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Synthesis of 2′-deoxy-2′-fluororibo- and 2′-deoxy-2′,2′-difluororibonucleosides derived from 6-(het)aryl-7-deazapurines

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ABSTRACT

A series of novel sugar-modified derivatives of cytostatic 6-hetaryl-7-deazapurine ribonucleosides (2′-deoxy-2′-fluororibo- and 2′-deoxy-2′,2-difluororibonucleosides) bearing an aryl or hetaryl group in position 6, was prepared and screened for biological activity. The fluororibo derivatives were prepared by aqueous palladium catalyzed cross-coupling reactions of the corresponding 6-chloro-7-deazapurine 2′-deoxy-2′-fluororibonucleoside **11** with (het)arylboronic acids. The key intermediate **11** was prepared by a six-step sequence from the corresponding arabinonucleoside by selective protection of 3′- and 5′-hydroxyls by acid-labile groups followed by stereoselective S_N2 fluorination and deprotection. The difluororibo-series was prepared by non-stereoselective glycosidation of 6-chloro-7-deazapurine with benzoyl-protected 2-deoxy-2,2-difluoro-D-*erythro*-pentofuranosyl-1-mesylate followed by cross-couplings, separation of anomers and deprotection. The title nucleosides did not show considerable cytostatic or antiviral activity.

1. Introduction

As a result of our long-term interest in synthesis and biological activity of modified purine ribonucleoside derivatives and analogues,[1] we have recently discovered a new group[2] of nucleoside cytostatics: 6-hetaryl-7-deazapurine ribonucleosides (Fig. 1). These nucleosides showed a potent in vitro cytostatic effect against a broad spectrum of leukaemia and tumour cell-lines in nanomolar concentrations, as well as non-selective anti-HCV activities (probably caused by cytotoxicity). Attempts to improve their activities and/or pharmacokinetic properties by the preparation of *cyclo*Sal-phosphate and ProTide prodrugs[3] were not efficient due to efflux from the cells. Further efforts to modulate the activities and/or to achieve selectivity to HCV RNA-polymerase were focused on sugar modifications. In our recent study,[4] we have prepared 2′-*C*-methyl-ribonucleosides, arabinonucleosides and 2′-fluoroarabinonucleosides (Fig. 1). None of these derivatives showed any cytostatic or anti-HCV activities indicating that the *ribo*-configuration of the sugar might be crucial for the activity. However, there are as yet unexplored types of derivatives that should be tested to prove or disprove this hypothesis and to complete the structure–activity relationship of this class of cytostatics: nucleosides with a fluorine in the *ribo*-configuration. The 2′,2′-difluororibo motif is represented by gemcitabine[5] (2′,2′-difluorodeoxycytidine), which is a clinical anti-cancer drug with a broad spectrum of activity. It is the only nucleoside analogue that is used for the treatment of solid tumours (pancreas and lung cancer). Also some 2′-deoxy-2′-fluororibonucleosides were reported to show cytostatic activities.[6] Therefore, we report here the synthesis of the title 2′-deoxy-2′-fluororibo- and 2′-deoxy-2′,2′-difluororibonucleosides derived from 6-hetaryl-7-deazapurines.

2. Results and discussion

The synthetic route to 7-deazapurine 2′-deoxy-2′-fluororibonucleosides was similar to the literature procedure for the synthesis of purine 2′-deoxy-2′-fluororibonucleosides.[7] The synthesis was based on selective acid-labile tetrahydropyran-2-yl (THP–) protection of the 3′- and 5′-hydroxy groups in the *arabino*-derivative followed by fluorination with DAST (Scheme 1). The starting material for the synthesis was silyl-protected arabinonucleoside **5**.[4] First, the 2′-hydroxyl group was protected by acetylation with acetic anhydride in the presence of Et_3N and catalytic amount of DMAP in acetonitrile to obtain acetate **6** in 98% yield. Then, the silyl groups were removed using $Et_3N{\cdot}3HF$ in THF[8] to prepare nucleoside **7** (95%). Subsequently, THP-protecting groups were introduced to positions 3′ and 5′ by reaction with 2,3-dihydropyran in presence of TsOH in DMF. THP-protected acetate **8** was obtained in a high yield of 97%. The synthesis continued with

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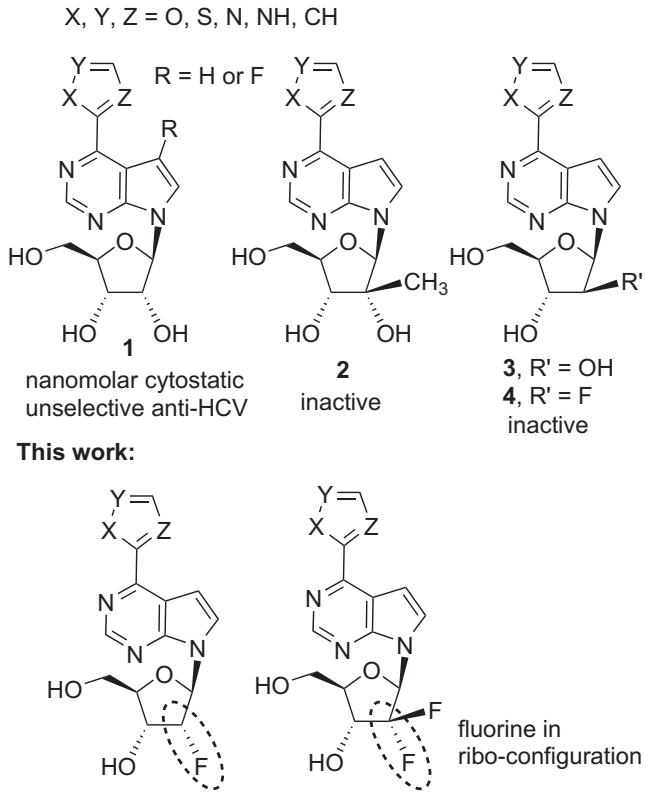


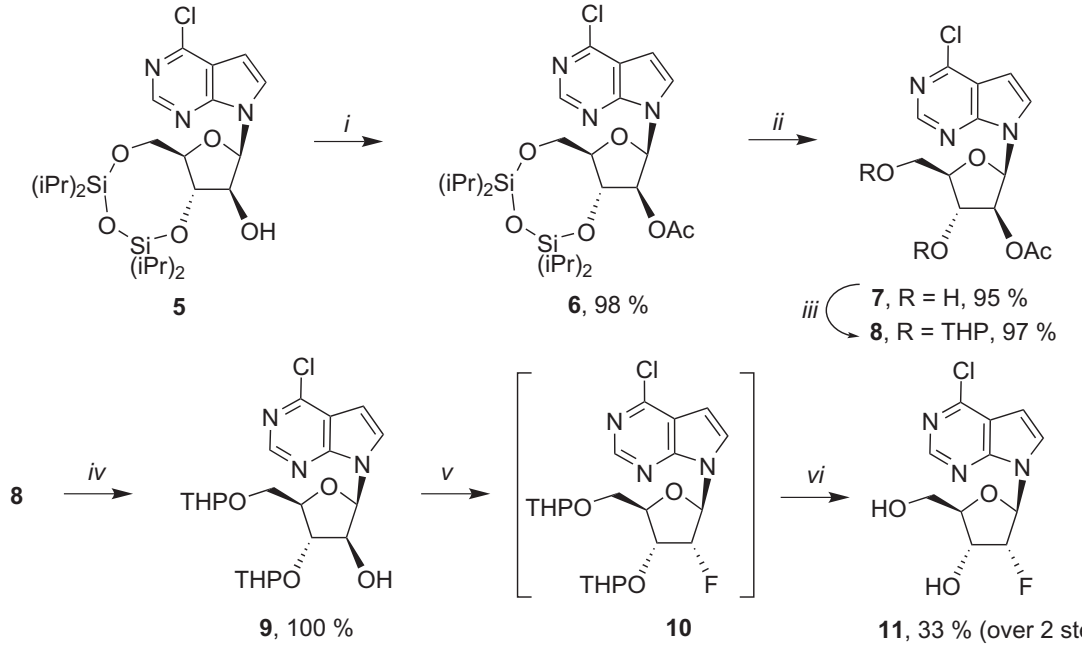
Fig. 1. Structures of biologically active 6-hetaryl-7-deazapurine nucleosides and their sugar-modified derivatives.

aminolysis of the acetyl group in position 2′ using methanolic ammonia at 0 °C to obtain 3′,5′-*O*-protected arabinoside **9** in quantitative yield. Fluorine was stereoselectively introduced to 2′-position by S_N2-reaction of arabinoside **9** with DAST in presence of pyridine in dichloromethane. The crude 2′-fluoro-2′-deoxyribonucleoside **10** was directly deprotected under acidic conditions to obtain free 2′-fluoro-2′-deoxyribonucleoside **11** in moderate yield (33% over two steps).

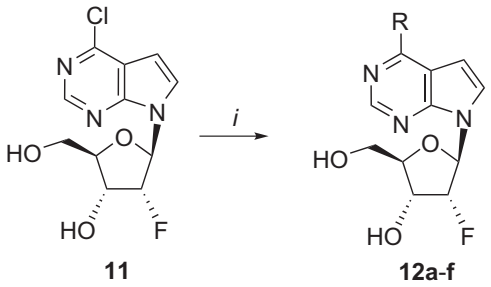
Fluoroderivative **11** was then used as a starting material for a series of aqueous-phase Suzuki cross-coupling reactions[9] to synthesize 6-(het)aryl-7-deazapurine 2′-fluoro-2′-deoxyribonucleosides **12a**–**f** (Scheme 2). The Suzuki cross-coupling reactions with (het)arylboronic acids were performed in the presence of sodium carbonate, TPPTS and palladium acetate in acetonitrile/water (2:1) at 100 °C. The desired title 6-(het)aryl-7-deazapurine 2′-fluoro-2′-deoxyribonucleosides **12a**–**f** were obtained in moderate to good yields (37–89%).

The synthesis of 6-hetaryl-7-deazapurine 2′-deoxy-2′,2′-difluoro-D-*erythro*-pentofuranosyl nucleosides **18** was based on glycosylation of 6-chloro-7-deazapurine (**14**) with commercially available mesylate **13** (Scheme 3). Catalysis with TMSOTf that was previously used[10] for the synthesis of purine 2′-deoxy-2′,2′-difluoro-L-*erythro*-pentofuranosyl nucleosides did not lead to formation of any product. Therefore, we decided to use a glycosylation protocol utilizing KOH and TDA-1 in toluene that was successfully used for glycosylation of 7-deazapurine derivatives with halogenoses.[2,11] At ambient temperature, the conversion was very low. Only at 50 °C and with prolonged reaction time was the yield of nucleoside **15** raised to maximum of 19% (Table 1). However, any higher temperatures led to degradation. Crude difluoronucleoside **15** was always obtained as an inseparable mixture of α- and β-anomers (1:2).

As attempts to separate anomers of nucleoside **15** failed, we decided to directly use the crude glycosylation product mixture **15** for the cross-coupling reactions to introduce the heterocyclic group to position 6 of the 7-deazapurine moiety. We supposed that the presence of a bulky group might help the separation of anomers. Thus the mixture **15** was subjected to a series of the Stille and Suzuki couplings. The Suzuki cross-coupling reactions of nucleoside **15** with hetarylboronic acids were performed in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in toluene at 85 °C and the Stille cross-coupling reactions with hetarylstannanes under $Pd(PPh_3)_2Cl_2$ catalysis in DMF at 105 °C and proceeded with full conversion. The separation of anomers of the protected fluorinated 6-hetaryl-7-deazapurine nucleosides **16** and **17** was again very difficult and several repeated HPFC chromatographies



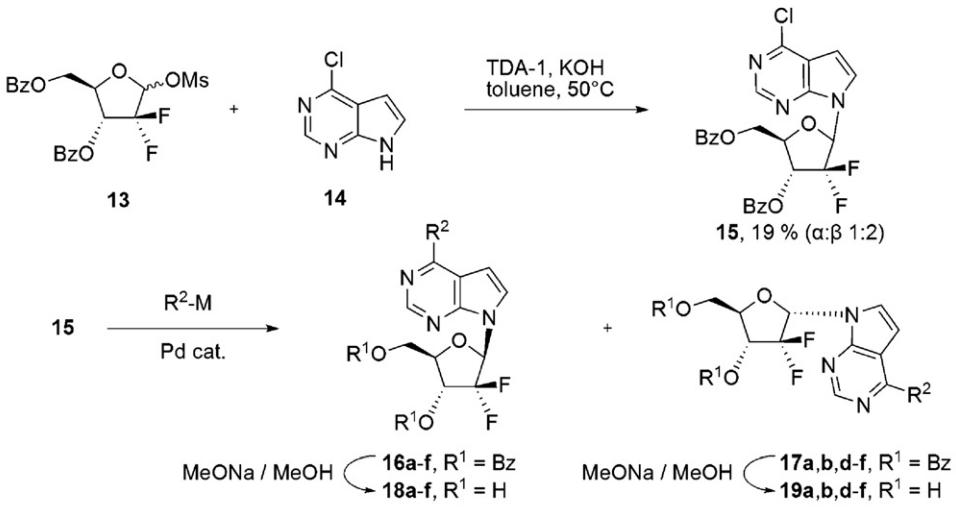
Scheme 1. (i): Ac_2O, Et_3N, DMAP/CH_3CN, rt; (ii) $Et_3N{\cdot}3HF$/THF, rt; (iii) DHP, TsOH/DMF, rt; (iv) NH_3/MeOH, 0 °C; (v) DAST, Py/DCM, rt; (vi) AcOH/THF/H_2O 4:2:1, reflux.



