RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 15815

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

Alejandro Carnero,[a] Virginia Martín-Nieves,[a] Yogesh S. Sanghvi,[b] Olivia O. Russel,[c] Leda Bassit,[c] Raymond F. Schinazi,[c] Susana Fernández *[a] and Miguel Ferrero *[a]

Received 13th February 2020
Accepted 14th April 2020

DOI: 10.1039/d0ra03254a

rsc.li/rsc-advances

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.

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 analogs, 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-ribo[11] and α-ribo[12] 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

[a]*Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, 33006-Oviedo, Asturias, Spain. E-mail: mferrero@uniovi.es; fernandezgsusana@uniovi.es*

[b]*Rasayan Inc., 2802 Crystal Ridge Road, Encinitas, CA 92024-6615, USA*

[c]*Center for AIDS Research, Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322, USA*

† Electronic supplementary information (ESI) available: Copies of 1D and 2D spectra. CCDC 1980305. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra03254a

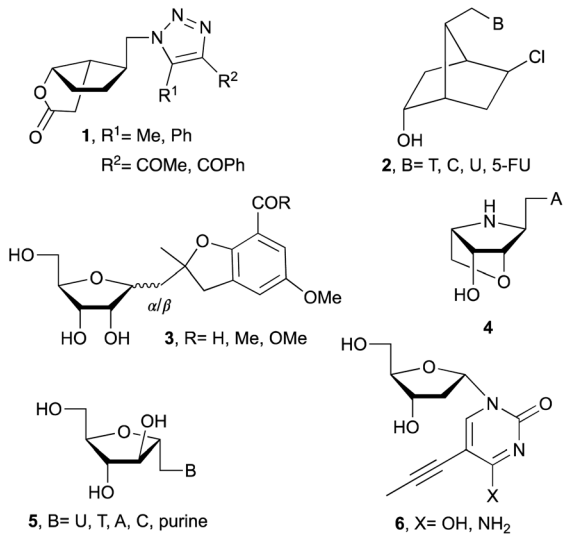


Fig. 1 Structures of 1′-homo-*N*-nucleosides and/or α-nucleosides.

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-workers[14] 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/H_2O. 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

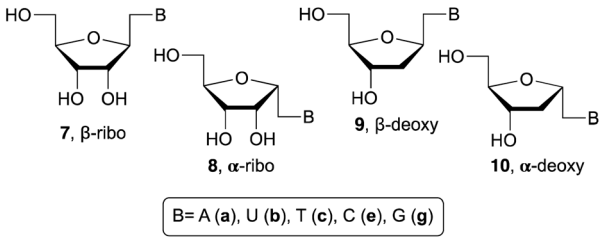


Fig. 2 Structures of α/β-ribo and α/β-2′-deoxy 1′-homo-*N*-nucleosides.

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 K_2CO_3 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

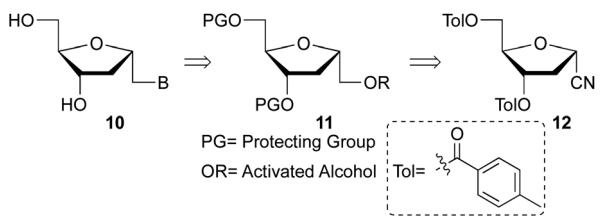
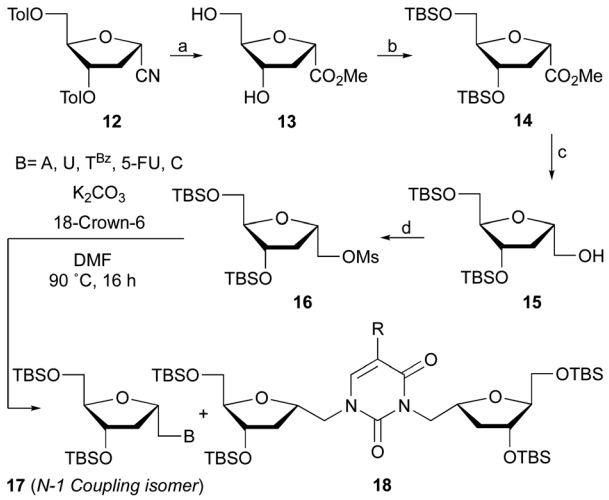


Fig. 3 Retrosynthetic analysis to 1′-homo-*N*-2′-deoxy-α-nucleosides.



	yield (%)		yield (%)
B= A	**17a**	84	**18** ——
B= U	**17b**	45	**18b** (R= H) 25
B= T	**17c**	12	**18c** (R= Me) 55
B= 5-FU	**17d**	14	**18d** (R= F) 73
B= C[a]	**17e**	20	**18e** ——

[a]A mixture of *N*-1 and *N*-3 coupling compounds was obtained

Scheme 1 Reaction conditions: (a) KOH, MeOH/H_2O, rt, 3 h (75%); (b) TBSCl, imidazole, CH_2Cl_2, 50 °C, 5 h (85%); (c) $LiAlH_4$, 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 ^{13}C–^{1}H 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 conditions[17] required acetate **19** (Scheme 2), which was easily prepared from **15** by treatment with acetic anhydride, Et_3N, and DMAP in CH_2Cl_2. 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, Ph_3P 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.

