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Original article

Stereospecific synthesis and biological evaluations of β-L-pentofuranonucleoside derivatives of 5-fluorouracil and 5-fluorocytosine

Jean-François Griffon[a], Christophe Mathé[a,*], Abdesslem Faraj[b], Anne-Marie Aubertin[c], Erik De Clercq[d], Jan Balzarini[d], Jean-Pierre Sommadossi[e], Gilles Gosselin[a,b]

[a]Laboratoire de Chimie Organique Biomoléculaire de Synthèse, UMR 5625 CNRS-UM II, Université Montpellier II, case courrier 008, Place Eugène Bataillon, F-34095 Montpellier, France
[b]Laboratoire Coopératif Novirio, CNRS-UM II, Université Montpellier II, France
[c]Université Louis Pasteur, INSERM U 74, F-67000 Strasbourg, France
[d]Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium
[e]Novirio-Pharmaceuticals, Inc., Cambridge, MA, USA

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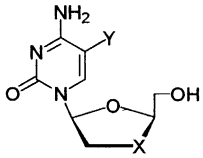
Abstract – In the search for new chemotherapeutic agents, we have focused our work on the synthesis and the study of several unnatural β-L-nucleoside analogues. In this paper, we report on the synthesis of β-L-pentofuranonucleosides (and their 2′-deoxy derivatives) of 5-fluorouracil and their inhibitory effects on the proliferation of several murine and human tumor cells. The corresponding 5-fluorocytosine derivatives were also synthesized and their anti-HIV and anti-HBV activities have been evaluated.

β-L-nucleoside analogues / 5-fluorouracil / anti-tumoral activity / 5-fluorocytosine / anti-HIV activity / anti-HBV activity

1. Introduction

5-Fluorouracil (**1**) (5FU) is widely used in the treatment of various solid tumors. This 5-fluorinated analogue of the natural pyrimidine base uracil exerts its anti-tumoral activity through various mechanisms [1, 2]. In fact, 5FU can be converted intracellularly into 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP), which is a mechanism-based inhibitor of the thymidylate synthase (TS) [3]. TS is an essential enzyme in pyrimidine de novo biosynthesis; it catalyses the methylation of 2′-deoxyuridine 5′-monophosphate (dUMP) to 2′-deoxythymidine 5′-monophosphate (dTMP) with concomitant conversion of N^5,N^{10}-methylene-5,6,7,8-tetrahydrofolate (CH_2H_4-folate) to 7,8-dihydrofolate (H_2-folate). The direct effect of TS inhibition is a depletion of dTMP, and subsequently, of 2′-deoxythymidine 5′-triphosphate (dTTP). The 2′-deoxy-β-D-ribofuranonucleoside of 5-fluorouracil (β-D-5FdU) is a very potent cytotoxic agent in cell culture systems, but it suffers in vivo from substantial degradation by thymidine phosphorylase to the pyrimidine base 5FU and deoxyribose-1-phosphate before reaching the target tissues [4]. In the search for new anti-neoplastic agents, many sugar-modified nucleoside analogues of 5FU have been synthesized earlier and their interactions with TS or thymidine phosphorylase studied [5–8]. Only very few studies have dealt with the unnatural β-L nucleoside analogues of 5FU. Holý et al. [9, 10] have reported the anti-bacterial effects and the enzymatic degradation of the β-L-2′-deoxyribo-, ribo- and *arabino*-furanosyl derivatives. Recently, Weis et al. [11] have evaluated the inhibitory effect of the β-L-2′-deoxyribo- and ribofuranosyl derivatives on the proliferation of several human tumor cell lines. These compounds were found to be either weakly active or not active at all.

* Correspondence and reprints
E-mail address: cmathe@univ-montp2.fr (C. Mathé).



3TC (X = S, Y = H)
(-)-FTC (X = S, Y = H)
β-L-ddC (X = CH_2, Y = H)
β-L-FddC (X = CH_2, Y = F)

Figure 1. Cytosine or 5-fluorocytosine nucleoside analogues endowed with the unnatural L configuration with potent anti-viral activity.

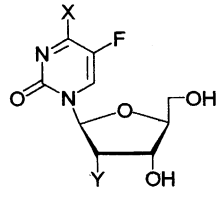
Nucleoside analogues endowed with the unnatural L configuration have drawn considerable attention as potential anti-viral drugs. The possibility that L-nucleoside derivatives may be more efficient than the corresponding D-counterparts, owing to their powerful anti-viral activity and favorable toxicity profile, has been demonstrated for some of them [12]. Particularly, those bearing a cytosine or 5-fluorocytosine base moieties were found to possess very potent anti-viral activity (*figure 1*). For instance, β-L(-)-2′,3′-dideoxy-3′-thiacytidine (3TC, Lamivudine,) was approved recently by the Food and Drug Administration (FDA) as an anti-human immunodeficiency virus (HIV) and anti-hepatitis B virus (HBV) drug and its 5-fluoro derivative [(−)-FTC] was also found to exhibit not only anti-HIV but also anti-HBV activities [13–15]. Additionally, β-L-2′,3′-dideoxycytidine (β-L-ddC) and its 5-fluoro derivative (β-L-FddC), widely studied by our group [16–20] and others [21–24] show potent anti-HIV and anti-HBV activities in cell culture systems.

As part of our ongoing research on β-L-nucleoside analogues, the stereospecific syntheses of the unnatural β-L-pento- and 2′-deoxy-β-L-pentofuranonucleosides of 5FU and 5-fluorocytosine (*figure 2*) are presented in this work. β-L-Nucleoside derivatives of 5FU were evaluated for their inhibitory effect on the proliferation of several murine and human tumor cells, while β-L-nucleoside derivatives of 5-fluorocytosine were evaluated for their anti-HIV and anti-HBV activities.

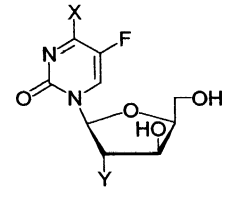
2. Chemistry

*2.1. β-L-Pentofuranonucleosides of 5FU (**4**, **7**, **11** and **15**)*

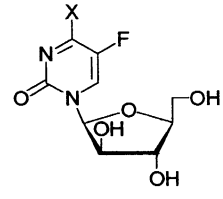
From a synthetic viewpoint, the dissymetrically peracylated 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose



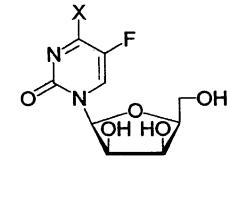
4 (X = OH, Y = OH) β-L-5FU
23 (X = NH_2, Y =OH) β-L-5FC
20 (X = OH, Y = H) β-L-5FdU
26 (X = NH_2, Y = H)β-L-5FdC



7 (X = OH, Y = OH) β-L-*xylo*-5FU
24 (X = NH_2, Y = OH) β-L-*xylo*-5FC
17 (X = OH, Y = H) β-L-*threo*-5FdU
25 (X = NH_2, Y = H) β-L-*threo*-5FdC



11 (X = OH) β-L-*ara*-5FU
27 (X = NH_2) β-L-*ara*-5FC



15 (X = OH) β-L-*lyxo*-5FU
28 (X = NH_2) β-L-*lyxo*-5FC

Figure 2. β-L-Pento- and 2′-deoxy-β-L-pentofuranonucleosides of 5FU and 5-fluorocytosine.

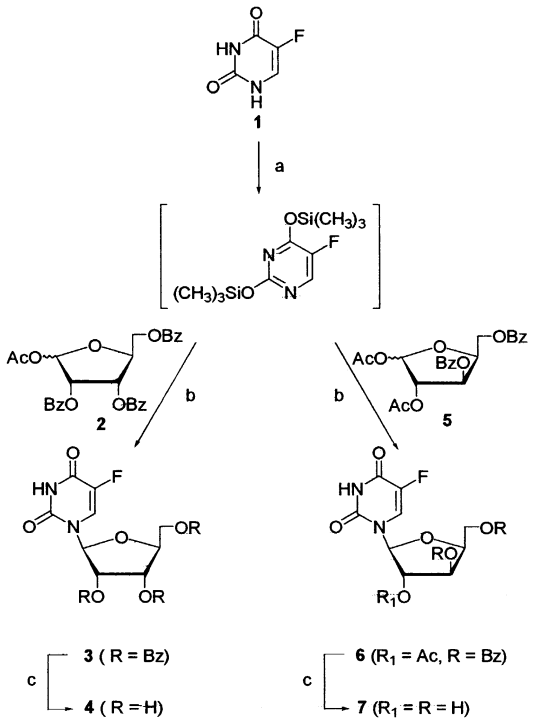


Figure 3. Synthesis of compounds **4** and **7**. Reagents and conditions: (a) HMDS, $(NH_4)SO_4$, reflux; (b) TMSTf, $(CH_2Cl)_2$, r.t.; (c) MeOH–NH_3, r.t.