	R	yield
12a	2-furyl	47 %
12b	3-furyl	39 %
12c	2-thienyl	65 %
12d	3-thienyl	37 %
12e	phenyl	89 %
12f	2-benzofuryl	89 %

Scheme 2. (i) R–$B(OH)_2$, Na_2CO_3, TPPTS, $Pd(OAc)_2$, CH_3CN/H_2O, (2:1), 100 °C.

were required for successful isolation and purification of the β-anomers **16a**,**b**,**d**–**f** and α-anomers **17a**,**b**. Nucleosides **16c** and **17d**–**f** were obtained as crude compounds and were used in the following step without further purification. Although α-anomer **17c** was formed in the reaction with 2-thienyl-tributylstannane, we did not manage to separate it from the β-anomer **16c**. The moderate isolated yields of benzoylated difluoronucleosides **16** and **17** (11–33%) were caused by significant loss of the material by repeated chromatographic



16-19	R^2	M	Products (yields) cross-coupling		deprotection[a]	
a	2-furyl	$SnBu_3$	**16a** (33 %)	**17a** (11 %)	**18a** (67 %)	**19a** (40 %)
b	3-furyl	$B(OH)_2$	**16b** (28 %)	**17b** (11 %)	**18b** (78 %)	**19b** (40 %)
c	2-thienyl	$SnBu_3$	**16c** n.i.		**18c** (10 %[b])	
d	3-thienyl	$B(OH)_2$	**16d** (31 %)	**17d** n.i.	**18d** (51 %)	**19d** (9 %[b])
e	phenyl	$B(OH)_2$	**16e** (32 %)	**17e** n.i.	**18e** (73 %)	**19e** (8 %[b])
f	2-benzofuryl	$B(OH)_2$	**16f** (30 %)	**17f** n.i.	**18f** (61 %)	**19f** (9 %[b])

n.i. = not isolated
[a] Pure β-anomers **16** or α-anomers **17** were used for deprotection
[b] overall yield over 2 steps

Scheme 3.

Table 1
Optimization of synthesis of difluoroderivative **15**

Base (equiv)	PTC (equiv)	Solvent	Other conditions	Yield (%)	α/β ratio
KOH (2)	TDA-1 (0.5)	Toluene	rt, 24 h	3	1:2
KOH (2)	TDA-1 (0.5)	Toluene	50 °C, 24 h	10	1:2
KOH (2)	TDA-1 (0.5)	Toluene	50 °C, 48 h	19	1:2
KOH (2.5)	TDA-1 (2)	Toluene	50 °C, 48 h	6	1:2

separations. The deprotection of benzoyl groups with sodium methoxide in methanol led to the target free 6-hetaryl-7-deazapurine 2′-deoxy-2′,2′-difluoro-D-*erythro*-pentofuranosyl nucleosides **18a**–**f** and **19a**,**b**,**d**–**f** in moderate to good yields (40–73%). Relative configuration of selected compounds **15**–**19** was established by two-dimensional ROESY NMR spectra, where it was possible to observe typical spacial contacts between some protons in a molecule. The characteristic spacial interactions for β-anomer found in the spectra were between protons H-1′ and H-4′, further between H-6 and H-3′ and sometimes also between proton H-6 and proton from hydroxyl group OH-5′. On the other hand, crosspeaks observed in the spectra of α-anomer usually correspond with spacial contacts between proton H-6 and H-4′ and H-1′ and H-3′, respectively.

3. Conclusion

We have developed a synthesis of two new series of fluorinated sugar-modified derivatives of previously discovered cytostatic 6-hetaryl-7-deazapurine ribonucleosides. The synthesis of the fluororibo derivatives was a seven-step (but efficient) sequence concluded by aqueous Suzuki cross-coupling reactions of 6-chloro-7-deazapurine 2′-deoxy-2′-fluororibonucleoside **11** with (het)arylboronic acids. The synthesis of the 2′,2′-difluororibonucleosides was more straightforward but much less selective and efficient. The glycosidation of **14** with the sugar mesylate **13** gave a low yield of an unseparable anomeric mixture of products. Only after the follow-up cross-coupling and/or deprotection, the desired anomerically pure title nucleosides were obtained in moderate yields. All the title compounds were tested for in vitro cytostatic (HL60, HeLa S3, CCRF-CEM, Hep G2) and for anti-HCV activity. None of them showed any considerable activity in any of these assays, apart from ca. μM cytotoxic and anti-HCV activities of bulky benzofuran-linked nucleosides **18f** and **9f**. This lack of activity confirms that the potent cytostatic effect of 6-hetaryl-7-deazapurine nucleosides is only limited to ribonucleosides and sugar modification does not bring any selectivity in this particular class of compounds.

4. Experimental

4.1. General

NMR spectra were recorded using a 400 MHz (400 MHz for ^{1}H), 500 MHz (500 MHz for ^{1}H, 125.7 MHz for ^{13}C, 470.3 MHz for ^{19}F), or 600 MHz (600 MHz for ^{1}H, 151 MHz for ^{13}C) spectrometer. Melting points were determined using a Kofler block and are uncorrected. High-resolution mass spectra were measured using electrospray ionization. High performance flash chromatography (HPFC) purifications were performed either using silica gel columns with hexane/EtOAc gradient or C-18 columns with H_2O/MeOH gradient.

4.2. 4-Chloro-7-[2-*O*-acetyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (6)

Arabinoside **5**[4] (3.41 g, 6.46 mmol) was dissolved in anhydrous acetonitrile (127 ml) and DMAP (79 mg, 0.65 mmol), triethylamine (1.08 ml, 7.75 mmol) and acetic anhydride (731 μl, 7.75 mmol) were added. The reaction mixture was stirred for 1 h. Then, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (60 ml), extracted with water and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and evaporated to give acetate **6** (3.61 g; 98%) as a colourless foam. IR (ATR): 1749, 1587, 1545, 1509, 1455, 1357, 1224, 1204, 1058, 1034 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 0.97–1.30 (m, 28H, $(CH_3)_2CH$); 1.62 (s, 3H, CH_3CO); 3.90 (dt, 1H, $J_{4',3'}$=8.6 Hz, $J_{4',5'a}$=$J_{4',5'b}$=3.1 Hz, H-4′); 4.07 (dd, 1H, J_{gem}=13.0 Hz, $J_{5'a,4'}$=3.1 Hz, H-5′a); 4.19 (dd, 1H, J_{gem}=13.0 Hz, $J_{5'b,4'}$=3.1 Hz, H-5′b); 4.80 (t, 1H, $J_{3',4'}$=$J_{3',2'}$=8.4 Hz, H-3′); 5.57 (dd, 1H, $J_{2',3'}$=8.2 Hz, $J_{2',1'}$=6.6 Hz, H-2′); 6.62 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 6.70 (d, 1H, $J_{1',2'}$=6.6 Hz, H-1′); 7.55 (d, 1H, $J_{6,5}$=3.8 Hz, H-6); 8.61 (s, 1H, H-2). MS (ESI) *m*/*z* (%): 592 (100) [(^{35}Cl)M+Na], 594 (48) [(^{37}Cl)M+Na]; HRMS (ESI) calcd for $C_{25}H_{40}O_6N_3ClNaSi_2$ [M+Na]: 592.20364; found: 592.20348.

4.3. 4-Chloro-7-[2-*O*-acetyl-β-D-arabinofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (7)

Silylated acetate **6** (1.30 g, 2.28 mmol) was dissolved in anhydrous THF (40 ml) and $Et_3N\cdot 3HF$ (743 μl, 4.56 mmol) was added. The reaction mixture was stirred overnight. Then, the mixture was co-evaporated with silica gel (10 g) and chromatographed on silica in 2% methanol in $CHCl_3$. The title compound **7** (710 mg; 95%) was obtained as a white solid. Mp 166–168 °C. $[\alpha]_D^{20}$ +4.9 (*c* 0.387, DMSO). IR (ATR): 3468, 3269, 1733, 1592, 1551, 1507, 1460, 1412, 1363, 1223, 1203, 1136, 1096, 1047, 1021 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 1.63 (s, 3H, CH_3CO); 3.66 (br dt, 1H, J_{gem}=12.2 Hz, $J_{5'a,OH}$=$J_{5'a,4'}$=5.0 Hz, H-5′a); 3.74 (br dt, 1H, J_{gem}=12.2 Hz, $J_{5'b,OH}$=$J_{5'b,4'}$=4.3 Hz, H-5′b); 3.87 (ddd, 1H, $J_{4',3'}$=6.5 Hz, $J_{4',5'a}$=4.8 Hz, $J_{4',5'b}$=3.6 Hz, H-4′); 4.38 (br dt, 1H, $J_{3',4'}$=6.5 Hz, $J_{3',OH}$=$J_{3',2'}$=5.5 Hz, H-3′); 5.08 (br t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.5 Hz, OH-5′); 5.30 (t, 1H, $J_{2',1'}$=$J_{2',3'}$=5.8 Hz, H-2′); 5.83 (d, 1H, $J_{OH,3'}$=5.3 Hz, OH-3′); 6.72 (d, 1H, $J_{1',2'}$=5.9 Hz, H-1′); 6.73 (br d, 1H, $J_{5,6}$=3.7 Hz, H-5); 7.88 (d, 1H, $J_{6,5}$=3.8 Hz, H-6); 8.65 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 20.05 (CH_3); 60.27 (CH_2-5′); 71.78 (CH-3′); 77.87 (CH-2′); 81.56 (CH-1′); 83.00 (CH-4′); 99.61 (CH-5); 117.00 (C-4a); 129.72 (CH-6); 150.77 (CH-2); 150.85 and 150.88 (C-4, 7a); 169.19 (CO). MS (ESI) *m*/*z* (%): 328 (50) [(^{35}Cl)M+H], 330 [(^{37}Cl)M+H] (22), 350 (100) [(^{35}Cl)M+Na], 352 (46) [(^{37}Cl)M+Na]; HRMS (ESI) calcd for $C_{13}H_{14}O_5N_3ClNa$ [M+Na]: 350.05142; found: 350.05136.

4.4. 4-Chloro-7-[2-*O*-acetyl-3,5-di-*O*-(tetrahydropyran-2-yl)-β-D-arabinofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (8)

Acetate **7** (658 mg, 2.01 mmol) and $TsOH\cdot H_2O$ (764 mg, 4.02 mmol) were dissolved in anhydrous DMF (60 ml). The solution was cooled to 0 °C and 3,4-dihydro-2*H*-pyran (2.75 ml, 30.12 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and then was allowed to warm to rt and stirred overnight. Afterwards, the reaction mixture was diluted with EtOAc (50 ml) and extracted with saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica (hexane/EtOAc 4:1) to give title compound **8** (968 mg; 97%) as a colourless oil. Mixture of four diastereomers (1:1:1:1). ^{1}H NMR (400 MHz, $CDCl_3$): 1.46–1.97 (m, 48H, H-3,4,5-*THP*); 1.73, 1.75, 1.781 and 1.783 (4×s, 4×3H, CH_3CO); 3.45–3.60 (m, 8H, H-6a-*THP*); 3.66–3.77 (m, 4H, H-5′a); 3.78–3.95 (m, 8H, H-6b-*THP*); 3.99–4.30 (m, 8H, H-4′,5′b); 4.46–4.62 (m, 4H, H-3′); 4.67–4.91 (m, 8H, H-2-*THP*); 5.39–5.42 and 5.58–5.64 (2×m, 4H, H-2′); 6.60–6.63 (m, 4H, H-5); 6.80–6.86 (m, 4H, H-1′); 7.58, 7.616, 7.620 and 7.64 (4×d, 4H, 4×$J_{6,5}$=3.8 Hz, H-6); 8.63 and 8.64 (4×s, 4H, H-2). MS (ESI) *m*/*z* (%): 518 (100) [(^{35}Cl)M+Na], 520 (32) [(^{37}Cl)M+Na]; HRMS (ESI) calcd for $C_{23}H_{30}O_7N_3ClNa$ [M+Na]: 518.16700; found: 518.16721.

