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Synthesis of some cyclic and acyclic nucleoside analogues derived from 4-(trifluoromethyl)pyrimidines

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Abstract—Cyclic nucleoside analogues **10**, **11**, **13b–d** and **17** and acyclic derivatives **19** and **20b–d** were prepared from 4-trifluoromethylpyrimidones **4a** and **5b–d**.

1. Introduction

Introduction of trifluoromethyl groups into bioactive molecules is known to improve their therapeutic efficacy. This result is related to an increased lipophilicity brought by the substituent.[1–3] The high electronegativity of fluorine and the great strength of the C–F bond are also contributing factors.

A wide variety of methods for the synthesis of trifluoromethylated organic compounds has been developed and efforts in this field are in constant progress. Two general approaches may be envisioned: the direct introduction of a CF_3 group into a prebuilt molecule[1,2] or the use of trifluoromethylated building-blocks.[2,3]

Along the second route, we previously studied the preparation of various trifluoromethylated heterocyclic compounds starting from enaminodiketones.[4,5]

The present paper describes the further application of this methodology to the synthesis of 4-trifluoromethylpyrimidones and their coupling with modified sugars toward potential antiviral nucleosides.

2. Results and discussion

2.1. Synthesis of 4-trifluoromethylpyrimidones (Scheme 1)

The benzoylpyrimidone **4a** was obtained as previously reported.[5]

In order to introduce other substituents at C-5 position of the pyrimidine nucleus, we envisioned the preparation of new enaminoketones by a classical enamine chemistry.[6]

Thus, 3-phenylpropionaldehyde,[7] butyraldehyde and 3-methylbutyraldehyde, were converted into enamines **1b–d**, respectively, by reacting with pyrrolidine or diethylamine in the presence of a dehydrating reagent.[6] Enamines **1b–d** were not isolated (their formation was monitored by ^{1}H NMR). They were directly trifluoroacylated to enaminoketones **2b–d**. With R^1=CH_2Ph, the pyrrolidinoenamine **2b** was obtained with 64% yield and was fully characterised. Subsequent cyclocondensation of **2b** with *O*-methylisourea afforded the 2-methoxypyrimidine **3b** in 74% yield. With R^1=Et or *i*Pr, the cyclocondensation step of the pyrrolidino derivatives failed, so diethylamine was preferred to pyrrolidine. Enaminoketones **2c** and **2d** proved to be very unstable and were immediately treated by *O*-methylisourea to give pyrimidines **3c** and **3d** in overall poor yields of 16 and 26%, respectively. Hydrolysis of **3b–d** by hydrobromic acid/acetic acid provided pyrimidones **5b–d** or 4-methoxydihydropyrimidones **6b–d** depending on the method of purification (column chromatography with CH_2Cl_2/MeOH 98:2 as eluent or recrystallisation from methanol). This result agrees with a previous observation for **4a**:[5] the 3,4-double bond easily undergoes addition of nucleophiles.

Keywords: enaminones; pyrimidones; nucleosides; fluorine compounds.

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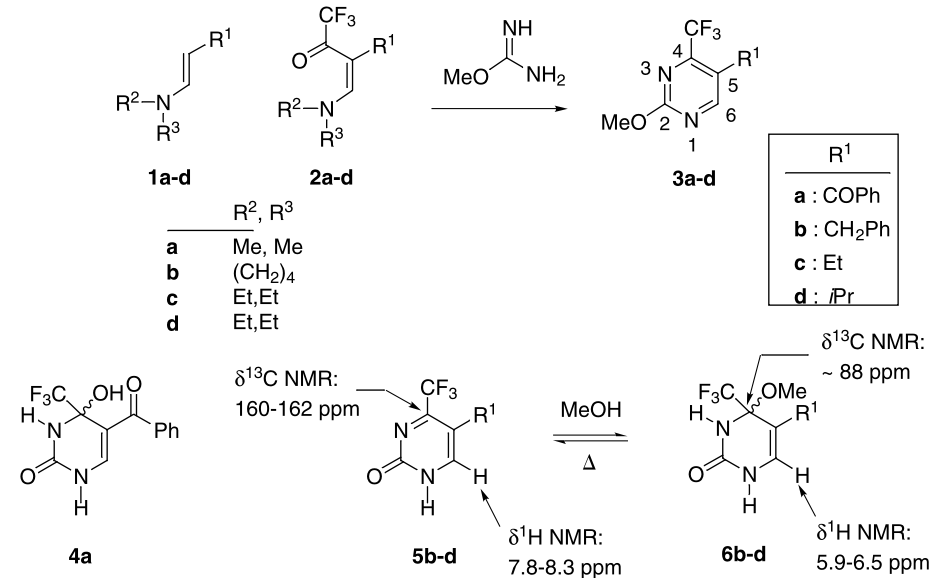
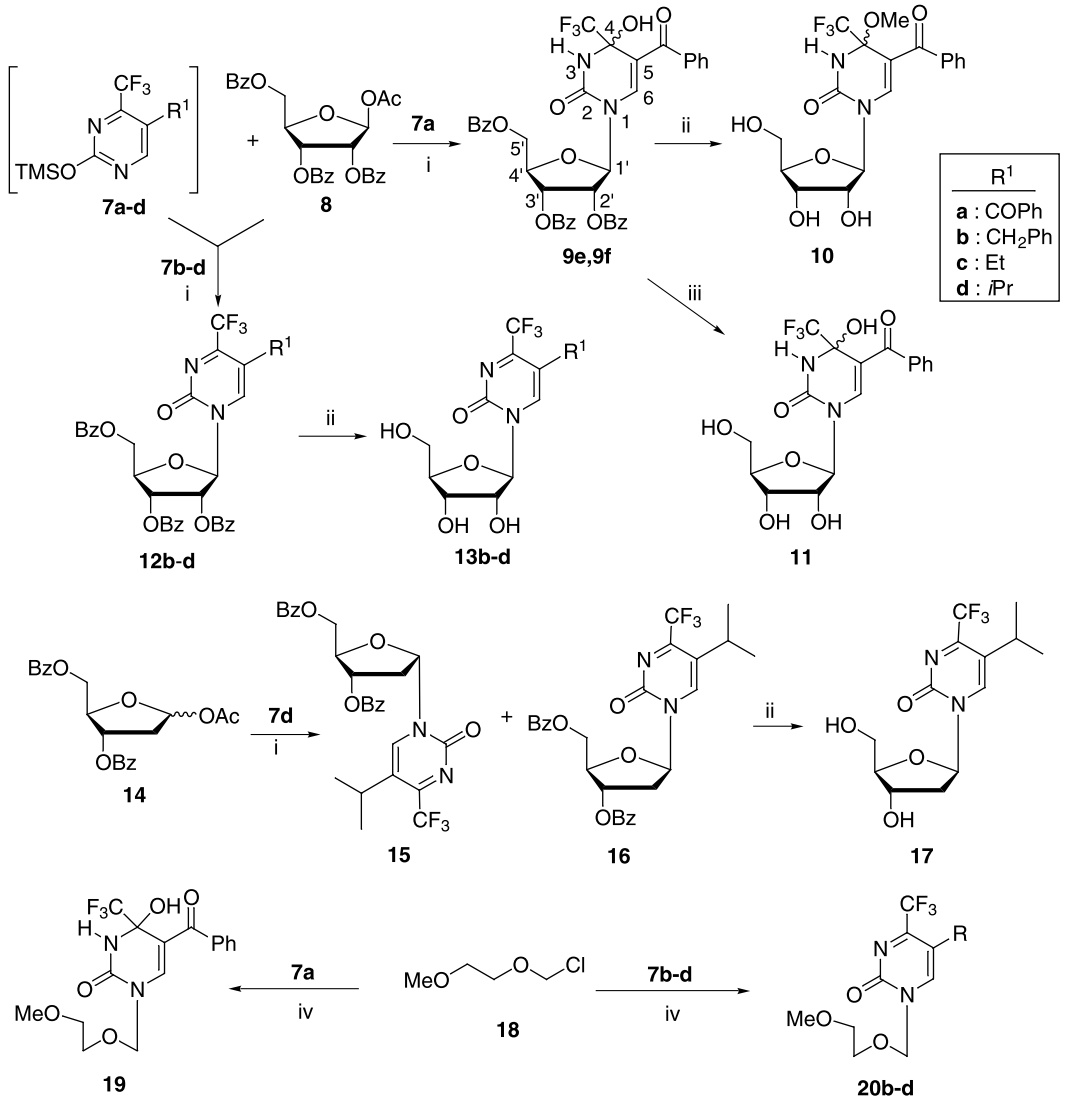