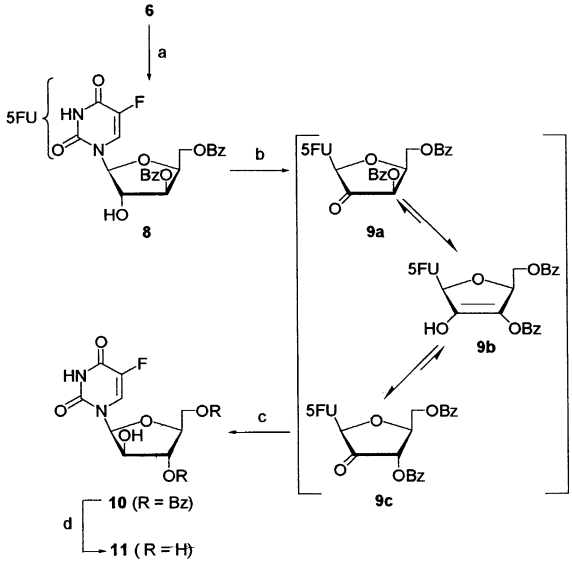


Figure 4. Synthesis of compound **11**. Reagents and conditions: (a) $H_2NNH_2{\cdot}H_2O$, AcOH, pyridine, r.t.; (b) DCC, DMSO, Cl_2CHCO_2H, benzene, pyridine, r.t.; (c) $NaBH_4$, EtOH, benzene, r.t.; (d) MeONa, MeOH, benzene, r.t.

(**2**) [25] or 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanose (**5**) [26] were, respectively, condensed with the commercially available 5-fluorouracil **1**, under Vörbruggen [27] conditions, using (trimethylsilyl)trifluoromethane sulfonate (TMSTf) as a catalyst, to exclusively give (owing to 2-*O*-acyl participation [28]) the corresponding fully protected β-L-nucleosides **3** and **6** (*figure 3*). These compounds were deacylated with saturated methanolic ammonia to afford the desired 1-(β-L-ribofuranosyl)-5-fluorouracil (**4**) and 1-(β-L-*xylo*-furanosyl)-5-fluorouracil (**7**) after silica gel column chromatography.

Regioselective 2′-*O*-deacylation (*figure 4*) of the fully protected *xylo*-nucleoside **6** with hydrazine hydrate gave **8**, which was then subjected to an oxidation–reduction process to obtain the *arabino*-nucleoside derivative as reported earlier by Gosselin et al. [29]. Oxidation of compound **8** was accomplished with dimethylsulfoxide (DMSO), dicyclohexylcarbodiimide (DCC) and dichloroacetic acid. The resulting 2′-keto nucleoside **9a** undergoes an epimerization at C-3′, via a keto–enol equilibrium as shown in square brackets (*figure 4*), to give the 2′-keto intermediate **9c**. Reduction of **9c** with sodium borohydride ($NaBH_4$) proceeded stereoselectively leading to the formation of **10**, which was then debenzoylated with sodium methanolate in a methanol–toluene mixture to form 1-(β-L-*arabino*-furanosyl)-5-fluorouracil (**11**) after purification on a silica gel column.

Additionally, 1-(β-L-*lyxo*-furanosyl)-5-fluorouracil (**15**) was obtained in several steps from the β-L-*xylo*-furanonuc1eoside (**7**) (*figure 5*), according to a strategy described earlier by Fox et al. [30] in the β-D-pyrimidine series. Thus, the reaction of **7** with 2,2-dimethoxypropane and *p*-toluene sulfonic acid (*p*-TsOH) gave 3′,5′-*O*-isopropylidene nucleoside (**12**), which was treated with methanesulfonyl chloride (MsCl) followed by hydrolysis with 80% aqueous acetic acid to form the 2′-*O*-mesyl derivative (**13**). Treatment of **13** with water under reflux allowed the inversion of configuration at C-2′ via 2,2′-*O*-anhydro intermediate (**14**) and led to the formation of 1-(β-L-*lyxo*-furanosyl)-5-fluorouracil (**15**) after silica gel column chromatography.

*2.2. 2′-Deoxy-β-L-pentofuranonucleosides of 5FU (**17** and **20**)*

1-(2-Deoxy-β-L-*threo*-pentofuranosyl)-5-fluorouracil (**17**) was obtained from **8** via a Barton–McCombie reductive process [31]. Thus, the treatment of **8** (*figure 6*) with *O*-phenyl chloro(thio)formate [PhOC(=S)Cl] and 4-(dimethyamino)pyridine (DMAP) formed the corre-

sponding 2′-*O*-[phenoxy(thiocarbonyl)] intermediate, which was subsequently deoxygenated with tris-(trimethylsilyl)silane [32] in the presence of α,α′-azoisobutyronitrile (AIBN). Finally, debenzoylation with saturated methanolic ammonia formed **17** as a crystalline solid after silica gel column chromatography. To prepare compound **20**, 2′-deoxy-β-L-*threo*-pentofuranonucleoside (**17**) was selectively converted into the 5′-*O*-benzoyl derivative (**18**). Inversion of the hydroxyl group at C-3′ was achieved via the Mitsunobu reaction

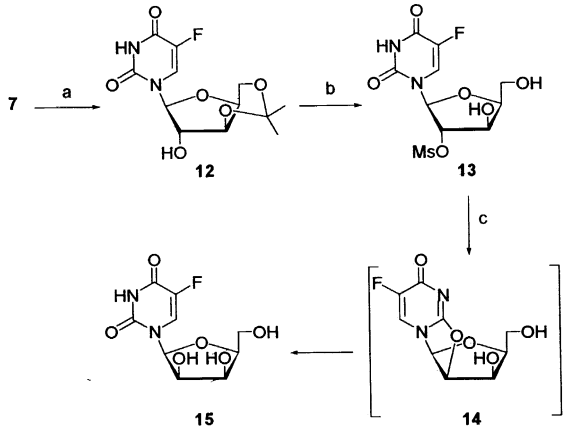


Figure 5. Synthesis of compound **15**. Reagents and conditions: (a) 2,2-dimethoxy-propane, *p*-TsOH, DMF, r.t.; (b) (1) MsCl, pyridine, 0 °C, (2) AcOH 80%, reflux; (c) H_2O, reflux.

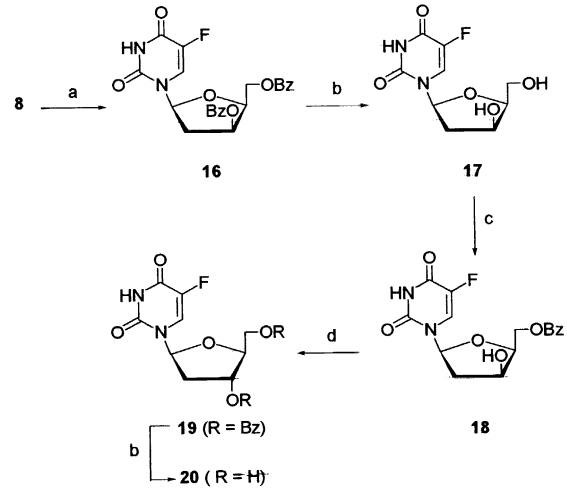


Figure 6. Synthesis of compounds **17** and **20**. Reagents and conditions: (a) (1) DMAP, PhO(C=S)Cl, CH_3CN, r.t, (2) $(Me_3Si)_3SiH$, AIBN, dioxane, 100 °C; (b) MeOH–NH_3, r.t; (c) BzCl, pyridine, DMF, 0 °C; (d) DEAD, benzoic acid, PPh_3, THF, 0 °C.

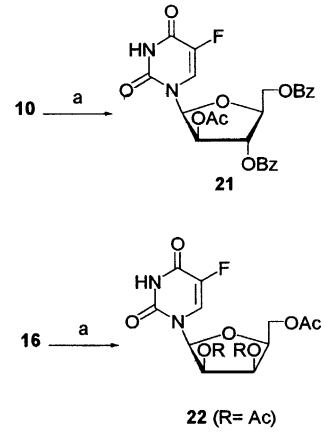


Figure 7. Synthesis of compounds **21** and **22**. Reagents and conditions: (a) Ac_2O, pyridine, r.t.

[33], using as incoming nucleophile benzoic acid. Thus, the reaction of **18** with diethyl azodicarboxylate (DEAD), triphenyl phosphine (PPh_3) and benzoic acid in anhydrous tetrahydrofuran (THF) at 0 °C gave nucleoside **19** which upon deprotection with methanolic ammonia formed 1-(2-deoxy-β-L-*erythro*-pentofuranosyl)-5-fluorouracil **20** as a crystalline solid after purification on silica gel column.

*2.3. β-L-Pento- and 2′-deoxy-β-L-pentofurano-nucleosides of 5-fluorocytosine (**23**–**28**)*

The synthesis of the 5-fluorocytosine nucleosides was carried out from the corresponding 5FU peracylated nucleosides. For the *arabino*- and *xylo*-nucleoside derivatives, **10** and **16**, an additional step of acetylation with acetic anhydride was necessary to obtain the fully protected nucleosides **21** and **22** (*figure 7*).

Conversion of peracylated 5FU derivatives **3**, **6**, **16**, **19**, **21**, and **22** to the corresponding 5-fluorocytosine nucleosides **23**–**28** was carried out via a treatment with Lawesson's reagent [34, 35], followed by the treatment of 4-thioamide intermediates with methanolic ammonia at 100 °C in a stainless-steel bomb (*figure 8*).

