleotides which leads to more stable duplexes.¹⁰

Related with the research described in this manuscript, β -ribo¹¹ and α -ribo¹² 1'-homo-*N*-nucleosides (**7** and **8**, respectively) have been prepared with variable success due to the use of multistep process and undesired side reactions. Whereas, fewer examples are available related to the synthesis of 1'-homo-*N*-2'-deoxynucleosides. For example, β -deoxy derivatives (**9**) were

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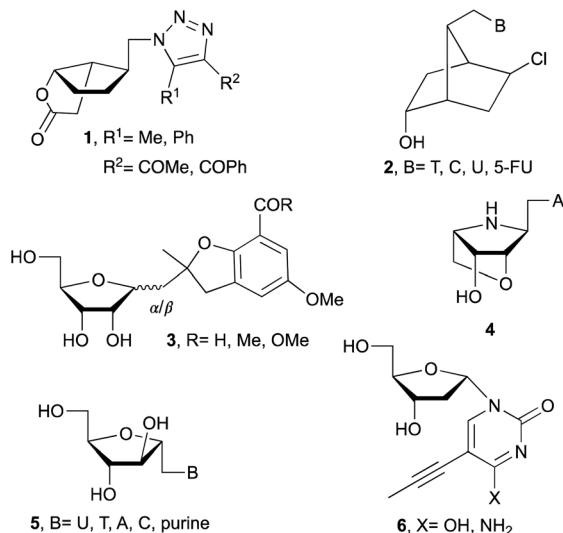


Fig. 1 Structures of 1'-homo-*N*-nucleosides and/or α -nucleosides.

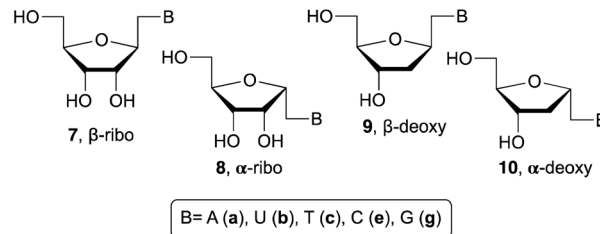


Fig. 2 Structures of α/β -ribo and α/β -2'-deoxy 1'-homo-*N*-nucleosides.

described by Saladino and Crucianelli,^{13a} Doboszewski,^{13b,c} and Herdewijn.^{13d} In relation to the closest work described here, that is, the synthesis of α -deoxy 1'-homo-*N*-2'-nucleosides only Beaucage and co-workers¹⁴ have reported the synthesis with one nucleobase, thymine (10c).

Our pursuit for the design of novel nucleosides and the development of their synthesis protocols,^{8,15} here we wish to report the synthesis of 1'-homo-*N*-2'-deoxy- α -nucleosides 10 with both purine and pyrimidine nucleobases. Installation of bioactive 5-fluoro and 5-iodo uracil derivatives is also demonstrated to access new structures and test their biological activities. Eight modified nucleosides reported herein were tested for their biological activity as antiviral against HIV-1 and HBV. Their cytotoxicity assay is also included in this study.

2. Results and discussion

Synthesis of 1'-homo-*N*-2'-deoxy- α -nucleosides

Beaucage and coworkers reported on the synthesis of 1'-homo- α -thymidine where pyrimidine ring was constructed *via* an acyclic analog.¹⁴ This approach is not practical for the synthesis of multiple analogs containing both natural and unnatural nucleobases. Therefore, we wish to develop a new synthetic route which permits the synthesis of any 1'-homo- α -nucleoside analog from a single precursor such as sugar derivative 11. To prepare the 1'-homo-*N*-2'-deoxy- α -nucleoside derivatives 10, we envisioned a synthetic approach wherein the nucleobase was introduced by nucleophilic displacement of a leaving group in sugar precursor 11, readily obtained from the α -cyano sugar derivative 12 (Fig. 2 and 3).¹⁶

Therefore, nitrile 12 was converted into the corresponding methyl ester by treatment with potassium hydroxide in MeOH/H₂O. Under these conditions, removal of the toluoyl protecting groups is also observed, affording compound 13 in 75% isolated yield after chromatography (Scheme 1). One-pot deprotection of toluoyl groups, hydrolysis of nitrile and *in situ* esterification

demonstrates a highly efficient protocol compared to the literature report for the corresponding β -anomer.^{16b}

Protection of the hydroxyl groups with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole gave silyl ether derivative 14. The reduction of ester 14 with lithium aluminum hydride in THF at -45 °C afforded after 30 min alcohol 15 in 90% yield. It is noteworthy that higher reaction temperatures during reduction leads to deprotection of the silyl groups and low temperature is critical to the successful outcome. Transformation of the alcohol into the mesylate 16 was achieved in excellent yield with methanesulfonyl chloride and catalytic DMAP in pyridine.

With mesylate 16 in hand, the stage was set for rapid synthesis of α -homonucleosides 10. Next, we opted for the base mediated displacement reaction using K₂CO₃ and 18-crown-6 in DMF. To our delight, the coupling of unprotected adenine base with mesylate 16 under these conditions at 90 °C furnished 1'-homo-*N*-2'-deoxy- α -adenosine (17a) in 84% yield after column chromatography purification. With the guanine base, the reaction of mesylate 16 under similar conditions furnished a complex mixture of products.

Under identical reaction conditions, uracil, a pyrimidine base when coupled with mesylate 16 furnished a mixture of two products. The expected 1'-homo-*N*-2'-deoxy- α -uridine (17b) was isolated in 45% yield. The second product was characterized as a dimer 18b, in which the uracil is linked with two deoxyribose moieties at the *N*-1 and *N*-3 positions of the base. The structure of dimer 18b was supported by spectral data.

Interestingly, the coupling of thymine base with mesylate 16 furnished two products where desired homonucleoside 17c was isolated in 12% yield and dimer 18c in 55% yield (Scheme 1). Similarly, the coupling of 5-fluorouracil base with mesylate 16 resulted in the formation of dimer 18d in 73% yield as a major

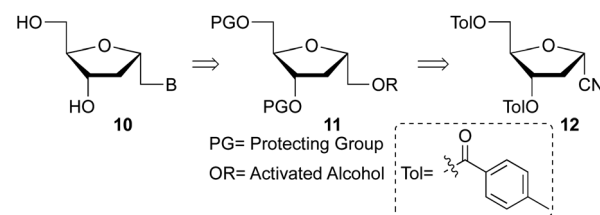
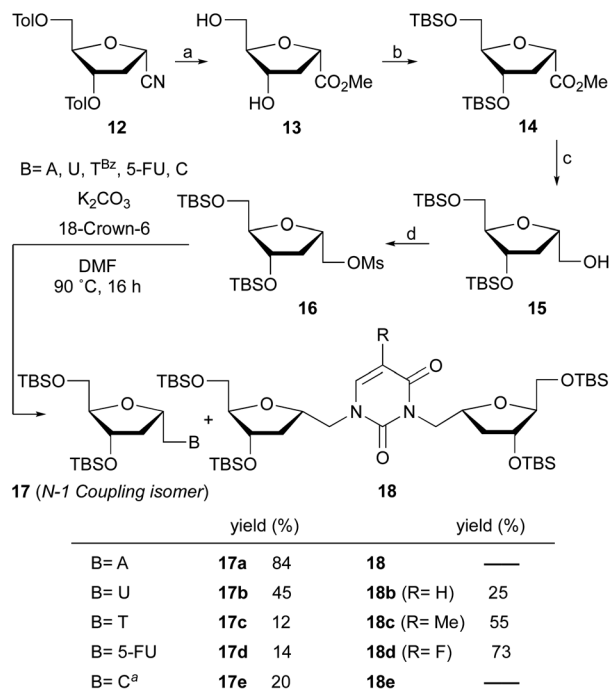


Fig. 3 Retrosynthetic analysis to 1'-homo-*N*-2'-deoxy- α -nucleosides.





Scheme 1 Reaction conditions: (a) KOH, MeOH/H₂O, rt, 3 h (75%); (b) TBSCl, imidazole, CH₂Cl₂, 50 °C, 5 h (85%); (c) LiAlH₄, THF, -45 °C, 30 min (90%); (d) MsCl, DMAP, Py, 0 °C to rt, 24 h (95%).

product along with **17d** in 14% yield. This observation is unprecedented where a dimer is obtained as a major product and offers a new synthetic pathway to the assembly of unique nucleoside scaffolds.

