Synthesis and Biological Activity of 2′-Fluoro-D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine Nucleosides

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Dedicated to Prof. Dr. *Frank Seela* on the occasion of his 60th birthday

Coupling of 2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl bromide with 4-methoxypyrazolo[3,4-*d*]pyrimidine gave an α-D/β-D mixture of N^1- and N^2-coupled products. All the anomers were separated and deblocked to yield the corresponding nucleosides. The β-D-anomer **7** was converted to the 4-amino derivative **11**, which was deaminated by adenosine deaminase to give the 4-oxo compound **12**. Compound **7** showed significant activity against human cytomegalovirus and hepatitis B virus, and compound **11** showed activity against human herpes virus 8. All the compounds were noncytotoxic in several human tumor-cell lines in culture.

1. Introduction. – Since the approval of 6-mercaptopurine by the FDA in 1953 for the treatment of human cancer, eight other nucleobases or nucleosides thereof have been approved for cancer treatment. All of the nucleosides are 2′-deoxyribonucleosides or biochemical analogs (*i.e.*, nucleosides that behave metabolically like 2′-deoxyribonucleosides) [1]. In the ongoing program to develop antiviral and anticancer agents in our laboratory, we have developed fludarabine [2][3], identified the anticancer activity of cladribine [4], and are developing clofarabine [5], another rationally designed drug which is undergoing clinical trials at the present time. This latter drug, which contains an F substituent at C(2) of the furanose ring in the *arabino*-configuration, behaves metabolically like a 2′-deoxyribonucleoside[1]) [6].

To explore other nucleosides containing the fluoro-*arabino*-sugar, we turned to purine ring analogs. *Seela* et al. have prepared the 2′-deoxyribonucleosides [7] and the arabinonucleosides [8] of the pyrazolo[3,4-*d*]pyrimidine ring system. Prior work had shown that 4-aminopyrazolo[3,4-*d*]pyrimidine was active against experimental animal tumors [9] but proved too toxic for human use [10].

We report herein the synthesis and biological activity of some pyrazolo[3,4-*d*]-pyrimidine nucleosides with an F substituent in the 2′-*arabino*-position.

2. Results and Discussion. – Since the introduction of phase-transfer glycosylation [11] and the sodium-salt procedure [12] for nucleoside synthesis, various modified

[1]) In the *ribo*-configuration, the nucleosides behave biologically like ribonucleosides [6].

purines have been coupled with 1-α-halo sugars. In theory, these coupling reactions proceed mainly by an S_N2 mechanism that should provide the desired β-D-anomer as the major product. In practice, the outcome depends on various factors, including the particular heterocycle and the halo sugar used and the reaction solvent and temperature. In our present work (*Scheme 1*), we used the sodium-salt method [12] to couple 4-methoxypyrazolo[3,4-*d*]pyrimidine (**1**) [13] with α-bromo sugar **2** [14]. However, these reactions gave poor yields and an unfavorable distribution of products, caused in part by the low solubility of the sodium salt of **1** (*Table 1, Entries a* and *b*).