3. Biological results

The β-L-nucleosides analogues of 5FU, **4**, **7**, **11**, **15**, **17** and **20** (*table I*) were tested for their in vitro inhibitory effect on the proliferation of murine leukemia cells (L1210), murine mammary carcinoma cells (FM3A) and human T-lymphocyte cells (Molt4/

C8 and CEM). 5FU **1** and β-D-5FdU were used as reference compounds. From these data, it appears that only β-L-*xylo*-5FU (**7**) shows some activity, albeit restricted to the murine L1210 and FM3A cells. The weak activity of compound **7** and the lack of an inhibitory effect for the other β-L-nucleoside derivatives of 5FU highlights the fact that these compounds are probably not able: (i) to release 5FU, via a chemical or enzymatic cleavage of the glycosidic bound, from the parent nucleoside; (ii) to serve as substrates for intracellular enzymes involved in the anabolic pathway.

β-L-Nucleoside analogues of 5-fluorocytosine **23**–**28** were evaluated for their in vitro inhibitory effect on the replication of HIV-1 in CEM-SS and MT-4 cell systems, but none of them showed any anti-viral activity or cytotoxicity (up to 100 μM, data not shown). When evaluated in anti-HBV assays in the HBV DNA-transfected Hep-G2 cells (2.2.15 cells), only β-L-5FdC (**26**) showed anti-viral activity ($EC_{50} = 4$ μM for HBV RI, $EC_{50} = 5$ μM for HBV virion). In the same assays, the others β-L-nucleoside analogues were inactive (up to a concentration of 10 μM). All β-L-nucleoside derivatives of 5-fluorocytosine did not show any cytotoxicity in Hep-G2 cells (up to a concentration of 200 μM).

4. Conclusion

The β-L-pento- and 2′-deoxypentofuranonucleosides of 5FU, **4**, **7**, **11**, **15**, **17** and **20**, were stereospecifically and conveniently prepared by following multi-step reaction sequences. When evaluated for their inhibitory effect on the proliferation of several murine and human tumor cells, it appeared that only β-L-*xylo*-5FU (**7**) showed some inhibitory activity. The β-L-5-fluorocytosine derivatives (**23**–**28**), synthesized from the corresponding 5-fluorouracil

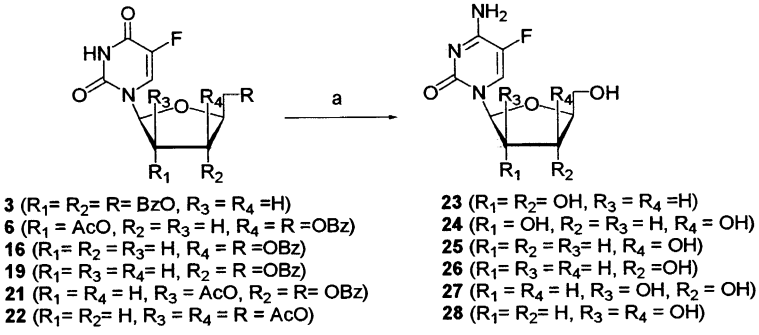


Figure 8. General synthetic procedure for compounds **23**–**28**. Reagents and conditions: (a) (1) Lawesson's reagent, $(CH_2Cl)_2$, reflux; (2) MeOH–NH_3, 100 °C.

Table I. Inhibitory effect of β-L-nucleoside analogues of 5-fluorouracil on the proliferation of murine leukemia cells (L1210), murine mammary carcinoma cells (FM3A) and human T-lymphocyte cells (Molt4/C8 and CEM).

Compound	IC_{50} [a](μM)			
	L1210	FM3A	Molt4/C8	CEM
β-D-5FdU	0.001 ± 0.0001	0.003 ± 0.0004	11 ± 2.7	0.014 ± 0.001
1 (5-fluorouracil)	0.282 ± 0.143	0.183 ± 0.090	23 ± 3.0	89 ± 0.43
4 (β-L-5FU)	294 ± 95	>500	>500	>500
7 (β-L-*xylo*-5FU)	43 ± 5.6	67 ± 8.4	>500	395 ± 148
11 (β-L-*ara*-5FL)	>500	>500	>500	>250
15 (β-L-*lyxo*-5FU)	>500	>500	>500	>500
17 (β-L-*threo*-5FdU)	319 ± 133	465 ± 61	>500	>500
20 (β-L-5FdU)	135 ± 53	129 ± 61	>500	>250

[a] IC_{50} value represents the drug concentration (μM) required to inhibit the proliferation of malignant cells by 50%.

nucleosides, were evaluated against HIV-1 in cell cultures, but none of them showed any anti-viral activity. When evaluated in anti-HBV assays, only β-L-5FdC (**26**) showed moderate anti-viral activity without concomitant cytotoxicity.

5. Experimental

5.1. Chemistry

Melting points (m.p. (dec.)) were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. The UV absorption spectra were recorded on an Uvikon 931 (KONTRON) spectrophotometer in ethanol. ^{1}H NMR spectra were run at room temperature (r.t.) in DMSO-d_6 with a Bruker AC 250 or 400 spectrometer. Chemical shifts are given in ppm, DMSO-d_5 being set at 2.49 ppm as reference. Deuterium exchange, decoupling experiments or 2D-COSY spectra were carried out to confirm the proton assignments. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), m (multiplet). All *J*-values are in Hz. FAB mass spectra were recorded in the positive- (FAB>0) or negative- (FAB<0) ion mode on a JEOL DX 300 mass spectrometer; the matrix was 3-nitrobenzyl alcohol (NBA) or a mixture (50:50, v/v) of glycerol and thioglycerol (GT). Specific rotations were measured on a Perkin–Elmer 241 spectropolarimeter (path length, 1 cm) and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the 'Service de Microanalyses du CNRS, Division de Vernaison' (France). Analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical values. Thin layer chromatography was performed on precoated aluminum sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbency followed by charring with 10% ethanolic sulphuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385) at atmospheric pressure.

5.1.1. General procedure for the preparation of compounds *4*, *7*, *11*, *17* and *20*

A solution of the protected nucleoside in methanolic ammonia (saturated earlier at −10 °C and stoppered tightly), (ca. 25 mL mmol^{-1}) was stirred overnight at r.t. The solution was evaporated to dryness under reduced pressure and the residue co-evaporated several times with methanol. The crude material was dissolved in water and the resulting solution was washed four times with methylene chloride. The aqueous layer was evaporated under reduced pressure and the residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–10%) in chloroform or gradient of methanol (0–5%) in ethyl acetate). Finally, the appropriate fractions were evaporated under reduced pressure, diluted with methanol and filtered through a unit Millex HV-4 (0.45 μm, Millipore).

5.1.2. General procedure for the preparation of compounds *23*–*28*

Lawesson's reagent (0.7 equiv.) was added under argon to a solution of the peracylated 5-fluorouracil nucleoside in anhydrous 1,2-dichloroethane (ca. 25 mL mmol^{-1}) and the reaction mixture was stirred overnight under reflux. The solvent was then evaporated under reduced pressure and the residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–2%) in chloroform) to give the corresponding 4-thio intermediate. A solution of the 4-thio intermediate in methanolic ammonia (saturated beforehand at −10 °C and stoppered tightly), (ca. 25 mL mmol^{-1}) was heated at 100 °C in a stainless-steel bomb for 3 h, and then cooled to r.t. The solution was evaporated to dryness under reduced pressure and the residue was co-evaporated several times in methanol. The crude material was dissolved in water and the resulting solution was washed with methylene chloride. The aqueous layer was evaporated under reduced pressure and the residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–15%) in chloroform or ethyl acetate). The appropriate fractions were pooled and evaporated under reduced pressure, diluted with methanol and filtered through a unit Millex HV-4 (0.45 μm, Millipore).

5.1.3. 1-(2,3,5-Tri-O-benzoyl-β-L-ribofuranosyl)-5-fluorouracil (*3*)

A suspension of 5-fluorouracil (**1**) (387 mg, 297 mmol) was treated with hexamethyldisilazane (HMDS, 20 mL) and a catalytic amount of ammonium sulfate during 18 h under reflux. After cooling to r.t., the mixture was evaporated under reduced pressure, and the residue obtained as a colorless oil was diluted with anhydrous 1,2-dichloroethane (20 mL). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (**2**) [25] (1.0 g, 1.98 mmol) in anhydrous 1,2-dichloroethane (11 mL) was added to the resulting solution followed by the addition of TMSTf

(0.72 mL, 3.96 mmol). The solution was stirred for 6 h at r.t. under argon atmosphere, then diluted with chloroform (150 mL), washed with the same volume of a saturated aqueous sodium hydrogen carbonate solution and finally with water (2×100 mL). The organic phase was dried over sodium sulfate, and then evaporated under reduced pressure. The resulting crude material was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–4%) in methylene chloride) to give pure **3** (1.08 g, yield: 95%), which was crystallized from chloroform; m.p. = 200–202 °C (lit. value = 204 °C [10]); UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 230 (37 400), 266 (11 500), λ_{min} (nm): 253 (10 200); ^{1}H NMR (DMS0-d_6): δ 13.0 (br s, 1H, NH), 8.19 (d, 1H, H-6, $J_{6\text{-}F5}$ = 6.8 Hz), 8.0–7.4 (m, 15H, 3 C_6H_5CO), 6.16 (d, 1H, H-1′, $J_{1'\text{-}2'}$ = 3,3 Hz), 5.9–5.8 (m, 2H, H-2′, H-3′), 4.8–4.6 (m, 3H, H-4′, H-5′, H-5″); FABMS (FAB>0); m/z (GT): 1149 $[2M+H]^+$, 575 $[M+H]^+$, 445 $[S]^+$, 105 $[C_6H_5CO]^+$; FABMS (FAB<0); m/z (GT): 1721 $[3M-H]^-$, 1147 $[2M-H]^-$, 665 $[M+G-H]^-$, 573 $[M-H]^-$, 129 $[B]^-$, 121 $[C_6H_5CO_2]^-$; $[\alpha]_D^{20}$ = +45 (*c* 0.94, DMSO) (lit. value = +76.8 (*c* 0.50, DMF) [10]); Anal. $C_{30}H_{23}FN_2O_9\cdot 0.1CH_3Cl$ (C, H, N).