The synthesis of 1'-homo-*N*-2'-deoxy- α -cytidine was also complicated due to the formation of two products. Reaction of **16** with cytosine gave a mixture of *N*-1 (compound **17e**) and *N*-3 (see Fig. 4b) coupled nucleosides. The structure of these products was established by homonuclear (COSY) and heteronuclear (HSQC, HMBC) correlations. In the ¹³C-¹H HMBC experiment for **17e**, a correlation cross-peak was observed between the H6 proton of the base and the methylene carbon at 6'-position. However, in the *N*-3 derivative this cross-peak does not exist.

In an attempt to improve the yield of the desired pyrimidine coupled products, other strategies were tested. Glycosylation under Vorbrüggen's conditions¹⁷ required acetate **19** (Scheme 2), which was easily prepared from **15** by treatment with acetic anhydride, Et₃N, and DMAP in CH₂Cl₂. Reaction of **19** with silylated bases such as uracil or 5-fluorouracil or 5-iodouracil in the presence of trimethylsilyl triflate failed to provide the coupled product, while deprotection of the TBS groups was observed.

The Mitsunobu reaction is an important technique in nucleoside synthesis for the direct coupling of alcohols with bases under mild conditions. Thus, treatment of **15** with uracil, Ph₃P and DIAD generated 1'-homo-*N*-2'-deoxy- α -uridine (**17b**), but with only 15% yield. The low yield is due, in part, to the difficulty of isolating the product during chromatography, since several byproducts are obtained post Mitsunobu reaction.

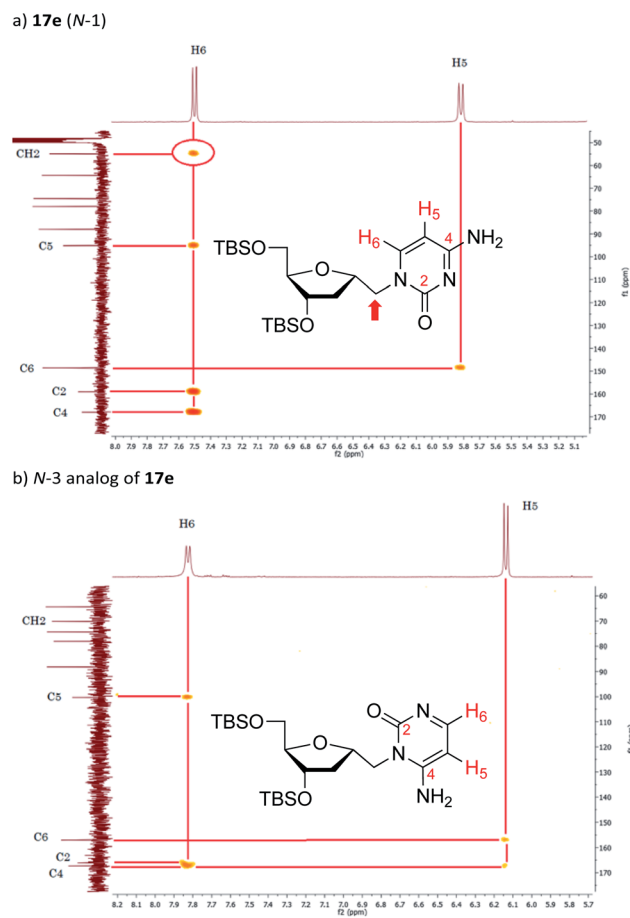
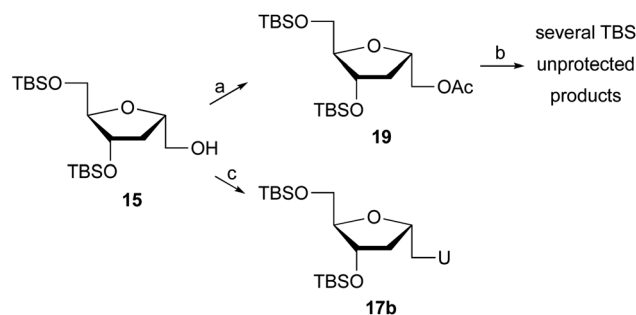


Fig. 4 HMBC spectra enlargements of: (a) **17e** and (b) its *N*-3 analog.

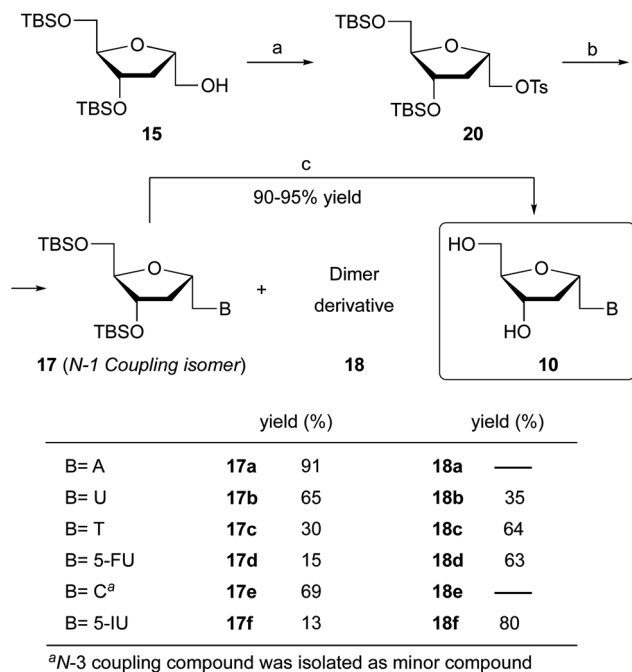
Since alternative coupling protocol failed to improve the outcome of the reaction and the formation of desired product, we revisited the first protocol offering a viable option. This time, we replaced the mesylate with tosylate hoping that we might observe better coupling efficiency and overall yield.

The synthesis of tosylate **20** (Scheme 3) was straightforward by the reaction of alcohol **15** with *p*-toluenesulfonyl chloride (TsCl) and catalytic DMAP in pyridine. Next, we performed the coupling reaction of **20** with the corresponding nucleobase in



Scheme 2 Reaction conditions: (a) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt, 2 h (90%); (b) (i) Base (U, 5-FU, 5-IU), BSA, MeCN, 80 °C, 1 h, (ii) TMSOTf, 0 °C to 80 °C; (c) Ph₃P, DIAD, uracil, THF, -10 °C to 25 °C, 24 h (15%).





Scheme 3 Reaction conditions: (a) TsCl, DMAP, Py, 0 °C to rt, 9 h (90%); (b) B = A, U, T^{Bz}, 5-FU, C, 5-IU, K₂CO₃, 18-crown-6, DMF, 90 °C, 7–8 h; (c) TBAF, THF, 25 °C, 2 h (90–95%).

the presence of K₂CO₃ and 18-crown-6. The reaction of **20** with adenine proceeds with excellent yield, giving rise to α -homonucleoside **17a** with a 91% isolated yield, slightly higher than when the reaction was carried out with mesylated **16**. Significant improvement was observed when **20** reacted with uracil or cytosine, isolating 1'-homo-*N*-2'-deoxy- α -uridine (**17b**) and 1'-homo-*N*-2'-deoxy- α -cytidine (**17e**) with 65% and 69% yield, respectively, *versus* 45% and 20% yield obtained from the mesylate derivative. However, the coupling of the tosylated derivative **20** with thymine led exclusively to the dimer **18c**. To the best of our knowledge, this is first report of dimer **18c** synthesis in high yield. Next, in order to control the regioselectivity of the coupling with thymine, the *N*-3-position of the base was protected. The reaction was carried out according to the procedure described by Ludek and Meier.¹⁸ For that, thymine was allowed to react with benzoyl chloride in acetonitrile-pyridine to give *N*³-benzoylthymine. Reaction of **20** and *N*³-benzoylthymine under the reaction conditions indicated above afforded 1'-homo-*N*-2'-deoxy- α -thymidine (**17c**) in 30% yield, although the major product of the reaction was still the dimer **18c**, probably due to the *in situ* deprotection of the base during the coupling. Nevertheless, the formation of the desired product **17c** has been considerably improved when *N*³ protected thymine was utilized.

The coupling of **20** and 5-fluorouracil or 5-iodouracil was performed next. The major product was the dimer derivative but the *N*-1 coupled analog was also formed in 15% and 13% yield, respectively. In both cases, the *N*-3 protection of the base did not improve the yield of the *N*-1 substituted product. Multiple

products were observed when **20** was coupled with the guanine base.