4.5. 4-Chloro-7-[3,5-di-*O*-(tetrahydropyran-2-yl)-β-D-arabino-furanosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (9)

THP-protected acetate **8** (968 mg, 1.95 mmol) was dissolved in methanolic ammonia (50 ml, 27%) at 0 °C and stirred for 3 h. Then the solution was evaporated in vacuo, resulting in arabinoside **9** (886 mg, 100%) as colourless foam. Mixture of four diastereomers (1:1:1:1). ^{1}H NMR (400 MHz, $CDCl_3$): 1.50–1.93 (m, 48H, H-3,4,5-*THP*); 3.51–3.69, 3.74–3.98, 4.01–4.57 and 4.66–4.86 (4×m, 44H, H-2′,3′,4′,5′ and H-2,6-*THP*); 6.57–6.65 (m, 6H, H-1′, 5); 6.72 and 6.75 (2×dd, 2H, 2×$J_{1',2'}$=5.6 Hz, H-1′); 7.73, 7.847, 7.850 and 7.75 (4×d, 4H, 4×$J_{6,5}$=3.8 Hz, H-6); 8.631, 8.633 and 8.64 (4×s, 4H, H-2). MS (ESI) *m*/*z* (%): 454 (11) [(^{35}Cl)M+H], 476 (100) [(^{35}Cl)M+Na], 478 (32) [(^{37}Cl)M+Na]; HRMS (ESI) calcd for $C_{21}H_{28}O_6N_3ClNa$ [M+Na]: 476.15588; found: 476.15585.

4.6. 4-Chloro-7-[2-deoxy-2-fluoro-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (11)

Arabinoside **9** (575 mg, 1.27 mmol) was dissolved in anhydrous dichloromethane (35 ml) in a plastic vial. Anhydrous pyridine (765 μl, 9.50 mmol) was added and the solution was cooled to 0 °C. Then DAST (836 μl, 6.33 mmol) was added. The reaction mixture was allowed to warm to rt and was stirred overnight. The reaction mixture was diluted with $CHCl_3$ (30 ml) and extracted with aqueous $NaHCO_3$ (saturated, 30 ml) and water (30 ml). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to obtain crude fluoroderivative **10**, which was subsequently dissolved in AcOH/THF/water mixture (4:2:1; 80.5 ml) and the solution was heated to reflux for 1 h. The reaction mixture was co-evaporated several times with toluene and the residue was chromatographed on silica gel column in 1.5% methanol in $CHCl_3$. 2-Deoxy-2-fluororibonucleoside **11** (120 mg, 33%) was obtained as a white crystalline solid after recrystallization (methanol/water 1:2). Mp 165–167 °C. $[\alpha]_D^{20}$ −25.0 (*c* 0.395, DMSO). IR (ATR): 3187, 1590, 1546, 1503, 1452, 1419, 1354, 1274, 1201, 1086, 1057, 1025 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): 3.78 (dd, 1H, J_{gem}=12.4 Hz, $J_{5'a,4'}$=3.5 Hz, H-5′a); 3.93 (dd, 1H, J_{gem}=12.4 Hz, $J_{5'b,4'}$=2.5 Hz, H-5′b); 4.11 (br dddd, 1H, $J_{4',3'}$=6.5 Hz, $J_{4',5'a}$=3.5 Hz, $J_{4',5'b}$=2.5 Hz, $J_{4',F}$=1.5 Hz, H-4′); 4.57 (ddd, 1H, $J_{3',F}$=16.5 Hz, $J_{3',4'}$=6.5 Hz, $J_{3',2'}$=4.7 Hz, H-3′); 5.30 (ddd, 1H, $J_{2',F}$=53.0 Hz, $J_{2',3'}$=4.7 Hz, $J_{2',1'}$=3.0 Hz, H-2′); 6.53 (dd, 1H, $J_{1',F}$=16.8 Hz, $J_{1',2'}$=3.0 Hz, H-1′); 6.72 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.88 (d, 1H, $J_{6,5}$=3.8 Hz, H-6); 8.60 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, CD_3OD): 61.89 (CH_2-5′); 70.36 (d, $J_{C,F}$=16.2 Hz, CH-3′); 85.26 (CH-4′); 88.25 (d, $J_{C,F}$=33.2 Hz, CH-1′); 95.21 (d, $J_{C,F}$=188.5 Hz, CH-2′); 101.36 (CH-5); 119.61 (C-4a); 129.64 (CH-6); 151.59 (CH-2); 152.22 (C-7a); 152.96 (C-4). ^{19}F NMR (470.3 MHz, CD_3OD): −202.12. MS (ESI) *m*/*z* (%): 288 (8) [(^{35}Cl)M+H], 310 (100) [(^{37}Cl)M+Na], 312 (48) [(^{37}Cl)M+Na]; HRMS (ESI) calcd for $C_{11}H_{12}O_3N_3ClF$ [M+H]: 288.05457; found: 228.05457.

4.7. 4-(Furan-2-yl)-7-[2-deoxy-2-fluoro-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (12a)

An argon purged mixture of compound **11** (100 mg, 0.35 mmol), furan-2-boronic acid (52 mg, 0.43 mmol), Na_2CO_3 (37 mg, 0.35 mmol), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol) and TPPTS (30 mg, 0.053 mmol) in water/MeCN (1:2, 2 ml) was stirred at 100 °C for 2 h. After cooling the mixture was neutralized by the addition of aqueous HCl (1 M), and volatiles were removed in vacuo. Purification of the residue by column chromatography on silica (1% methanol in $CHCl_3$) and crystallization (H_2O/methanol 2:1) afforded compound **12a** (52 mg, 47%) as a white crystalline solid. Mp 159–161 °C. $[\alpha]_D^{20}$ −42.7 (*c* 0.145, DMSO). IR (ATR): 3426, 1597, 1561, 1458, 1080, 1019 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): 3.61 (ddd, 1H, J_{gem}=12.2 Hz, $J_{5'a,OH}$=5.5 Hz, $J_{5'a,4'}$=3.9 Hz, H-5′a); 3.75 (ddd, 1H, J_{gem}=12.2 Hz, $J_{5'b,OH}$=5.2 Hz, $J_{5'b,4'}$=2.9 Hz, H-5′b); 3.97–4.01 (m, 1H, H-4′); 4.43 (dtd, 1H, $J_{3',F}$=16.5 Hz, $J_{3',4'}$=$J_{3',OH}$=6.0 Hz, $J_{3',2'}$=4.6 Hz, H-3′); 5.16 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.4 Hz, OH-5′); 5.34 (ddd, 1H, $J_{2',F}$=53.0 Hz, $J_{2',3'}$=4.6 Hz, $J_{2',1'}$=3.3 Hz, H-2′); 5.73 (d, 1H, $J_{OH,3'}$=6.0 Hz, OH-3′); 6.52 (dd, 1H, $J_{1',F}$=16.7 Hz, $J_{1',2'}$=3.4 Hz, H-1′); 6.79 (dd, 1H, $J_{4,3}$=3.5 Hz, $J_{4,5}$=1.8 Hz, H-4-furyl); 7.08 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.49 (dd, 1H, $J_{3,4}$=3.5 Hz, $J_{3,5}$=0.8 Hz, H-3-furyl); 7.94 (d, 1H, $J_{6,5}$=3.8 Hz, H-6); 8.06 (dd, 1H, $J_{5,4}$=1.8 Hz, $J_{5,3}$=0.8 Hz, H-5-furyl); 8.80 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 60.57 (CH_2-5′); 68.62 (d, $J_{C,F}$=15.8 Hz, CH-3′); 84.01 (d, $J_{C,F}$=1.8 Hz, CH-4′); 85.30 (d, $J_{C,F}$=32.7 Hz, CH-1′); 93.89 (d, $J_{C,F}$=187.2 Hz, C-2′); 101.71 (CH-5); 112.80 (C-4a); 112.87 (CH-4-furyl); 113.62 (CH-3-furyl); 128.01 (CH-6); 146.61 (CH-5-furyl); 146.74 (C-4); 151.36 (CH-2); 151.73 (C-7a); 152.51 (C-2-furyl). ^{19}F NMR (470.3 MHz, DMSO-d_6): −200.36 (s, 1F, F-2′). MS (ESI) *m*/*z* (%): 320 (100) [M+H], 342 (15) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{15}O_4N_3F$ [M+H]: 320.10411; found: 320.10413. For $C_{15}H_{14}O_4N_3F\cdot H_2O$ calcd: 53.41% C, 4.78% H, 12.46% N; found: 53.43% C, 4.70% H, 12.06% N.

4.8. 4-(Furan-3-yl)-7-[2-deoxy-2-fluoro-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (12b)

Compound **12b** was prepared as described for compound **12a** from compound **11** (100 mg, 0.54 mmol) and furan-3-boronic acid. The crude product was purified by column chromatography on silica (1% methanol in $CHCl_3$) and by reverse phase HPFC on C-18 (0→100% MeOH in water). Compound **12b** (43 mg, 39%) was obtained as an off-white crystalline solid after recrystallization (10% MeOH in water). Mp 69–71 °C. $[\alpha]_D^{20}$ −32.2 (*c* 0.205, DMSO). IR (ATR): 3243, 1580, 1518, 1454, 1432, 1102, 1079, 1020 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.61 (ddd, 1H, J_{gem}=12.2 Hz, $J_{5'a,OH}$=5.5 Hz, $J_{5'a,4'}$=3.9 Hz, H-5′a); 3.76 (ddd, 1H, J_{gem}=12.2 Hz, $J_{5'b,OH}$=5.2 Hz, $J_{5'b,4'}$=2.9 Hz, H-5′b); 3.97–4.01 (m, 1H, H-4′); 4.43 (br dq, 1H, $J_{3',F}$=16.7 Hz, $J_{3',4'}$=$J_{3',OH}$=$J_{3',2'}$=5.4 Hz, H-3′); 5.17 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.4 Hz, OH-5′); 5.33 (ddd, 1H, $J_{2',F}$=53.0 Hz, $J_{2',3'}$=4.6 Hz, $J_{2',1'}$=3.3 Hz, H-2′); 5.73 (d, 1H, $J_{OH,3'}$=5.7 Hz, OH-3′); 6.52 (dd, 1H, $J_{1',F}$=16.7 Hz, $J_{1',2'}$=3.3 Hz, H-1′); 7.12 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.26 (dd, 1H, $J_{4,5}$=1.9 Hz, $J_{4,2}$=0.8 Hz, H-4-furyl); 7.90 (dd, 1H, $J_{5,4}$=1.8 Hz, $J_{5,2}$=1.6 Hz, H-5-furyl); 7.93 (d, 1H, $J_{6,5}$=3.9 Hz, H-6); 8.74 (dd, 1H, $J_{2,5}$=1.5 Hz, $J_{2,4}$=0.8 Hz, H-2-furyl); 8.81 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.56 (CH_2-5′); 68.60 (d, $J_{C,F}$=15.8 Hz, CH-3′); 83.98 (d, $J_{C,F}$=1.8 Hz, CH-4′); 85.35 (d, $J_{C,F}$=32.6 Hz, CH-1′); 93.94 (d, $J_{C,F}$=187.2 Hz, C-2′); 101.28 (CH-5); 109.53 (CH-4-furyl); 114.65 (C-4a); 125.11 (C-3-furyl); 127.57 (CH-6); 144.82 (CH-5-furyl); 145.14 (CH-2-furyl); 150.40 (C-4); 151.24 (C-7a); 151.35 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): −200.28 (s, 1F, F-2′). MS (ESI) *m*/*z* (%): 320 (100) [M+H], 342 (95) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{15}O_4N_3F$ [M+H]: 320.10411; found: 320.10412. For $C_{15}H_{14}O_4N_3F\cdot 2.4H_2O$ calcd: 49.70% C, 5.23% H, 11.59% N; found: 50.09% C, 4.89% H, 11.15% N.