5.1.4. 1-(β-L-Ribofuranosyl)-5-fluorouracil (4)

Compound **3** (350 mg, 0.61 mmol) was deacylated by treating with methanolic ammonia following the general procedure to form **4** (130 mg, Yield: 82%), which was crystallized from a diethyl ether–ethanol mixture; m.p. = 180–182 °C (lit. values = 184 °C [10], 208–209 °C [11]); UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 269 (8900), λ_{min} (nm): 235 (1900); ^{1}H NMR (DMSO-d_6): δ 11.9 (br s, 1H, NH), 8.27 (d, 1H, H-6, $J_{6\text{-}F5}$ = 7.3 Hz), 5.72 (dd, 1H, H-1′, $J_{1'\text{-}2'}$ = 4.5 Hz, $J_{1'\text{-}F5}$ = 1.7 Hz), 5.4 (br s, 1H, OH-2′), 5.3 (br s, 1H, OH-5′), 5.1 (br s, 1H, OH-3′), 4.0–3.9 (m, 2H, H-2′, H-3″), 3.8 (m, 1H, H-4′), 3.7–3.4 (m, 2H, H-5′, H-5″); FABMS (FAB>0); m/z (GT): 525 $[2M+H]^+$, 355 $[M+G+H]^+$, 263 $[M+H]^+$, 133 $[S]^+$, 131 $[BH_2]^+$; FABMS (FAB<0); m/z (GT): 523 $[2M-H]^-$, 353 $[M+G-H]^-$, 261 $[M-H]^-$, 129 $[B]^-$; $[\alpha]_D^{20}$ = −20 (*c* 0.60, DMSO) ($[\alpha]_D^{20}$ = +18 (*c* 1.00, DMSO) for commercial β-D-5-fluorouridine [Fluka, Ref. 47 576]); Anal. $C_9H_{11}FN_2O_6\cdot 0.25H_2O$ (C, H, N).

5.1.5. 1-(2-O-Acetyl-3,5-di-O-benzoyl-β-L-xylo-furanosyl)-5-fluorouracil (6)

Condensation of 5-fluorouracil (**1**) (5.0 g, 38.4 mmol) with 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanose (**5**) [26] (11.3 g, 25.6 mmol) was carried out by following the same procedure as described for the preparation of compound **3**, and outlined for compound **6** (11.0 g, Yield: 84%) as a white foam; m.p. = 96–98 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 228 (25 900), 266 (9000), λ_{min} (nm): 250 (7200); ^{1}H NMR (DMSO-d_6): δ 11.1 (br s, 1H, NH), 8.05 (1H, H-6, $J_{6\text{-}F5}$ = 6.8 Hz), 7.9–7.4 (m, 10H, $2C_6H_5CO$), 5.99 (d, 1H, H-1′, $J_{1'\text{-}2'}$ = 3.1 Hz), 5.74 (dd, 1H, H-3′, $J_{3'\text{-}2'}$ = 4.2 Hz, $J_{3'\text{-}4'}$ = 2.3 Hz), 5.54 (t, 1H, H-2′, J = 2.9 Hz), 4.8–4.6 (m, 3H, H-4′, H-5′, H-5″); FABMS (FAB>0); m/z (GT): 513 $[M+H]^+$, 383 $[S]^+$, 105 $[C_6H_5CO]^+$; FABMS (FAB<0); m/z (GT): 511 $[M-H]^-$, 469 $[M-CH_3CO]^-$, 129 $[B]^-$, 121 $[C_6H_5CO_2]^-$; $[\alpha]_D^{20}$ = −91 (*c* 0.88, DMSO); Anal. $C_{25}H_{21}FN_2O_9$ (C, H, N).

5.1.6. 1-(β-L-xylo-furanosyl)-5-fluorouracil (7)

Compound **6** (500 mg, 0.98 mmol) was deacylated by treating with methanolic ammonia following the general procedure to form **7** (240 mg, Yield: 94%), which was crystallized from ethanol; m.p. = 161–162 °C (lit. value = 203 °C for 1-(β-D-*xylo*-furanosyl)-5-fluorouracil [10]); UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 268 (10 200), λ_{min} (nm): 234 (2500); ^{1}H NMR (DMSO-d_6): δ 11.9 (br, s, 1H, NH), 7.99 (d, 1H, H-6, $J_{6\text{-}F5}$ = 7.4 Hz), 5.78 (d, 1H, OH-2′, J = 4.2 Hz), 5.6 (br s, 1H, H-1′), 5.50 (d, 1H, OH-3′, J = 3.5 Hz), 4.78 (t, 1H, OH-5′, J = 5.6 Hz), 4.1–4.0 (m, 1H, H-4′), 3.98 (d, 1H, H-2′), 3.9 (m, 1H, H-3′), 3.8–3.6 (m, 2H, H-5′, H-5″); FABMS (FAB>0); m/z (GT): 263 $[M+H]^+$, 133 $[S]^+$, 131 $[BH_2]^+$; FABMS (FAB<0); m/z (GT): 261 $[M-H]^-$, 129 $[B]^-$; $[\alpha]_D^{20}$ = +21 (*c* 0.87, DMSO); Anal $C_9H_{11}FN_2O_6\cdot$ 0.25EtOH (C, H, N).

5.1.7. 1-(3,5-Di-O-benzoyl-β-L-xylo-furanosyl)-5-fluorouracil (8)

Hydrazine hydrate (80%, 2.80 mL, 57.4 mmol) was added to a solution of 1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)-5-fluorouracil (**6**) (9.80 g, 19.1 mmol) in acetic acid (35 mL) and pyridine (150 mL). The resulting solution was stirred overnight at r.t. Acetone (50 mL) was added and the mixture was stirred continuously for 2 h. The reaction mixture was concentrated to a small volume and partitioned between ethyl acetate (200 mL) and water (200 mL). Ther layers formed were separated and the organic phase was washed with a saturated aqueous sodium hydrogen carbonate solution (2×200 mL) and finally with water (2×200 mL). The organic phase was dried over sodium sulfate, and then evaporated under reduced pressure. The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–5%) in methylene

chloride) to give pure **8** (7.82 g, Yield: 87%), which was crystallized from methylene chloride; m.p. = 93–97 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 227 (22 800), 267 (8200), λ_{min}: 249 (5900); ^{1}H NMR (DMSO-d_6): δ 11.9 (br s, 1H, NH), 8.06 (d, 1H, H-6, $J_{6\text{-}F5} = 6.9$ Hz), 8.0–7.4 (m, 10H, $2C_6H_5CO$), 6.35 (d, 1H, OH-2′, $J = 3.8$ Hz), 5.77 (d, 1H, H-1′, $J_{1'\text{-}2'} = 3.3$ Hz), 5.43 (dd, 1H, H-3′, $J_{3'\text{-}2'} = 3.1$ Hz, $J_{3'\text{-}4'} = 1.9$ Hz), 4.8–4.6 (m, 3H, H-4′, H-5′, H-5″), 4.43 (t, 1H, H-2′, $J = 2.3$ Hz); FABMS (FAB>0); m/z (GT): 941 $[2M+H]^+$, 471 $[M+H]^+$, 341 $[S]^+$, 131 $[BH_2]^+$, 105 $[C_6H_5CO]^+$; FABMS (FAB<0); m/z (GT): 939 $[2M-H]^-$, 469 $[MH]^-$, 129 $[B]^-$, 121 $[C_6H_5CO_2]^-$; $[\alpha]_D^{20} = -110$ (c 1.55, DMSO); Anal. $C_{23}H_{19}FN_2O_8 \cdot 1.1CH_2C1_2$ (C, H, N).