Scheme 1

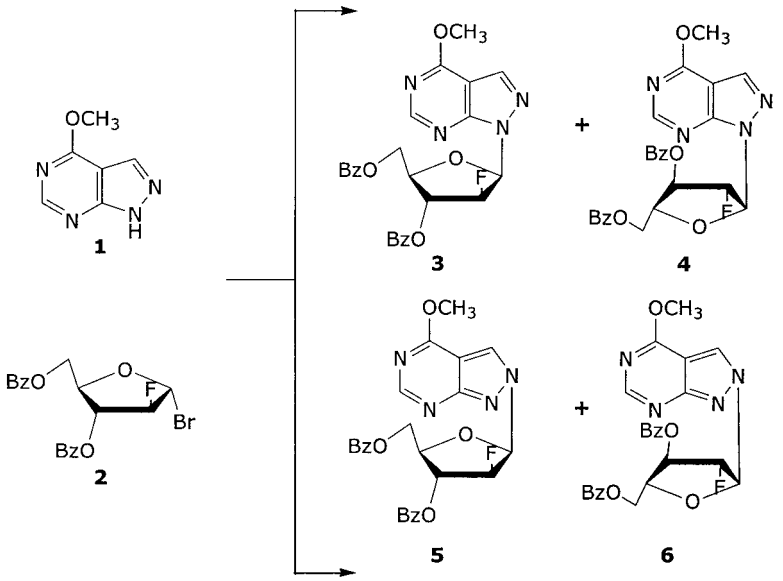


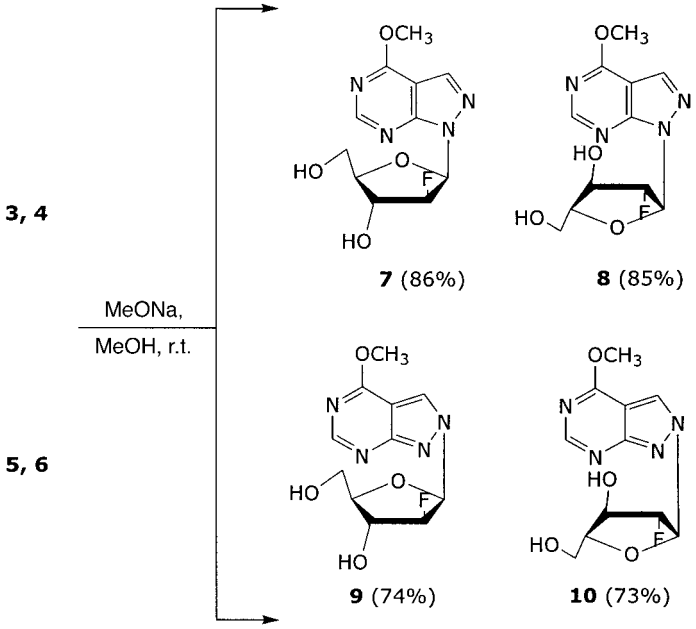
Table 1. *Coupling Studies*

Entry	Base [equiv.]	Conditions	Nucleoside distribution	Total yield
a [12]	NaH (1.6)	DME, 45°, 3 h	**3** (6%), **4** (4%), **5** (33%), **6** (–)	43%
b [12]	NaH (1.5)	MeCN, r.t., 23 h	**3** (24%), **4** (17%), **5** (14%), **6** (8%)	63%
c [15]	DBU[a]) (1.0)	MeCN, r.t., 4 h	**3** (45%), **4** (17%), **5** (26%), **6** (6%)	94%

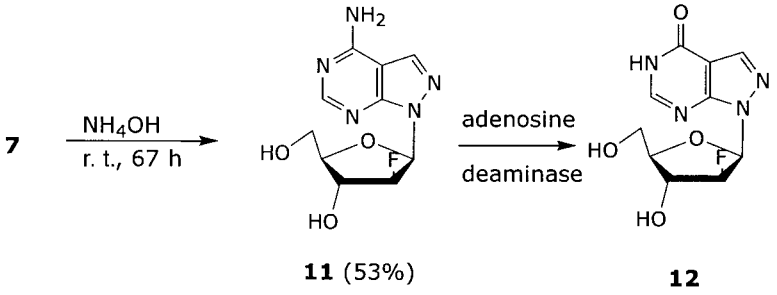
[a]) 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Employing a new method reported by *Jungmann* and *Pfleiderer* [15], we treated an MeCN suspension of **1** with an equimolar amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to provide a clear solution. This easily soluble DBU salt of **1** was reacted with **2** to give a 94% total nucleoside yield (*Table 1, Entry c*). Debenzoylation of **3**–**6** with MeONa/MeOH produced **7**–**10** (*Scheme 2*) [7]. As depicted in *Scheme 3*, nucleoside **7** was aminated in conc. aqueous NH_3, giving **11**, which was readily deaminated by adenosine deaminase (HPLC experiment) [7][8].

Scheme 2



Scheme 3



Compounds **3**–**11** were characterized by UV, NMR, and mass spectra. The anomeric configuration and point of attachment of the sugar to the heterocyclic moiety was confirmed by ^{1}H-NMR spectra with decoupling experiments and coupling constants. Correlation with published literature on 2′-deoxynucleosides in this series further verified assignments [7]. ^{19}F-NMR Spectra of β-D-anomers **7** and **9** showed signals upfield from $CFCl_3$ at -204 and -202 ppm, respectively. In contrast, signals from the α-anomers **8** and **10** appeared at -194 and -189 ppm, respectively.