Scheme 1.



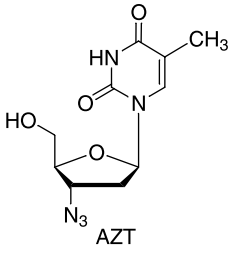
Scheme 2. (i) $SnCl_4$, CH_3CN, −25°C, 3 h; (ii) NH_3/MeOH, rt, 20 h; (iii) NH_4OH/MeOH 1:1, rt, 22 h; (iv) NaI, dichloroethane, reflux, 4 h.

However whereas **6b–d** were converted into **5b–d** by heating, dehydration of **4a** could not be achieved. Structural distinction between **5b–d** and **6b–d** was deduced from the ^{1}H and ^{13}C NMR spectra which showed significant differences in the chemical shifts for H-6 and C-4.

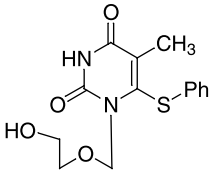
2.2. Nucleoside analogues (Scheme 2)

Extensive studies on the synthesis and biological activity of 5-trifluoromethylpyrimidine-nucleosides have been reported.[8,9,10]

However 4-substituted derivatives are quite rare in the literature. Therefore it seemed to be of interest to attempt glycosylation and alkylation of pyrimidones **4a** and **5b–d** or **6b–d** by several protected sugars or hydroxyalkylchlorides in order to synthesize analogues of the heading antiviral nucleosides AZT and HEPT.



AZT



HEPT

Nucleosides were prepared according to the Vorbrüggen's procedure (Scheme 2).[11] Activation of pyrimidones **4a** and **5b–d** or **6b–d** was achieved with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate,[12] leading to the monosilylated derivatives **7b–d** (the C-4 signal deshielded to ~160 ppm on the ^{13}C NMR spectrum was in agreement with an aromatic structure).

Couplings of the activated bases with protected sugars were performed with tin(IV)chloride in acetonitrile at low temperature.

Thus, condensation of **7a** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **8** gave the protected nucleoside analogues **9e**, **f** as a 1:1 diastereomeric mixture. As generally observed for syntheses using that procedure, the glycosylation reaction was regioselective and stereoselective and gave the *N*-1 substituted pyrimidine (a three-bond correlation was observed between the anomeric proton H-1′ and C-6 in HMBC NMR experiments) and β-nucleoside (low coupling constant between H-1′ and H-2′).[11b] Thus compounds **9e** and **9f** only differed by their configuration at C-4. They were separated by repeated column chromatographies. The available data did not allow us to assign the definitive configuration at C-4. Removal of the benzoyl protecting groups of **9e**, **f** was performed with methanolic ammonia yielding **10**. When the cleavage was carried out with aqueous ammonia diluted with methanol the 4-hydroxy derivative **11** was obtained.

Similarly the ribonucleosides **13b–d** were prepared from **7b–d** and **8**. Nucleosides **9e**, **f** compare with the pyrimidone **4a** (hydrated form), while nucleosides **12b–d**, in the absence of electrowithdrawing substituents at C-5, only occured as aromatic, non hydrated forms.

In order to prepare 2-deoxyribonucleoside analogues, condensation of 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-D-erythro-pentafuranose **14**[13] with **7d** was attempted. As expected an α,β-mixture of **15** and **16** was obtained in a 28:72 ratio. After separation of the two anomers by column chromatography, the β-anomer **16** was deprotected to **17**. Determination of the anomeric configuration of **17** was supported by NMR experiments, especially by observation of ^{1}H nuclear Overhauser effects (nOe) between proton H-1′ and proton H-2′α and between proton H-3′ and proton H-2′β.

The acyclic nucleoside analogues **19** and **20b–d** were also prepared starting from 2-methoxy-ethoxymethylchloride **18** (MEMCl) and silylated pyrimidines **7a–d**, using sodium iodide in order to favour the nucleophilic displacement.[14]

2.3. Biological assays

These nucleoside analogues, **10**, **13b–d**, **17**, **19**, **20b–d** were evaluated for their ability to inhibit HIV-1 multiplication in human T4-lymphoblastoid cells, CEM-SS and MT4. Virus released from CEM-SS in culture supernatant was quantified by a measure of the reverse transcriptase activity associated with the particles. None of the compounds reduced virus production when present at concentrations ranging from 100 μg/ml to 10 μg/ml. Under these conditions, the IC50 of AZT is 6 nM. To verify the lack of antiviral activity a second type of assay was performed on infected MT4 cells following virus multiplication by the associated cytopathogenicity. The molecules were found inactives. In parallel evaluations, the compounds used at the same concentrations, did not reveal any cytotoxicity for uninfected CEM-SS and MT4 cells.

3. Experimental

3.1. Antiviral assays

The antiviral HIV-1 activity of a given compound was measured in HIV-1 Lai infected CEM-SS cells by quantification of the reverse transcriptase activity (RT) associated with virus particles released from the cells and in HIV-1 IIIb infected MT4 cells by the inhibition of virus-induced cytopathogenicity as already described.[15]

The CEM-SS cells were obtained from P. Nara through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH.