4.9. 4-(Thiophene-2-yl)-7-[2-deoxy-2-fluoro-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (12c)

Compound **12c** was prepared as described for compound **12a** from compound **11** (100 mg, 0.54 mmol) and thiophene-2-boronic acid. The crude product was purified by reverse phase HPFC on C-18 (0→100% MeOH in water). Compound **12c** (76 mg, 65%) was obtained as a white crystalline solid after recrystallization (H_2O/MeOH 2:1). Mp 177–179 °C. $[\alpha]_D^{20}$ −37.0 (*c* 0.181, DMSO). IR (ATR): 3352, 1567, 1514, 1459, 1352, 1078, 1031, 1017 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.62 (ddd, 1H, J_{gem}=12.3 Hz, $J_{5'a,OH}$=5.5 Hz, $J_{5'a,4'}$=3.8 Hz, H-5′a); 3.76 (ddd, 1H, J_{gem}=12.3 Hz, $J_{5'b,OH}$=5.3 Hz, $J_{5'b,4'}$=2.9 Hz, H-5′b); 3.97–4.02 (m, 1H, H-4′); 4.44 (dtd, 1H, $J_{3',F}$=16.8 Hz, $J_{3',4'}$=$J_{3',OH}$=6.1 Hz, $J_{3',2'}$=4.6 Hz, H-3′); 5.17 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.4 Hz, OH-5′); 5.34 (ddd, 1H, $J_{2',F}$=53.0 Hz,

$J_{2',3'}$=4.5 Hz, $J_{2',1'}$=3.3 Hz, H-2′); 5.73 (d, 1H, $J_{OH,3'}$=6.0 Hz, OH-3′); 6.53 (dd, 1H, $J_{1',F}$=16.7 Hz, $J_{1',2'}$=3.3 Hz, H-1′); 7.21 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.31 (dd, 1H, $J_{4,5}$=5.0 Hz, $J_{4,3}$=3.8 Hz, H-4-thienyl); 7.87 (dd, 1H, $J_{5,4}$=5.0 Hz, $J_{5,3}$=1.1 Hz, H-5-thienyl); 7.98 (d, 1H, $J_{6,5}$=3.9 Hz, H-6); 8.18 (dd, 1H, $J_{3,4}$=3.8 Hz, $J_{3,5}$=1.1 Hz, H-3-thienyl); 8.78 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.52 (CH_2-5′); 68.58 (d, $J_{C,F}$=15.8 Hz, CH-3′); 83.99 (d, $J_{C,F}$=1.8 Hz, CH-4′); 85.41 (d, $J_{C,F}$=32.6 Hz, CH-1′); 93.96 (d, $J_{C,F}$=187.1 Hz, C-2′); 101.33 (CH-5); 113.12 (C-4a); 128.18 (CH-6); 129.26 (CH-4-thienyl); 129.87 (CH-3-thienyl); 131.05 (CH-5-thienyl); 142.42 (C-2-thienyl); 150.45 (C-4); 151.12 (CH-2); 151.64 (C-7a). ^{19}F NMR (470.3 MHz, DMSO-d_6): −200.19 (s, 1F, F-2′). MS (ESI) *m*/*z* (%): 336 (100) [M+H]; HRMS (ESI) calcd for $C_{15}H_{15}O_3N_3FS$ [M+H]: 336.08127; found: 336.08121. For $C_{15}H_{14}O_3N_3FS$ calcd: 53.72% C, 4.21% H, 12.53% N; found: 53.45% C, 4.10% H, 12.18% N.

4.10. 4-(Thiophene-3-yl)-7-[2-deoxy-2-fluoro-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (12d)

Compound **12d** was prepared as described for compound **12a** from compound **11** (100 mg, 0.54 mmol) and thiophene-3-boronic acid. The crude product was purified by column chromatography on silica (1% methanol in $CHCl_3$) and by reverse phase HPFC on C-18 (0→100% MeOH in water). Compound **12d** (43 mg, 37%) was obtained as an off-white crystalline solid after recrystallization (H_2O/EtOH 3:1). Mp 179–181 °C. $[\alpha]_D^{20}$ −41.3 (*c* 0.234, DMSO). IR (ATR): 3351, 1566, 1518, 1463, 1350, 1079, 1033, 1019 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.62 (ddd, 1H, J_{gem}=12.2 Hz, $J_{5'a,OH}$=5.5 Hz, $J_{5'a,4'}$=3.9 Hz, H-5′a); 3.76 (ddd, 1H, J_{gem}=12.2 Hz, $J_{5'b,OH}$=5.2 Hz, $J_{5'b,4'}$=2.9 Hz, H-5′b); 3.98–4.02 (m, 1H, H-4′); 4.44 (br dq, 1H, $J_{3',F}$=16.7 Hz, $J_{3',4'}$=$J_{3',OH}$=$J_{3',2'}$=5.5 Hz, H-3′); 5.17 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.4 Hz, OH-5′); 5.34 (ddd, 1H, $J_{2',F}$=53.0 Hz, $J_{2',3'}$=4.6 Hz, $J_{2',1'}$=3.4 Hz, H-2′); 5.73 (d, 1H, $J_{OH,3'}$=5.9 Hz, OH-3′); 6.54 (dd, 1H, $J_{1',F}$=16.8 Hz, $J_{1',2'}$=3.4 Hz, H-1′); 7.17 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.75 (dd, 1H, $J_{5,4}$=5.1 Hz, $J_{5,2}$=2.9 Hz, H-5-thienyl); 7.96 (dd, 1H, $J_{4,5}$=5.1 Hz, $J_{4,2}$=1.3 Hz, H-4-thienyl); 7.96 (d, 1H, $J_{6,5}$=3.8 Hz, H-6); 8.55 (dd, 1H, $J_{2,5}$=2.9 Hz, $J_{2,4}$=1.3 Hz, H-2-thienyl); 8.84 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.56 (CH_2-5′); 68.62 (d, $J_{C,F}$=15.9 Hz, CH-3′); 83.99 (d, $J_{C,F}$=1.8 Hz, CH-4′); 85.36 (d, $J_{C,F}$=32.7 Hz, CH-1′); 93.94 (d, $J_{C,F}$=187.2 Hz, C-2′); 101.51 (CH-5); 114.68 (C-4a); 127.37 (CH-5-thienyl); 127.58 (CH-4-thienyl); 127.86 (CH-6); 128.88 (CH-2-thienyl); 139.93 (C-3-thienyl); 151.30 (CH-2); 151.68 (C-7a); 151.81 (C-4). ^{19}F NMR (470.3 MHz, DMSO-d_6): −200.27 (s, 1F, F-2′). MS (ESI) *m*/*z* (%): 336 (100) [M+H]; HRMS (ESI) calcd for $C_{15}H_{15}O_3N_3FS$ [M+H]: 336.08127; found: 336.08141. For $C_{15}H_{14}O_3N_3FS$ calcd: 53.72% C, 4.21% H, 12.53% N; found: 53.54% C, 4.11% H, 12.21% N.

4.11. 4-Phenyl-7-[2-deoxy-2-fluoro-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (12e)

Compound **12e** was prepared as described for compound **12a** from compound **11** (100 mg, 0.54 mmol) and phenylboronic acid. The crude product was purified by reverse phase HPFC on C-18 (0→100% MeOH in water). Compound **12e** (102 mg, 89%) was obtained as a white crystalline solid after recrystallization (H_2O/MeOH 2:1). Mp 70–73 °C. $[\alpha]_D^{20}$ −31.6 (*c* 0.263, DMSO). IR (ATR): 3273, 1560, 1521, 1467, 1360, 1238, 1113, 1061, 1041 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.62 (ddd, 1H, J_{gem}=12.3 Hz, $J_{5'a,OH}$=5.4 Hz, $J_{5'a,4'}$=3.9 Hz, H-5′a); 3.76 (ddd, 1H, J_{gem}=12.2 Hz, $J_{5'b,OH}$=5.3 Hz, $J_{5'b,4'}$=2.9 Hz, H-5′b); 3.98–4.02 (m, 1H, H-4′); 4.45 (dtd, 1H, $J_{3',F}$=16.6 Hz, $J_{3',4'}$=$J_{3',OH}$=6.1 Hz, $J_{3',2'}$=4.6 Hz, H-3′); 5.18 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.4 Hz, OH-5′); 5.36 (ddd, 1H, $J_{2',F}$=53.0 Hz, $J_{2',3'}$=4.6 Hz, $J_{2',1'}$=3.4 Hz, H-2′); 5.75 (d, 1H, $J_{OH,3'}$=6.0 Hz, OH-3′); 6.56 (dd, 1H, $J_{1',F}$=16.7 Hz, $J_{1',2'}$=3.4 Hz, H-1′); 7.04 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.58 (m, 1H, H-*p*-Ph); 7.60 (m, 2H, H-*m*-Ph); 7.98 (d, 1H, $J_{6,5}$=3.8 Hz, H-6); 8.17 (m, 2H, H-*o*-Ph); 8.92 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.58 (CH_2-5′); 68.64 (d, $J_{C,F}$=15.8 Hz, CH-3′); 84.03 (d, $J_{C,F}$=1.8 Hz, CH-4′); 85.43 (d, $J_{C,F}$=32.6 Hz, CH-1′); 93.97 (d, $J_{C,F}$=187.2 Hz, C-2′); 101.53 (CH-5); 115.66 (C-4a); 128.09 (CH-6); 128.87 (CH-*o*-Ph); 129.16 (CH-*m*-Ph); 130.58 (CH-*p*-Ph); 137.57 (C-*i*-Ph); 151.42 (CH-2); 151.66 (C-7a); 156.54 (C-4). ^{19}F NMR (470.3 MHz, DMSO-d_6): −200.36 (s, 1F, F-2′). MS (ESI) *m*/*z* (%): 330 (100) [M+H]; HRMS (ESI) calcd for $C_{17}H_{17}O_3N_3F$ [M+H]: 330.12485; found: 330.12484. For $C_{17}H_{16}O_3N_3F\cdot 2.2H_2O$ calcd: 55.34% C, 5.57% H, 11.39% N; found: 55.42% C, 5.38% H, 11.08% N.

4.12. 4-(Benzofuran-2-yl)-7-[2-deoxy-2-fluoro-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (12f)

Compound **12f** was prepared as described for compound **12a** from compound **11** (100 mg, 0.54 mmol) and benzofuran-2-boronic acid. The crude product was purified by reverse phase HPFC on C-18 (0→100% MeOH in water). Compound **12f** (114 mg, 89%) was obtained as an off-white amorphous solid. Mp 189–193 °C. $[\alpha]_D^{20}$ −47.8 (*c* 0.209, DMSO). IR (ATR): 3241, 1599, 1567, 1549, 1461, 1228, 1101, 1057 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.63 (br dm, 1H, J_{gem}=12.2 Hz, H-5′a); 3.76 (br dm, 1H, J_{gem}=12.2 Hz, H-5′b); 3.98–4.03 (m, 1H, H-4′); 4.46 (br dq, 1H, $J_{3',F}$=16.8 Hz, $J_{3',4'}$=$J_{3',OH}$=$J_{3',2'}$=5.0 Hz, H-3′); 4.98–5.24 (m, 1H, OH-5′); 5.37 (ddd, 1H, $J_{2',F}$=53.0 Hz, $J_{2',3'}$=4.6 Hz, $J_{2',1'}$=3.4 Hz, H-2′); 5.78 (br d, 1H, $J_{OH,3'}$=5.5 Hz, OH-3′); 6.56 (dd, 1H, $J_{1',F}$=16.8 Hz, $J_{1',2'}$=3.3 Hz, H-1′); 7.30 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.36 (br td, 1H, $J_{5,4}$=$J_{5,6}$=7.5 Hz, $J_{5,7}$=0.9 Hz, H-5-benzofuryl); 7.48 (ddd, 1H, $J_{6,7}$=8.3 Hz, $J_{6,5}$=7.2 Hz, $J_{6,4}$=1.3 Hz, H-6-benzofuryl); 7.81 (br dq, 1H, $J_{7,6}$=8.4 Hz, $J_{7,5}$=$J_{7,4}$=$J_{7,3}$=0.8 Hz, H-7-benzofuryl); 7.82 (br dm, 1H, $J_{4,5}$=7.8 Hz, H-4-benzofuryl); 7.94 (d, 1H, $J_{3,7}$=1.0 Hz, H-3-benzofuryl); 8.05 (d, 1H, $J_{6,5}$=3.8 Hz, H-6); 8.90 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.33 (CH_2-5′); 68.59 (d, $J_{C,F}$=15.8 Hz, CH-3′); 84.03 (d, $J_{C,F}$=1.7 Hz, CH-4′); 85.43 (d, $J_{C,F}$=32.7 Hz, CH-1′); 93.98 (d, $J_{C,F}$=187.3 Hz, C-2′); 102.02 (CH-5); 109.33 (CH-3-benzofuryl); 112.12 (CH-7-benzofuryl); 114.16 (C-4a); 122.66 (CH-4-benzofuryl); 124.02 (CH-5-benzofuryl); 126.77 (CH-6-benzofuryl); 127.94 (C-3a-benzofuryl); 128.74 (CH-6); 146.64 (C-4); 151.42 (CH-2); 152.00 (C-7a); 154.10 (C-2-benzofuryl); 155.52 (C-7a-benzofuryl). ^{19}F NMR (470.3 MHz, DMSO-d_6): −200.18 (s, 1F, F-2′). MS (ESI) *m*/*z* (%): 370 (100) [M+H]; HRMS (ESI) calcd for $C_{19}H_{17}O_4N_3F$ [M+H]: 370.11976; found: 370.11969. For $C_{19}H_{16}O_4N_3F$ calcd: 61.79% C, 4.37% H, 11.38% N; found: 61.50% C, 4.12% H, 11.09% N.