Finally, the treatment of compounds **17a–f** with tetrabutylammonium fluoride (TBAF) in THF afforded the 1'-homo-*N*-2'-deoxy- α -nucleosides **10a–f** in 90–95% yield. The structure of all derivatives was established by NMR homonuclear (COSY) and heteronuclear (HSQC, HMBC) correlations. Unambiguous confirmation of the structure of the synthesized compounds was obtained by a single crystal X-ray analysis of **10a** (Fig. 5).

Single crystal X-ray data for compound **10a** is given in Table 1. Homo-*N*-2'-deoxynucleoside analog **10a** crystallized as colourless small crystals. Fig. 5 is a Chimera drawing,¹⁹ which corresponds to asymmetric unit X-ray diffraction studies of compound **10a**.²⁰ Note that the sugar conformation is North type with the 2'-*exo* and 3'-*endo* configurations. The structure shows three molecules per asymmetric unit linked by H-bonds, that is, six molecules per crystal.

The formation of various dimers **18** is synthetically important because it offers an access to the assembly of bifunctional 2'-deoxynucleoside analogs. Literature search for reports on similar structures has been limited to two examples. First report by Prystas and Sorm²¹ describing the formation of *N*¹,*N*³-diribofuranosyl derivative as a byproduct during ribosylation of 6-methyl-4-methoxy-2(1*H*)-pyrimidinone with a ribofuranosyl chloride derivative. In the second example, Zhang and co-workers²² reported the isolation of a similar derivative in the synthesis of isonucleosides. In order to further investigate the importance of this bifunctional nucleoside, we have evaluated the biological activity of dimeric compounds **21** (Scheme 4). For that, desilylation of **18d** and **18f** with TBAF in THF furnished the desired derivatives **21d** and **21f** in 80% and 75% yield, respectively.

Biological evaluation

Antiviral assays against HIV-1.²³ A set of eight compounds **10a–f** and **21d,f** were tested against HIV-1 (strain LAI) and compared to 3'-azido-3'-deoxythymidine (AZT, zidovudine) as a control in an assay with human peripheral blood mononuclear (PBM) cells. Positive control AZT exhibited expected anti-HIV-1 activity, with EC₅₀ of 0.006 μ M. There was no anti-HIV activity observed from the six homonucleosides **10a–f** and the two dimeric compounds **21d,f** tested, all with an EC₅₀ > 10 μ M.

Antiviral assays against HBV.^{23c,24} As expected, the control Lamivudine demonstrates desired antiviral response, with an

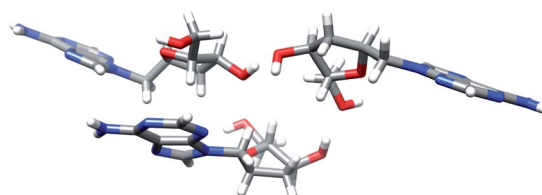
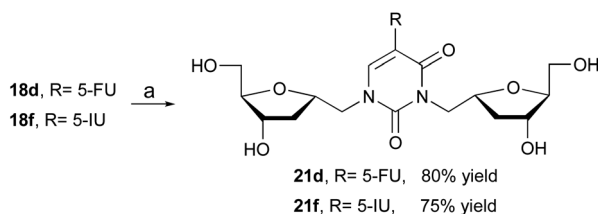


Fig. 5 X-ray structure of 1'-homo-*N*-2'-deoxy- α -adenosine (**10a**). The structure shows three molecules per asymmetric unit.



Table 1 Crystal data for homo-*N*-nucleoside analog 10a

Formula	C ₁₁ H ₁₅ N ₅ O ₃
Molecular weight	265.28
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁
<i>a</i> , Å	15.8711 (6)
<i>b</i> , Å	8.04111 (18)
<i>c</i> , Å	16.4342 (5)
<i>Z</i>	6
Final <i>R</i>	0.035
Reflections	4865



Scheme 4 Reaction conditions: (a) TBAF, THF, 25 °C, 2 h.

EC₅₀ value < 10 μM (97% HBV DNA inhibition at 10 μM). Among eight derivatives, none displayed anti-HBV activity, with EC₅₀ values > 10 μM.

Cytotoxicity profile.^{23c,25} These assays were performed in human PBM, T lymphoblast CEM-CCRF (CEM), African green monkey kidney (Vero) or human liver (HepG2) cells. Results represent means from triplicate wells. Positive control cycloheximide exhibited expected toxicity in the PBM, CEM, Vero, and HepG2 cells, with an IC₅₀ (μM) of 0.6, 0.08, 0.5, and 0.8, respectively (data not shown). None of the eight compounds exhibited apparent cytotoxicity (IC₅₀ values > 100 μM) in four cell types tested.

3. Experimental

General

TLC plates were visualized with 2.5% *p*-anisaldehyde, 3.5% sulfuric acid, and 1% acetic acid in ethanol. Pure α-cyano-sugar **12** is commercially available^{16a} and T^{Bz} was prepared as previously reported.¹⁸ Unless otherwise specified column chromatography was performed over silica 60 Å (230–400 mesh).

General procedure for desilylation of 17. Synthesis of 10

TBAF (6 eq., 1.0 M in THF) was added dropwise to a stirred solution of **17** (1 eq.) in anhydrous THF (0.1 M) at 0 °C. After 5 min, the ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h. Next, solvents were evaporated, and the residue was purified by column chromatography (gradient eluent 15–20% MeOH/CH₂Cl₂ for **10a–c**, **10e**; gradient eluent 5–20% MeOH/CH₂Cl₂ for **10d** and **10f**) to afford **10a–f** in 90–95% yield.

1'-Homo-*N*-2'-deoxy-α-adenosine (10a). 95% yield. *R*_f: 0.18 (20% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.69 (dt, 1H, H_{2'}, *J* = 13.1, 5.8 Hz), 2.38 (dt, 1H, H_{2'}, *J* = 13.3, 6.7 Hz),

3.50 (m, 1H, H_{5'}), 3.59 (dd, 1H, H_{5'}, *J* = 11.8, 3.9 Hz), 3.85 (q, 1H, H_{4'}, *J* = 4.5 Hz), 4.25 (dt, 1H, H_{3'}, *J* = 6.6, 5.2 Hz), 4.38 (m, 2H, H_{6'}), 4.45 (m, 1H, H_{1'}), 8.16 (s, 1H, H₂) 8.20 (s, 1H, H₈) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 38.5 (C_{2'}), 48.8 (C_{6'}), 63.3 (C_{5'}), 73.2 (C_{3'}), 77.8 (C_{1'}), 87.6 (C_{4'}), 119.7 (C₄), 143.6 (C₂), 150.8 (C₅), 153.6 (C₈), 157.2 (C₆) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₁H₁₆N₅O₃ [M + H]⁺: 266.1248, found: 266.1251.

1'-Homo-*N*-2'-deoxy-α-uridine (10b). 95% yield. *R*_f: 0.13 (10% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.70 (ddd, 1H, H_{2'}, *J* = 13.1, 5.9, 4.9 Hz), 2.33 (m, 1H, H_{2'}), 3.53 (m, 2H, H_{5'}), 3.87 (m, 2H, H_{4'} + H_{6'}), 3.96 (dd, 1H, H_{6'}, *J* = 14.1, 3.4 Hz), 4.25 (dt, 1H, H_{3'}, *J* = 6.6, 4.6 Hz), 4.34 (m, 1H, H_{1'}), 5.63 (d, 1H, H₅, *J* = 7.9 Hz), 7.60 (d, 1H, H₆, *J* = 7.9 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 38.4 (C_{2'}), 53.2 (C_{6'}), 63.3 (C_{5'}), 73.3 (C_{3'}), 77.7 (C_{1'}), 87.6 (C_{4'}), 101.6 (C₅), 148.5 (C₆), 153.0 (C₂), 166.9 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₀H₁₄N₂NaO₅ [M + Na]⁺: 265.0795, found: 265.0797.