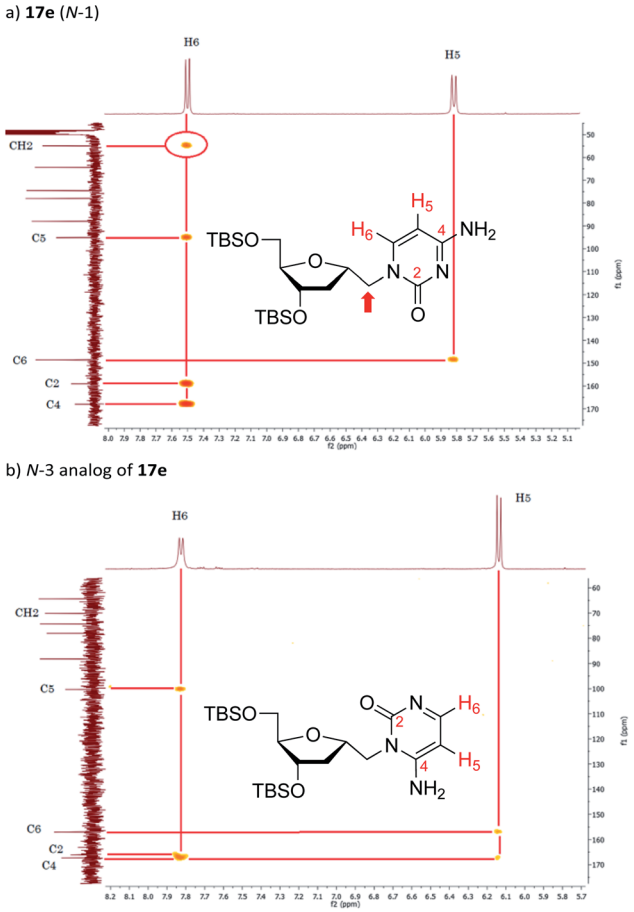
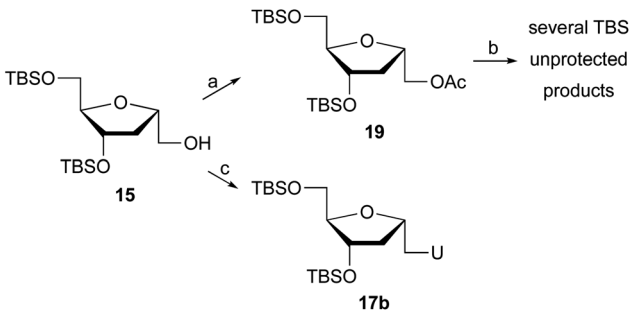


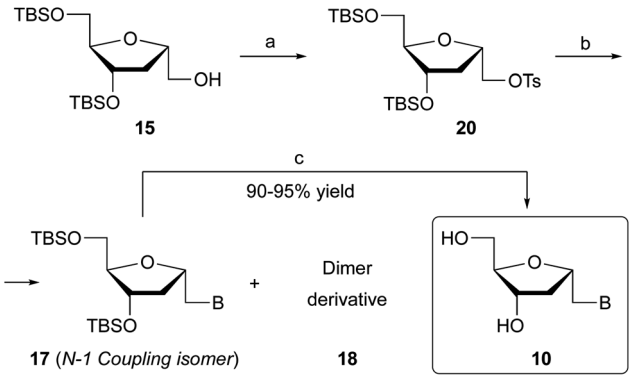
Fig. 4 HMBC spectra enlargements of: (a) **17e** and (b) its *N*-3 analog.

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*-toluensulfonyl 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) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 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) Ph_3P, DIAD, uracil, THF, −10 °C to 25 °C, 24 h (15%).



		yield (%)		yield (%)
B= A	**17a**	91	**18a**	——
B= U	**17b**	65	**18b**	35
B= T	**17c**	30	**18c**	64
B= 5-FU	**17d**	15	**18d**	63
B= C[a]	**17e**	69	**18e**	——
B= 5-IU	**17f**	13	**18f**	80

[a]*N*-3 coupling compound was isolated as minor compound

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, K_2CO_3, 18-crown-6, DMF, 90 °C, 7–8 h; (c) TBAF, THF, 25 °C, 2 h (90–95%).

the presence of K_2CO_3 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 Sorm[21] 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-workers[22] 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 EC_{50} of 0.006 μM. There was no anti-HIV activity observed from the six homonucleosides **10a–f** and the two dimeric compounds **21d,f** tested, all with an EC_{50} > 10 μM.

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

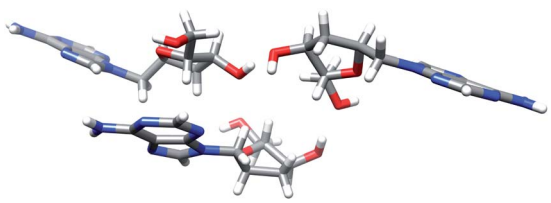
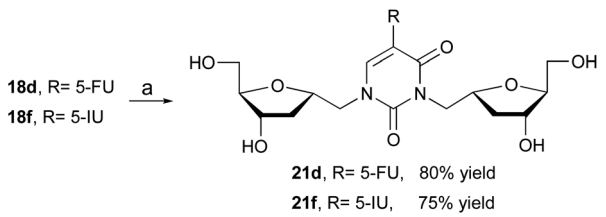


Fig. 5 X-ray structure of 1′-homo-*N*-2′-deoxy-α-adenosine (**10a**). The structure shows three molecules per asymmetric unit.

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

Formula	$C_{11}H_{15}N_5O_3$
Molecular weight	265.28
Crystal system	Monoclinic
Space group	$P2_1$
a, Å	15.8711 (6)
b, Å	8.04111 (18)
c, Å	16.4342 (5)
Z	6
Final *R*	0.035
Reflections	4865



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

EC_{50} value < 10 μM (97% HBV DNA inhibition at 10 μM). Among eight derivatives, none displayed anti-HBV activity, with EC_{50} 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 IC_{50} (μM) of 0.6, 0.08, 0.5, and 0.8, respectively (data not shown). None of the eight compounds exhibited apparent cytotoxicity (IC_{50} 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/CH_2Cl_2 for **10a–c**, **10e**; gradient eluent 5–20% MeOH/CH_2Cl_2 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/CH_2Cl_2); ^{1}H 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, H_2) 8.20 (s, 1H, H_8) ppm; ^{13}C 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 (C_4), 143.6 (C_2), 150.8 (C_5), 153.6 (C_8), 157.2 (C_6) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{11}H_{16}N_5O_3$ $[M + H]^+$: 266.1248, found: 266.1251.