5.1.8. 1-(3,5-Di-O-benzoyl-β-L-arabino-furanosyl)-5-fluorouracil (**10**)

DCC (5.26 g, 25.5 mmol) was added to a solution of **8** in a mixture of anhydrous benzene (75 mL), DMSO (50 mL) and pyridine (0.68 mL). The resulting solution was stirred at r.t. under argon for 4 h and diluted with ethyl acetate (300 mL). Oxalic acid (2.3 g, 25.5 mmol) dissolved in methanol (6.8 mL) was added and the reaction mixture was then stirred at r.t. for 1 h and filtered to eliminate dicyclohexylurea. The filtrate was washed with brine (3×300 mL), saturated aqueous sodium hydrogen carbonate solution (2×300 mL), water (3×200 mL), dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was co-evaporated several times with absolute ethanol and dissolved in a mixture of absolute ethanol (45 mL) and anhydrous benzene (15 mL). The resulting solution was then cooled to 0 °C after which $NaBH_4$ (0.48 g, 12.8 mmol) was added. The reaction mixture was stirred at r.t. under argon for 1 h and diluted with ethyl acetate (300 mL) and then filtered. The filtrate was washed with brine (3×300 mL), water (2×200 mL), dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified using silica gel column chromatography (eluent: stepwise gradient of ethyl acetate (0–50%) in chloroform) to give pure **10** (2.41 g, Yield: 60%), which was crystallized from methanol; m.p. = 223–224 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 231 (29 100), 268 (11 900), λ_{min} (nm): 251 (8600); ^{1}H NMR (DMSO-d_6): δ 11.9 (br s, 1H, NH), 8.1–7.5 (m, 11H, $2C_6H_5CO$, H-6), 6.2 (br s, 1H, OH-2′), 6.13 (d, 1H, H-1′, $J_{1'\text{-}2'} = 3.6$ Hz), 5.36 (d, 1H, H-3′, $J_{3'\text{-}4'} = 1.8$ Hz), 4.8 (m, 1H, H-5′), 4.6 (m, 1H, H-5″), 4.5 (m, 1H, H-4′), 4.4 (m, 1H, H-2′); FABMS (FAB>0); m/z (NBA): 471 $[M+H]^+$, 341 $[S]^+$; $[\alpha]_D^{20} = -22$ (c 1.01, DMSO); Anal. $C_{23}H_{19}FN_2O_8$ (C, H, N).

5.1.9. 1-(β-L-Arabino-furanosyl)-5-fluorouracil (**11**)

Sodium (0.87 g, 37.8 mmol) was added to a solution of **10** (8.05 g, 17.1 mmol) in a mixture of anhydrous toluene (80 mL) and methanol (160 mL). The resulting solution was stirred at r.t. under argon for 2 h, and then neutralized by the addition of Dowex 50 W X 2 resin (H^+ form). The resin was filtered and washed with warm methanol, and the combined filtrates were evaporated to dryness. Column chromatography of the residue on silica gel (eluent: stepwise gradient of methanol (0–5%) in ethyl acetate) and filtration through a unit Millex HV-4 (0.45 μm, Millipore) gave **11** (3.81 g, Yield: 85%), which was crystallized from a methylene chloride–methanol mixture; m.p. = 183–185 °C (lit. value = l87–188 °C for 1-(β-D-*arabino*-furanosyl)-5-fluorouracil [36]); UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 270 (9100), λ_{min} (nm): 235 (1600); ^{1}H NMR (DMSO-d_6): δ 11.8 (br s, 1H, NH), 7.94 (1H, H-6, $J_{6\text{-}F5} = 7.4$ Hz), 5.94 (d, 1H, H-1′, $J_{1'\text{-}2'} = 3.9$ Hz), 5.6 (br s, 1H, OH-2′), 5.5 (br s, 1H, OH-3′), 5.2 (br s, 1H, OH-5′), 4.0 (br s, 1H, H-2′), 3.9 (br s, 1H, H-3′), 3.7 (m, 1H, H-4′), 3.6 (m, 2H, H-5′, H-5″); FABMS (FAB>0); m/z (GT): 787 $[3M+H]^+$, 525 $[2M+H]^+$ 447 $[M+2G+H]^+$, 263 $[M+H]^+$, 133 $[S]^+$, 131 $[BH_2]^+$; FABMS (FAB<0); m/z (GT): 1309 $[5M-H]^-$, 1047 $[4M-H]^-$, 785 $[3M-H]^-$, 523 $[2M-H]^-$, 369 $[M+T-H]^-$, 261 $[M-H]^-$, 129 $(B)^-$; $[\alpha]_D^{20} = -127$ (c 1.02, DMSO); Anal. $C_9H_{11}FN_20_6$ (C, H, N).

5.1.10. 1-(3,5-O-Isopropylidene-β-L-xylo-furanosyl)-5-fluorouracil (**12**)

2,2-Dimethoxypropane (10.8 mL, 87.7 mmol) and *p*-TsOH (170 mg, 0.88 mmol) were added to a solution of 1-(β-L-*xylo*-furanosyl)-5-fluorouracil (**7**) (2.3 g, 8.77 mmol) in anhydrous DMF (60 mL). The resulting solution was stirred at r.t. under argon for 2 h, and then evaporated under reduced pressure (0.02 mbar, 45 °C). The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–8%) in chloroform) to give pure **12** (2.04 g, 77%), which was crystallized from methanol; m.p. = 112–114 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 270 (9200), λ_{min} (nm): 235 (1700); ^{1}H NMR (DMSO-d_6): δ 11.67 (br s, 1H, NH), 7.96 (d, H-6, $J_{6\text{-}F5} = 7.5$ Hz), 5.84 (br d, 1H, H-1′, $J_{1'\text{-}2'} = 3.1$ Hz), 5.40 (d, 1H, OH-2′, $J_{OH\text{-}2'} = 1.3$ Hz), 4.0–3.8 (m, 4H, H-3′, H-4′, H-5′, H-5″), 3.79 (s, 1H, H-2′), 1.20 (s, 3H, C–CH_3), 1.06 (s, 3H, C–CH_3); FABMS (FAB>0); m/z (GT): 907 $[3M+H]^+$, 605 $[2M+$

H]$^+$, 303 [M+H], 245 [M−[$(CH_3)_2CO$]+H], 173 [S]$^+$, 131 [BH_2]$^+$, 59 [[$(CH_3)_2CO$]+H]$^+$; FABMS (FAB<0); *m/z* (GT): 1309 [5M−H]$^-$, 1207 [4M−H]$^-$, 905 [3M−H]$^-$, 603 [2M−H]$^-$, 301 [M−H]$^-$, 129 [B]$^-$.

5.1.11. 1-(2-O-Mesyl-β-L-xylo-furanosyl)-5-fluorouracil (13)

MsCl (1.86 mL, 24.0 mmol) was added dropwise to a stirred suspension of **12** (2.07 g, 6.85 mmol) in dry pyridine (100 mL) at 0 °C. The reaction mixture was stirred overnight at 0 °C, then poured into icewater (300 mL) and extracted with chloroform (3×150 mL). Combined extracts were washed with 5% aqueous sodium hydrogen carbonate solution (2×300 mL), water (2×300 mL), dried over sodium sulfate and evaporated under reduced pressure. The crude material was treated with 80% acetic acid (55 mL) for 40 mn under reflux, cooled to r.t. and evaporated under reduced pressure. The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (7.5–15%) in chloroform) and filtered through a unit Millex HV-4 (0.45 μm, Millipore) to give pure **13** (1.75 g, Yield: 75%), which was crystallized from ethanol; m.p. = 188–189 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 267 (10 100), λ_{min} (nm): 233 (2400); ^{1}H NMR (DMSO-d_6): δ 12.0 (br s, 1H, NH), 7.97 (d, 1H, H-6, $J_{6\text{-}F5}$ = 7.2 Hz), 6.04 (d, 1H, OH-3′, J = 4.1 Hz), 5.9 (br s, 1H, H-1′), 5.0 (m, 2H, H-2′, OH-5′), 4.3 (m, 1H, H-3′), 4.1 (m, 1H, H-4′), 3.7 (m, 2H, H-5′, H-5″), 3.33 (s, 3H, CH_3SO_2); FABMS (FAB>0); *m/z* (GT): 773 [2M+G+H]$^+$, 681 [2M+H]$^+$, 525 [M+2G+H]$^+$, 433 [M+G+H]$^+$, 341 [M+H]$^+$, 131 [BH_2]$^+$; FABMS (FAB<0); *m/z* (GT): 679 [2M−H]$^-$, 339 [M−H]$^-$, 129 [B]$^-$, 95 [CH_3SO_3]$^-$; $[\alpha]_D^{50}$ = −15 (*c* 1.01, DMSO).

5.1.12. 1-(β-L-lyxo-Furanosy1)-5-fluorouracil (15)

A suspension of **13** (1.70 g, 5.00 mmol) in water (100 mL) was boiled overnight under reflux. The mixture was then cooled to r.t. and evaporated under reduced pressure. The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (7.5–15%) in ethyl acetate) and filtered through a unit Millex HV-4 (0.45 μm, Millipore) to give pure **15** (1.12 g, Yield: 81%), which was crystallized from ethanol; m.p. = 208–209 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 269 (9300), λ_{min} (nm): 234 (1800); ^{1}H NMR (DMSO-d_6): δ 11.8 (br s, 1H, NH), 8.15 (1H, H-6, $J_{6\text{-}F5}$ = 7.7 Hz), 6.01 (dd, 1H, H-1′, $J_{1'\text{-}2'}$ = 6.9 Hz, $J_{1'\text{-}}$F5 = 1.8 Hz), 5.50 (d, 1H, OH-2′, J = 4.2 Hz), 5.40 (d, 1H, OH-3′, J = 3.7 Hz), 4.77 (t, 1H, OH-5′, J = 5.1 Hz), 4.36 (q, 1H, H-2′, J = 11.0 Hz, J = 5.8 Hz), 4.0 (m, 1H, H-3′), 3.8 (m, 1H, H-4′), 3.7–3.5 (m, 2H, H-5′, H-5″); FABMS (FAB>0); *m/z* (GT): 263 [M+H]$^+$, 131 [BH_2]$^+$; FABMS (FAB<0); *m/z* (GT): 261 [M−H]$^-$, 129 [B]$^-$; $[\alpha]_D^{20}$ = −120 (*c* 1.00, DMSO); Anal. $C_9H_{11}FN_2O_6$ (C, H, N).