1'-Homo-*N*-α-thymidine (10c).¹⁴ 95% yield. *R*_f: 0.40 (15% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.69 (m, 1H, H_{2'}), 1.87 (d, 3H, *Me*-H₅, *J* = 1.1 Hz), 2.33 (dt, 1H, H_{2'}, *J* = 13.9, 7.1 Hz), 3.55 (qd, 2H, H_{5'}, *J* = 11.8, 4.6 Hz), 3.87 (m, 3H, H_{4'} + 2H_{6'}), 4.24 (dt, 1H, H_{3'}, *J* = 6.6, 4.7 Hz), 4.34 (m, 1H, H_{1'}), 7.44 (s, 1H, H₆, *J* = 1.2 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 12.2 (CH₃), 38.5 (C_{2'}), 53.1 (C_{6'}), 63.4 (C_{5'}), 73.3 (C_{3'}), 77.7 (C_{1'}), 87.6 (C_{4'}), 110.4 (C₅), 144.3 (C₆), 153.1 (C₂), 167.0 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₁H₁₇N₂O₅ [M + H]⁺: 257.1132, found: 257.1134.

1'-Homo-*N*-2'-deoxy-α-5-fluorouridine (10d). 90% yield. *R*_f: 0.29 (15% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.70 (ddd, 1H, H_{2'}, *J* = 13.2, 5.9, 4.8 Hz), 2.34 (dt, 1H, H_{2'}, *J* = 12.0, 6.0 Hz), 3.55 (m, 2H, H_{5'}), 3.88 (m, 3H, H_{4'} + 2H_{6'}), 4.24 (m, 1H, H_{3'}), 4.35 (m, 1H, H_{1'}), 7.81 (d, 1H, H₆, *J* = 6.4 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 38.4 (C_{2'}), 53.2 (C_{6'}), 63.3 (C_{5'}), 73.3 (C_{3'}), 77.7 (C_{1'}), 87.6 (C_{4'}), 132.4 (d, C₆, *J* = 33.5 Hz), 141.3 (d, C₅, *J* = 231.1 Hz), 151.7 (C₂), 159.9 (d, C₄, *J* = 25.7 Hz) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₀H₁₄FN₂O₅ [M + H]⁺: 261.0881, found: 261.0874 and calcd for C₁₀H₁₃FN₂NaO₅ [M + Na]⁺: 283.0701, found: 283.0695.

1'-Homo-*N*-2'-deoxy-α-cytidine (10e). 95% yield. *R*_f: 0.07 (15% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.68 (ddd, 1H, H_{2'}, *J* = 13.1, 6.0, 5.2 Hz), 2.33 (dt, 1H, H_{2'}, *J* = 13.8, 7.0 Hz), 3.50 (m, 1H, H_{5'}), 3.58 (dd, 1H, H_{5'}, *J* = 11.8, 4.0 Hz), 3.80 (m, 1H, H_{6'}), 3.84 (m, 1H, H_{4'}), 4.04 (dd, 1H, H_{6'}, *J* = 13.8, 3.1 Hz), 4.24 (dt, 1H, H_{3'}, *J* = 6.6, 4.9 Hz), 4.36 (m, 1H, H_{1'}), 5.82 (d, 1H, H₅, *J* = 7.2 Hz), 7.58 (d, 1H, H₆, *J* = 7.3 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 38.6 (C_{2'}), 54.7 (C_{6'}), 63.4 (C_{5'}), 73.3 (C_{3'}), 77.6 (C_{1'}), 87.4 (C_{4'}), 95.2 (C₅), 148.6 (C₆), 159.1 (C₂), 168.0 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₀H₁₆N₃O₄ [M + H]⁺: 242.1135, found: 242.1138.

1'-Homo-*N*-2'-deoxy-α-5-iodouridine (10f). 92% yield. *R*_f: 0.47 (15% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.69 (dt, 1H, H_{2'}, *J* = 13.1, 5.6 Hz), 2.33 (dt, 1H, H_{2'}, *J* = 13.9, 7.3 Hz), 3.54 (m, 2H, H_{5'}), 3.89 (m, 3H, H_{4'} + 2H_{6'}), 4.25 (m, 1H, H_{3'}), 4.33 (m, 1H, H_{1'}), 8.05 (s, 1H, H₆) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₀H₁₄IN₂O₅ [M + H]⁺: 368.9942, found: 368.9943 and calcd for C₁₀H₁₃IN₂NaO₅ [M + Na]⁺: 390.9761, found: 390.9764.



1,2-Dideoxy-1 α -(methoxycarbonyl)-D-ribofuranose (13)

To a solution of **12** (500 mg, 1.3 mmol) in MeOH (15 mL) at room temperature were added 3.1 mL of a 2.5 M KOH solution (25% MeOH : H₂O). The progress of the reaction was monitored by TLC (10% MeOH/CH₂Cl₂) until no further reaction was apparent (3 h). Next, the mixture was neutralized with DOWEX 50WX8 hydrogen form (50–100 mesh). After removal of the resin by filtration, the solution was evaporated, and the residue was purified by column chromatography (5% MeOH/CH₂Cl₂) to afford **13** as a yellowish oil in 75% yield. *R*_f: 0.22 (5% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 2.11 (dt, 1H, H₂, *J* = 13.2, 3.9 Hz), 2.47 (ddd, 1H, H₂, *J* = 13.2, 8.8, 6.2 Hz), 3.59 (m, 2H, H₅), 3.73 (s, 3H, *Me*), 3.99 (q, 1H, H₄, *J* = 4.2 Hz), 4.23 (dt, 1H, H₃, *J* = 6.3, 3.6 Hz), 4.60 (dd, 1H, H₁, *J* = 8.8, 4.2 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 39.7 (C₂), 52.5 (Me), 63.1 (C₅), 72.7 (C₃), 77.3 (C₁), 88.6 (C₄), 175.6 (C=O) ppm; HRMS (ESI⁺, *m/z*): calcd for C₇H₁₂NaO₅ [M + Na]⁺: 199.0577, found: 199.0578.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1 α -(methoxycarbonyl)-D-ribofuranose (14)

TBSCl (904.3 mg, 6 mmol) was added to a solution of **13** (210 mg, 1.2 mmol) and imidazole (408.5 mg, 6 mmol) in anhydrous CH₂Cl₂ (4 mL) at room temperature. The reaction mixture was stirred at 50 °C for 5 h, then diluted with water/ice, and extracted with CH₂Cl₂. The organic layers were dried (Na₂SO₄) and evaporated in a vacuum. The residue was purified by column chromatography (10% EtOAc/hexane) to yield **14** as a viscous liquid in 85% yield. *R*_f: 0.65 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.088 (s, 3H, Si-*Me*), 0.095 (s, 3H, Si-*Me*), 0.098 (s, 3H, Si-*Me*), 0.102 (s, 3H, Si-*Me*), 0.87 (s, 9H, Si-*t*Bu), 0.92 (s, 9H, Si-*t*Bu), 2.16 (dt, 1H, H₂, *J* = 13.0, 2.4 Hz), 2.39 (ddd, 1H, H₂, *J* = 13.0, 8.9, 5.2 Hz), 3.53 (dd, 1H, H₅, *J* = 11.0, 5.8 Hz), 3.67 (dd, 1H, H₅, *J* = 11.0, 3.8 Hz), 3.71 (s, 3H, O-*Me*), 4.01 (ddd, 1H, H₄, *J* = 5.7, 3.7, 2.0 Hz), 4.36 (dt, 1H, H₃, *J* = 5.2, 2.1 Hz), 4.59 (dd, 1H, H₁, *J* = 8.9, 2.7 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (Si-CH₃), -5.2 (Si-CH₃), -4.7 (Si-CH₃), -4.6 (Si-CH₃), 18.7 (SiCMe₃), 19.2 (SiCMe₃), 26.2 (3CH₃-*t*Bu), 26.4 (3CH₃-*t*Bu), 39.9 (C₂), 52.5 (Me), 64.3 (C₅), 74.2 (C₃), 77.7 (C₁), 89.5 (C₄), 175.4 (C=O) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₉H₄₀NaO₅Si₂ [M + Na]⁺: 427.2306, found: 427.2302.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1 α -(hydroxymethyl)-D-ribofuranose (15)