1′-Homo-*N*-2′-deoxy-α-uridine (10b). 95% yield. R_f: 0.13 (10% MeOH/CH_2Cl_2); ^{1}H 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, H_5, J = 7.9 Hz), 7.60 (d, 1H, H_6, J = 7.9 Hz) ppm; ^{13}C 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 (C_5), 148.5 (C_6), 153.0 (C_2), 166.9 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{10}H_{14}N_2NaO_5$ $[M + Na]^+$: 265.0795, found: 265.0797.

1′-Homo-*N*-α-thymidine (10c).[14] 95% yield. R_f: 0.40 (15% MeOH/CH_2Cl_2); ^{1}H NMR (300.13 MHz, MeOH-d_4): δ 1.69 (m, 1H, $H_{2'}$), 1.87 (d, 3H, *Me*–H_5, 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, H_6, J = 1.2 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ 12.2 (CH_3), 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 (C_5), 144.3 (C_6), 153.1 (C_2), 167.0 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{11}H_{17}N_2O_5$ $[M + H]^+$: 257.1132, found: 257.1134.

1′-Homo-*N*-2′-deoxy-α-5-fluorouridine (10d). 90% yield. R_f: 0.29 (15% MeOH/CH_2Cl_2); ^{1}H 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, H_6, J = 6.4 Hz) ppm; ^{13}C 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, C_6, J = 33.5 Hz), 141.3 (d, C_5, J = 231.1 Hz), 151.7 (C_2), 159.9 (d, C_4, J = 25.7 Hz) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{10}H_{14}FN_2O_5$ $[M + H]^+$: 261.0881, found: 261.0874 and calcd for $C_{10}H_{13}FN_2NaO_5$ $[M + Na]^+$: 283.0701, found: 283.0695.

1′-Homo-*N*-2′-deoxy-α-cytidine (10e). 95% yield. R_f: 0.07 (15% MeOH/CH_2Cl_2); ^{1}H 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, H_5, J = 7.2 Hz), 7.58 (d, 1H, H_6, J = 7.3 Hz) ppm; ^{13}C 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 (C_5), 148.6 (C_6), 159.1 (C_2), 168.0 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{10}H_{16}N_3O_4$ $[M + H]^+$: 242.1135, found: 242.1138.

1′-Homo-*N*-2′-deoxy-α-5-iodouridine (10f). 92% yield. R_f: 0.47 (15% MeOH/CH_2Cl_2); ^{1}H 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, H_6) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{10}H_{14}IN_2O_5$ $[M + H]^+$: 368.9942, found: 368.9943 and calcd for $C_{10}H_{13}IN_2NaO_5$ $[M + Na]^+$: 390.9761, found: 390.9764.

1,2-Dideoxy-1α-(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 : H_2O). The progress of the reaction was monitored by TLC (10% MeOH/CH_2Cl_2) 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/CH_2Cl_2) to afford **13** as a yellowish oil in 75% yield. R_f: 0.22 (5% MeOH/CH_2Cl_2); ^{1}H NMR (300.13 MHz, MeOH-d_4): δ 2.11 (dt, 1H, H_2, J = 13.2, 3.9 Hz), 2.47 (ddd, 1H, H_2, J = 13.2, 8.8, 6.2 Hz), 3.59 (m, 2H, H_5), 3.73 (s, 3H, *Me*), 3.99 (q, 1H, H_4, J = 4.2 Hz), 4.23 (dt, 1H, H_3, J = 6.3, 3.6 Hz), 4.60 (dd, 1H, H_1, J = 8.8, 4.2 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ 39.7 (C_2), 52.5 (Me), 63.1 (C_5), 72.7 (C_3), 77.3 (C_1), 88.6 (C_4), 175.6 (*C*=O) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_7H_{12}NaO_5$ [M + Na]$^+$: 199.0577, found: 199.0578.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1α-(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 CH_2Cl_2 (4 mL) at room temperature. The reaction mixture was stirred at 50 °C for 5 h, then diluted with water/ice, and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) 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); ^{1}H 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, H_2, J = 13.0, 2.4 Hz), 2.39 (ddd, 1H, H_2, J = 13.0, 8.9, 5.2 Hz), 3.53 (dd, 1H, H_5, J = 11.0, 5.8 Hz), 3.67 (dd, 1H, H_5, J = 11.0, 3.8 Hz), 3.71 (s, 3H, O–*Me*), 4.01 (ddd, 1H, H_4, J = 5.7, 3.7, 2.0 Hz), 4.36 (dt, 1H, H_3, J = 5.2, 2.1 Hz), 4.59 (dd, 1H, H_1, J = 8.9, 2.7 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (Si–*C*H$_3$), −5.2 (Si–*C*H$_3$), −4.7 (Si–*C*H$_3$), −4.6 (Si–*C*H$_3$), 18.7 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.2 (3*C*H$_3$–^{t}Bu), 26.4 (3*C*H$_3$–^{t}Bu), 39.9 (C_2), 52.5 (Me), 64.3 (C_5), 74.2 (C_3), 77.7 (C_1), 89.5 (C_4), 175.4 (*C*=O) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{19}H_{40}NaO_5Si_2$ [M + Na]$^+$: 427.2306, found: 427.2302.