5.1.13. 1-(2-Deoxy-3,5-di-O-benzoyl-β-L-threo-pentofuranosyl)-5-fluorouracil (16)

O-phenyl chlorothioformate (6.80 mL, 49.1 mmol) and DMAP (12.0 g, 98.2 mmol) were added to a solution of 1-(3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)-5-fluorouracil (**8**) (15.4 g, 32.7 mmol) in anhydrous acetonitrile (650 mL). The resulting solution was stirred at r.t. under argon for 1 h, and then evaporated under reduced pressure. The residue was dissolved in methylene chloride (350 mL) and the solution was successively washed with water (2×250 mL), ice-cold 0.5 N hydrochloric acid (250 mL), water (2×250 mL), dried over sodium sulfate and evaporated under reduced pressure. The crude material was co-evaporated several times with anhydrous dioxane and dissolved in the same solvent (265 mL). To the resulting solution were added under argon tris(trimethylsilyl)silane (12,1 mL, 39.3 mmol) and AIBN (1.74 g, 10.8 mmol). The reaction mixture was then heated and stirred at 100 °C for 2.5 h under argon. The mixture was then cooled to r.t. and evaporated under reduced pressure. The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–2%) in chloroform) to give pure **16** (13.0 g, Yield: 87%), which was crystallized from a diethyl ether–methanol mixture; m.p. = 182–184 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 229 (25 800), 269 (9300), λ_{min} (nm): 251 (6500); ^{1}H NMR (DMSO-d_6): δ 11.8 (br s, 1H, NH), 8.05 (d, 1H, H-6, $J_{6\text{-}F5}$ = 7.0 Hz), 8.0–7.4 (m, 10H, 2C_6H_5CO), 6.15 (d, 1H, H-1′, $J_{1'\text{-}2'}$ = 7.4 Hz), 5.68 (t, 1H, H-3′, J = 4.2 Hz), 4.8–4.6 (m, 2H, H-5′, H″-5), 4.6 (m, 1H, H-4′), 3.0–2.8 (m, 1H, H-2′), 2.40 (d, 1H, H-2″, $J_{2''\text{-}2'}$ = 14.8 Hz); FABMS (FAB>0); *m/z* (GT): 455 [M+H]$^+$, 325 [S]$^+$, 131 [BH_2]$^+$, 105 [C_6H_5CO]$^+$; FABMS (FAB<0); *m/z* (GT): 452 [M−H]$^-$, 129 [B]$^-$; $[\alpha]_D^{20}$ = −125 (*c* 1.05, DMSO); Anal. $C_{23}H_{19}FN_2O_7$ (C, H, N).

5.1.14. 1-(2-Deoxy-β-L-threo-pentofuranosyl)-5-fluorouracil (17)

Compound **16** (3.25 g, 7.15 mmol) was debenzoylated by treating with methanolic ammonia following the general procedure to give **17** (1.60 g, Yield: 91%), which was crystallized from methanol; m.p. = 198–200 °C;

UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 267 (8500), λ_{min} (nm): 233 (2100); ^{1}H NMR (DMSO-d_6): δ 11.8 (br s, 1H, NH), 8.16 (d, 1H, H-6, $J_{6\text{-}F5} = 7.4$ Hz), 6.05 (dd, 1H, H-1′, $J_{1'\text{-}2'} = 6.5$ Hz, $J_{1'\text{-}F5} = 1.8$ Hz), 5.38 (d, 1H, OH-3′, $J = 3.3$ Hz), 4.72 (t, 1H OH-5′, $J = 5.4$ Hz), 4.22 (q, 1H, H-3′, $J = 3.1$ Hz, $J = 7.5$ Hz), 3.8–3.6 (m, 3H, H-4′, H-5′, H″-5), 2.6 (m, 1H, H-2′), 1.83 (d, 1H, H-2″, $J_{2''\text{-}2'} = 14.7$ Hz); FABMS (FAB>0); m/z (GT): 339 [M+G+H]$^+$, 247 [M+H]$^+$, 131 [BH_2]$^+$, 115 [S]$^+$; FABMS (FAB<0); m/z (GT): 245 [M−H]$^-$, 129 [B]$^-$; $[\alpha]_D^{20} = +16$ (c 0.86, DMSO); Anal. $C_9H_{11}FN_2O_5$ (C, H, N).

*5.1.15. 1-(2-Deoxy-5-O-benzoyl-β-L-threo-pentofuranosyl)-5-fluorouracil (**18**)*

A solution of benzoyl chloride(1.39 mL, 12.0 mmol) in anhydrous pyridine (22 mL) was added dropwise to a suspension of **17** (2.68 g, 10.9 mmol) in anhydrous pyridine (88 mL) and DMF (22 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, then poured onto icewater (200 mL) and extracted with chloroform (3×100 mL). Combined extracts were washed with a saturated aqueous sodium hydrogen carbonate solution (150 mL), water (2×150 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–5%) in methylene chloride) to give pure **18** (3.0 g, Yield: 81%), which was crystallized from methylene chloride; m.p. = 187–189 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 228 (16 100), 269 (8500), λ_{min} (nm): 217 (6000); ^{1}H NMR (DMSO-d_6): δ 11.8 (br s, 1H, NH), 8.21 (d, 1H, H-6, $J_{6\text{-}F5} = 7.3$ Hz), 8.0–7.5 (m, 5H, C_6H_5CO), 6.13 (dd, 1H, H-1′, $J_{1'\text{-}2'} = 6.6$ Hz and $J_{6-5F} = 1.7$ Hz), 5.72 (d, 1H, OH-3′, $J = 3.5$ Hz), 4.6–4.5 (m, 2H, H-5′ et H″-5), 4.37 (dd, 1H, H-3′, $J = 7.8$ Hz), 4.2–4.1 (m, 1H, H-4′), 2.7–2.6 (m, 1H, H-2′), 1.97 (d, 1H, H-2″, $J_{2''\text{-}2'} =$ 14.8 Hz); FABMS (FAB>0); m/z (GT): 701 [2M+H]$^+$, 351 [M+H]$^+$, 221 [S]$^+$, 131 [BH_2]$^+$, 105 [C_6H_5CO]$^+$; FABMS (FAB<0); m/z (GT): 699 [2M−H]$^-$, 349 [M−H]$^-$, 121 [$C_6H_5CO_2$]$^-$; $[\alpha]_D^{20} = -46$ (c 1.10, DMSO); Anal. $C_{16}H_{15}FN_2O_6{\cdot}0.2CH_2C1_2$ (C, H, N).

*5.1.16. 1-(2-Deoxy-3,5-di-O-benzoyl-β-L-erythro-pentofuranosyl)-5-fluorouracil (**19**)*

DEAD (0.83 mL, 5.30 mmol) and benzoic acid (647 mg, 5.30 mmol) in anhydrous THF (7.5 mL) were added dropwise to a solution of **18** (619 mg, 1.77 mmol) and PPh_3 (1,39 g, 5.30 mmol) in anhydrous THF (28.5 mL) at 0 °C. The reaction mixture was stirred for 2 h at r.t. The reaction was quenched by the addition of ethanol and solvents were removed under reduced pressure. The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–2.5%) in chloroform) to give **19** (483 mg, Yield: 60%), which was precipitated in chloroform; m.p. = 243–244 °C (lit. value >250 °C for the D-enantiomer [9]); UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 231 (31 200), 268 (11 500), λ_{min} (nm): 251 (8500); ^{1}H NMR (DMSO-d_6): δ 11.9 (br s, 1H, NH), 8.1–7.4 (m, 11H, 2C_6H_5CO, H-6), 6.21 (t, 1H, H-1′, $J = 6.6$ Hz), 5.6 (m, 1H, H-3′), 4.6–4.5 (m, 2H, H-5′, H″-5), 4.5 (m, 1H, H-4′), 2.7–2.5 (m, 2H, H-2′, H-2″); FABMS (FAB<0); m/z (GT): 453 [M−H]$^-$, 129 [B]$^-$, 121 [$C_6H_5CO_2$]$^-$.