3.2. General techniques

Melting points were taken on a Reichert melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AC 300 spectrometer. ^{19}F NMR spectra (235 MHz) were recorded on a Bruker AC 250 spectrometer. Chemical shifts

are expressed in parts per million from TMS (^{1}H and ^{13}C) or $CFCl_3$ (^{19}F) as internal reference and coupling constants are in Hz. Unless otherwise noted, NMR samples were dissolved in $CDCl_3$. IR spectra were recorded on a BOMEM MB Series apparatus (in cm^{-1}). Mass spectra were recorded on a Fison VG Autospec spectrometer. Elemental analyses were performed with a Perkin-Elmer CHN 2400 apparatus. Solvents were dried before use.

3.3. General procedure for the synthesis of methoxypyrimidines 3b–d

To a stirred suspension of K_2CO_3 (1.2 equiv.) and Et_2NH (1.01 equiv.) in CH_2Cl_2 was added dropwise aldehyde at 0°C. After stirring for 3 h at rt, the precipitate was filtered off. To the stirred solution of the resulting oil in CH_2Cl_2, under N_2, was added dropwise $(CF_3CO)_2O$ (1.2 equiv.) at 0°C. The reaction mixture was gradually warmed to room temperature over 3 h, then quenched by careful addition of saturated aqueous Na_2CO_3 solution. The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting brown oil was added to a stirred suspension of K_2CO_3 (1.5 equiv.) and *O*-methylisourea hemisulfate (1.5 equiv.) in CH_3CN. After stirring for 20 h at rt or 60°C, the precipitate was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/cyclohexane 1:1) to yield methoxypyrimidines (**3b–d**).

3.3.1. 3-Benzyl-1,1,1-trifluoro-4-pyrrolidin-1-yl-but-3-en-2-one (2b). Yellow oil, 64%; EIMS *m/z* 283 (M^+, 100), 214 (65), 206 (26), 186 (31); δ_H 1.82 (t, ^3J=6.6 Hz, 4H), 3.50 (t, ^3J=6.6 Hz, 4H), 3.91 (s, 2H, CH_2), 7.04–7.32 (m, 5H), 7.73 (s, 1H, CH); δ_C 26.0, 29.4, 47.3, 118.5 (q, $^1J_{C-F}$=291.9 Hz, CF_3), 125.6, 127.2, 128.4, 141.4, 151.9 (CH), 177.7 (q, $^2J_{C-F}$=30.6 Hz, C=O).

3.3.2. 5-Benzyl-2-methoxy-4-(trifluoromethyl)pyrimidine (3b). Pale yellow oil, 74%; ν_{max}(film) 1595, 1478, 1389, 1316, 1194, 1136, 1044; EIMS *m/z* 268 (M^+, 100), 238 (26), 183 (17); HRMS calcd for $C_{13}H_{11}F_3N_2O$: 268.0819. Found: 268.0823; δ_H 4.02 (s, 3H, CH_3–O), 4.10 (s, 2H, CH_2), 7.08–7.38 (m, 5H), 8.46 (s, 1H, H-6); δ_C 33.4, 55.4, 119.1 (q, $^1J_{C-F}$=276.7 Hz, CF_3), 126.0 (C-5), 126.9, 128.7, 128.9, 137.8, 154.3 (q, $^2J_{C-F}$=34.3 Hz, C-4), 164.0 (C-2), 164.2 (C-6); δ_F −66.3 (s, 3F, CF_3).

3.3.3. 5-Ethyl-2-methoxy-4-(trifluoromethyl)pyrimidine (3c). Oil, 16%; ν_{max}(film) 1595, 1480, 1393, 1190, 1138; EIMS *m/z* 206 (M^+, 100), 191 (60), 176 (86); HRMS calcd for $C_8H_9F_3N_2O$: 206.0689. Found: 206.0667; δ_H 1.24 (t, ^3J=7.6 Hz, 3H, CH_3), 2.79 (q, ^3J=7.6 Hz, 2H, CH_2), 4.05 (s, 3H, CH_3–O), 8.59 (s, 1H, H-6); δ_C 15.3, 21.3, 55.2, 121.0 (q, $^1J_{C-F}$=276.5 Hz, CF_3), 127.3 (C-5), 154.0 (q, $^2J_{C-F}$=34.5 Hz, C-4), 163.3 (C-6), 163.8 (C-2); δ_F −66.8 (s, 3F, CF_3).

3.3.4. 5-Isopropyl-2-methoxy-4-(trifluoromethyl)pyrimidine (3d). Oil, 26%; ν_{max}(film) 1593, 1480, 1391, 1188, 1138, 1045; EIMS *m/z* 220 (M^+, 40), 205 (100); HRMS calcd for $C_9H_{11}F_3N_2O$: 220.0817. Found: 220.0823; δ_H 1.31 (d, ^3J=6.9 Hz, 6H), 3.30 (sept, ^3J=6.9 Hz, 1H), 4.05 (s, 3H, CH_3), 8.71 (s, 1H, H-6); δ_C 23.6, 23.7, 26.1, 55.2, 121.0 (q, $^1J_{C-F}$=275.0 Hz, CF_3), 132.1 (C-5), 153.1 (q, $^2J_{C-F}$=34.0 Hz, C-4), 161.2 (C-6), 163.5 (C-2); δ_F −65.7 (s, 3F, CF_3).

3.4. Hydrolysis of pyrimidines 3b–d

A solution of pyrimidine and 33% HBr in acetic acid (20 mL for 1.5 mmol) was left at rt for two days. The reaction mixture was then concentrated under reduced pressure. According to the cases, the residue was purified by recrystallisation or by flash column chromatography.

3.4.1. 5-Benzyl-4-methoxy-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (6b). The solid residue obtained starting from **3b** (448 mg, 1.67 mmol) was recrystallised from MeOH to give dihydropyrimidone **6b** as a white solid (379 mg, 79%); ν_{max}(KBr) 3450, 1707, 1684, 1179; EIMS *m/z* 286 (M^+, 42), 255 (23), 217 (100); Anal. calcd for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79. Found: C, 54.27; H, 4.55; N, 9.65; (DMSO-d_6) δ_H 3.10 (s, 3H, CH_3O), 3.29 (s, 2H, CH_2), 5.89 (d, ^3J=4.7 Hz, 1H, H-6), 7.16–7.40 (m, 5H), 8.11 (br s, 1H), 9.00 (d, ^3J=4.7 Hz,1H, NH); δ_C 32.6, 48.7, 88.3 (q, $^2J_{C-F}$=31.3 Hz, C-4), 102.4 (C-5), 123.2 (q, $^1J_{C-F}$=288.6 Hz, CF_3), 126.6, 128.7, 129.6, 130.6 (C-6), 138.5, 151.2 (C-2); δ_F −75.2 (s, 3F, CF_3).