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

$LiAlH_4$ (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); ^{1}H 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, H_2, J = 12.8, 5.9, 4.8 Hz), 2.24 (ddd, 1H, H_2, J = 12.9, 7.5, 6.5 Hz), 3.54 (dd, 1H, H_6, J = 11.4, 4.6 Hz), 3.62 (m, 3H, 2H_5 + H_6), 3.81 (q, 1H, H_4, J = 4.1 Hz), 4.13 (m, 1H, H_1), 4.40 (ddd, 1H, H_3, J = 6.4, 4.7, 3.9 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (Si–*C*H$_3$), −5.2 (Si–*C*H$_3$), −4.6 (Si–*C*H$_3$), −4.5 (Si–*C*H$_3$), 18.8 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.3 (3*C*H$_3$–^{t}Bu), 26.4 (3*C*H$_3$–^{t}Bu), 37.9 (C_2), 64.4 (C_5), 66.0 (C_6), 74.4 (C_3), 80.9 (C_1), 87.9 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{18}H_{40}NaO_4Si_2$ [M + Na]$^+$: 399.2357, found: 399.2358.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1α-(((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 μL, 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 Et_2O. The organic layers were dried (Na_2SO_4) 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); ^{1}H 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, H_2, J = 13.0, 3.9 Hz), 2.32 (m, 1H, H_2), 3.09 (s, 3H, Ms–*Me*), 3.61 (dq, 2H, H_5, J = 11.0, 4.6 Hz), 3.89 (q, 1H, H_4, J = 4.3 Hz), 4.20 (m, 1H, H_6), 4.39 (m, 3H, H_1 + H_3 + H_6) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (Si–*C*H$_3$), −5.2 (Si–*C*H$_3$), −4.62 (Si–*C*H$_3$), −4.57 (Si–*C*H$_3$), 18.8 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.3 (3*C*H$_3$–^{t}Bu), 26.4 (3*C*H$_3$–^{t}Bu), 37.5 (Ms–*Me*), 37.6 (C_2), 64.4 (C_5), 73.4 (C_6), 74.4 (C_3), 78.0 (C_1), 88.6 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{19}H_{42}NaO_6SSi_2$ [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 K_2CO_3 (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/CH_2Cl_2) until no further reaction was apparent (7–8 h). Solvents were evaporated and the residue was purified by column chromatography (5% MeOH/CH_2Cl_2) 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/CH_2Cl_2); ^{1}H 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, $H_{2'}$, J = 13.1, 5.0 Hz), 2.38 (dt, 1H, $H_{2'}$, J = 13.4, 6.6 Hz), 3.60 (m, 2H, $H_{5'}$), 3.87 (q, 1H, $H_{4'}$, J = 4.0 Hz), 4.40 (m, 4H, $H_{1'}$ + $H_{3'}$ + 2$H_{6'}$), 8.09 (s, 1H, H_2), 8.20 (s, 1H, H_8) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (2Si–*C*H$_3$), −4.6 (2Si–*C*H$_3$), 18.9 (Si*C*Me$_3$), 19.1 (Si*C*Me$_3$), 26.29 (3*C*H$_3$–^{t}Bu), 26.34 (3*C*H$_3$–^{t}Bu), 39.1 ($C_{2'}$), 48.9 ($C_{6'}$), 64.4 ($C_{5'}$), 74.6 ($C_{3'}$), 78.3 ($C_{1'}$), 88.3 ($C_{4'}$), 119.7 (C_4), 143.5 (C_2), 150.8 (C_5), 153.6 (C_8), 157.2 (C_6) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{23}H_{44}N_5O_3Si_2$ [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/CH_2Cl_2); ^{1}H 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–^{t}*Bu*), 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; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (Si–*C*H$_3$), −5.2 (Si–*C*H$_3$), −4.6 (Si–*C*H$_3$), −4.5 (Si–*C*H$_3$), 18.9 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.3 (3*C*H$_3$–^{t}Bu), 26.4 (3*C*H$_3$–^{t}Bu), 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 (C_5), 148.4 (C_6), 152.9 (C_2), 166.8 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{22}H_{42}N_2NaO_5Si_2$ [M + Na]$^+$: 493.2524, found: 493.2529.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1′-homo-*N*-α-thymidine (17c). R_f: 0.16 (50% Et_2O/hexane); ^{1}H 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–^{t}*Bu*), 1.70 (ddd, 1H, $H_{2'}$, J = 12.9, 5.9, 4.5 Hz), 1.86 (d, 3H, *Me*–C_5, 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, H_6) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.30 (Si–*C*H$_3$), −5.26 (Si–*C*H$_3$), −4.6 (Si–*C*H$_3$), −4.5 (Si–*C*H$_3$), 12.3 (*C*H$_3$–C_5) 18.9 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.3 (3*C*H$_3$–^{t}Bu), 26.4 (3*C*H$_3$–^{t}Bu), 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 (C_5), 144.2 (C_6), 152.9 (C_2), 167.0 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{23}H_{45}N_2O_5Si_2$ [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/CH_2Cl_2); ^{1}H 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–^{t}*Bu*), 0.91 (s, 9H, Si–^{t}*Bu*), 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, H_6, J = 6.3 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.31 (Si–*C*H$_3$), −5.26 (Si–*C*H$_3$), −4.6 (Si–*C*H$_3$), −4.55 (Si–*C*H$_3$), 18.9 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.3 (3*C*H$_3$–^{t}Bu), 26.4 (3*C*H$_3$–^{t}Bu), 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, C_6, J = 33.5 Hz), 141.2 (d, C_5, J = 131.5 Hz), 151.6 (C_2), 159.9 (d, C_4, J = 25.3 Hz) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{22}H_{42}FN_2O_5Si_2$ [M + H]$^+$: 489.2611, found: 489.2635 and calcd for $C_{22}H_{41}FN_2NaO_5Si_2$ [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/CH_2Cl_2); ^{1}H 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–^{t}*Bu*), 0.92 (s, 9H, Si–^{t}*Bu*), 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, H_6, J = 7.2 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (Si–*C*H$_3$), −5.2 (Si–*C*H$_3$), −4.6 (Si–*C*H$_3$), −4.5 (Si–*C*H$_3$), 18.9 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.3 (3*C*H$_3$–^{t}Bu), 26.4 (3*C*H$_3$–^{t}Bu), 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 (C_5), 148.5 (C_6), 159.0 (C_2), 168.0 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{22}H_{44}N_3O_4Si_2$ [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/CH_2Cl_2); ^{1}H 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–^{t}*Bu*), 0.92 (s, 9H, Si–^{t}*Bu*), 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, H_6) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.2 (2Si–*C*H$_3$), −4.56 (Si–*C*H$_3$), −4.52 (Si–*C*H$_3$), 18.9 (Si*C*Me$_3$), 19.2 (Si*C*Me$_3$), 26.37 (3*C*H$_3$–^{t}Bu), 26.42 (3*C*H$_3$–^{t}Bu), 38.9 ($C_{2'}$), 53.2 ($C_{6'}$), 64.4 ($C_{5'}$), 67.2 (C_5), 74.7 ($C_{3'}$), 78.0 ($C_{1'}$), 88.3 ($C_{4'}$), 152.6 (C_6), 152.7 (C_2), 163.4 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{22}H_{42}IN_2O_5Si_2$ [M + H]$^+$: 597.1671, found: 597.1684 and calcd for $C_{22}H_{41}IN_2NaO_5Si_2$ [M + Na]$^+$: 619.1491, found: 619.1504.