4.13. 4-Chloro-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-α,β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (15)

6-Chloro-7-deazapurine (**14**) (5 g, 32.6 mmol) was dissolved in anhydrous toluene (250 ml) and KOH (3.71 g, 65.1 mmol), TDA-1 (5.21 ml, 16.3 mmol) and mesylate **13** (29.71 g, 65.1 mmol) were added. The reaction mixture was stirred at 50 °C for 48 h. Then, the reaction mixture was diluted with EtOAc (100 ml) and extracted with aqueous HCl (1 M, 150 ml) and water (150 ml). Organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude reaction product was purified by column chromatography on silica (hexane/EtOAc 10:1) to obtain crude nucleoside **15** (3.16 g, 19%) as a mixture of anomers (α/β 1:2). Colourless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): 4.63–4.68 (m, 2H, β-H-4′); 4.71–4.75 (m, 4H, β-H-5′a, α-H-5′a, α-H-5′b); 4.85 (dd, 2H, J_{gem}=12.4 Hz, $J_{4',5'}$=3.6 Hz, β-H-5′b); 4.96–5.02 (m, 1H, α-H-4′); 5.84–5.92 (m, 3H, α-H-3′, β-H-3′); 6.69–6.76 (m, 5H, β-H-1′, α-H-5, β-H-5); 6.98 (dd, 1H, $J_{1',F}$=12.4 Hz, $J_{1',F}$=6.4 Hz, α-H-1′); 7.44–7.68 (m, 21H, α-H-6, β-H-6, α-H-*m*-Bz, β-H-*m*-Bz, α-H-*p*-Bz, β-H-*p*-Bz); 8.02–8.14 (m, 12H, α-H-*o*-Bz, β-H-*o*-Bz); 8.68 (s, 2H, β-H-2), 8.69 (s, 1H, α-H-2). MS (ESI) *m*/*z* (%): 514 (36) [(^{35}Cl)M+H], 516 (9) [(^{37}Cl)M+H], 536

(100) [(^{35}Cl)M+Na], 538 (32) [(^{37}Cl)M+Na]; HRMS (ESI) calcd for $C_{25}H_{19}O_5N_3ClF_2$ [M+H]: 514.09758, found 514.09760.

4.14. 4-(Furan-2-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (16a) and 4-(furan-2-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (17a)

An argon purged mixture of compound **15** (750 mg, 1.46 mmol), 2-(tributylstannanyl)furan (781 mg, 2.19 mmol) and $PdCl_2(PPh_3)_2$ (51 mg, 0.073 mmol) in anhydrous DMF (5 ml) was stirred at 105 °C for 2 h. After cooling, volatiles were removed in vacuo. The residue was purified by multiple HPFC on silica column (0–100% EtOAc in hexane) to give **16a** (262 mg, 33%) and **17a** (86 mg, 11%) as yellowish oils. Compound **16a**: IR (ATR): 1730, 1602, 1453, 1270, 1095, 1071 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 4.66 (br q, 1H, $J_{4',5'b}$=$J_{4',5'a}$=$J_{3',4'}$=4.4 Hz, H-4′); 4.74 (dd, 1H, J_{gem}=12.0 Hz, $J_{4',5'}$=4.4 Hz, H-5′a); 4.86 (dd, 1H, J_{gem}=12.0 Hz, $J_{4',5'}$=3.2 Hz, H-5′b); 5.85 (ddd, 1H, $J_{3',F}$=14.0 Hz, $J_{3',F}$=5.2 Hz, $J_{3',4'}$=3.2 Hz, H-3′); 6.67 (dd, 1H, $J_{3,4}$=3.6 Hz, $J_{4,5}$=2.0 Hz, H-4-furyl); 6.83 (dd, 1H, $J_{1',F}$=12.4 Hz, $J_{1',F}$=6.4 Hz, H-1′); 7.16 (d, 1H, $J_{5,6}$=4.0 Hz, H-5); 7.44–7.68 (m, 8H, H-6, H-*m*-Bz, H-*p*-Bz, H-3-furyl); 7.74 (d, 1H, $J_{5,4}$=0.9 Hz, H-5-furyl); 8.07–8.16 (m, 4H, H-*o*-Bz); 8.90 (s, 1H, H-2). MS (ESI) *m*/*z* (%): 546 (40) [M+H], 568 (100) [M+Na]; HRMS (ESI) calcd for $C_{29}H_{22}O_6N_3F_2$ [M+H]: 546.14712, found 536.14685. **17a:** IR (ATR): 1730, 1453, 1266, 1109, 1096, 1071 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 4.73 (br d, 2H, $J_{4',5'}$=4.4 Hz, H-5′a, H-5′b); 4.97–5.01 (m, 1H, H-4′); 5.91 (dt, 1H, $J_{3',F}$=11.6 Hz, $J_{3',F}$=$J_{3',4'}$=4.8 Hz, H-3′); 6.67 (dd, 1H, $J_{3,4}$=3.6 Hz, $J_{4,5}$=2.0 Hz, H-4-furyl); 7.06 (dd, 1H, $J_{1',F}$=8.8 Hz, $J_{1',F}$=6.4 Hz, H-1′); 7.21 (d, 1H, $J_{5,6}$=4.0 Hz, H-5); 7.44–7.67 (m, 8H, H-6, H-*m*-Bz, H-*p*-Bz, H-3-furyl); 7.74 (d, 1H, $J_{5,4}$=1.2 Hz, H-5-furyl); 8.06–8.12 (m, 4H, H-*o*-Bz); 8.90 (s, 1H, H-2). MS (ESI) *m*/*z* (%): 546 (35) [M+H], 568 (100) [M+Na]; HRMS (ESI) calcd for $C_{29}H_{22}O_6N_3F_2$ [M+H]: 546.14712, found 536.14666.

4.15. 4-(Furan-3-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (16b) and 4-(furan-3-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (17b)

An argon purged mixture of compound **15** (1.00 g, 1.95 mmol), furan-3-boronic acid (326 mg, 2.92 mmol), K_2CO_3 (537 mg, 3.89 mmol) and $Pd(PPh_3)_4$ (112 mg, 0.097 mmol) in anhydrous toluene (16 ml) was stirred at 85 °C for 2 h. After cooling, the reaction mixture was diluted with EtOAc (30 ml) and extracted with aqueous HCl (1 M, 20 ml) and water (20 ml). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by multiple HPFC on silica column (0–100% EtOAc in hexane) to give **16b** (298 mg, 28%) and **17b** (120 mg, 11%) as yellowish oils. Compound **16b**: IR (ATR): 1722, 1600, 1572, 1518, 1452, 1263, 1090, 1068, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 4.67 (br q, 1H, $J_{4',5'b}$=$J_{4',5'a}$=$J_{3',4'}$=4.4 Hz, H-4′); 4.74 (dd, 1H, J_{gem}=12.4 Hz, $J_{4',5'}$=4.8 Hz, H-5′a); 4.86 (dd, 1H, J_{gem}=12.0 Hz, $J_{4',5'}$=3.2 Hz, H-5′b); 5.85 (ddd, 1H, $J_{3',F}$=14.0 Hz, $J_{3',F}$=5.2 Hz, $J_{3',4'}$=3.2 Hz, H-3′); 6.81–6.87 (m, 2H, H-1′, H-5); 7.18 (br s, 1H, H-4-furyl); 7.44–7.68 (m, 8H, H-6, H-*m*-Bz, H-*p*-Bz, H-5-furyl); 8.08–8.15 (m, 4H, H-*o*-Bz); 8.34 (br s, 1H, H-2-furyl); 8.90 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 62.88 (CH_2-5′); 71.75 (dd, $J_{C,F}$=34.6 and 16.8 Hz, CH-3′); 77.80 (dd, $J_{C,F}$=4.0 and 2.3 Hz, CH-4′); 82.33 (dd, $J_{C,F}$=37.0 and 21.1 Hz, CH-1′); 102.22 (CH-5); 109.41 (CH-4-furyl); 115.11 (C-4a); 120.69 (dd, $J_{C,F}$=265.0 and 259.1 Hz, C-2′); 124.89 (C-3-furyl); 126.83 (d, $J_{C,F}$=4.1 Hz, CH-6); 127.95 (C-*i*-Bz); 128.53, 128.67 (CH-*m*-Bz); 129.21 (C-*i*-Bz); 129.70, 130.11 (CH-*o*-Bz); 133.46, 134.15 (CH-*p*-Bz); 144.08, 144.10 (CH-2,5-furyl); 151.35 (C-4); 151.81 (CH-2); 152.34 (C-7a); 164.84, 166.01 (CO-Bz). ^{19}F{^{1}H} NMR (470.3 MHz, $CDCl_3$): −117.00 and −110.74 (2×d, 2×1F, J_{gem}=246.0 Hz). MS (ESI) *m*/*z* (%): 546 (75) [M+H], 568 (100) [M+Na]; HRMS (ESI) calcd for $C_{29}H_{22}O_6N_3F_2$ [M+H]: 546.14712, found 536.14740. Compound **17b**: IR (ATR): 1725, 1601, 1572, 1452, 1264, 1108, 1095, 1070, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 4.73 (br d, 2H, $J_{4',5'}$=4.4 Hz, H-5′a, H-5′b); 4.97–5.01 (m, 1H, H-4′); 5.92 (dt, 1H, $J_{3',F}$=12.0 Hz, $J_{3',F}$=$J_{3',4'}$=5.2 Hz, H-3′); 6.87 (d, 1H, $J_{5,6}$=4.0 Hz, H-5); 7.07 (dd, 1H, $J_{1',F}$=8.8 Hz, $J_{1',F}$=6.4 Hz, H-1′); 7.19 (br s, 1H, H-4-furyl); 7.44–7.67 (m, 8H, H-6, H-*m*-Bz, H-*p*-Bz, H-5-furyl); 8.07–8.13 (m, 4H, H-*o*-Bz); 8.34 (br s, 1H, H-2-furyl); 8.93 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 63.35 (CH_2-5′); 72.51 (dd, $J_{C,F}$=33.2 and 17.1 Hz, CH-3′); 80.23 (dd, $J_{C,F}$=5.3 and 1.9 Hz, CH-4′); 83.63 (dd, $J_{C,F}$=41.3 and 21.0 Hz, CH-1′); 102.23 (CH-5); 109.45 (CH-4-furyl); 114.88 (C-4a); 121.90 (dd, $J_{C,F}$=268.6 and 256.7 Hz, C-2′); 124.85 (C-3-furyl); 126.36 (CH-6); 127.99 (C-*i*-Bz); 128.53, 128.77 (CH-*m*-Bz); 129.12 (C-*i*-Bz); 129.82, 130.03 (CH-*o*-Bz); 133.48, 134.21 (CH-*p*-Bz); 144.14, 144.17 (CH-2,5-furyl); 151.30 (C-4); 151.84 (CH-2); 152.46 (C-7a); 164.75, 166.06 (CO-Bz). ^{19}F{^{1}H} NMR (470.3 MHz, $CDCl_3$): −116.41 and −104.41 (2×d, 2×1F, J_{gem}=249.2 Hz). MS (ESI) *m*/*z* (%): 546 (55) [M+H], 568 (100) [M+Na]; HRMS (ESI) calcd for $C_{29}H_{22}O_6N_3F_2$ [M+H]: 546.14712, found 536.14742.

4.16. 4-(Thiophene-2-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (16c)

Compound **16c** was prepared as described for compounds **16a** and **17a** from compound **15** (750 mg, 1.46 mmol) and 2-(tributylstannyl)thiophene. The crude reaction mixture was partially separated by multiple HPFC on silica gel column (0→100% EtOAc in hexane). Crude compound **16c** (121 mg) was used for the next step without further purification.

4.17. 4-(Thiophene-3-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (16d) and 4-(thiophene-3-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (17d)

Compounds **16d** and **17d** were prepared as described for compounds **16b** and **17b** from compound **15** (1.00 g, 1.95 mmol) and thiophene-3-boronic acid. The crude reaction mixture was partially separated by multiple HPFC on silica gel column (0→100% EtOAc in hexane). Compounds **16d** (337 mg, 31%) and crude compound **17d** (210 mg) were obtained as yellowish oils. Compound **17d** was used for the next step without further purification. Compound **16d**: IR (ATR): 1725, 1568, 1519, 1453, 1265, 1094, 1070, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 4.65–4.70 (m, 1H, H-4′); 4.74 (dd, 1H, J_{gem}=12.0 Hz, $J_{4',5'}$=4.4 Hz, H-5′a); 4.86 (dd, 1H, J_{gem}=12.0 Hz, $J_{4',5'}$=3.2 Hz, H-5′b); 5.86 (ddd, 1H, $J_{3',F}$=14.0 Hz, $J_{3',F}$=5.2 Hz, $J_{3',4'}$=2.8 Hz, H-3′); 6.86 (dd, 1H, $J_{1',F}$=12.4 Hz, $J_{1',F}$=6.4 Hz, H-1′); 6.93 (d, 1H, J_i=3.6 Hz, H-5); 7.43–7.68 (m, 8H, H-6, H-*m*-Bz, H-*p*-Bz, H-5-thienyl); 7.90 (br d, 1H, $J_{5,4}$=4.8, H-4-thienyl); 8.07–8.16 (m, 4H, H-*o*-Bz); 8.29 (br s, 1H, H-2-thienyl); 8.97 (s, 1H, H-2). MS (ESI) *m*/*z* (%): 562 (100) [M+H], 584 (70) [M+Na]; HRMS (ESI) calcd for $C_{29}H_{22}O_5N_3F_2S$ [M+H]: 562.12427, found 562.12425.