3.4.2. 5-Benzyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (5b). 5b was characterized by NMR experiments starting from **6b** by heating at 60°C in $CDCl_3$. δ_H 3.95 (s, 2H, CH_2), 6.96–7.40 (m, 5H), 7.80 (s, 1H, H-6), 10.00 (br s, 1H); δ_C 33.0, 116.4 (C-5), 119.9 (q, $^1J_{C-F}$=278.6 Hz, CF_3), 127.4, 128.9, 129.2, 136.8, 150.9 (C-6), 157.5 (C-2), 161.4 (q, $^2J_{C-F}$=31.3 Hz, C-4).

3.4.3. 5-Ethyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (5c). The residue obtained starting from **3c** (300 mg, 1.46 mmol) was purified by flash column chromatography (CH_2Cl_2/MeOH 97:3) to give pyrimidone **5c** as a white solid (260 mg, 93%); mp 138–140°C; ν_{max}(KBr) 3400, 1655, 1275, 1194, 1142; EIMS *m/z* 192 (M^+, 55), 177 (100), 150 (24); HRMS calcd for $C_7H_7F_3N_2O$: 192.0515. Found: 192.0510. δ_H 1.20 (t, ^3J=7.5 Hz, 3H, CH_3), 2.68 (q, ^3J=7.5 Hz, 2H, CH_2), 8.20 (s, 1H, H-6), 11.4 (br s, 1H); δ_C 14.2, 20.4, 118.0 (C-5), 120.0 (q, $^1J_{C-F}$=278.6 Hz, CF_3), 149.5 (C-6), 157.6 (C-2),162.0 (q, $^2J_{C-F}$=34.5 Hz, C-4); δ_F −68.7 (s, 3F, CF_3).

3.4.4. 5-Ethyl-4-methoxy-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (6c). The solid residue obtained starting from **3c** (300 mg, 1.46 mmol) was recrystallised from MeOH to give **6c** as a white solid (235 mg, 72%); (DMSO-d_6) δ_H 1.00 (t, ^3J=7.3 Hz, 3H, CH_3), 1.98 (q, ^3J=7.3 Hz, 2H, CH_2), 3.06 (s, 3H, CH_3O), 6.38 (d, ^3J=5.1 Hz, 1H, H-6), 8.00 (br s, 1H), 9.08 (br s, 1H); δ_C 12.2, 18.9, 48.5, 88.3 (q, $^2J_{C-F}$=30.9 Hz, C-4), 103.1 (C-5), 123.0 (q, $^1J_{C-F}$=288.5 Hz, CF_3), 128.0 (C-6), 151.1 (C-2).

3.4.5. 5-Isopropyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (5d). The solid residue obtained starting from **3d** (404 mg, 1.84 mmol) was recrystallised from (CH_2Cl_2/cyclohexane 1:1) and the mother liquor was chromatographied

(CH_2Cl_2/MeOH 97:3) to give pyrimidone **5d** all together as a white solid (354 mg, 93%); mp 168–169°C; ν_{max}(KBr) 3437, 1643, 1190, 1142, 1049; EIMS *m/z* 206 (M^+, 24), 191 (100); δ_H 1.22 (d, ^3J=6.9 Hz, 6H, 2×CH_3), 3.13 (m, 1H, CH), 8.36 (s, 1H, H-6), 9.95 (br s, 1H); δ_C 23.4, 23.6, 25.7, 120.1 (q, $^1J_{C-F}$=276.7 Hz, CF_3), 123.4 (C-5), 149.2 (C-6), 157.7 (C-2), 160.6 (q, $^2J_{C-F}$=34.0 Hz, C-4); δ_F −67.6 (s, 3F, CF_3).

3.4.6. 5-Isopropyl-4-methoxy-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (6d). The solid residue obtained starting from **3d** (706 mg, 3.20 mmol) was recrystallised from MeOH to give the product **6d** as a white solid (480 mg, 63%); EIMS *m/z* 238 (M^+, 5), 207 (34), 191 (13), 169 (100); HRMS calcd for $C_9H_{13}F_3N_2O_2$: 238.0929. Found: 238.0929; (DMSO-d_6) δ_H 1.04 (d, ^3J=6.8 Hz, 3H), 1.10 (d, ^3J=6.8 Hz, 3H), 2.32 (sept, ^3J=6.8 Hz, 1H), 3.11 (s, 3H, CH_3O), 6.50 (d, ^3J=5.4 Hz, 1H, H-6), 8.00 (br s, 1H), 9.10 (d, ^3J=3.9 Hz, 1H, NH); δ_C 24.1, 24.3, 25.7, 49.1, 88.5 (q, $^2J_{C-F}$=31.0 Hz, C-4), 108.6 (C-5), 123.2 (q, $^1J_{C-F}$= 288.4 Hz, CF_3), 128.6 (C-6), 151.1 (C-2).

3.5. General procedure for the preparation of nucleoside analogues

Pyrimidone **4a** or **5** vs **6** (1.2 equiv./sugar) was refluxed with an excess of HMDS (2–4 mL) and a catalytic amount of $(NH_4)_2SO_4$ until a clear solution was obtained (for 3 h). The excess of HMDS was removed by distillation in vacuo and the silylated base was dissolved in CH_3CN. A solution of the protected sugar **8** or **14** in CH_3CN was then added at rt under N_2. $SnCl_4$ (1.8–2 equiv./sugar) (1 M in CH_2Cl_2) was added dropwise at −25°C. After stirring for 3 h at rt, the reaction mixture was diluted with CH_2Cl_2, then quenched with aqueous saturated $NaHCO_3$ solution. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic phases were washed with water and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (cyclohexane/AcOEt 80:20) to obtain nucleoside analogues.