LiAlH₄ (44 mg, 1.16 mmol) was added to a solution of **14** (360 mg, 0.89 mmol) in anhydrous THF (6 mL) at -45 °C, and the reaction was stirred for 30 min at the same temperature. Next, the mixture was diluted with THF and MeOH, the residue was filtered on Celite and concentrated to afford **15** as a viscous liquid (90% yield), which was sufficiently pure for the next step. *R*_f: 0.34 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.082 (s, 3H, Si-*Me*), 0.084 (s, 3H, Si-*Me*), 0.10 (s, 6H, Si-*Me*), 0.91 (s, 9H, Si-*t*Bu), 0.92 (s, 9H, Si-*t*Bu), 1.73 (ddd, 1H, H₂, *J* = 12.8, 5.9, 4.8 Hz), 2.24 (ddd, 1H, H₂, *J* = 12.9, 7.5, 6.5 Hz), 3.54 (dd, 1H, H₆, *J* = 11.4, 4.6 Hz), 3.62 (m, 3H, 2H₅ + H₆), 3.81 (q, 1H, H₄, *J* = 4.1 Hz), 4.13 (m, 1H, H₁), 4.40 (ddd, 1H, H₃, *J* = 6.4, 4.7,

3.9 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (Si-CH₃), -5.2 (Si-CH₃), -4.6 (Si-CH₃), -4.5 (Si-CH₃), 18.8 (SiCMe₃), 19.2 (SiCMe₃), 26.3 (3CH₃-*t*Bu), 26.4 (3CH₃-*t*Bu), 37.9 (C₂), 64.4 (C₅), 66.0 (C₆), 74.4 (C₃), 80.9 (C₁), 87.9 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₈H₄₀NaO₄Si₂ [M + Na]⁺: 399.2357, found: 399.2358.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1 α -(((methylsulfonyl)oxy)methyl)-D-ribofuranose (16)

To a solution of **15** (135 mg, 0.36 mmol) in anhydrous pyridine (0.65 mL) at 0 °C were added MsCl (62 μ L, 0.8 mmol) and catalytic DMAP (5 mg). The solution was stirred at room temperature for 24 h. Then, the solvent was removed in a vacuum, and the residue was dissolved in water and extracted with Et₂O. The organic layers were dried (Na₂SO₄) and evaporated in a vacuum. The residue was purified by column chromatography (20% EtOAc/hexane) to yield **16** as a viscous liquid in 95% yield. *R*_f: 0.42 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.08 (s, 6H, Si-*Me*), 0.11 (s, 6H, Si-*Me*), 0.92 (s, 18H, Si-*t*Bu), 1.75 (dt, 1H, H₂, *J* = 13.0, 3.9 Hz), 2.32 (m, 1H, H₂), 3.09 (s, 3H, Ms-*Me*), 3.61 (dq, 2H, H₅, *J* = 11.0, 4.6 Hz), 3.89 (q, 1H, H₄, *J* = 4.3 Hz), 4.20 (m, 1H, H₆), 4.39 (m, 3H, H₁ + H₃ + H₆) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (Si-CH₃), -5.2 (Si-CH₃), -4.62 (Si-CH₃), -4.57 (Si-CH₃), 18.8 (SiCMe₃), 19.2 (SiCMe₃), 26.3 (3CH₃-*t*Bu), 26.4 (3CH₃-*t*Bu), 37.5 (Ms-*Me*), 37.6 (C₂), 64.4 (C₅), 73.4 (C₆), 74.4 (C₃), 78.0 (C₁), 88.6 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₉H₄₂NaO₆Si₂ [M + Na]⁺: 477.2133, found: 477.2134.

General procedure for coupling of **20** with nucleobases.

Synthesis of **17** and **18**

To a solution of **20** in anhydrous DMF (0.1 M) was added K₂CO₃ (1.5 eq. for A, C, 5-FU, and 5-IU; 1.2 eq. for U; 2.1 eq. for T^{Bz}), 18-crown-6 (1.5 eq.), and the nucleobase (1.2 eq. for A, U, C, and T^{Bz}; 1.5 eq. for 5-FU and 5-IU). The mixture was stirred at 90 °C and the reaction progress followed by TLC (5% MeOH/CH₂Cl₂) until no further reaction was apparent (7–8 h). Solvents were evaporated and the residue was purified by column chromatography (5% MeOH/CH₂Cl₂) to yield **17** (or **18**). Yields are indicated in Scheme 3.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1'-homo-*N*-2'-deoxy- α -adenosine (17a**).** White solid. mp 137–138 °C; *R*_f: 0.32 (5% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ -0.02 (s, 3H, Si-*Me*), 0.01 (s, 3H, Si-*Me*), 0.06 (s, 3H, Si-*Me*), 0.08 (s, 3H, Si-*Me*), 0.86 (s, 9H, Si-*t*Bu), 0.87 (s, 9H, Si-*t*Bu), 1.72 (dt, 1H, H₂, *J* = 13.1, 5.0 Hz), 2.38 (dt, 1H, H₂, *J* = 13.4, 6.6 Hz), 3.60 (m, 2H, H₅), 3.87 (q, 1H, H₄, *J* = 4.0 Hz), 4.40 (m, 4H, H₁' + H₃' + 2H₆'), 8.09 (s, 1H, H₂), 8.20 (s, 1H, H₈) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (2Si-CH₃), -4.6 (2Si-CH₃), 18.9 (SiCMe₃), 19.1 (SiCMe₃), 26.29 (3CH₃-*t*Bu), 26.34 (3CH₃-*t*Bu), 39.1 (C₂'), 48.9 (C₆'), 64.4 (C₅'), 74.6 (C₃'), 78.3 (C₁'), 88.3 (C₄'), 119.7 (C₄), 143.5 (C₂), 150.8 (C₅), 153.6 (C₈), 157.2 (C₆) ppm; HRMS (ESI⁺, *m/z*): calcd for C₂₃H₄₄N₅O₃Si₂ [M + H]⁺: 494.2977, found: 494.2984.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1'-homo-*N*-2'-deoxy- α -uridine (17b**).** White solid. mp 102–103 °C; *R*_f: 0.49 (5% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.05 (s, 3H, Si-*Me*), 0.06 (s, 3H, Si-*Me*), 0.11 (s, 6H, Si-*Me*), 0.90 (s, 9H, Si-*t*Bu), 0.92