*5.1.17. 1-(2-Deoxy-β-L-erythro-pentofuranosyl)-5-fluorouracil (**20**)*

Compound **19** (190 mg, 0.42 mmol) was debenzoylated by treating with methanolic ammonia following the general procedure, giving **20** (95 mg, Yield: 92%), which was crystallized from ethanol; m.p. = 148–150 °C (lit. value 147–149 °C [10]); UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 269 (11 100), λ_{min} (nm): 234 (1800); ^{1}H NMR (DMSO-d_6): δ 11.8 (br s, 1H, NH), 8.20 (1H, H-6, $J_{6\text{-}F5} = 7.2$ Hz), 6.11 (t, 1H, H-1′, $J = 6.6$ Hz), 5.3–5.1 (m, 2H, OH-5′ and OH-3′), 4.2 (br d, 1H, H-3′, $J = 3.0$ Hz), 3.8 (m, 1H, H-4′), 3.6–3.5 (m, 2H, H-5′, H-5″), 2.0 (m, 2H, H-2′, H-2″); FABMS (FAB>0); m/z (GT): 247 [M+H]$^+$, 131 [BH_2]$^+$, 117 [S]$^+$; FABMS (FAB<0); m/z (GT): 245 [M−H]$^-$, 129 [B]$^-$; $[\alpha]_D^{20} = -44$ ($c = 0.77$, DMSO) (+37 (c 1.00, DMSO)) for the commercial 2′-deoxy-β-D-5-fluorouridine [Pharma-Waldhof Gmbh, Ref. 6717 60]; Anal. $C_9H_{11}FN_20_5$ (C, H, N).

*5.1.18. 1-(2-O-Acetyl-3,5-di-O-benzoyl-β-L-arabino-furanosyl)-5-fluorouracil (**21**)*

Acetic anhydride (0.17 mL, 1.81 mmol) was added to a solution of 1-(3,5-di-*O*-benzoyl-β-L-*arabino*-furanosyl)-5-fluorouracil (**10**) (709 mg, 1.51 mmol) in dry pyridine (11 mL) under argon at 0 °C. The resulting mixture was stirred at r.t. for 22 h. Ethanol was then added and the solvents were removed under reduced pressure. The residue was purified using silica gel column chromatography (eluent: stepwise gradient of methanol (0–4%) in chloroform) to give pure **21** (518 mg, Yield: 67%) as a white foam; m.p. = 94–95 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 231 (27 400), 267 (10 300), λ_{min} (nm): 251 (8400); ^{1}H NMR (DMSO-d_6): δ 12.0 (br s, 1H, NH), 8.1–7.5 (m, 11H, 2C_6H_5CO, H-6), 6.35 (d, 1H, H-1′, $J_{1'\text{-}2'} = 4.9$ Hz), 5.7 (m, 1H, H-3′), 5.6 (m, 1H, H-2′), 4.7 (m, 2H, H-5′, H-5″), 4.5 (br s, 1H,

H-4′), 1.90 (s, 3H, CH_3CO); FABMS (FAB>0); *m/z* (GT): 513 $[M+H]^+$, 383 $[S]^+$, 105 $[C_6H_5CO]^+$, 43 $[CH_3CO]^+$; FABMS (FAB<0); *m/z* (GT): 1023 $[2M-H]^-$, 511 $[M-H]^-$, 129 $[B]^-$, 121 $[C_6H_5CO_2]^-$, 59 $[CH_3CO_2]^-$; $[\alpha]_D^{20} = -49$ (*c* 1.01, DMSO).

*5.1.19. 1-(2,3,5-Tri-O-acetyl-β-L-lyxo-furanosyl)-5-fluorouracil (**22**)*

Acetylation of 1-(β-L-*lyxo*-furanosyl)-5-fluorouracil (**16**) (0.75 g, 2.86 mmol) with acetic anhydride (2.03 mL, 21.5 mmol), was carried out following the same procedure as described for the preparation of **21** giving compound **22** (1.00 g, Yield: 90%) as a white foam; m.p. = 84–86 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 266 (9400), λ_{min} (nm): 233 (2400); ^1H NMR (DMSO-d_6): δ 11.9 (br s, 1H, NH), 7.82 (1H, H-6, $J_{6\text{-}F5} = 7.1$ Hz), 6.19 (dd, 1H, H-1′, $J_{1'\text{-}2'} = 6.5$ Hz, $J_{1'\text{-}F5} = 1.7$ Hz), 5.69 (dd, 1H, H-2′, $J_{2'\text{-}3'} = 5.1$ Hz), 5.46 (dd, 1H, H-3′, $J_{3'\text{-}4'} = 3.3$ Hz), 4.4–4.3 (m, 3H, H-4′, H-5′, H-5″), 2.06 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 1.90 (s, 3H, CH_3CO); FABMS (FAB>0); *m/z* (GT): 777 $[2M+H]^+$, 388 $[M+H]^+$, 329 $[M-[CH_3CO_2]]^+$, 259 $[S]^+$, 131 $[BH_2]^+$, 43 $[CH_3CO]^+$; FABMS (FAB<0); *m/z* (GT): 775 $[2M-H]^-$, 387 $[M-H]^-$, 345 $[M-[CH_3CO]]^-$, 59 $[CH_3C0_2]^-$; $[\alpha]_D^{20} = -66$ (*c* 1.05, DMSO).

*5.1.20. 1-(β-L-Ribofuranosyl)-5-fluorocytosine (**23**)*

Thiation of 1-(2,3,5-tri-*O*-benzoyl-β-L-ribofuranosyl)-5-fluorouracil (**3**) (720 mg, 1.25 mmol), with Lawesson's reagent (355 mg, 0.88 mmol), was carried out following the general procedure giving the corresponding 4-thio intermediate (530 mg, Yield: 72%) as a yellow foam. The 4-thio intermediate (500 mg, 0.85 mmol) was treated with methanolic ammonia following the general procedure to give **23** (188 mg, Yield: 85%) as a white solid; m.p. = 70–71 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 241 (7600), 284 (6900), λ_{min} (nm): 226 (6600), 264 (5200); ^1H NMR (DMSO-d_6): δ 8.20 (d, 1H, H-6, $J_{6\text{-}F5} = 7.4$ Hz), 7.7–7.5 (br d, 2H, NH_2), 5.69 (dd, 1H, H-1′, $J_{1'\text{-}2'} = 3.6$ Hz, $J_{1'\text{-}F5} = 1.8$ Hz), 5.35 (d, 1H, OH-2′, $J = 5.1$ Hz), 5.20 (t, 1H, OH-5′, $J = 4.9$ Hz), 4.99 (d, 1H, OH-3′, $J = 5.5$ Hz), 4.0–3.9 (m, 2H, H-2′, H-3″), 3.8 (m, 1H, H-4′), 3.7–3.5 (m, 2H, H-5′, H-5″); FABMS (FAB>0); *m/z* (GT): 523 $[2M+H]^+$, 262 $[M+H]^+$, 130 $[BH_2]^+$; FABMS (FAB<0); *m/z* (GT): 260 $[M-H]^-$, 128 $[B]^-$; $[\alpha]_D^{20} = -28$ (*c* 0.96, DMSO); Anal. $C_9H_{12}FN_3O5{\cdot}2H_2O$ (C, H, N).

*5.1.21. 1-(β-L-xylo-Furanosyl)-5-fluorocytosine (**24**)*

Thiation of 1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)-5-fluorouracil (**6**) (500 mg, 0.976 mmol), with Lawesson's reagent (276 mg, 0.68 mmol), was carried out following the general procedure giving the corresponding 4-thio intermediate (469 mg, Yield: 91%) as a yellow foam. The 4-thio intermediate (410 mg, 0.78 mmol) was treated with methanolic ammonia following the general procedure to give **24** (180 mg, Yield: 89%), which was crystallized from methanol; m.p. = 221–225 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 238 (8700), 280 (8100), λ_{min} (nm): 226 (8000), 261 (6100); ^1H NMR (DMSO-d_6): δ 7.84 (d, 1H, H-6, $J_{6\text{-}F5} = 7.4$ Hz), 7.7–7.4 (br d, 2H, NH_2), 5.70 (d, 1H, OH-2′, $J = 4.2$ Hz), 5.6 (br s, 1H, H-1′), 5.37 (d, 1H, OH-3′, $J = 3.5$ Hz), 4.75 (t, 1H, OH-5′, $J = 5.6$ Hz), 4.1–4.0 (m, 1H, H-4′), 3.9–3.8 (m, 2H, H-2′, H-3″), 3.7–3.6 (m, 2H, H-5′, H-5″); FABMS (FAB>0); *m/z* (GT): 1045 $[4M+H]^+$, 784 $[3M+H]^+$, 523 $[2M+H]^+$, 262 $[M+H]^+$, 130 $[BH_2]^+$; FABMS (FAB<0); *m/z* (GT): 521 $[2M-H]^-$, 260 $[M-H]^-$, 128 $[B]^-$; $[\alpha]_D^{20} = +10$ (*c* 0.90, DMSO); Anal. $C_9H_{12}FN_3O_5$ (C, H, N).