***N*^{1},*N*^{3}-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-α-ribofuranosylmethyl]uracil (18b).** Colourless oil. R_f: 0.40 (20% EtOAc/hexane); ^{1}H 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–^{t}*Bu*), 0.90 (s, 9H, Si–^{t}*Bu*), 0.92 (s, 9H, Si–^{t}*Bu*), 0.93 (s, 9H, Si–^{t}*Bu*), 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, H_6, J = 7.9 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (2Si–*C*H$_3$), −5.2 (2Si–*C*H$_3$), −4.6 (2Si–*C*H$_3$), −4.5 (2Si–*C*H$_3$), 18.8 (Si*C*Me$_3$), 18.9 (Si*C*Me$_3$), 19.2 (2Si*C*Me$_3$), 26.36 (6*C*H$_3$–^{t}Bu), 26.42 (3*C*H$_3$–^{t}Bu), 26.44 (3*C*H$_3$–^{t}Bu), 39.0 ($C_{2'}$), 39.8 ($C_{2'}$), 46.2 ($C_{7'}$), 54.5 ($C_{6'}$), 64.4 (2$C_{5'}$), 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 (C_5), 146.4 (C_6), 153.2 (C_2), 165.7 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{40}H_{81}N_2O_8Si_4$ [M + H]$^+$: 829.5065, found: 829.5065.

***N*^{1},*N*^{3}-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-α-ribofuranosylmethyl]thymine (18c).** Colourless oil. R_f: 0.50 (20% EtOAc/hexane); ^{1}H 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–^{t}*Bu*), 0.893 (s, 9H, Si–^{t}*Bu*), 0.92 (s, 9H, Si–^{t}*Bu*), 0.93 (s, 9H, Si–^{t}*Bu*), 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, H_6, J = 1.0 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (2Si–*C*H$_3$), −5.2 (2Si–*C*H$_3$), −4.6 (2Si–*C*H$_3$), −4.5 (2Si–*C*H$_3$), 13.1 (C_7), 18.8 (Si*C*Me$_3$), 18.9 (Si*C*Me$_3$), 19.2 (2Si*C*Me$_3$), 26.36 (6*C*H$_3$–^{t}Bu), 26.42 (6*C*H$_3$–^{t}Bu), 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 (C_5), 142.4 (C_6), 153.2 (C_2), 166.0 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{41}H_{83}N_2O_8Si_4$ [M + H]$^+$: 843.5221, found: 843.5218.

***N*^{1},*N*^{3}-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-α-ribofuranosylmethyl]-5-fluorouracil (18d).** Colourless oil. R_f: 0.50 (20% EtOAc/hexane); ^{1}H 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–^{t}*Bu*), 0.892 (s, 9H, Si–^{t}*Bu*), 0.91 (s, 9H, Si–^{t}*Bu*), 0.93 (s, 9H, Si–^{t}*Bu*), 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, H_6, J = 5.9 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.24 (2Si–*C*H$_3$), −5.17 (Si–*C*H$_3$), −5.1 (Si–*C*H$_3$), −4.54 (2Si–*C*H$_3$), −4.48 (2Si–*C*H$_3$), 18.8 (Si*C*Me$_3$), 18.9 (Si*C*Me$_3$), 19.2 (2Si*C*Me$_3$), 26.38 (6*C*H$_3$–^{t}Bu), 26.43

($3CH_3$–^{t}Bu), 26.5 ($3CH_3$–^{t}Bu), 39.0 ($C_{2'}$), 39.7 ($C_{2'}$), 46.9 ($C_{7'}$), 54.3 ($C_{6'}$), 64.4 ($C_{5'}$), 64.5 ($C_{5'}$), 74.6 ($C_{3'}$), 74.8 ($C_{3'}$), 77.3 ($C_{1'}$), 78.1 ($C_{1'}$), 88.1 ($2C_{4'}$), 130.6 (d, C_6, $J = 33.3$ Hz), 140.8 (d, C_5, $J = 229.4$ Hz), 151.7 (C_2), 159.5 (d, C_4, $J = 25.2$ Hz) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{40}H_{79}FN_2NaO_8Si_4$ [M + Na]$^+$: 869.4790, found: 869.4762.