The cell-culture cytotoxicities of the target compounds **7**–**11** were determined against eight human cancer-cell lines, namely CCRF-CEM (leukemia), CAKI-I (renal), DLD-1 (colon), LOXIMVI (colon), NCI-H-23 (lung), PC-3 (prostate), SNB-7 (CNS), and ZR-75-1 (mammary) [16]. All compounds were found to be non-

cytotoxic at the highest level tested (40 μg/ml). In addition, **7**, **9**, and **11** were screened for activity against a variety of viruses (*i.e.*, CMV, influenza A, HBV, HHV-8, HSV-1, and respiratory syncytial). Those compounds with significant antiviral activity are identified in *Table 2*. Compound **7** showed good activity against CMV and in the HBV screen [17]. Its isomer **9** exhibited moderate activity only against CMV. Compound **11**, which is the 6-amino analog of **7**, was active against HHV8 [18].

Table 2. *Virus Screening Summary*

Virus Cell line Compound	IC_{50} [μM][a])	TC_{50} [μM])[b])
Cytomegalovirus (CMV AD169) in MRC-5 cells		
Ganciclovir[c])	8.6	> 1000
7	0.42	> 10
9	3.8	> 10
Hepatitis B virus (HBV EC50) in HepG2 2.2.15 cells		
3TC[c])	0.14	> 1000
7	0.98	> 100
Herpes virus 8 (HHV8) in TPA-induced BCBL-1 cells		
Cidofovir[c])	0.63	> 350
11	0.59	> 10

[a]) IC_{50}: Inhibitory concentration at 50% cell viability. [b]) TC_{50}: Toxic concentration at 50% cell viability. [c]) Control drug.

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Experimental Part

General. 2-Fluoro-1,3,5-tri-*O*-benzoyl-α-D-arabinofuranose was purchased from *Pfanstiehl Laboratories, Inc*. TLC: *Analtech* precoated (250 μm) silica gel (*GF*) plates. Flash chromatography (FC): 230–400-mesh silica gel from *E. Merck*. HPLC: *Hewlett-Packard 1100 Series* liquid chromatograph with a *Phenomenex SphereClone 5 μ ODS (1)* column (250 × 4.6 mm), UV monitoring (254 nm). M.p.: *Mel-Temp* apparatus; uncorrected. UV Spectra: *Perkin-Elmer lambda 9* spectrometer in MeOH; extinction coefficients ($\varepsilon \times 10^{-3}$) in parentheses. ^{1}H-NMR Spectra: *Nicolet NT-300 NB* spectrometer, at 300.635 MHz; chemical shifts (δ) in ppm downfield from Me_4Si. ^{19}F-NMR Spectra: *Bruker CXP-200* spectrometer, at 188.2 MHz; chemical shifts (δ) in ppm upfield relative to $CFCl_3$ (δ 0.0). MS: *Varian/MAT 311A* double-focusing mass spectrometer in the fast-atom-bombardment (FAB) mode. Microanalyses were performed by the *Molecular Spectroscopy Section* of *Southern Research Institute*. Where solvents are noted as part of the elemental analyses, they were seen in the ^{1}H-NMR spectra in the proper amounts.

1- and 2-(2-Deoxy-2-fluoro-3,5-di-O-*benzoyl-β*-D- *and* -α-D-*arabinofuranosyl)-4-methoxy-1*H- *and* -2H-*pyrazolo[3,4*-d*]pyrimidine* (**3**–**6**). To a suspension of *4-methoxy-1*H-*pyrazolo[3,4*-d*]pyrimidine* (**1**; 329 mg, 2.20 mmol) in anh. MeCN (24 ml) under Ar was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 329 μl, 2.20 mmol), and the mixture was stirred 15 min. The resulting clear soln. was treated dropwise over 5 min with a soln. of **2** (1.02 g, 2.42 mmol) in MeCN (6 ml). The soln. was stirred at r.t. for 4 h and then evaporated to a yellow foam. This material was dissolved in a minimum of CH_2Cl_2 and applied to a flash column containing 50 g silica gel previously equilibrated with hexane/AcOEt 3:1. Elution with a gradient from 3:1 to 1:1 hexane/

AcOEt provided N^1-isomers followed by N^2-isomers. After further chromatography of mixed bands, four pure isomers were obtained for a 94% total nucleoside yield. A small sample of each was crystallized from i-PrOH for analysis.