3.5.1. 5-Benzoyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-hydroxy-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (9e,f). White solid, 85%, 2 diastereomers; ν_{max}(KBr) 3427, 3308, 2924, 1728, 1651, 1267; EIMS *m/z* 712 (M^+-H_2O, 11), 687 (21), 590 (75), 445 (99), 201 (100); Anal. calcd for $C_{38}H_{29}F_3N_2O_{10}$: C, 62.47; H, 4.00; N, 3.83. Found: C, 62.37; H, 3.99; N, 3.68. **9e** (*less polar*): mp 90–92°C; $[\alpha]^{26}_D$=−254.9 (*c* 1.00, CH_2Cl_2); δ_H 4.44 (dd, $^2J_{5'a\text{-}5'b}$=12.3 Hz, $^3J_{5'a\text{-}4'}$=2.1 Hz, 1H, H-5′a), 4.64 (dd, $^2J_{5'b\text{-}5'a}$=12.3 Hz, $^3J_{5'b\text{-}4'}$=3.3 Hz, 1H, H-5′b), 4.68 (m, 1H, H-4′), 5.58 (t, $^3J_{2'\text{-}3'}$=$^3J_{2'\text{-}1'}$=6.3 Hz, 1H, H-2′), 5.75 (dd, $^3J_{3'\text{-}4'}$=2.7 Hz, $^3J_{3'\text{-}2'}$=5.7 Hz, 1H, H-3′), 6.39 (d, $^3J_{1'\text{-}2'}$=6.8 Hz, 1H, H-1′), 7.13–8.03 (m, 22H); δ_C 64.9 (C-5′), 71.8 (C-3′), 73.6 (C-2′), 80.7 (C-4′), 82.3 (q, $^2J_{C-F}$=34.0 Hz, C-4), 86.7 (C-1′), 105.9 (C-5), 123.3 (q, $^1J_{C-F}$=287.8 Hz, CF_3), 128.3–133.8 (CH-ar), 135.5, 140.5 (C-6), 147.8 (C-2), 165.36, 165.40, 165.45, 195.5; δ_F −86.4 (s, 3F, CF_3). ***9f*** (*more polar*): mp 70–72°C; $[\alpha]^{23}_D$=−23.7 (*c* 1.01, CH_2Cl_2); δ_H 4.50 (d, $^3J_{5'\text{-}4'}$=4.3 Hz, 2H, H-5′), 4.65 (q, $^3J_{4'\text{-}5'}$=$^3J_{4'\text{-}3'}$=4.3 Hz, 1H, H-4′), 5.69 (t, $^3J_{2'\text{-}3'}$=$^3J_{2'\text{-}1'}$=5.7 Hz, 1H, H-2′), 5.75 (dd, $^3J_{3'\text{-}4'}$=4.3, $^3J_{3'\text{-}2'}$=5.7 Hz, 1H, H-3′), 6.16 (d, $^3J_{1'\text{-}2'}$=5.7 Hz, 1H, H-1′), 7.28–8.03 (m, 22H); δ_C 64.0 (C-5′), 71.1 (C-3′), 73.1 (C-2′), 79.9 (C-4′), 82.2 (q, $^2J_{C-F}$=34.6 Hz, C-4), 87.7 (C-1′), 106.3 (C-5), 123.3 (q, $^1J_{C-F}$=290.0 Hz, CF_3), 128.3–133.8 (CH-ar), 136.3, 141.7 (C-6), 148.2 (C-2), 165.2, 165.3, 165.9, 196.0; δ_F −87.1 (s, 3F, CF_3).

3.5.2. 5-Benzyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (12b). White solid, 90%, mp 65–67°C; ν_{max}(KBr) 1730, 1686, 1269, 710; EIMS *m/z* 698 (M^+, 7), 445 (M^+, 62), 201 (52), 105 (100); Anal. calcd for $C_{38}H_{29}F_3N_2O_8$: C, 65.33; H, 4.18; N, 4.01. Found: C, 65.64; H, 4.21; N, 3.72; δ_H 3.69 (d, ^2J=16.4 Hz, 1H, CH_a-Ph), 3.83 (d, ^2J=16.4 Hz, 1H, CH_b-Ph), 4.51 (m, 2H, H-5′), 4.76 (m, 1H, H-4′), 5.78 (m, 2H), 6.39 (d, ^3J=4.3 Hz, 1H, H-1′), 7.00–7.60 (m, 14H), 7.64 (s, 1H, H-6), 7.96 (m, 6H, H_o); δ_C 33.0, 63.9 (C-5′), 71.5, 75.0, 81.3 (C-4′), 90.2 (C-1′), 114.1 (C-5), 119.7 (q, $^1J_{C-F}$=278.7 Hz, CF_3), 127.3–136.5 (C-ar), 146.2 (C-6), 153.3 (C-2), 161.7 (q, $^2J_{C-F}$=35.3 Hz, C-4), 165.2, 165.8; δ_F −68.6 (s, 3F, CF_3).

3.5.3. 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-ethyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (12c). White solid, 76%, mp 67–69°C; ν_{max}(KBr) 1728, 1683, 1269, 710; CIMS *m/z* 637 (M^++1, 13), 514 (32), 445 (100), 201 (24), 105 (67); Anal. calcd for $C_{33}H_{27}F_3N_2O_8$: C, 62.26; H, 4.27; N, 4.40. Found: C, 62.49; H, 3.94; N, 4.20; δ_H 0.95 (t, ^3J=7.5 Hz, 3H, CH_3), 2.36 (m, 2H, CH_2), 4.72 (dd, $^2J_{5'a\text{-}5'b}$=12.4 Hz, $^3J_{5'a\text{-}4'}$=4.0 Hz, 1H, H-5′a), 4.83 (m, 1H, H-4′), 4.94 (dd, $^2J_{5'b\text{-}5'a}$=12.4 Hz, $^3J_{5'b\text{-}4'}$=2.5 Hz, 1H, H-5′b), 5.79 (t, $^3J_{2'\text{-}3'}$=$^3J_{2'\text{-}1'}$=5.7 Hz, 1H, H-2′), 5.95 (dd, $^3J_{3'\text{-}2'}$=5.7, $^3J_{3'\text{-}4'}$=4.4 Hz, 1H, H-3′), 6.56 (d, $^3J_{1'\text{-}2'}$=5.6 Hz, 1H, H-1′), 7.30–7.69 (m, 9H), 7.88 (s, 1H, H-6), 8.00 (m, 4H, H_o), 8.10 (m, 2H, H_o); δ_C 14.1, 20.5, 63.7 (C-5′), 71.3 (C-3′), 75.0 (C-2′), 81.6 (C-4′), 89.2 (C-1′), 116.6 (C-5), 119.7 (q, $^1J_{C-F}$=279.2 Hz, CF_3), 128.3–133.8 (C-ar), 144.4 (C-6), 153.5 (C-2), 162.0 (q, $^2J_{C-F}$=35.0 Hz, C-4), 165.3,165.4, 166.0; δ_F −68.7 (s, 3F, CF_3).