4.18. 4-Phenyl-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (16e) and 4-phenyl-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (17e)

Compounds **16e** and **17e** were prepared as described for compounds **16b** and **17b** from compound **15** (750 mg, 1.46 mmol) and phenylboronic acid. The crude reaction mixture was partially separated by multiple HPFC on silica gel column (0→100% EtOAc in

hexane). Compounds **16e** (267 mg, 32%) and crude compound **17e** (236 mg) were obtained as yellowish oils. Compound **17e** was used for the next step without further purification. Compound **16e**: IR (ATR): 1724, 1568, 1519, 1452, 1264, 1093, 1069, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 4.65–4.70 (m, 1H, H-4′); 4.75 (dd, 1H, J_{gem}=12.0 Hz, $J_{4',5'}$=4.4 Hz, H-5′a); 4.86 (dd, 1H, J_{gem}=12.4 Hz, $J_{4',5'}$=3.6 Hz, H-5′b); 5.87 (ddd, 1H, $J_{3',F}$=14.0 Hz, $J_{3',F}$=5.2 Hz, $J_{3',4'}$=3.2 Hz, H-3′); 6.87 (dd, 1H, $J_{1',F}$=12.4 Hz, $J_{1',F}$=6.4 Hz, H-1′); 6.93 (d, 1H, $J_{5,6}$=3.6 Hz, H-5); 7.44–7.68 (m, 10H, H-6, H-*m*-Bz, H-*p*-Bz, H-*m*-Ph, H-*p*-Ph); 8.08–8.15 (m, 6H, H-*o*-Bz, H-*o*-Ph); 9.04 (s, 1H, H-2). MS (ESI) *m*/*z* (%): 556 (80) [M+H], 578 (100) [M+Na]; HRMS (ESI) calcd for $C_{31}H_{24}O_5N_3F_2$ [M+H]: 556.16785, found 556.16784.

4.19. 4-(Benzofuran-2-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (16f) and 4-(benzofuran-2-yl)-7-[3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (17f)

Compounds **16f** and **17f** were prepared as described for compounds **16b** and **17b** from compound **15** (750 mg, 1.46 mmol) and benzofuran-2-boronic acid. The crude reaction mixture was partially separated by multiple HPFC on silica gel column (0→100% EtOAc in hexane). Compounds **16f** (262 mg, 30%) and crude compound **17f** (289 mg) were obtained as yellowish oils. Compound **17f** was used for the next step without further purification. Compound **16f**: IR (ATR): 1725, 1600, 1573, 1453, 1264, 1248, 1094, 1070, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 4.65–4.469 (m, 1H, H-4′); 4.75 (dd, 1H, J_{gem}=12.4 Hz, $J_{4',5'}$=4.8 Hz, H-5′a); 4.87 (dd, 1H, J_{gem}=12.4 Hz, $J_{4',5'}$=3.6 Hz, H-5′b); 5.88 (ddd, 1H, $J_{3',F}$=14.0 Hz, $J_{3',F}$=5.2 Hz, $J_{3',4'}$=3.2 Hz, H-3′); 6.85 (dd, 1H, $J_{1',F}$=12.4 Hz, $J_{1',F}$=6.4 Hz, H-1′); 7.28–7.34 (m, 2H, H-5, H-5-benzofuryl); 7.40–7.67 (m, 9H, H-6, H-*m*-Bz, H-*p*-Bz, H-*6*-benzofuryl, H-4-benzofuryl); 7.73 (d, 1H, $J_{6,7}$=7.6 Hz, H-7-benzofuryl); 7.79 (s, 1H, H-3-benzofuryl); 8.07–8.17 (m, 4H, H-*o*-Bz); 8.97 (s, 1H, H-2). MS (ESI) *m*/*z* (%): 596 (52) [M+H], 618 (100) [M+Na]; HRMS (ESI) calcd for $C_{33}H_{24}O_6N_3F_2$ [M+H]: 596.16277, found 596.16276.

4.20. 4-(Furan-2-yl)-7-[2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (18a)

Compound **16a** (171 mg, 0.31 mmol) was dissolved in anhydrous methanol (5 ml) and a solution of sodium methoxide in methanol (1 M, 940 μl, 0.94 mmol) was added. The reaction mixture was stirred at rt for 1 h, then it was neutralized with aqueous HCl (1 M) and co-evaporated with silica (10 g). The residue was purified by column chromatography on silica (2% of methanol in $CHCl_3$) to obtain compound **18a** (75 mg, 67%) as an off-white crystalline solid after recrystallization (H_2O/methanol 10:1). Mp 184–186 °C. $[\alpha]_D^{20}$ +14.8 (*c* 0.200, DMSO). IR (ATR): 3145, 1587, 1566, 1487, 1263, 1205, 1069, 1052, 1022 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.70 (ddd, 1H, J_{gem}=12.6 Hz, $J_{5'a,OH}$=5.9 Hz, $J_{5'a,4'}$=4.2 Hz, H-5′a); 3.82 (br dm, 1H, J_{gem}=12.5 Hz, H-5′b); 3.94–3.98 (m, 1H, H-4′); 4.42–4.51 (m, 1H, H-3′); 5.26 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.6 Hz, OH-5′); 6.35 (d, 1H, $J_{OH,3'}$=6.5 Hz, OH-3′); 6.60 (dd, 1H, $J_{1',F}$=11.0 and 5.2 Hz, H-1′); 6.80 (dd, 1H, $J_{4,3}$=3.5 Hz, $J_{4,5}$=1.8 Hz, H-4-furyl); 7.14 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.51 (dd, 1H, $J_{3,4}$=3.5 Hz, $J_{3,5}$=0.8 Hz, H-3-furyl); 7.90 (dd, 1H, $J_{6,5}$=3.8 Hz, $J_{6,F}$=1.3 Hz, H-6); 8.08 (dd, 1H, $J_{5,4}$=1.8 Hz, $J_{5,3}$=0.8 Hz, H-5-furyl); 8.82 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 59.63 (CH_2-5′); 68.88 (dd, $J_{C,F}$=25.9 and 18.3 Hz, CH-3′); 81.26 (d, $J_{C,F}$=8.3 Hz, CH-4′); 82.50 (dd, $J_{C,F}$=39.9 and 23.8 Hz, CH-1′); 102.24 (CH-5); 112.47 (C-4a); 112.92 (CH-4-furyl); 113.82 (CH-3-furyl); 123.23 (dd, $J_{C,F}$=260.3 and 255.1 Hz, C-2′); 127.93 (CH-6); 146.75 (CH-5-furyl); 146.91 (C-4); 151.66 (CH-2);152.09 (C-7a); 152.38 (C-2-furyl). ^{19}F NMR (470.3 MHz, DMSO-d_6): −113.94 and −112.88 (2×d, 2×1F, J_{gem}=234.3 Hz). MS (ESI) *m*/*z* (%): 338 (50) [M+H], 360 (100) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{14}O_4N_3F_2$ [M+H]: 338.09469; found: 338.09466. For $C_{15}H_{13}O_4N_3F_2$ calcd: 53.42% C, 3.88% H, 12.46% N; found: 53.03% C, 4.12% H, 12.20% N.

4.21. 4-(Furan-3-yl)-7-[2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (18b)

Compound **18b** was prepared as described for compound **18a**. Compound **16b** (193 mg, 0.35 mmol) was used. The crude product was purified by column chromatography (2% MeOH in $CHCl_3$) and reverse phase HPFC on C-18 column (methanol in H_2O 0–100%) to give compound **18b** (92 mg, 78%) as a yellowish crystalline solid after recrystallization (H_2O/methanol 2:1). Mp 85–86 °C. $[\alpha]_D^{20}$ +17.1 (*c* 0.211, DMSO). IR (ATR): 3432, 1596, 1574, 1512, 1212, 1071, 1056, 1030, 1010 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.70 (ddd, 1H, J_{gem}=12.6 Hz, $J_{5'a,OH}$=5.9 Hz, $J_{5'a,4'}$=4.1 Hz, H-5′a); 3.82 (br dm, 1H, J_{gem}=12.6 Hz, H-5′b); 3.93–3.97 (m, 1H, H-4′); 4.42–4.51 (m, 1H, H-3′); 5.27 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.5 Hz, OH-5′); 6.35 (d, 1H, $J_{OH,3'}$=6.5 Hz, OH-3′); 6.60 (dd, 1H, $J_{1',F}$=10.9 and 5.1 Hz, H-1′); 7.18 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.27 (dd, 1H, $J_{4,5}$=1.9 Hz, $J_{4,2}$=0.8 Hz, H-4-furyl); 7.89 (dd, 1H, $J_{6,5}$=3.9 Hz, $J_{6,F}$=0.9 Hz, H-6); 7.91 (br dd, 1H, $J_{5,4}$=1.8 Hz, $J_{5,2}$=1.5 Hz, H-5-furyl); 8.76 (dd, 1H, $J_{2,5}$=1.5 Hz, $J_{2,4}$=0.8 Hz, H-2-furyl); 8.83 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 59.63 (CH_2-5′); 68.82 (dd, $J_{C,F}$=25.8 and 18.8 Hz, CH-3′); 81.23 (d, $J_{C,F}$=8.0 Hz, CH-4′); 82.53 (dd, $J_{C,F}$=39.5 and 24.6 Hz, CH-1′); 101.79 (CH-5); 109.51 (CH-4-furyl); 114.32 (C-4a); 123.24 (dd, $J_{C,F}$=260.5 and 255.8 Hz, C-2′); 124.98 (C-3-furyl); 127.45 (CH-6); 144.87 (CH-5-furyl); 145.27 (CH-2-furyl); 150.60 (C-4); 151.59 (C-7a); 151.62 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): −113.94 and −113.03 (2×d, 2×1F, J_{gem}=234.1 Hz). MS (ESI) *m*/*z* (%): 338 (82) [M+H], 360 (100) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{14}O_4N_3F_2$ [M+H]: 338.09469; found: 338.09457. For $C_{15}H_{13}O_4N_3F_2 \cdot 1.3H_2O$ calcd: 49.95% C, 4.36% H, 11.65% N; found: 50.05% C, 4.33% H, 11.42% N.

4.22. 4-(Thiophene-2-yl)-7-[2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (18c)

Compound **18c** was prepared as described for compound **18a**. Crude product **16c** (121 mg) was used. The crude product was purified by column chromatography (1.5% MeOH in $CHCl_3$) to give compound **18c** (50 mg, 10% over two steps) as a white crystalline solid after recrystallization (H_2O/methanol 10:1). Mp 176–179 °C. $[\alpha]_D^{20}$ +5.0 (*c* 0.06, DMSO). IR (ATR): 3333, 1559, 1518, 1353, 1196, 1058, 1035 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.71 (ddd, 1H, J_{gem}=12.6 Hz, $J_{5'a,OH}$=5.9 Hz, $J_{5'a,4'}$=4.1 Hz, H-5′a); 3.83 (br dm, 1H, J_{gem}=12.5 Hz, H-5′b); 3.94–3.98 (m, 1H, H-4′); 4.47 (tdd, 1H, 2×$J_{3',F}$=12.6 Hz, $J_{3',4'}$=8.1 Hz, $J_{3',OH}$=6.5 Hz, H-3′); 5.28 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.6 Hz, OH-5′); 6.36 (d, 1H, $J_{OH,3'}$=6.5 Hz, OH-3′); 6.60 (dd, 1H, $J_{1',F}$=11.0 and 5.0 Hz, H-1′); 7.27 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.32 (dd, 1H, $J_{4,5}$=5.1 Hz, $J_{4,3}$=3.8 Hz, H-4-thienyl); 7.89 (dd, 1H, $J_{5,4}$=5.1 Hz, $J_{5,3}$=1.1 Hz, H-5-thienyl); 7.94 (dd, 1H, $J_{6,5}$=3.9 Hz, $J_{6,F}$=1.1 Hz, H-6); 8.20 (dd, 1H, $J_{3,4}$=3.8 Hz, $J_{3,5}$=1.1 Hz, H-3-thienyl); 8.80 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 59.60 (CH_2-5′); 68.80 (dd, $J_{C,F}$=25.7 and 18.6 Hz, CH-3′); 81.26 (d, $J_{C,F}$=8.0 Hz, CH-4′); 82.58 (dd, $J_{C,F}$=39.9 and 24.5 Hz, CH-1′); 101.87 (CH-5); 112.80 (C-4a); 123.24 (dd, $J_{C,F}$=260.2 and 255.5 Hz, C-2′); 128.05 (CH-6); 129.30 (CH-4-thienyl); 130.05 (CH-3-thienyl); 131.25 (CH-5-thienyl); 142.22 (C-2-thienyl); 150.65 (C-4); 151.41 (CH-2); 151.99 (C-7a). ^{19}F NMR (470.3 MHz, DMSO-d_6): −113.93 and −112.99 (2×d, 2×1F, J_{gem}=234.3 Hz). MS (ESI) *m*/*z* (%): 354 (63) [M+H], 376 (100) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{14}O_3N_3F_2S$ [M+H]: 354.07184; found: 354.07189. For $C_{15}H_{13}O_3N_3F_2S$ calcd: 50.99% C, 3.71% H, 11.89% N; found: 50.82% C, 3.76% H, 11.43% N.