Data of N^1-*β*-D-*Isomer* (**3**; 486 mg, 45%): m.p. 148–150°. TLC (hexane/AcOEt 2:1): R_f 0.42. HPLC: MeCN/H_2O 65:35. UV (MeOH): 231 (32.2), 266 (sh). ^{1}H-NMR ($CDCl_3$): 8.60 (*s*, H–C(6)); 8.15 (*s*, H–C(3)); 8.06 (*m*, 4 H_o of Ph); 7.62 (*m*, 2 H_p of Ph); 7.42 (*m*, 4 H_m of Ph); 6.94 (*br. d*, J = 8, H–C(1′)); 6.64 (*m*, J(3′,4′) = 6, J(3′,F) = 24, H–C(3′)); 5.73 (*ddd*, J(2′,3′) = 4, J(2′,F) = 62, H–C(2′)); 4.93 (J(5′a,5′b) = 14, J(4′,5′a) = 4, H–C(5′)); 4.80 (J(4′,5′b) = 6, H–C(5′)); 4.16 (*s*, MeO). MS 493 ([M + H]$^+$). Anal. calc. for $C_{25}H_{21}FN_4O_6 \cdot 0.10$ H_2O (494.27): C 60.75, H 4.32, N 11.34; found: C 60.50, H 4.48, N 11.32.

Data of N^1-*α*-D-*Isomer* (**4**; 186 mg, 17%): m.p. 92–93°. TLC (hexane/AcOEt 2:1): R_f 0.54. HPLC: MeCN/H_2O 65:35. UV (MeOH): 231 (31.4), 266 (sh). ^{1}H-NMR ($CDCl_3$): 8.62 (*s*, H–C(6)); 8.12 (*s*, H–C(3)); 8.02–8.10 (*m*, 4 H_o of Ph); 7.40–7.65 (*m*, 6 arom. H); 6.90 (*dd*, J(1′,2′) = 2, J(1′,F) = 20, H–C(1′)); 6.14 (*ddd*, J(2′,3′) = 2, J(2′,F) = 54, H–C(2′)); 5.90 (*m*, J(3′,4′) = 2, J(3′,F) = 18, H–C(3′)); 4.93 (*dt*, H–C(4′)); 4.74 (J(5′a,5′b) = 14, J(4′,5′a) = 4, H–C(5′)); 4.64 (J(4′,5′b) = 5, H–C(5′)); 4.18 (*s*, MeO). MS 493 ([M + H]$^+$). Anal. calc. for $C_{25}H_{21}FN_4O_6 \cdot 0.20$ H_2O (496.07): C 60.53, H 4.35, N 11.29; found: C 60.42, H 4.30, N 11.30.

Data of N^2-*β*-D-*Isomer* (**5**; 282 mg, 26%): m.p. 175–176°; TLC: (hexane/AcOEt 1:1), R_f 0.30. HPLC: MeCN/H_2O 65:35. UV (MeOH): 224 (32.0), 260 (12.4). ^{1}H-NMR ($CDCl_3$): 8.68 (*s*, H–C(6)); 8.39 (*br. d*, H–C(3)); 8.10 (*m*, 4 H_o of Ph); 7.56 (*m*, 6 arom. H); 6.58 (*dd*, J(1′,2′) = 2, J(1′,F) = 20, H–C(1′)); 5.82 (*m*, H–C(2′)); 5.48 (*dd*, J(3′,4′) = 2, J(3′,F) = 50, H–C(3′)); 4.86 (*m*, H–C(4′), H–C(5′)); 4.72 (*m*, H–C(5′)); 4.15 (*s*, MeO). ^{19}F-NMR ($CDCl_3$ + $CFCl_3$): −201.32. (J(2) = 50, J(3) = 16.4, J(3) = 32.7). MS 493 ([M + H]$^+$). Anal. calc. for $C_{25}H_{21}FN_4O_6 \cdot 0.20$ H_2O (496.07): C 60.53, H 4.35, N 11.29; found: C 60.60, H 4.18, N 11.32.