3.5.4. 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-isopropyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (12d). White solid, 82%, mp 68–69°C; ν_{max}(KBr) 1728, 1682, 1269, 710; EIMS *m/z* 650 (M^+, 9), 445 (42), 105 (100); Anal. calcd for $C_{34}H_{29}F_3N_2O_8$: C, 62.77; H, 4.49; N, 4.31. Found: C, 62.58; H, 4.32; N, 4.02; δ_H 0.90 (d, ^3J=6.8 Hz, 3H, CH_3), 1.10 (d, ^3J=6.8 Hz, 3H, CH_3), 3.02 (sept, ^3J=6.8 Hz, 1H), 4.76 (dd, $^2J_{5'a\text{-}5'b}$=12.1 Hz, $^3J_{5'a\text{-}4'}$= 4.2 Hz, 1H, H-5′a), 4.82 (m, 1H, H-4′), 4.91 (dd, $^2J_{5'b\text{-}5'a}$= 12.1 Hz, $^3J_{5'b\text{-}4'}$=2.4 Hz, 1H, H-5′b), 5.76 (t, $^3J_{2'\text{-}3'}$=$^3J_{2'\text{-}1'}$= 5.9 Hz, 1H, H-2′), 5.96 (dd, $^3J_{3'\text{-}2'}$=5.9 Hz, $^3J_{3'\text{-}4'}$=3.9 Hz, 1H, H-3′), 6.57 (d, $^3J_{1'\text{-}2'}$=5.9 Hz, 1H, H-1′), 7.30–7.68 (m, 9H), 8.00 (m, 5H), 8.11 (m, 2H); δ_C 23.4, 23.5, 25.6, 64.0 (C-5′), 71.5 (C-3′), 75.1 (C-2′), 81.7 (C-4′), 89.3 (C-1′), 119.8 (q, $^1J_{C-F}$=278.0 Hz, CF_3), 122.1 (C-5), 128.3–133.8 (C-ar), 143.6 (C-6), 153.3 (C-2), 161.4 (q, $^2J_{C-F}$=34.0 Hz, C-4), 165.3,165.4, 166.1; δ_F −67.6 (s, 3F, CF_3).

3.5.5. 1-(3,5-Di-*O*-benzoyl-2-deoxy-α,β-D-*erythro*-pentofuranosyl)-5-isopropyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (15 and 16). 67%. α *anomer* (**15**): white solid, 19%; δ_H 0.80 (d, ^3J=6.8 Hz, 3H), 1.16 (d, ^3J=6.8 Hz, 3H), 2.86–3.14 (m, 3H), 4.68 (d, ^3J=3.9 Hz, 2H, H-5′), 4.92 (t, ^3J=3.9 Hz, 1H, H-4′), 5.59 (d, ^3J=5.5 Hz, 1H, H-3′), 6.30

(d, ^3J=5.9 Hz, 1H, H-1′), 7.21–7.70 (m, 8H), 8.01–8.15 (m, 3H); δ_C 23.0, 24.3, 25.6, 38.2 (CH_2, C-2′), 63.8 (CH_2, C-5′), 74.9, 86.7, 90.7 (C-1′), 120.0 (q, $^1J_{C-F}$=278.6, CF_3), 121.0 (C-5), 128.4–133.9 (C-ar), 143.5 (C-6), 153.4 (C-2), 160.3 (q, $^2J_{C-F}$=34.3 Hz, C-4), 165.5, 165.9. β *anomer* (**16**): white solid, 48%; ν_{max}(KBr) 1723, 1678, 1512, 1453, 1271, 1196, 1105, 712; δ_H 0.90 (d, ^3J=6.9 Hz, 3H, CH_3), 1.13 (d, ^3J=6.9 Hz, 3H, CH_3), 2.31 (m, 1H, H-2′a), 3.03 (m, 1H, CH), 3.32 (dd, $^2J_{2'b-2'a}$=14.7 Hz, $^3J_{2'b-1'}$=5.6 Hz, 1H, H-2′b), 4.70–4.88 (m, 3H), 5.65 (d, ^3J=6.4 Hz, 1H, H-3′), 6.32 (dd, $^3J_{1'-2'a}$=8.1 Hz, $^3J_{1'-2'b}$=5.6 Hz, 1H, H-1′), 7.38–7.70 (m, 6H), 7.90 (m, 2H), 8.09 (m, 2H), 8.21 (s, 1H, H-6); δ_C 23.4, 23.6, 25.7, 39.5 (C-2′), 64.4 (C-5′), 75.3, 84.5, 88.9 (C-1′), 119.9 (q, $^1J_{C-F}$=279.0 Hz, CF_3), 121.5 (C-5), 128.3–133.7 (C-ar), 143.2 (C-6), 153.2 (C-2), 160.4 (q, $^2J_{C-F}$= 34.3 Hz, C-4), 165.9, 166.0.

3.5.6. 5-Benzoyl-4-hydroxy-1-(β-D-ribofuranosyl)-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (11). To a solution of NH_4OH (7 mL) in MeOH (7 mL) was added **9e**, **f** (220 mg, 0.3 mmol) and the solution was stirred at rt for 22 h. The reaction mixture was neutralized by diluted HCl and the aqueous layer was separated and extracted with AcOEt (3×15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 96:4) to give **11** as a white solid (63 mg, 2 diastereomers, 50%); ν_{max}(KBr) 3435, 1705, 1643, 1279, 1194; EIMS *m*/*z* 418 (M^+, 0.5), 400 (M^+-H_2O, 31), 349 (13), 269 (100), 133 (37); Anal. calcd. for $C_{17}H_{17}F_3N_2O_7$: C, 48.81; H, 4.09; N, 6.70. Found: C, 48.45; H, 4.01; N, 6.51; (CD_3OD) δ_H 3.25–3.60 (m, 2H, H-5′), 3.85–4.10 (m, 3H, H-2′, H-3′ and H-4′), 5.80 (d, $^3J_{1'-2'}$=4.9 Hz, 0.5H, H-1′), 5.89 (d, $^3J_{1'-2'}$=5.5 Hz, 0.5H, H-1′), 7.50–7.90 (m, 7H, H-ar and H-6); δ_C 62.5 and 62.7 (2×C-5′), 71.9 and 72.0 (2×CH), 75.4 and 75.7 (2×CH), 76.0–76.3 (m, 2×C-4), 86.1 and 86.3 (2×CH), 89.4 and 90.8 (2×C-1′), 107.5 and 107.7 (2×C-5), 125.2 (q, $^1J_{C-F}$=288.8 Hz, CF_3), 125.3 (q, $^1J_{C-F}$=289.6 Hz, CF_3), 128.1–140.3 (C-ar), 144.2 and 144.4 (2×C-6), 150.8 and 150.9 (2×C-2), 197.0 and 197.3 (2×C=O); δ_F −83.3 and −82.8 (2×(s, 3F, CF_3)).

3.6. General procedure for the deprotection of nucleoside analogues

The benzoylated nucleoside analogues were saponified with methanolic ammonia (20 mL for 1 mmol). After stirring for 20 h at rt, MeOH and NH_3 were evaporated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 96:4) to give nucleoside analogues.