4.23. 4-(Thiophene-3-yl)-7-[2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (18d)

Compound **18d** was prepared as described for compound **18a**. Compound **16d** (322 mg, 0.59 mmol) was used. The crude product was purified by column chromatography (2% MeOH in $CHCl_3$) and reverse phase HPFC on C-18 column (methanol in H_2O 0–100%) to give compound **18d** (104 mg, 51%) as a white crystalline solid after recrystallization (H_2O/methanol 2:1). Mp 87–90 °C. $[\alpha]_D^{20}$ +14.0 (*c* 0.214, DMSO). IR (ATR): 3422, 1578, 1568, 1515, 1466, 1201, 1066, 1043, 1032 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.71 (ddd, 1H, J_{gem}=12.6 Hz, $J_{5'a,OH}$=5.8 Hz, $J_{5'a,4'}$=4.1 Hz, H-5′a); 3.83 (br dm, 1H, J_{gem}=12.6 Hz, H-5′b); 3.94–3.98 (m, 1H, H-4′); 4.42–4.52 (m, 1H, H-3′); 5.27 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.5 Hz, OH-5′); 6.36 (d, 1H, $J_{OH,3'}$=3.9 Hz, OH-3′); 6.61 (dd, 1H, $J_{1',F}$=11.0 and 5.1 Hz, H-1′); 7.23 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.76 (dd, 1H, $J_{5,4}$=5.1 Hz, $J_{5,2}$=2.9 Hz, H-5-thienyl); 7.92 (dd, 1H, $J_{6,5}$=3.9 Hz, $J_{6,F}$=1.1 Hz, H-6); 7.96 (br dd, 1H, $J_{4,5}$=5.1 Hz, $J_{4,2}$=1.3 Hz, H-4-thienyl); 8.58 (dd, 1H, $J_{2,5}$=2.9 Hz, $J_{2,4}$=1.3 Hz, H-2-thienyl); 8.86 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 59.63 (CH_2-5′); 68.84 (br dd, $J_{C,F}$=26.0 and 18.1 Hz, CH-3′); 81.24 (d, $J_{C,F}$=7.9 Hz, CH-4′); 82.55 (br dd, $J_{C,F}$=39.9 and 24.2 Hz, CH-1′); 102.04 (CH-5); 114.35 (C-4a); 123.27 (br t, $J_{C,F}$=258.0 Hz, C-2′); 127.43 (CH-5-thienyl); 127.57 (CH-4-thienyl); 127.75 (CH-6); 129.07 (CH-2-thienyl); 139.75 (C-3-thienyl); 151.58 (CH-2); 151.98 and 152.02 (C-4,7a). ^{19}F NMR (470.3 MHz, DMSO-d_6): −113.93 and −112.96 (2×d, 2×1F, J_{gem}=234.2 Hz). MS (ESI) *m*/*z* (%): 354 (100) [M+H], 376 (82) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{14}O_3N_3F_2S$ [M+H]: 354.07184; found: 354.07179. For $C_{15}H_{13}O_3N_3F_2S$ calcd: 50.99% C, 3.71% H, 11.89% N; found: 50.81% C, 3.70% H, 11.72% N.

4.24. 4-Phenyl-7-[2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (18e)

Compound **18e** was prepared as described for compound **18a**. Compound **16e** (227 mg, 0.41 mmol) was used. The crude product was purified by column chromatography (1.5% MeOH in $CHCl_3$) to give compound **18e** (104 mg, 73%) as a white crystalline solid after recrystallization (H_2O/methanol 9:1). Mp 201–202 °C. $[\alpha]_D^{20}$ +12.0 (*c* 0.283, DMSO). IR (ATR): 3271, 1575, 1557, 1463, 1429, 1338, 1201, 1061, 1034 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.71 (ddd, 1H, J_{gem}=12.5 Hz, $J_{5'a,OH}$=5.9 Hz, $J_{5'a,4'}$=4.1 Hz, H-5′a); 3.83 (br dm, 1H, J_{gem}=12.5 Hz, H-5′b); 3.95–3.99 (m, 1H, H-4′); 4.48 (tdd, 1H, 2×$J_{3',F}$=12.5 Hz, $J_{3',4'}$=8.1 Hz, $J_{3',OH}$=6.5 Hz, H-3′); 5.27 (br dd, 1H, $J_{OH,5'a}$=5.8 Hz, $J_{OH,5'b}$=5.3 Hz, OH-5′); 6.37 (d, 1H, $J_{OH,3'}$=6.5 Hz, OH-3′); 6.64 (dd, 1H, $J_{1',F}$=11.0 and 5.1 Hz, H-1′); 7.10 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.56–7.63 (m, 3H, H-*m*,*p*-Ph); 7.93 (dd, 1H, $J_{6,5}$=3.9 Hz, $J_{6',F}$=1.3 Hz, H-6); 8.16–8.20 (m, 2H, H-*o*-Ph); 8.95 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 59.63 (CH_2-5′); 68.87 (dd, $J_{C,F}$=26.1 and 18.4 Hz, CH-3′); 81.28 (d, $J_{C,F}$=8.2 Hz, CH-4′); 82.60 (dd, $J_{C,F}$=40.0 and 24.1 Hz, CH-1′); 102.02 (CH-5); 115.32 (C-4a); 123.26 (dd, $J_{C,F}$=260.3 and 255.3 Hz, CH-2′); 127.97 (CH-6); 128.86 (CH-*o*-Ph); 129.13 (CH-*m*-Ph); 130.62 (CH-*p*-Ph); 137.37 (C-*i*-Ph); 151.65 (CH-2); 151.99 (C-7a); 156.70 (C-4). ^{19}F NMR (470.3 MHz, DMSO-d_6): −113.93 and − −112.86 (2×d, 2×1F, J_{gem}=234.3 Hz). MS (ESI) *m*/*z* (%): 338 (100) [M+H], 370 (56) [M+Na]; HRMS (ESI) calcd for $C_{17}H_{16}O_3N_3F_2$ [M+H]: 348.11542; found: 348.11543. For $C_{17}H_{15}O_3N_3F_2$ calcd: 58.79% C, 4.35% H, 12.10% N; found: 58.57% C, 4.53% H, 11.71% N.

4.25. 4-(Benzofuran-2-yl)-7-[2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (18f)

Compound **18f** was prepared as described for compound **18a**. Compound **16f** (214 mg, 0.36 mmol) was used. The crude product was purified by column chromatography (1.5% MeOH in $CHCl_3$) to give compound **18f** (86 mg, 61%) as a white crystalline solid after recrystallization (H_2O/methanol 9:1). Mp 209–211 °C. $[\alpha]_D^{20}$ +8.3 (*c* 0.216, DMSO). IR (ATR): 3317, 1598, 1576, 1548, 1461, 1360, 1345, 1197, 1078, 1055, 1037 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.72 (ddd, 1H, J_{gem}=12.6 Hz, $J_{5'a,OH}$=5.8 Hz, $J_{5'a,4'}$=4.1 Hz, H-5′a); 3.84 (br dm, 1H, J_{gem}=12.6 Hz, H-5′b); 3.96–4.00 (m, 1H, H-4′); 4.44–4.53 (m, 1H, H-3′); 5.30 (t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.6 Hz, OH-5′); 6.38 (d, 1H, $J_{OH,3'}$=6.5 Hz, OH-3′); 6.64 (dd, 1H, $J_{1',F}$=10.9 and 5.1 Hz, H-1′); 7.36 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.37 (ddd, 1H, $J_{5,4}$=7.8 Hz, $J_{5,6}$=7.2 Hz, $J_{5,7}$=0.9 Hz, H-5-benzofuryl); 7.49 (ddd, 1H, $J_{6,7}$=8.4 Hz, $J_{6,5}$=7.2 Hz, $J_{6,4}$=1.3 Hz, H-6-benzofuryl); 7.81 (dq, 1H, $J_{7,6}$=8.4 Hz, $J_{7,5}$=$J_{7,4}$=$J_{7,3}$=0.9 Hz, H-7-benzofuryl); 7.83 (dm, 1H, $J_{4,5}$=7.8 Hz, H-4-benzofuryl); 7.96 (d, 1H, $J_{3,7}$=1.0 Hz, H-3-benzofuryl); 8.00 (dd, 1H, $J_{6,5}$=3.8 Hz, $J_{6,F}$=1.0 Hz, H-6); 8.93 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 59.65 (CH_2-5′); 68.87 (dd, $J_{C,F}$=25.9 and 18.3 Hz, CH-3′); 81.32 (d, $J_{C,F}$=8.2 Hz, CH-4′); 82.60 (dd, $J_{C,F}$=39.9 and 24.0 Hz, CH-1′); 102.56 (CH-5); 109.51 (CH-3-benzofuryl); 112.12 (CH-7-benzofuryl); 113.82 (C-4a); 122.70 (CH-4-benzofuryl); 123.26 (dd, $J_{C,F}$=260.2 and 255.8 Hz, C-2′);124.03 (CH-5-benzofuryl); 126.84 (CH-6-benzofuryl); 127.90 (C-3a-benzofuryl); 128.61 (CH-6); 146.85 (C-4); 151.71 (CH-2); 152.35 (C-7a); 153.95 (C-2-benzofuryl); 155.56 (C-7a-benzofuryl). ^{19}F NMR (470.3 MHz, DMSO-d_6): −113.92 and −112.82 (2×d, 2×1F, J_{gem}=234.2 Hz, F-2′). MS (ESI) *m*/*z* (%): 388 (58) [M+H], 410 (100) [M+Na]; HRMS (ESI) calcd for $C_{19}H_{16}O_4N_3F_2$ [M+H]: 388.11034; found: 388.11031. For $C_{19}H_{15}O_4N_3F_2$ calcd: 58.92% C, 3.90% H, 10.85% N; found: 58.92% C, 4.17% H, 11.35% N.

4.26. 4-(Furan-2-yl)-7-[2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (19a)

Compound **19a** was prepared as described for compound **18a**. Compound **17a** (68 mg, 0.12 mmol) was used. The crude product was purified by column chromatography (1.5% MeOH in $CHCl_3$) to give compound **19a** (17 mg, 40%) as an off-white lyophilizate (*tert*-butanol). Mp 88–90 °C. $[\alpha]_D^{20}$ +30.0 (*c* 0.033, DMSO). IR (ATR): 3257, 1600, 1567, 1458, 1244, 1054, 1016 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.62 (br dm, 1H, J_{gem}=12.5 Hz, H-5′a); 3.70 (br dm, 1H, J_{gem}=12.5 Hz, H-5′b); 4.31–4.35 (m, 1H, H-4′); 4.46–4.55 (m, 1H, H-3′); 5.12 (br t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.8 Hz, OH-5′); 6.47 (d, 1H, $J_{OH,3'}$=6.0 Hz, OH-3′); 6.78 (dd, 1H, $J_{1',F}$=10.1 and 7.2 Hz, H-1′); 6.80 (dd, 1H, $J_{4,3}$=3.5 Hz, $J_{4,5}$=1.8 Hz, H-4-furyl); 7.14 (d, 1H, $J_{5,6}$=3.8 Hz, H-5); 7.50 (dd, 1H, $J_{3,4}$=3.5 Hz, $J_{3,5}$=0.8 Hz, H-3-furyl); 7.81 (dd, 1H, $J_{6,5}$=3.8 Hz, $J_{6,F}$=2.8 Hz, H-6); 8.08 (dd, 1H, $J_{5,4}$=1.8 Hz, $J_{5,3}$=0.8 Hz, H-5-furyl); 8.81 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.37 (CH_2-5′); 69.79 (dd, $J_{C,F}$=26.1 and 17.8 Hz, CH-3′); 82.24 (dd, $J_{C,F}$=40.0 and 20.1 Hz, CH-1′); 84.06 (d, $J_{C,F}$=7.3 Hz, CH-4′); 102.30 (CH-5); 112.27 (C-4a); 112.94 (CH-4-furyl); 113.81 (CH-3-furyl); 123.15 (dd, $J_{C,F}$=261.3 and 255.2 Hz, C-2′); 128.65 (d, $J_{C,F}$=3.0 Hz, CH-6); 146.77 (CH-5-furyl); 146.86 (C-4); 151.67 (CH-2);152.39 and 152.42 (C-7a, 2-furyl). ^{19}F NMR (470.3 MHz, DMSO-d_6): −119.04 and −110.38 (2×d, 2×1F, J_{gem}=233.6 Hz). MS (ESI) *m*/*z* (%): 338 (62) [M+H], 360 (100) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{14}O_4N_3F_2$ [M+H]: 338.09469; found: 338.09466. For $C_{15}H_{13}O_4N_3F_2$ calcd: 53.42% C, 3.88% H, 12.46% N; found: 53.15% C, 3.92% H, 12.06% N.