(s, 9H, Si-^tBu), 1.70 (dt, 1H, H_{2'}, *J* = 13.0, 4.9 Hz), 2.32 (dt, 1H, H_{2'}, *J* = 13.5, 6.9 Hz), 3.62 (m, 2H, H_{5'}), 3.87 (m, 2H, H_{4'} + H_{6'}), 3.96 (dd, 1H, H_{6'}, *J* = 14.1, 3.0 Hz), 4.32 (m, 1H, H_{1'}), 4.43 (m, 1H, H_{3'}), 5.62 (d, 1H, H_{5'}, *J* = 7.8 Hz), 7.53 (d, 1H, H_{6'}, *J* = 7.9 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (Si-CH₃), -5.2 (Si-CH₃), -4.6 (Si-CH₃), -4.5 (Si-CH₃), 18.9 (SiCMe₃), 19.2 (SiCMe₃), 26.3 (3CH₃-^tBu), 26.4 (3CH₃-^tBu), 38.9 (C_{2'}), 53.4 (C_{6'}), 64.4 (C_{5'}), 74.6 (C_{3'}), 78.1 (C_{1'}), 88.2 (C_{4'}), 101.6 (C₅), 148.4 (C₆), 152.9 (C₂), 166.8 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₂₂H₄₂N₂O₅Si₂ [M + Na]⁺: 493.2524, found: 493.2529.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1'-homo-*N*- α -thymidine (17c). *R*_f: 0.16 (50% Et₂O/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.05 (s, 3H, Si-*Me*), 0.06 (s, 3H, Si-*Me*), 0.11 (s, 6H, Si-*Me*), 0.90 (s, 9H, Si-^tBu), 0.92 (s, 9H, Si-^tBu), 1.70 (ddd, 1H, H_{2'}, *J* = 12.9, 5.9, 4.5 Hz), 1.86 (d, 3H, *Me*-C₅, *J* = 1.1 Hz), 2.32 (dt, 1H, H_{2'}, *J* = 13.6, 6.6 Hz), 3.62 (dd, 2H, H_{5'}, *J* = 4.4, 1.9 Hz), 3.88 (m, 3H, H_{4'} + 2H_{6'}), 4.31 (m, 1H, H_{1'}), 4.41 (m, 1H, H_{3'}), 7.37 (s, 1H, H₆) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.30 (Si-CH₃), -5.26 (Si-CH₃), -4.6 (Si-CH₃), -4.5 (Si-CH₃), 12.3 (CH₃-C₅), 18.9 (SiCMe₃), 19.2 (SiCMe₃), 26.3 (3CH₃-^tBu), 26.4 (3CH₃-^tBu), 39.0 (C_{2'}), 53.1 (C_{6'}), 64.4 (C_{5'}), 74.6 (C_{3'}), 78.2 (C_{1'}), 88.2 (C_{4'}), 110.4 (C₅), 144.2 (C₆), 152.9 (C₂), 167.0 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₂₃H₄₅N₂O₅Si₂ [M + H]⁺: 485.2862, found: 485.2851.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1'-homo-*N*-2'-deoxy- α -5-fluorouridine (17d). White solid. mp 134–136 °C; *R*_f: 0.57 (5% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.05 (s, 3H, Si-*Me*), 0.07 (s, 3H, Si-*Me*), 0.10 (s, 3H, Si-*Me*), 0.11 (s, 3H, Si-*Me*), 0.90 (s, 9H, Si-^tBu), 0.91 (s, 9H, Si-^tBu), 1.70 (ddd, 1H, H_{2'}, *J* = 13.0, 5.7, 4.4 Hz), 2.34 (dt, 1H, H_{2'}, *J* = 13.7, 7.0 Hz), 3.62 (dd, 2H, H_{5'}, *J* = 4.3, 1.7 Hz), 3.88 (m, 3H, H_{4'} + 2H_{6'}), 4.33 (m, 1H, H_{1'}), 4.42 (m, 1H, H_{3'}), 7.74 (d, 1H, H₆, *J* = 6.3 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.31 (Si-CH₃), -5.26 (Si-CH₃), -4.6 (Si-CH₃), -4.55 (Si-CH₃), 18.9 (SiCMe₃), 19.2 (SiCMe₃), 26.3 (3CH₃-^tBu), 26.4 (3CH₃-^tBu), 38.9 (C_{2'}), 53.2 (C_{6'}), 64.4 (C_{5'}), 74.6 (C_{3'}), 78.2 (C_{1'}), 88.2 (C_{4'}), 132.3 (d, C₆, *J* = 33.5 Hz), 141.2 (d, C₅, *J* = 131.5 Hz), 151.6 (C₂), 159.9 (d, C₄, *J* = 25.3 Hz) ppm; HRMS (ESI⁺, *m/z*): calcd for C₂₂H₄₂FN₂O₅Si₂ [M + H]⁺: 489.2611, found: 489.2635 and calcd for C₂₂H₄₁FN₂NaO₅Si₂ [M + Na]⁺: 511.2430, found: 511.2456.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1'-homo-*N*-2'-deoxy- α -cytidine (17e). *R*_f: 0.22 (5% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.04 (s, 3H, Si-*Me*), 0.05 (s, 3H, Si-*Me*), 0.11 (s, 6H, Si-*Me*), 0.89 (s, 9H, Si-^tBu), 0.92 (s, 9H, Si-^tBu), 1.68 (dt, 1H, H_{2'}, *J* = 12.8, 5.2 Hz), 2.32 (dt, 1H, H_{2'}, *J* = 13.3, 6.8 Hz), 3.61 (m, 2H, H_{5'}), 3.77 (dd, 1H, H_{6'}, *J* = 13.7, 8.5 Hz), 3.85 (q, 1H, H_{4'}, *J* = 4.1 Hz), 4.05 (dd, 1H, H_{6'}, *J* = 13.8, 2.7 Hz), 4.32 (m, 1H, H_{1'}), 4.41 (dt, 1H, H_{3'}, *J* = 5.9, 4.2 Hz), 5.82 (d, 1H, H_{5'}, *J* = 7.2 Hz), 7.50 (d, 1H, H₆, *J* = 7.2 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (Si-CH₃), -5.2 (Si-CH₃), -4.6 (Si-CH₃), -4.5 (Si-CH₃), 18.9 (SiCMe₃), 19.2 (SiCMe₃), 26.3 (3CH₃-^tBu), 26.4 (3CH₃-^tBu), 39.0 (C_{2'}), 54.9 (C_{6'}), 64.4 (C_{5'}), 74.5 (C_{3'}), 78.0 (C_{1'}), 88.0 (C_{4'}), 95.2 (C₅), 148.5 (C₆), 159.0 (C₂), 168.0 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₂₂H₄₄N₃O₄Si₂ [M + H]⁺: 470.2865, found: 470.2868.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1'-homo-*N*-2'-deoxy- α -5-iodouridine (17f). *R*_f: 0.63 (5% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.05 (s, 3H, Si-*Me*), 0.07 (s, 3H, Si-*Me*), 0.11 (s, 6H, Si-*Me*), 0.90 (s, 9H, Si-^tBu), 0.92 (s, 9H, Si-^tBu), 1.70 (ddd,

1H, H_{2'}, *J* = 13.0, 5.9, 4.4 Hz), 2.33 (ddd, 1H, H_{2'}, *J* = 13.5, 7.6, 6.4 Hz), 3.62 (dd, 2H, H_{5'}, *J* = 4.4, 1.6 Hz), 3.90 (m, 3H, H_{4'} + 2H_{6'}), 4.30 (m, 1H, H_{1'}), 4.42 (m, 1H, H_{3'}), 7.98 (s, 1H, H₆) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.2 (2Si-CH₃), -4.56 (Si-CH₃), -4.52 (Si-CH₃), 18.9 (SiCMe₃), 19.2 (SiCMe₃), 26.37 (3CH₃-^tBu), 26.42 (3CH₃-^tBu), 38.9 (C_{2'}), 53.2 (C_{6'}), 64.4 (C_{5'}), 67.2 (C₅), 74.7 (C_{3'}), 78.0 (C_{1'}), 88.3 (C_{4'}), 152.6 (C₆), 152.7 (C₂), 163.4 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₂₂H₄₂IN₂O₅Si₂ [M + H]⁺: 597.1671, found: 597.1684 and calcd for C₂₂H₄₁IN₂NaO₅Si₂ [M + Na]⁺: 619.1491, found: 619.1504.

N¹,N³-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy- α -ribofuranosylmethyl]uracil (18b). Colourless oil. *R*_f: 0.40 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.04 (s, 6H, Si-*Me*), 0.05 (s, 3H, Si-*Me*), 0.06 (s, 3H, Si-*Me*), 0.11 (s, 12H, Si-*Me*), 0.89 (s, 9H, Si-^tBu), 0.90 (s, 9H, Si-^tBu), 0.92 (s, 9H, Si-^tBu), 0.93 (s, 9H, Si-^tBu), 1.74 (m, 2H, H_{2'}), 2.27 (m, 2H, H_{2'}), 3.60 (m, 4H, H_{5'}), 3.78 (dd, 1H, H_{7'}, *J* = 12.9, 3.9 Hz), 3.92 (m, 4H, 2H_{4'} + 2H_{6'}), 4.38 (m, 4H, 2H_{1'} + 2H_{3'}), 4.56 (dd, 1H, H_{7'}, *J* = 12.9, 8.8 Hz), 5.69 (d, 1H, H_{5'}, *J* = 7.9 Hz), 7.51 (d, 1H, H₆, *J* = 7.9 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (2Si-CH₃), -5.2 (2Si-CH₃), -4.6 (2Si-CH₃), -4.5 (2Si-CH₃), 18.8 (SiCMe₃), 18.9 (SiCMe₃), 19.2 (2SiCMe₃), 26.36 (6CH₃-^tBu), 26.42 (3CH₃-^tBu), 26.44 (3CH₃-^tBu), 39.0 (C_{2'}), 39.8 (C_{2'}), 46.2 (C_{7'}), 54.5 (C_{6'}), 64.4 (2C_{5'}), 74.6 (C_{3'}), 74.7 (C_{3'}), 77.4 (C_{1'}), 78.1 (C_{1'}), 88.0 (C_{4'}), 88.2 (C_{4'}), 101.0 (C₅), 146.4 (C₆), 153.2 (C₂), 165.7 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₄₀H₈₁N₂O₈Si₄ [M + H]⁺: 829.5065, found: 829.5065.