3.6.1. 5-Benzoyl-4-methoxy-1-(β-D-ribofuranosyl)-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one(10). White solid, 2 diastereomers, 77%; ν_{max}(KBr) 3441, 1701, 1653, 1281, 1180, 1082; EIMS *m*/*z* 401 (M^+-MeO, 10), 269 (100), 191 (19), 133 (24); Anal. calcd for $C_{18}H_{19}F_3N_2O_7$: C, 50.01; H, 4.43; N, 6.48. Found: C, 50.02; H, 4.38; N, 6.27; (CD_3OD) δ_H 3.45 (2×(s, 3H, CH_3)), 3.46 and 3.55 (m, 2H, 2×H-5′), 3.80 and 4.05 (m, 3H, 2×(H-2′,3′,4′)), 5.84 (d, $^3J_{1'-2'}$=5.4 Hz, 0.5H, H-1′), 5.90 (d, $^3J_{1'-2'}$=5.5 Hz, 0.5H, H-1′), 7.40–7.90 (m, 6H); δ_C 51.1 and 51.3 (2×CH_3), 62.5 and 62.8 (2×C-5′), 72.0 and 72.1 (2×CH), 75.4 and 75.5 (2×CH), 75.7–76.3 (m, 2×C-4), 86.3 and 86.7 (2×CH), 89.4 and 90.2 (2×C-1′), 105.8 and 106.0 (2×C-5), 124.2 (q, $^1J_{C-F}$=288.1 Hz, CF_3), 124.3 (q, $^1J_{C-F}$=287.4 Hz, CF_3), 128.1–140.3 (m, C-ar), 145.7 and 145.8 (2×C-6), 151.9 and 152.0 (2×C-2), 193.7 and 193.9 (2×C=O); δ_F −80.2 and −79.8 (2×(s, 3F, CF_3)).

3.6.2. 5-Benzyl-1-(β-D-ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (13b). White solid, 92%, mp 177–179°C; ν_{max}(KBr) 3440, 1665, 1287, 1202, 1144; EIMS *m*/*z* 386 (M^+, 26), 297 (14), 255 (100), 133 (16); Anal. calcd for $C_{17}H_{17}F_3N_2O_5$: C, 52.85; H, 4.43; N, 7.25. Found: C, 52.66; H, 4.33; N, 7.28; (CD_3OD) δ_H 3.51 (dd, $^2J_{5'a-5'b}$=12.4 Hz, $^3J_{5'a-4'}$=2.7 Hz, 1H, H-5′a), 3.90 (dd, $^2J_{5'b-5'a}$=12.4 Hz, $^3J_{5'b-4'}$=2.2 Hz, 1H, H-5′b), 3.95 (s, 2H, CH_2), 4.04–4.14 (m, 2H), 4.18 (dd, $^3J_{2'-3'}$=4.5 Hz, $^3J_{2'-1'}$=1.4 Hz, 1H, H-2′), 5.87 (d, $^3J_{1'-2'}$=1.4 Hz, 1H, H-1′), 7.10–7.38 (m, 5H), 8.84 (s, 1H, H-6); δ_C 34.2, 60.9 (C-5′), 69.5, 76.5 (C-2′), 86.0, 94.1 (C-1′), 115.4 (C-5), 121.5 (q, $^1J_{C-F}$=278.1 Hz, CF_3), 127.8, 129.5, 129.8, 139.7, 150.7 (C-6), 155.9 (C-2), 161.6 (q, $^2J_{C-F}$=34.3 Hz, C-4); δ_F −65.2 (s, 3F, CF_3).

3.6.3. 5-Ethyl-1-(β-D-ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (13c). White solid, 94%, mp 180–182°C; ν_{max}(KBr) 3400, 1676, 1289, 1198, 1146; EIMS *m*/*z* 324 (M^+, 48), 193 (100), 133 (28); Anal. calcd for $C_{12}H_{15}F_3N_2O_5$: C, 44.45; H, 4.66; N, 8.64. Found: C, 44.20; H, 4.24; N, 8.30; (CD_3OD) δ_H 1.21 (t, ^3J=7.5 Hz, 3H), 2.62 (q, ^3J=7.5 Hz, 2H), 3.83 (dd, $^2J_{5'a-5'b}$=12.4 Hz, $^3J_{5'a-4'}$=1.8 Hz, 1H, H-5′a), 4.04 (dd, $^2J_{5'b-5'a}$=12.4 Hz, $^3J_{5'b-4'}$=2.0 Hz, 1H, H-5′b), 4.10–4.23 (m, 3H), 5.88 (s, 1H, H-1′), 9.03 (s, 1H, H-6); δ_C 14.8, 21.7, 60.3 (C-5′), 69.0, 76.5, 85.8, 94.0 (C-1′), 118.1 (C-5), 121.6 (q, $^1J_{C-F}$=277.9 Hz, CF_3), 149.4 (C-6), 156.0 (C-2), 161.4 (q, $^2J_{C-F}$=34.3 Hz, C-4); δ_F −65.7 (s, 3F, CF_3).

3.6.4. 5-Isopropyl-1-(β-D-ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (13d). White solid, 94%, mp 186–188°C; ν_{max}(KBr) 3410, 1659; EIMS *m*/*z* 338 (M^+, 15), 191 (27), 207 (100), 133 (17); Anal. calcd for $C_{13}H_{17}F_3N_2O_5$: C, 46.16; H, 5.06; N, 8.28. Found: C, 46.43; H, 4.76; N, 8.17; (CD_3OD) δ_H 1.24 (m, 6H), 3.10 (m, 1H), 3.85 (dd, $^2J_{5'a-5'b}$=12.2 Hz, $^3J_{5'a-4'}$=1.4 Hz, 1H, H-5′a), 4.06 (dd, $^2J_{5'b-5'a}$=12.2 Hz, $^3J_{5'b-4'}$=1.7 Hz, 1H, H-5′b), 4.10–4.20 (m, 3H), 5.89 (s, 1H, H-1′), 9.13 (s, 1H, H-6); δ_C 23.9, 24.1, 27.5, 60.0 (C-5′), 68.7, 76.6, 85.6, 94.1 (C-1′), 121.7 (q, $^1J_{C-F}$=277.8 Hz, CF_3), 123.6 (C-5), 148.9 (C-6), 155.8 (C-2), 160.5 (q, $^2J_{C-F}$=33.9 Hz, C-4); δ_F −64.7 (s, 3F, CF_3).