***N*^{1},*N*^{3}-Bis-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-α-ribofuranosylmethyl]-5-iodouracil (18f).** Colourless oil. R_f: 0.56 (20% EtOAc/hexane); ^{1}H 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–^{t}*Bu*), 0.90 (s, 9H, Si–^{t}*Bu*), 0.92 (s, 9H, Si–^{t}*Bu*), 0.93 (s, 9H, Si–^{t}*Bu*), 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, H_6) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.24 (Si–CH_3), −5.19 (Si–CH_3), −5.1 (2Si–CH_3), −4.5 (4Si–CH_3), 18.8 (SiCMe_3), 18.9 (SiCMe_3), 19.2 ($2SiCMe_3$), 26.4 ($6CH_3$–^{t}Bu), 26.5 ($6CH_3$–^{t}Bu), 38.9 ($C_{2'}$), 39.8 ($C_{2'}$), 47.8 ($C_{7'}$), 54.4 ($C_{6'}$), 64.4 ($2C_{5'}$), 66.5 (C_5), 74.6 ($C_{3'}$), 74.7 ($C_{3'}$), 77.4 ($C_{1'}$), 78.0 ($C_{1'}$), 88.0 ($C_{4'}$), 88.3 ($C_{4'}$), 150.9 (C_6), 152.9 (C_2), 162.4 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{40}H_{80}IN_2O_8Si_4$ [M + H]$^+$: 955.4031, found: 955.4033 and calcd for $C_{40}H_{79}IN_2NaO_8Si_4$ [M + Na]$^+$: 977.3850, found: 977.3851.

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

To a solution of **15** (44 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (1.2 mL) at room temperature was added Et_3N (50 μL, 0.36 mmol), Ac_2O (170 μL, 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); ^{1}H 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–^{t}*Bu*), 0.92 (s, 9H, Si–^{t}*Bu*), 1.71 (dt, 1H, H_2, $J = 13.1$, 4.5 Hz), 2.05 (s, 3H, Ac–*Me*), 2.28 (dt, 1H, H_2, $J = 13.6$, 6.9 Hz), 3.63 (qd, 2H, H_5, $J = 11.0$, 4.5 Hz), 3.85 (q, 1H, H_4, $J = 3.9$ Hz), 4.05 (dd, 1H, H_6, $J = 10.9$, 3.7 Hz), 4.24 (m, 1H, H_6), 4.27 (m, 1H, H_1), 4.40 (dt, 1H, H_3, $J = 6.2$, 3.9 Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (Si–CH_3), −5.2 (Si–CH_3), −4.6 (Si–CH_3), −4.5 (Si–CH_3), 18.8 (SiCMe_3), 19.2 (SiCMe_3), 20.8 (Ac–CH_3), 26.3 ($3CH_3$–^{t}Bu), 26.4 ($3CH_3$–^{t}Bu), 38.1 (C_2), 64.4 (C_5), 68.1 (C_6), 74.4 (C_3), 78.1 (C_1), 88.4 (C_4), 172.6 (C=O) ppm.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-1α-((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); ^{1}H 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–^{t}*Bu*), 0.90 (s, 9H, Si–^{t}*Bu*), 1.64 (dt, 1H, H_2, $J =$ 13.3, 3.4 Hz), 2.21 (ddd, 1H, H_2, $J = 13.7$, 8.1, 5.8 Hz), 2.45 (s, 3H, Ts–*Me*), 3.46 (dd, 1H, H_5, $J = 10.9$, 5.6 Hz), 3.57 (dd, 1H, H_5, $J =$ 10.9, 3.8 Hz), 3.69 (m, 1H, H_4), 3.98 (dd, 1H, H_6, $J = 10.0$, 4.0 Hz), 4.12 (dd, 1H, H_6, $J = 10.0$, 7.6 Hz), 4.27 (m, 1H, H_1), 4.33 (m, 1H, H_3), 7.43 (d, 2H, H_{arom}, $J = 8.5$ Hz), 7.79 (d, 2H, H_{arom}, $J = 8.4$ Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ −5.3 (Si–CH_3), −5.2 (Si–CH_3), −4.6 (2Si–CH_3), 18.7 (SiCMe_3), 19.2 (SiCMe_3), 21.6 (CH_3–Ts), 26.3 ($3CH_3$–^{t}Bu), 26.4 (3^tBu–CH_3), 37.6 (C_2), 64.4 (C_5), 73.6 (C_6), 74.5 (C_3), 77.9 (C_1), 88.7 (C_4), 129.1 ($2C_{arom}$), 131.0 ($2C_{arom}$), 134.4 (C_{ipso}), 146.3 (C_{ipso}) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{25}H_{47}O_6SSi_2$ [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.

***N*^{1},*N*^{3}-Bis-(1,2-dideoxy-α-ribofuranosylmethyl)-5-fluorouracil (21d).** Colourless oil. R_f: 0.15 (15% MeOH/CH_2Cl_2); ^{1}H NMR (300.13 MHz, MeOH-d_4): δ 1.74 (m, 2H, $H_{2'}$), 2.33 (m, 2H, $H_{2'}$), 3.54 (m, 4H, $H_{5'}$), 3.90 (m, 5H, $2H_{4'} + 2H_{6'} + H_{7'}$), 4.22 (m, 2H, $H_{3'}$), 4.39 (m, 2H, $H_{1'}$), 4.50 (dd, 1H, $H_{7'}$, $J = 12.6$, 8.8 Hz), 7.84 (d, 1H, H_6, $J = 6.0$ Hz) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ 38.4 ($C_{2'}$), 39.3 ($C_{2'}$), 46.6 ($C_{7'}$), 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, C_6, $J = 33.5$ Hz), 140.8 (d, C_5, $J = 229.0$ Hz), 151.9 (C_2), 159.6 (d, C_4, $J = 25.0$ Hz) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{16}H_{24}FN_2O_8$ [M + H]$^+$: 391.1511, found: 391.1526 and calcd for $C_{16}H_{23}FN_2NaO_8$ [M + Na]$^+$: 413.1331, found: 413.1345.