*5.1.22. 1-(2-Deoxy-β-L-threo-pentofuranosyl)-5-fluorocytosine (**25**)*

Thiation of 1-(2-deoxy-3,5-di-*O*-benzoyl-β-L-*threo*-pentofuranosyl)-5-fluorouracil (**16**) (5.0 g, 11.0 mmol), with Lawesson's reagent (3.1 g, 7.70 mmol), was carried out following the general procedure, giving the corresponding 4-thio intermediate (4.6 g, Yield: 80% as a yellow foam. The 4-thio intermediate (1.0 g, 2.13 mmol) was treated with methanolic ammonia following the general procedure to give **25** (0.44 g, Yield: 84%), which was crystallized from an ethyl acetate–methanol mixture; m.p. = 199–201 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 226 (7700), 281 (8500), λ_{min} (nm): 262 (6300); ^1H NMR (DMSO-d_6): δ 7.99 (d, 1H, H-6, $J_{6\text{-}F5} = 7.4$ Hz), 7.7–7.4 (br d, 2H, NH_2), 5.98 (d, 1H, H-1′, $J_{1'\text{-}2'} = 8.1$ Hz), 5.25 (d, 1H, OH-3′, $J = 3.4$ Hz), 4.71 (t, 1H, OH-5′, $J = 5.6$ Hz), 4.2 (m, 1H, H-3′), 3.8–3.6 (m, 3H, H-4′, H-5′, H-5″), 2.5 (m, 1H, H-2′), 1.8 (m, 1H, H-2″); FABMS (FAB>0); *m/z* (GT): 491 $[2M+H]^+$, 246 $[M+H]^+$, 130 $[BH_2]^+$; FABMS (FAB<0); *m/z* (GT): 489 $[2M-H]^-$, 244 $[M-H]^-$, 128 $[B]^-$; $[\alpha]_D^{20} = -21$ (*c* 0.92, DMSO); Anal. $C_9H_{12}FN_3O_4$ (C, H, N).

*5.1.23. 1-(2-Deoxy-β-L-erythro-pentofuranosyl)-5-fluorocytosin (**26**)*

Thiation of 1-(2-deoxy-3,5-di-*O*-benzoyl-β-L-*erythro*-pentofuranosyl)-5-fluorouracil (**19**) (670 mg, 1.47

mmol), with Lawesson's reagent (417 mg 1.03 mmol), was carried out following the general procedure, and forming the corresponding 4-thio intermediate (636 mg, Yield: 92%) as a yellow foam. The 4-thio intermediate (275 mg, 0.58 mmol) was treated with methanolic ammonia following the general procedure to give **26** (125 mg, Yield: 87%), which was crystallized from ethanol; m.p. = 200–201 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 242 (9500), 284 (9000), λ_{min} (nm): 226 (7200), 264 (6600); ^{1}H NMR (DMSO-d_6): δ 8.09 (d, 1H, H-6, $J_{6\text{-}F5} = 7.2$ Hz), 7.8–7.5 (br s, 2H, NH_2), 6.10 (t, 1H, H-1′, $J = 6.1$ Hz), 5.21 (d, 1H, OH-3′, $J = 4.0$ Hz), 5.09 (t, 1H, OH-5′, $J = 4.9$ Hz), 4.2 (br s, 1H, H-3′), 3.9 (br s, 1H, H-4′), 3.6–3.5 (m, 2H, H-5′, H-5″) 2.2 (m, 1H, H-2′), 2.0 (m, 1H, H-2″); FABMS (FAB>0); m/z (GT): 736 $[3M+H]^+$, 491 $[2M+H]^+$, 338 $[M+G+H]^+$, 246 $[M+H]^+$, 130 $[BH_2]^+$, 117 $[S]^+$; FABMS (FAB<0); m/z (GT): 244 $[M-H]^-$, 128 $[B]^-$; $[\alpha]_D^{20} = -71$ (c 0.82, DMSO); Anal. $C_9H_{12}FN_3O_4$ (C, H, N).

5.1.24. 1-(β-L-Arabino-furanosyl)-5-fluorocytosine (27)

Thiation of 1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-*arabino*-furanosyl)-5-fluorouracil (**21**) (750 mg, 1.46 mmol), with Lawesson's reagent (414 mg, 1.02 mmol), was carried out following the general procedure forming the corresponding 4-thio intermediate (610 mg, Yield: 80%) as a yellow foam. The 4-thio intermediate (308 mg, 0.58 mmol) was treated with methanolic ammonia following the general procedure to give **27** (126 mg, Yield: 83%), which was crystallized from methanol; m.p. = 237–239 °C (lit. value 232–233 °C for the D-enantiomer [36]); UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 240 (7800), 285 (7600), λ_{min} (nm): 226 (6800), 264 (5100); ^{1}H NMR (DMSO-d_6): δ 7.76 (1H, H-6, $J_{6\text{-}F5} = 7.2$ Hz), 7.7–7.4 (br d, 2H, NH_2), 6.0 (m, 1H, H-1′), 5.4 (m, 2H, OH-2′, OH-3′), 5.1 (br s, 1H, OH-5′), 4.0 (br S, 1H, H-2′), 3.9 (m, 1H, H-3′), 3.7 (m, 1H, H-4′), 3.6 (m, 2H, H-5′, H-5″); FABMS (FAB>0); m/z (GT): 523 $[2M+H]^+$, 262 $[M+H]^+$, 130 $[BH_2]^+$; FABMS (FAB<0); m/z (GT): 260 $[M-H]^-$; $[\alpha]_D^{20} = -15$ (c 0.89, DMSO); Anal. $C_9H_{12}FN_3O_5$ (C, H, N).

5.1.25. 1-(β-L-lyxo-Furanosyl)-5-fluorocytosine (28)

Thiation of 1-(2,3,5-tri-*O*-acetyl-β-L-*lyxo*-furanosyl)-5-fluorouracil (**22**) (0.96 g, 2.47 mmol), with Lawesson's reagent (0.70 g, 1.73 mmol), was carried out following the general procedure giving the corresponding 4-thio intermediate (0.97 g, Yield: 97%) as a yellow foam. The 4-thio intermediate (500 mg, 1.24 mmol) was treated with methanolic ammonia following the general procedure to give **28** (202 mg, Yield: 63%), which was crystallized from an ethyl acetate–methanol mixture; m.p. = 78–80 °C; UV: λ_{max} (nm) (ε, $M^{-1}\,cm^{-1}$) (ethanol): 241 (7700), 283 (7700), λ_{min} (nm): 226 (6600), 262 (5600); ^{1}H NMR (DMSO-d_6): δ 7.99 (1H, H-6, $J_{6\text{-}F5} = 7.6$ Hz), 7.7–7.4 (br d, 2H, NH_2), 6.03 (dd, 1H, H-1′, $J_{1'\text{-}2'} = 6.5$ Hz, $J_{1'\text{-}F5} = 2.0$ Hz), 5.38 (d, 1H, OH-2′, $J = 5.7$ Hz), 5.33 (d, 1H, OH-3′, $J = 3.6$ Hz), 4.81 (t, 1H, OH-5′, $J = 5.4$ Hz), 4.27 (br d, 1H, H-2′, $J = 5.4$ Hz), 4.1 (m, 1H, H-3′), 4.0 (m, 1H, H-4′), 3.7–3.5 (m, 2H, H-5′, H5″); FABMS (FAB>0); m/z (GT): 523 $[2M+H]^+$, 262 $[M+H]^+$, 130 $[BH_2]^+$; FABMS (FAB<0); m/z (GT): 521 $[2M-H]^-$, 260 $[M-H]^-$, 128 $[B]^-$; $[\alpha]_D^{20} = -33$ (c 1.00, DMSO).

5.2. Biology

5.2.1. Inhibition of cell proliferation

The test compounds were evaluated for their cytostatic activity against murine leukemia L1210, murine mammary carcinoma FM3A and human T-lymphocyte Molt4/C8 and CEM cells in 96-microtiter plates as described earlier [37–39]. Briefly, 100 μl of an appropriate dilution of the test compound and 100 μl of 5×10^4–7.5×10^4 tumor cells were added to each 200 μl well. After a 48 h (L1210 and FM3A) or 72 h (Molt4/C8, CEM) incubation period at 37 °C in a humidified CO_2-controlled atmosphere, cells were counted using an automated Coulter counter. The IC_{50} represents the compound concentration required to inhibit cell proliferation by 50%.

5.2.2. Anti-viral assays

The anti-HIV and anti-HBV assays in cell cultures were carried out following the procedures established earlier [40].

5.2.2.1. Anti-HIV evaluation

Briefly, in MT-4 cells, the determination of the antiviral activity of compounds was based on a reduction of HIV-1_{IIIB}-induced cytopathogenicity, the metabolic activity of the cells being measured by the property of mitochondrial deshydrogenase to reduce MTT into formazan. For CEM-SS cells, the production of virus HIV-1_{LAI} was measured by quantifying the reverse transcriptase activity associated with the virus particle released into the culture supernatant. In parallel experiments, cytotoxicity of the test compounds was

measured after incubating the uninfected cells for 5 days in their presence using the colorimetric MTT test.

5.2.2.2. Anti-HBV evaluation

Briefly, the 2.2.15. cells (HBV DNA-transfected human hepatoblastoma-derived Hep-G2 cells) were cultured and the inhibition of HBV extracellular DNA (HBV virion) or HBV intracellular DNA(HBV replicative intermediate, HBV RI) was determined. Cytotoxicity assays were conducted in Hep-G2 cells. Each compound was tested in four concentrations in triplicate cultures and the median inhibitory concentration (IC_{50}) was determined.

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