3.6.5. 1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-isopropyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (17). White solid, 78%; ν_{max}(KBr) 3450, 1653, 1281, 1198, 1144, 1096; EIMS *m*/*z* 322 (M^+, 9), 141 (77), 117 (100); HRMS calcd for $C_{13}H_{17}F_3N_2O_4$: 322.1127. Found: 322.1140; (CD_3OD) δ_H 1.26 (m, 6H, 2×CH_3), 2.27 (ddd, $^2J_{2'\beta-2'\alpha}$= 13.8 Hz, $^3J_{2'\beta-3'}$=6.3 Hz, $^3J_{2'\beta-1'}$=4.3 Hz, 1H, H-2′β), 2.60 (ddd, $^2J_{2'\alpha-2'\beta}$=13.8 Hz, $^3J_{2'\alpha-3'}$=5.7 Hz, $^3J_{2'\alpha-1'}$=6.2 Hz, 1H, H-2′α), 3.11 (m, 1H, CH), 3.78 (dd, $^2J_{5'a-5'b}$=12.1 Hz, $^3J_{5'a-4'}$=2.6 Hz, 1H, H-5′a), 3.92 (dd, $^2J_{5'b-5'a}$=12.1 Hz, $^3J_{5'b-4'}$=2.6 Hz, 1H, H-5′b), 4.05 (m, 1H, H-4′), 4.39 (m, 1H, H-3′), 6.19 (dd, $^3J_{1'-2'\alpha}$=6.2 Hz, $^3J_{1'-2'\beta}$=4.3 Hz, 1H, H-1′), 9.10 (s, 1H, H-6); δ_C 23.9, 24.1, 27.5, 42.6 (C-2′),

61.4 (C-5′), 70.3 (C-3′), 89.8 (C-4′), 90.0 (C-1′), 121.8 (q, $^1J_{C-F}$=277.9 Hz, CF_3), 123.4 (C-5), 148.5 (C-6), 155.7 (C-2), 160.4 (q, $^2J_{C-F}$=34.3 Hz, C-4).

3.7. General procedure for the synthesis of acyclonucleosides

Pyrimidone **4a** or **5** vs **6** was refluxed with an excess of HMDS (2–4 mL) and a catalytic amount of $(NH_4)_2SO_4$ until a clear solution was obtained (for 3 h). The excess of HMDS was removed by distillation in vacuo and **18** (1.4–2 equiv.) was added under N_2 at rt. Then a suspension of NaI (1.1 equiv.) in 1,2-dichloroethane was added at rt. The reaction mixture was refluxed for 4 h, then quenched with aqueous $Na_2S_2O_3$ solution at rt. After extraction with AcOEt (3×), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 98:2) to give acyclonucleosides.

3.7.1. 5-Benzoyl-4-hydroxy-1-(2-methoxy-ethoxymethyl)-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (19). White solid, 36%; ν_{max}(KBr) 3430, 1717, 1657, 1624, 1447, 1335, 1283, 1186, 1090; EIMS *m/z* 375 (M^+ +1, 17), 357 (34), 305 (100), 139 (52), 105 (91); Anal. calcd for $C_{16}H_{17}F_3N_2O_5$: C, 51.34; H, 4.58; N, 7.48. Found: C, 50.93; H, 4.45; N, 7.41; δ_H 3.32 (s, 3H, CH_3O), 3.50 (m, 2H, CH_2), 3.70 (m, 2H, CH_2), 5.05 (d, ^2J=10.7 Hz, 1H, CH_a), 5.11 (d, ^2J=10.7 Hz, 1H, CH_b), 6.00 (br s, 1H), 7.31 (s, 1H, H-6), 7.45–7.75 (m, 5H); δ_C 58.9, 68.6, 71.5, 76.7, 82.8 (q, $^2J_{C-F}$=34.2 Hz, C-4), 105.8 (C-5), 123.4 (q, $^1J_{C-F}$=289.7 Hz, CF_3), 128.9, 129.3, 133.4, 136.5, 144.9 (C-6), 149.0 (C-2), 196.2; δ_F −86.9 (s, 3F, CF_3).

3.7.2. 5-Benzyl-1-(2-methoxy-ethoxymethyl)-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (20b). 80%, oil; ν_{max}(film) 1680, 1510, 1198, 1142, 1107, 995; EIMS *m/z* 342 (M^+, 19), 305 (40), 268 (51), 255 (100), 238 (52); Anal. calcd for $C_{16}H_{17}F_3N_2O_3$: C, 56.14; H, 5.00; N, 8.18. Found: C, 56.06; H, 4.90; N, 8.12; δ_H 3.30 (s, 3H, CH_3), 3.75 (m, 2H, CH_2), 3.91 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 7.09–7.45 (m, 5H), 7.56 (s, 1H, H-6); δ_C 32.9, 57.8, 70.2, 71.2, 79.6, 106.6 (C-5), 120.3 (q, $^1J_{C-F}$=279.2 Hz, CF_3), 127.3, 128.7, 128.9, 136.8, 149.1 (C-6), 154.2 (C-2), 161.4 (q, $^2J_{C-F}$= 35.2 Hz, C-4); δ_F −68.5 (s, 3F, CF_3).

3.7.3. 5-Ethyl-1-(2-methoxy-ethoxymethyl)-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (20c). 63%, oil; ν_{max}(film) 1678, 1514, 1279, 1196, 1140, 1003; EIMS *m/z* 280 (M^+, 9), 205 (86), 193 (100); Anal. calcd for $C_{11}H_{15}F_3N_2O_3$: C, 47.14; H, 5.39; N, 10.00. Found: C, 46.74; H, 5.57; N, 9.87; δ_H 1.24 (t, ^3J=7.5 Hz, 3H, CH_3), 2.64 (q, ^3J=7.5 Hz, 2H, CH_2), 3.34 (s, 3H, CH_3), 3.57 (m, 2H, CH_2), 3.82 (m, 2H, CH_2), 5.42 (s, 2H, CH_2), 8.01 (s, 1H, H-6); δ_C 11.8, 20.4, 58.9, 70.2, 71.2, 79.4, 116.1 (C-5), 119.8 (q, $^1J_{C-F}$= 279.0 Hz, CF_3), 147.3 (C-6), 154.4 (C-2), 161.7(q, $^2J_{C-F}$= 34.2 Hz, C-4); δ_F −68.7 (s, 3F, CF_3).

3.7.4. 5-Isopropyl-1-(2-methoxy-ethoxymethyl)-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (20d). 63%, oil; ν_{max}(film) 1686, 1514, 1279, 1196, 1140; EIMS *m/z* 294 (M^+, 11), 220 (57), 207 (100), 191 (29), 107 (41); Anal. calcd for $C_{12}H_{17}F_3N_2O_3$: C, 48.98; H, 5.82; N, 9.52. Found: C, 49.05; H, 5.95; N, 9.37; δ_H 1.21 (d, ^3J=6.9 Hz, 6H, 2×CH_3), 3.12 (m, 1H, CH), 3.35 (s, 3H, CH_3O), 3.55 (m, 2H, CH_2), 3.81 (m, 2H, CH_2), 5.40 (s, 2H, CH_2), 8.04 (s, 1H, H-6); δ_C 23.6, 23.8, 25.6, 58.8, 70.2, 71.2, 79.4, 119.8 (q, $^1J_{C-F}$=279.0 Hz, CF_3), 121.5 (C-5), 149.2 (C-6), 154.1 (C-2), 160.7 (q, $^2J_{C-F}$=34.3 Hz, C-4); δ_F −65.6 (s, 3F, CF_3).

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