***N*^{1},*N*^{3}-Bis-(1,2-dideoxy-α-ribofuranosylmethyl)-5-iodouracil (21f).** Colourless oil. R_f: 0.24 (15% MeOH/CH_2Cl_2); ^{1}H NMR (300.13 MHz, MeOH-d_4): δ 1.73 (m, 2H, $H_{2'}$), 2.32 (m, 2H, $H_{2'}$), 3.53 (m, 4H, $H_{5'}$), 3.89 (m, 3H, $2H_{4'} + H_{7'}$), 3.96 (m, 2H, $H_{6'}$), 4.23 (m, 2H, $H_{3'}$), 4.39 (m, 2H, $H_{1'}$), 4.52 (dd, 1H, $H_{7'}$, $J = 12.9$, 8.7 Hz), 8.08 (s, 1H, H_6) ppm; ^{13}C NMR (75.5 MHz, MeOH-d_4): δ 38.4 ($C_{2'}$), 39.3 ($C_{2'}$), 47.6 ($C_{7'}$), 54.4 ($C_{6'}$), 63.2 ($C_{5'}$), 63.3 ($C_{5'}$), 66.4 (C_5), 73.4 ($2C_{3'}$), 76.7 ($C_{1'}$), 77.6 ($C_{1'}$), 87.0 ($C_{4'}$), 87.8 ($C_{4'}$), 151.2 (C_6), 153.1 (C_2), 162.5 (C_4) ppm; HRMS (ESI$^+$, *m*/*z*): calcd for $C_{16}H_{24}IN_2O_8$ [M + H]$^+$: 499.0572, found: 499.0577 and calcd for $C_{16}H_{23}IN_2NaO_8$ [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 (EC_{50}) were determined using described method.[23d]

HBV assay. HepAD38 cells[24] 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 μM. 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% (EC_{50}) 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% (IC_{50}) 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 K_2CO_3 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.

Acknowledgements

Financial support by the Spanish Ministerio de Ciencia e Innovación (MICINN, Project CTQ2014-55015-P) and Principado de Asturias (Project IDI/2018/000181) are gratefully acknowledged. This work was also supported in part by NIH grants 1-R01-AI-132833 (to R. F. S.) and 5P30-AI-50409 (CFAR) (to R. F. S.).

References

1 (*a*) E. De Clercq, *Curr. Opin. Microbiol.*, 2005, **8**, 552–560; (*b*) S. Rachakonda and L. Cartee, *Curr. Med. Chem.*, 2004, **11**, 775–793; (*c*) *Recent Advances in Nucleosides: Chemistry and Chemotherapy*, ed. C. K. Chu, Elsevier Science, New York, 2002; (*d*) *Nucleoside Analogs in Cancer Therapy*, ed. B. D. Chenson, M. J. Keating and W. Plunkett, Marcel Dekker, New York, 1997; (*e*) *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*, ed. C. K. Chu and D. C. Baker, Plenum Press, New York, 1993; (*f*) *Chemistry of Nucleosides and Nucleotides*, ed. L. B. Townsend, Plenum Press, New York, 1988.

2 See a recent review on α-nucleosides: G. Ni, Y. Du, F. Tang, J. Liu, H. Zhao and Q. Chen, *RSC Adv.*, 2019, **9**, 14302–14320.

3 A. E. Wróblewski, I. E. Glowacka and D. G. Piotrowska, *Eur. J. Med. Chem.*, 2016, **118**, 121–142.

4 C. Lamberth, *Org. Prep. Proced. Int.*, 2002, **34**, 149–167.

5 D. González-Calderón, M. G. Mejía-Dionicio, M. A. Morales-Reza, J. G. Aguirre-de Paz, A. Ramírez-Villalva, M. Morales-Rodríguez, A. Fuentes-Benítes and C. González-Romero, *Bioorg. Chem.*, 2016, **69**, 1–6.

6 C. I. Tanase, C. Draghici, A. Hanganu, L. Pintilie, M. Maganu, A. Volobueva, E. Sinegubova, V. V. Zarubaev, J. Neyts, D. Jochmans and A. V. Slita, *Molecules*, 2019, **24**, 2446.

7 Y. Okada, K. Shimada, Y. Kitano and K. Chiba, *Eur. J. Org. Chem.*, 2014, 1371–1375.

8 S. Martínez-Montero, S. Fernańdez, Y. S. Sanghvi, J. Chattopadhyaya, M. Ganesan, N. G. Ramesh, V. Gotor and M. Ferrero, *J. Org. Chem.*, 2012, **77**, 4671–4678.

9 (*a*) P. Busca, I. McCort, T. Prangé and Y. Le Merrer, *Eur. J. Org. Chem.*, 2006, 2403–2409; (*b*) P. Angibeaud, J. Defaye and H. Franconie, *Carbohydr. Res.*, 1980, **78**, 195–204.

10 F. Morvan, J. Zeidler and B. Rayner, *Tetrahedron*, 1998, **54**, 71–82.

11 (*a*) D. C. Pryde, D. S. Middleton, P. T. Stephenson, P. Wainwright, A. Maddaford, X. Zhang, D. Leese, R. Glen, J. Hart, N. Forrest and T. Guyot, *Tetrahedron Lett.*, 2011, **52**, 6415–6419; (*b*) J. Farkas, *Collect. Czech. Chem. Commun.*, 1971, **36**, 3043–3046; (*c*) J. A. Montgomery and K. Hewson, *J. Heterocycl. Chem.*, 1970, **7**, 443–445; (*d*) M. Bobek and J. Farkas, *Collect. Czech. Chem. Commun.*, 1969, **34**, 1684–1689.