4.27. 4-(Furan-3-yl)-7-[2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (19b)

Compound **19b** was prepared as described for compound **18a**. Compound **17b** (163 mg, 0.30 mmol) was used. The crude product was purified by column chromatography (2% MeOH in $CHCl_3$) and reverse phase HPFC on C-18 column (methanol in H_2O 0–100%) to give compound **19b** (40 mg, 40%) as a yellowish crystalline solid after recrystallization (H_2O/methanol 4:1). Mp 75–79 °C. $[\alpha]_D^{20}$ +4.3 (*c* 0.087, DMSO). IR (ATR): 3348, 1571, 1514, 1465, 1239, 1096, 1067, 1034 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 3.62 (ddd, 1H, J_{gem}=12.3 Hz, $J_{5'a,OH}$=6.2 Hz, $J_{5'a,4'}$=4.5 Hz, H-5′a); 3.70 (br dm, 1H, J_{gem}=12.3 Hz, H-5′b); 4.32–4.37 (m, 1H, H-4′); 4.46–4.56 (m, 1H, H-

3′); 5.12 (br t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.7 Hz, OH-5′); 6.46 (d, 1H, $J_{OH,3'}$=6.0 Hz, OH-3′); 6.78 (dd, 1H, $J_{1',F}$=9.9 and 7.3 Hz, H-1′); 7.18 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.27 (dd, 1H, $J_{4,5}$=1.9 Hz, $J_{4,2}$=0.8 Hz, H-4-furyl); 7.80 (dd, 1H, $J_{6,5}$=3.8 Hz, $J_{6,F}$=2.9 Hz, H-6); 7.91 (br t, 1H, $J_{5,4}$=$J_{5,2}$=1.7 Hz, H-5-furyl); 8.76 (dd, 1H, $J_{2,5}$=1.5 Hz, $J_{2,4}$=0.8 Hz, H-2-furyl); 8.83 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.35 (CH_2-5′); 69.80 (dd, $J_{C,F}$=26.2 and 16.2 Hz, CH-3′); 82.28 (dd, $J_{C,F}$=40.0 and 20.3 Hz, CH-1′); 84.04 (d, $J_{C,F}$=7.4 Hz, CH-4′); 101.80 (CH-5); 109.51 (CH-4-furyl); 114.10 (C-4a); 123.15 (dd, $J_{C,F}$=261.4 and 255.4 Hz, C-2′); 124.99 (C-3-furyl); 128.16 (CH-6); 144.85 (CH-5-furyl); 145.25 (CH-2-furyl); 150.54 (C-4); 151.62 (CH-2); 151.88 (C-7a). ^{19}F NMR (470.3 MHz, DMSO-d_6): −119.02 and −110.44 (2×d, 2×1F, J_{gem}=233.6 Hz). MS (ESI) m/z (%): 338 (100) [M+H], 360 (80) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{14}O_4N_3F_2$ [M+H]: 338.09469; found: 338.09460. For $C_{15}H_{13}O_4N_3F_2\cdot 2.3H_2O$ calcd: 47.57% C, 4.68% H, 11.10% N; found: 47.75% C, 4.56% H, 10.74% N.

4.28. 4-(Thiophene-3-yl)-7-[2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (19d)

Compound **19d** was prepared as described for compound **18a**. Crude compound **17d** (210 mg) was used. The crude product was purified by column chromatography (2% MeOH in $CHCl_3$) and reverse phase HPFC on C-18 column (methanol in H_2O 0–100%) to give compound **19d** (62 mg, 9% over two steps) as a pale pink crystalline solid after recrystallization (H_2O/methanol 4:1). Mp 157–160 °C. $[\alpha]_D^{20}$ +47.1 (*c* 0.193, DMSO). IR (ATR): 3336, 1585, 1569, 1514, 1260, 1240, 1115, 1059, 1038, 1009 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.62 (ddd, 1H, J_{gem}=12.3 Hz, $J_{5'a,OH}$=6.2 Hz, $J_{5'a,4'}$=4.5 Hz, H-5′a); 3.70 (br dm, 1H, J_{gem}=12.4 Hz, H-5′b); 4.32–4.37 (m, 1H, H-4′); 4.47–4.56 (m, 1H, H-3′); 5.12 (dd, 1H, $J_{OH,5'a}$=6.2 Hz, $J_{OH,5'b}$=5.2 Hz, OH-5′); 6.47 (d, 1H, $J_{OH,3'}$=3.8 Hz, OH-3′); 6.80 (dd, 1H, $J_{1',F}$=9.9 and 7.3 Hz, H-1′); 7.23 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.76 (dd, 1H, $J_{5,4}$=5.1 Hz, $J_{5,2}$=2.9 Hz, H-5-thienyl); 7.83 (dd, 1H, $J_{6,5}$=3.9 Hz, $J_{6,F}$=2.9 Hz, H-6); 7.96 (dd, 1H, $J_{4,5}$=5.1 Hz, $J_{4,2}$=1.3 Hz, H-4-thienyl); 8.58 (dd, 1H, $J_{2,5}$=2.9 Hz, $J_{2,4}$=1.3 Hz, H-2-thienyl); 8.86 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.35 (CH_2-5′); 69.81 (br dd, $J_{C,F}$=26.5 and 18.1 Hz, CH-3′); 82.31 (dd, $J_{C,F}$=40.1 and 20.2 Hz, CH-1′); 84.07 (d, $J_{C,F}$=7.2 Hz, CH-4′); 102.05 (CH-5); 114.13 (C-4a); 123.17 (br dd, $J_{C,F}$=261.8 and 255.0 Hz, C-2′); 127.42 (CH-5-thienyl); 127.56 (CH-4-thienyl); 128.45 (CH-6); 129.05 (CH-2-thienyl); 139.76 (C-3-thienyl); 151.57 (CH-2); 151.93 (C-4); 152.31 (C-7a). ^{19}F NMR (470.3 MHz, DMSO-d_6): −118.98 and −110.33 (2×d, 2×1F, J_{gem}=233.5 Hz). MS (ESI) m/z (%): 354 (100) [M+H], 376 (60) [M+Na]; HRMS (ESI) calcd for $C_{15}H_{14}O_3N_3F_2S$ [M+H]: 354.07184; found: 354.07176. For $C_{15}H_{13}O_3N_3F_2S$ calcd: 50.99% C, 3.71% H, 11.89% N; found: 50.59% C, 3.71% H, 11.41% N.

4.29. 4-Phenyl-7-[2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (19e)

Compound **19e** was prepared as described for compound **18a**. Crude compound **17e** (236 mg) was used. The crude product was purified by reverse phase HPFC on C-18 column (methanol in H_2O 0–100%) to give compound **19e** (41 mg, 8% over two steps) as a white lyophilizate (*tert*-butanol/benzene 2:1). Mp 39–41 °C. $[\alpha]_D^{20}$ +30.7 (*c* 0.101, DMSO). IR (ATR): 3150, 1562, 1517, 1459, 1359, 1238, 1054, 1032 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.63 (ddd, 1H, J_{gem}=12.4 Hz, $J_{5'a,OH}$=5.8 Hz, $J_{5'a,4'}$=4.5 Hz, H-5′a); 3.71 (ddd, 1H, J_{gem}=12.4 Hz, $J_{5'b,OH}$=$J_{5'b,4'}$=4.0 Hz, H-5′b); 4.33–4.37 (m, 1H, H-4′); 4.48–4.56(m, 1H, H-3′); 5.14 (br t, 1H, $J_{OH,5'a}$=$J_{OH,5'b}$=5.6 Hz, OH-5′); 6.50 (br d, 1H, $J_{OH,3'}$=5.5 Hz, OH-3′); 6.83 (dd, 1H, $J_{1',F}$=10.0 and 7.4 Hz, H-1′); 7.10 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.56–7.63 (m, 3H, H-*m*,*p*-Ph); 7.84 (dd, 1H, $J_{6,5}$=3.9 Hz, $J_{6',F}$=2.8 Hz, H-6); 8.17–8.20 (m, 2H, H-*o*-Ph); 8.94 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.36 (CH_2-5′); 69.83 (dd, $J_{C,F}$=26.5 and 18.0 Hz, CH-3′); 82.39 (dd, $J_{C,F}$=40.2 and 20.4 Hz, CH-1′); 84.12 (d, $J_{C,F}$=7.4 Hz, CH-4′); 102.04 (CH-5); 115.11 (C-4a); 123.19 (dd, $J_{C,F}$=261.5 and 255.2 Hz, CH-2′); 128.65 (d, $J_{C,F}$=2.8 Hz, CH-6); 128.86 (CH-*o*-Ph); 129.12 (CH-*m*-Ph); 130.61 (CH-*p*-Ph); 137.39 (C-*i*-Ph); 151.64 (CH-2); 152.29 (C-7a); 156.65 (C-4). ^{19}F NMR (470.3 MHz, DMSO-d_6): −118.91 and −110.27 (2×d, 2×1F, J_{gem}=233.8 Hz). MS (ESI) m/z (%): 348 (100) [M+H], 370 (93) [M+Na]; HRMS (ESI) calcd for $C_{17}H_{16}O_3N_3F_2$ [M+H]: 348.11542; found: 348.11540. For $C_{17}H_{15}O_3N_3F_2$ calcd: 58.79% C, 4.35% H, 12.10% N; found: 58.47% C, 4.46% H, 11.71% N.

4.30. 4-(Benzofuran-2-yl)-7-[2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (19f)

Compound **19f** was prepared as described for compound **18a**. Crude compound **17f** (289 mg) was used. The crude product was by column chromatography on silica (1.5% methanol in $CHCl_3$) to give compound **19f** (51 mg, 9% over two steps) as a white crystalline solid after recrystallization (H_2O/methanol 9:1). Mp 230–232 °C. $[\alpha]_D^{20}$ +34.9 (*c* 0.109, DMSO). IR (ATR): 3122, 1599, 1571, 1458, 1363, 1084, 1053 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.63 (ddd, 1H, J_{gem}=12.3 Hz, $J_{5'a,OH}$=6.2 Hz, $J_{5'a,4'}$=4.5 Hz, H-5′a); 3.72 (br dm, 1H, J_{gem}=12.4 Hz, H-5′b); 4.35–4.39 (m, 1H, H-4′); 4.49–4.58 (m, 1H, H-3′); 5.15 (dd, 1H, $J_{OH,5'a}$=6.2 Hz, $J_{OH,5'b}$=5.3 Hz, OH-5′); 6.49 (d, 1H, $J_{OH,3'}$=6.0 Hz, OH-3′); 6.82 (dd, 1H, $J_{1',F}$=10.2 and 7.2 Hz, H-1′); 7.36 (d, 1H, $J_{5,6}$=3.9 Hz, H-5); 7.37 (ddd, 1H, $J_{5,4}$=7.8 Hz, $J_{5,6}$=7.2 Hz, $J_{5,7}$=0.8 Hz, H-5-benzofuryl); 7.49 (ddd, 1H, $J_{6,7}$=8.3 Hz, $J_{6,5}$=7.2 Hz, $J_{6,4}$=1.3 Hz, H-6-benzofuryl); 7.82 (dq, 1H, $J_{7,6}$=8.4 Hz, $J_{7,5}$=$J_{7,4}$=$J_{7,3}$=0.9 Hz, H-7-benzofuryl); 7.83 (br dm, 1H, $J_{4,5}$=7.8 Hz, H-4-benzofuryl); 7.92 (dd, 1H, $J_{6,5}$=3.8 Hz, $J_{6,F}$=2.8 Hz, H-6); 7.96 (d, 1H, $J_{3,7}$=1.0 Hz, H-3-benzofuryl); 8.92 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 60.38 (CH_2-5′); 69.79 (dd, $J_{C,F}$=26.1 and 17.7 Hz, CH-3′); 82.34 (dd, $J_{C,F}$=39.7 and 20.2 Hz, CH-1′); 84.08 (d, J_i=7.4 Hz, CH-4′); 102.58 (CH-5); 109.47 (CH-3-benzofuryl); 112.11 (CH-7-benzofuryl); 113.61 (C-4a); 122.69 (CH-4-benzofuryl); 123.15 (dd, $J_{C,F}$=261.4 and 255.8 Hz, C-2′);124.03 (CH-5-benzofuryl); 126.82 (CH-6-benzofuryl); 127.90 (C-3a-benzofuryl); 129.31 (d, $J_{C,F}$=3.3 Hz, CH-6); 146.78 (C-4); 151.71 (CH-2); 152.65 (C-7a); 153.99 (C-2-benzofuryl); 155.56 (C-7a-benzofuryl). ^{19}F NMR (470.3 MHz, DMSO-d_6): −119.08 and −110.67 (2×d, 2×1F, J_i=233.4 Hz, F-2′). MS (ESI) m/z (%): 388 (67) [M+H], 410 (100) [M+Na]; HRMS (ESI) calcd for $C_{19}H_{16}O_4N_3F_2$ [M+H]: 388.11034; found: 388.11029. For $C_{19}H_{15}O_4N_3F_2$ calcd: 58.92% C, 3.90% H, 10.85% N; found: 59.13% C, 4.24%H, 10.59% N.

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