N¹,N³-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy- α -ribofuranosylmethyl]thymine (18c). Colourless oil. *R*_f: 0.50 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.04 (s, 6H, Si-*Me*), 0.049 (s, 3H, Si-*Me*), 0.054 (s, 3H, Si-*Me*), 0.108 (s, 6H, Si-*Me*), 0.114 (s, 6H, Si-*Me*), 0.891 (s, 9H, Si-^tBu), 0.893 (s, 9H, Si-^tBu), 0.92 (s, 9H, Si-^tBu), 0.93 (s, 9H, Si-^tBu), 1.74 (m, 2H, H_{2'}), 1.89 (d, 3H, H_{7'}, *J* = 0.8 Hz), 2.27 (m, 2H, H_{2'}), 3.60 (m, 4H, H_{5'}), 3.79 (dd, 1H, H_{7'}, *J* = 13.0, 3.9 Hz), 3.90 (m, 4H, 2H_{4'} + 2H_{6'}), 4.36 (m, 4H, 2H_{1'} + 2H_{3'}), 4.58 (dd, 1H, H_{7'}, *J* = 13.0, 8.8 Hz), 7.37 (d, 1H, H₆, *J* = 1.0 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (2Si-CH₃), -5.2 (2Si-CH₃), -4.6 (2Si-CH₃), -4.5 (2Si-CH₃), 13.1 (C₇), 18.8 (SiCMe₃), 18.9 (SiCMe₃), 19.2 (2SiCMe₃), 26.36 (6CH₃-^tBu), 26.42 (6CH₃-^tBu), 39.0 (C_{2'}), 39.9 (C_{2'}), 46.5 (C_{7'}), 54.2 (C_{6'}), 64.4 (C_{5'}), 64.5 (C_{5'}), 74.6 (C_{3'}), 74.7 (C_{3'}), 77.5 (C_{1'}), 78.2 (C_{1'}), 88.0 (C_{4'}), 88.1 (C_{4'}), 109.6 (C₅), 142.4 (C₆), 153.2 (C₂), 166.0 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₄₁H₈₃N₂O₈Si₄ [M + H]⁺: 843.5221, found: 843.5218.

N¹,N³-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy- α -ribofuranosylmethyl]-5-fluorouracil (18d). Colourless oil. *R*_f: 0.50 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.039 (s, 3H, Si-*Me*), 0.041 (s, 3H, Si-*Me*), 0.05 (s, 3H, Si-*Me*), 0.06 (s, 3H, Si-*Me*), 0.10 (s, 6H, Si-*Me*), 0.113 (s, 3H, Si-*Me*), 0.115 (s, 3H, Si-*Me*), 0.890 (s, 9H, Si-^tBu), 0.892 (s, 9H, Si-^tBu), 0.91 (s, 9H, Si-^tBu), 0.93 (s, 9H, Si-^tBu), 1.75 (m, 2H, H_{2'}), 2.28 (m, 2H, H_{2'}), 3.58 (m, 4H, H_{5'}), 3.77 (dd, 1H, H_{7'}, *J* = 13.1, 3.7 Hz), 3.92 (m, 4H, 2H_{4'} + 2H_{6'}), 4.38 (m, 4H, 2H_{1'} + 2H_{3'}), 4.62 (dd, 1H, H_{7'}, *J* = 12.9, 9.1 Hz), 7.75 (d, 1H, H₆, *J* = 5.9 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.24 (2Si-CH₃), -5.17 (Si-CH₃), -5.1 (Si-CH₃), -4.54 (2Si-CH₃), -4.48 (2Si-CH₃), 18.8 (SiCMe₃), 18.9 (SiCMe₃), 19.2 (2SiCMe₃), 26.38 (6CH₃-^tBu), 26.43



(3CH₃-^tBu), 26.5 (3CH₃-^tBu), 39.0 (C₂), 39.7 (C_{2'}), 46.9 (C₇), 54.3 (C_{6'}), 64.4 (C_{5'}), 64.5 (C₅), 74.6 (C₃), 74.8 (C_{3'}), 77.3 (C₁), 78.1 (C_{1'}), 88.1 (2C_{4'}), 130.6 (d, C₆, *J* = 33.3 Hz), 140.8 (d, C₅, *J* = 229.4 Hz), 151.7 (C₂), 159.5 (d, C₄, *J* = 25.2 Hz) ppm; HRMS (ESI⁺, *m/z*): calcd for C₄₀H₇₉FN₂NaO₈Si₄ [M + Na]⁺: 869.4790, found: 869.4762.

N¹,N³-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy- α -ribofuranosylmethyl]-5-iodouracil (18f). Colourless oil. *R*_f: 0.56 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.04 (s, 3H, Si-*Me*), 0.050 (s, 3H, Si-*Me*), 0.052 (s, 3H, Si-*Me*), 0.07 (s, 3H, Si-*Me*), 0.108 (s, 6H, Si-*Me*), 0.114 (s, 6H, Si-*Me*), 0.89 (s, 9H, Si-^tBu), 0.90 (s, 9H, Si-^tBu), 0.92 (s, 9H, Si-^tBu), 0.93 (s, 9H, Si-^tBu), 1.73 (m, 2H, H_{2'}), 2.28 (m, 2H, H_{2'}), 3.62 (m, 4H, H_{5'}), 3.82 (dd, 1H, H_{7'}, *J* = 13.1, 3.7 Hz), 3.89 (m, 2H, 2H_{4'}), 3.96 (m, 2H, 2H_{6'}), 4.38 (m, 4H, 2H_{1'} + 2H_{3'}), 4.63 (dd, 1H, H_{7'}, *J* = 13.0, 9.0 Hz), 7.99 (s, 1H, H₆) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.24 (Si-CH₃), -5.19 (Si-CH₃), -5.1 (2Si-CH₃), -4.5 (4Si-CH₃), 18.8 (SiCMe₃), 18.9 (SiCMe₃), 19.2 (2SiCMe₃), 26.4 (6CH₃-^tBu), 26.5 (6CH₃-^tBu), 38.9 (C₂), 39.8 (C_{2'}), 47.8 (C₇), 54.4 (C_{6'}), 64.4 (2C_{5'}), 66.5 (C₅), 74.6 (C₃), 74.7 (C_{3'}), 77.4 (C₁), 78.0 (C_{1'}), 88.0 (C_{4'}), 88.3 (C_{4'}), 150.9 (C₆), 152.9 (C₂), 162.4 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₄₀H₈₀IN₂O₈Si₄ [M + H]⁺: 955.4031, found: 955.4033 and calcd for C₄₀H₇₉IN₂NaO₈Si₄ [M + Na]⁺: 977.3850, found: 977.3851.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1 α -((acetoxy)methyl)-*D*-ribofuranose (19)

To a solution of **15** (44 mg, 0.12 mmol) in anhydrous CH₂Cl₂ (1.2 mL) at room temperature was added Et₃N (50 μ L, 0.36 mmol), Ac₂O (170 μ L, 1.8 mmol) and catalytic DMAP (2 mg). The solution was stirred for 2 h. Solvents were evaporated, and the residue purified by column chromatography (10% EtOAc/hexane) to afford **19** in 90% yield as a viscous liquid. *R*_f: 0.65 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.081 (s, 3H, Si-*Me*), 0.085 (s, 3H, Si-*Me*), 0.10 (s, 6H, Si-*Me*), 0.91 (s, 9H, Si-^tBu), 0.92 (s, 9H, Si-^tBu), 1.71 (dt, 1H, H₂, *J* = 13.1, 4.5 Hz), 2.05 (s, 3H, Ac-*Me*), 2.28 (dt, 1H, H₂, *J* = 13.6, 6.9 Hz), 3.63 (qd, 2H, H₅, *J* = 11.0, 4.5 Hz), 3.85 (q, 1H, H₄, *J* = 3.9 Hz), 4.05 (dd, 1H, H₆, *J* = 10.9, 3.7 Hz), 4.24 (m, 1H, H₆), 4.27 (m, 1H, H₁), 4.40 (dt, 1H, H₃, *J* = 6.2, 3.9 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (Si-CH₃), -5.2 (Si-CH₃), -4.6 (Si-CH₃), -4.5 (Si-CH₃), 18.8 (SiCMe₃), 19.2 (SiCMe₃), 20.8 (Ac-CH₃), 26.3 (3CH₃-^tBu), 26.4 (3CH₃-^tBu), 38.1 (C₂), 64.4 (C₅), 68.1 (C₆), 74.4 (C₃), 78.1 (C₁), 88.4 (C₄), 172.6 (C=O) ppm.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1 α -((tosyloxy)methyl)-*D*-ribofuranose (20)