12 M. W. Winkley, *Carbohydr. Res.*, 1973, **31**, 245–254.

13 (*a*) R. Saladino, V. Neri, P. Checconi, I. Celestino, L. Nencioni, A. T. Palamara and M. Crucianelli, *Chem.–Eur. J.*, 2013, **19**, 2392–2404; (*b*) B. Doboszewski, *Nucleos Nucleot. Nucleic Acids*, 2009, **28**, 875–901; (*c*) B. Doboszewski, *Nucleosides Nucleotides*, 1997, **16**, 1049–1052; (*d*) N. Hossain, N. Blaton, O. Peeters, J. Rozenski and P. Herdewijn, *Tetrahedron*, 1996, **52**, 5563–5578.

14 (*a*) C. L. Scremin, J. H. Boal, A. Wilk, L. R. Philips and S. L. Beaucage, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 207–212; (*b*) J. H. Boal, A. Wilk, C. L. Scremin, G. N. Gray, L. R. Philips and S. L. Beaucage, *J. Org. Chem.*, 1996, **61**, 8617–8626.

15 (*a*) A. Carnero, S. Pérez-Rentero, A. Alagia, A. Aviñó, Y. S. Sanghvi, S. Fernández, M. Ferrero and R. Eritja, *RSC Adv.*, 2017, **7**, 9579–9586; (*b*) A. Carnero, Y. S. Sanghvi, V. Gotor, S. Fernández and M. Ferrero, *Org. Process Res. Dev.*, 2015, **19**, 701–709; (*c*) S. Martínez-Montero, S. Fernández, Y. S. Sanghvi, E. A. Theodorakis, M. A. Detorio, T. R. Mcbrayer, T. Whitaker, R. F. Schinazi, V. Gotor and M. Ferrero, *Bioorg. Med. Chem.*, 2012, **20**, 6885–6893; (*d*) S. Martínez-Montero, S. Fernández, Y. S. Sanghvi, V. Gotor and M. Ferrero, *Eur. J. Org. Chem.*, 2012, 5483–5490; (*e*) S. Martínez-Montero, S. Fernández, Y. S. Sanghvi, V. Gotor and M. Ferrero, *Org. Biomol. Chem.*, 2011, **9**, 5960–5966; (*f*) T. Rodríguez-Pérez, S. Fernández, Y. S. Sanghvi, M. Detorio, R. F. Schinazi, V. Gotor and M. Ferrero, *Bioconjugate Chem.*, 2010, **21**, 2239–2249; (*g*) S. Martínez-Montero, S. Fernández, Y. S. Sanghvi, V. Gotor and M. Ferrero, *J. Org. Chem.*, 2010, **75**, 6605–6613; (*h*) T. Rodríguez-Pérez, S. Fernández, S. Martínez-Montero, T. González-García, Y. S. Sanghvi, V. Gotor and M. Ferrero, *Eur. J. Org. Chem.*, 2010, 1736–1744.

16 (*a*) Pure α-cyano-sugar **12** is available from Sapala Organics Pvt. Ltd, India, http://www.sapalaorganics.com; (*b*) T. H. Smith, M. A. Kent, S. Muthini, S. J. Boone and P. S. Nelson, *Nucleosides Nucleotides*, 1996, **15**, 1581–1594.

17 H. Vorbrüggen and C. Ruh-Pohlenz, *Handbook of Nucleoside Synthesis*, Wiley Interscience, 2001.

18 O. R. Ludek and C. Meier, *Eur. J. Org. Chem.*, 2006, 941–946.

19 Molecular graphics and analyses were performed with the UCSF Chimera package (http://www.rbvi.ucsf.edu/chimera). Chimera is developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco (supported by NIGMS P41-GM103311).

20 CCDC 1980305 contains the supplementary crystallographic data for compound **10a**.

21 M. Prystas and F. Sorm, *Collect. Czech. Chem. Commun.*, 1969, **34**, 2316–2347.

22 Z. J. Yang, H. W. Yu, J. M. Min, L. T. Ma and L. H. Zhang, *Tetrahedron Asymmetry*, 1997, **8**, 2739–2747.

23 (*a*) R. F. Schinazi, J.-P. Sommadossi, V. Saalmann, D. L. Cannon, M.-W. Xie, G. C. Hart, G. A. Smith and E. F. Hahn, *Antimicrob. Agents Chemother.*, 1990, **34**, 1061–1067; (*b*) R. F. Schinazi, A. McMillan, D. Cannon, R. M. Mathis, R. M. Lloyd, A. Peck, J.-P. Sommadossi, M. St. Clair, J. Wilson, P. A. Furman, G. Painter, W.-B. Choi and D. C. Liotta, *Antimicrob. Agents Chemother.*, 1992, **36**, 2423–2431; (*c*) L. J. Stuyver, S. Lostia, M. Adams, J. S. Mathew, B. S. Pai, J. Grier, P. M. Tharnish, Y. Choi, Y. Chong, H. Choo, C. K. Chu, M. J. Otto and R. F. Schinazi, *Antimicrob. Agents Chemother.*, 2002, **46**, 3854–3860; (*d*) M. S. Belen'kii and R. F. Schinazi, *Antiviral Res.*, 1994, **25**, 1–11.

24 S. K. Ladner, M. J. Otto, C. S. Barker, K. Zaifert, G. H. Wang, J. T. Guo, C. Seeger and R. W. King, *Antimicrob. Agents Chemother.*, 1997, **41**, 1715–1720.

25 T.-C. Chou and P. Talalay, *Adv. Enzym. Regul.*, 1984, **22**, 27–55.