To a solution of **15** (100 mg, 0.26 mmol) in anhydrous pyridine (0.5 mL) at 0 °C were added TsCl (111.3 mg, 0.58 mmol) and catalytic DMAP (5 mg). The solution was stirred at room temperature for 9 h. Solvents were evaporated, and the residue was purified by column chromatography (15% EtOAc/hexane) to yield **20** as a colourless viscous liquid in 90% yield. *R*_f: 0.60 (20% EtOAc/hexane); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 0.040 (s, 3H, Si-*Me*), 0.042 (s, 3H, Si-*Me*), 0.05 (s, 3H, Si-*Me*), 0.06 (s, 3H, Si-*Me*), 0.84 (s, 9H, Si-^tBu), 0.90 (s, 9H, Si-^tBu), 1.64 (dt, 1H, H₂, *J* =

13.3, 3.4 Hz), 2.21 (ddd, 1H, H₂, *J* = 13.7, 8.1, 5.8 Hz), 2.45 (s, 3H, Ts-*Me*), 3.46 (dd, 1H, H₅, *J* = 10.9, 5.6 Hz), 3.57 (dd, 1H, H₅, *J* = 10.9, 3.8 Hz), 3.69 (m, 1H, H₄), 3.98 (dd, 1H, H₆, *J* = 10.0, 4.0 Hz), 4.12 (dd, 1H, H₆, *J* = 10.0, 7.6 Hz), 4.27 (m, 1H, H₁), 4.33 (m, 1H, H₃), 7.43 (d, 2H, H_{arom}, *J* = 8.5 Hz), 7.79 (d, 2H, H_{arom}, *J* = 8.4 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ -5.3 (Si-CH₃), -5.2 (Si-CH₃), -4.6 (2Si-CH₃), 18.7 (SiCMe₃), 19.2 (SiCMe₃), 21.6 (CH₃-Ts), 26.3 (3CH₃-^tBu), 26.4 (3^tBu-CH₃), 37.6 (C₂), 64.4 (C₅), 73.6 (C₆), 74.5 (C₃), 77.9 (C₁), 88.7 (C₄), 129.1 (2C_{arom}), 131.0 (2C_{arom}), 134.4 (C_{ipso}), 146.3 (C_{ipso}) ppm; HRMS (ESI⁺, *m/z*): calcd for C₂₅H₄₇O₆SSi₂ [M + H]⁺: 531.2626, found: 531.2632.

General procedure for desilylation of 18d and 18f. Synthesis of 21d and 21f

A procedure analogous to that described for the synthesis of **10** was used.

N¹,N³-Bis-(1,2-dideoxy- α -ribofuranosylmethyl)-5-fluorouracil (21d). Colourless oil. *R*_f: 0.15 (15% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.74 (m, 2H, H₂), 2.33 (m, 2H, H₂), 3.54 (m, 4H, H₅), 3.90 (m, 5H, 2H_{4'} + 2H_{6'} + H_{7'}), 4.22 (m, 2H, H₃), 4.39 (m, 2H, H₁), 4.50 (dd, 1H, H₇, *J* = 12.6, 8.8 Hz), 7.84 (d, 1H, H₆, *J* = 6.0 Hz) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 38.4 (C₂), 39.3 (C_{2'}), 46.6 (C₇), 54.2 (C_{6'}), 63.2 (C_{5'}), 63.4 (C_{5'}), 73.3 (C_{3'}), 73.4 (C_{3'}), 76.7 (C_{1'}), 77.7 (C_{1'}), 87.1 (C_{4'}), 87.7 (C_{4'}), 130.9 (d, C₆, *J* = 33.5 Hz), 140.8 (d, C₅, *J* = 229.0 Hz), 151.9 (C₂), 159.6 (d, C₄, *J* = 25.0 Hz) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₆H₂₄FN₂O₈ [M + H]⁺: 391.1511, found: 391.1526 and calcd for C₁₆H₂₃FN₂NaO₈ [M + Na]⁺: 413.1331, found: 413.1345.

N¹,N³-Bis-(1,2-dideoxy- α -ribofuranosylmethyl)-5-iodouracil (21f). Colourless oil. *R*_f: 0.24 (15% MeOH/CH₂Cl₂); ¹H NMR (300.13 MHz, MeOH-*d*₄): δ 1.73 (m, 2H, H₂), 2.32 (m, 2H, H₂), 3.53 (m, 4H, H₅), 3.89 (m, 3H, 2H_{4'} + H_{7'}), 3.96 (m, 2H, H_{6'}), 4.23 (m, 2H, H_{3'}), 4.39 (m, 2H, H₁), 4.52 (dd, 1H, H₇, *J* = 12.9, 8.7 Hz), 8.08 (s, 1H, H₆) ppm; ¹³C NMR (75.5 MHz, MeOH-*d*₄): δ 38.4 (C₂), 39.3 (C_{2'}), 47.6 (C₇), 54.4 (C_{6'}), 63.2 (C_{5'}), 63.3 (C_{5'}), 66.4 (C₅), 73.4 (2C_{3'}), 76.7 (C_{1'}), 77.6 (C_{1'}), 87.0 (C_{4'}), 87.8 (C_{4'}), 151.2 (C₆), 153.1 (C₂), 162.5 (C₄) ppm; HRMS (ESI⁺, *m/z*): calcd for C₁₆H₂₄IN₂O₈ [M + H]⁺: 499.0572, found: 499.0577 and calcd for C₁₆H₂₃IN₂NaO₈ [M + Na]⁺: 521.0391, found: 521.0397.

Antiviral assays

HIV assay. The assay was performed as described previously,^{23a,b} with some modifications described elsewhere.^{23c} Briefly, human PBM cells were stimulated with PHA/IL-2 prior to infection with HIV-1 LAI (MOI 0.1) for 6 days in the presence of various concentrations of test compounds (**10a-f**, **21d**, and **21f**) or AZT (control). Supernatants were harvested, and HIV-1 RT was quantified. Median effective concentrations (EC₅₀) were determined using described method.^{23d}

HBV assay. HepAD38 cells²⁴ were seeded at 50 000 cells per well in collagen-coated 96-well plates. Test compounds or 3TC (control) were added to HepAD38 cells to a final concentration of 10 μ M. Real-time PCR for HBV DNA lasted 7 days. On day 7, total DNA was purified from supernatant using commercially available kit (DNeasy 96 Blood & Tissue kit, Qiagen). The HBV DNA was amplified in a real-time PCR assay using LightCycler



480 (Roche) as described elsewhere.^{23c} All samples were tested in triplicate. Analysis: the concentration of compound that inhibited HBV DNA replication by 50% (EC₅₀) was determined by linear regression.

Cytotoxicity assays. These were performed in primary blood mononuclear (PBM), T lymphoblast CEM-CCRF (CEM), African green monkey kidney (Vero) or human liver (HepG2) cells *via* MTT assay using the CellTiter 96[®]. Non-Radioactive Cell Proliferation (Promega) kit as previously described.^{23c} Cytotoxicity was expressed as the concentration of test compounds that inhibited cell proliferation by 50% (IC₅₀) and calculated using the Chou and Talalay method.²⁵

4. Conclusions

We have synthesized a series of novel 1'-homo-*N*-2'-deoxy- α -nucleoside analogs of A, U, T, 5-FU, C, and 5-IU *via* coupling of a nucleobase and a tosylated intermediate sugar precursor readily obtained from a cyano derivative, which is easily accessible on large-scale. Displacement reactions took place in the presence of K₂CO₃ and 18-crown-6 in DMF at elevated temperature. The structure of all derivatives was established by NMR spectroscopy and confirmation was obtained by a single crystal X-ray analysis of 1'-homo-*N*-2'-deoxy- α -adenosine. It is worthy of mention that only the thymine derivative has been previously described synthesized *via* a more complex route. In addition to the desired compounds we have obtained the corresponding dimer derivatives resulting from the coupling of the sugar moiety at the *N*-1 and *N*-3 positions of the base. The occurrence of these dimers is very interesting since few derivatives of this type have been reported in the literature, primarily as byproducts. Eight homonucleosides, including dimers, were tested as antiviral agents. These compounds did not exhibit selective antiviral activity against HIV-1 and HBV. Also, none of them exhibited apparent cytotoxicity in all four cells types tested. Although the results obtained from the preliminary biological screening led to no hit, we believe these novel α -nucleosides may serve as important building-blocks for therapeutic oligonucleotides.¹⁰ This study established a facile path for the synthesis of multifunctional nucleoside analogs that may elicit biological activity and make an attractive scaffold for drug discovery using the combinatorial approach.

Conflicts of interest

There are no conflicts to declare.

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