Data of N^2-*α*-D-*Isomer* (**6**; 67 mg, 6%): m.p. 128–130°; TLC (hexane/AcOEt 1:1): R_f 0.40; HPLC: MeCN/H_2O 65:35. UV (MeOH): 223 (28.7), 261 (10.1). ^{1}H-NMR ($CDCl_3$): 8.68 (*s*, H–C(6)); 8.36 (*s*, H–C(3)); 8.12 (m, 4 H_o of Ph); 7.54 (*m*, 6 arom. H); 6.52 (*br. dd*, J = 14, H–C(1′)); 6.18 (*br. dd* J = 50, H–C(2′)); 5.75 (*br. dd*, J(3′,4′) = 5, J(3′,F) = 20, H–C(3′)); 4.96 (*dt*, H–C(4′)); 4.75 (*m*, 2 H–C(5′)); 4.14 (*s*, MeO). MS 493 ([M + H]$^+$). Anal. calc. for $C_{25}H_{21}FN_4O_6 \cdot 0.20$ H_2O (496.07): C 60.53, H 4.35, N 11.29; found: C 60.62, H 4.20, N 11.18.

*1-(2-Deoxy-2-fluoro-β-*D-*arabinofuranosyl)-4-methoxy-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**7**). A suspension of **3** (486 mg, 0.99 mmol) in MeOH (12 ml) was treated in one portion with 0.50N MeONa in MeOH (5.9 ml). The mixture became a clear soln. after 10 min and was stirred an additional 2 h. The mixture was neutralized to pH 6 with glacial AcOH and evaporated. This residue was purified by prep. TLC (*Analtech GF*, 20 × 20 cm, 2,000 μ) with development in $CHCl_3$/MeOH 95:5. The product band was extracted with MeOH, and the extract was evaporated. The isolated material was crystallized from hot H_2O (10 ml) to give pure **7** (242 mg, 85%). M.p. 135–136°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.55. HPLC: H_2O/MeCN 80:20. UV (MeOH): 246 (8.44), 265 (sh, 4.83). ^{1}H-NMR ((D_6)DMSO): 8.66 (*s*, H–C(6)); 8.42 (*s*, H–C(3)); 6.76 (*br. d*, J = 8, H–C(1′)); 5.90 (*br. d*, J = 6, HO–C(3′)); 5.54 (*dt*, J(2′,3′) = 6, J(2′,F) = 52, H–C(2′)); 4.83 (*t*, HO–C(5′)); 4.74 (*m*, H–C(3′)); 4.14 (*s*, MeO); 3.84 (*m*, H–C(4′)); 3.66 (*m*, 2 H–C(5′)). ^{19}F-NMR (DMSO + $CFCl_3$): −204.11 (J(2) = 53.41, J(3) = 18.53, J(3) = 0). MS 285 ([M + H]$^+$). Anal. calc. for $C_{11}H_{13}FN_4O_4 \cdot 0.30$ H_2O (289.65): C 45.61, H 4.73, N 19.34; found: C 45.52, H 4.70, N 19.24.

*1-(2-Deoxy-2-fluoro-α-*D-*arabinofuranosyl)-4-methoxy-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**8**). Compound **4** (139 mg, 0.28 mmol) was treated with 0.50N MeONa as described for **3**. Similar workup and crystallization from H_2O provided pure **8** (68 mg, 85%). M.p. 163–164°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.57. HPLC: H_2O/MeCN 80:20. UV (MeOH): 246 (8.44), 265 (sh, 5.02). ^{1}H-NMR ((D_6)DMSO): 8.92 (*s*, H–C(6)); 8.42 (*s*, H–C(3)); 6.48 (*dd*, J(1′,2′) = 4, J(1′,F) = 18, H–C(1′)); 6.02 (*d*, J = 6, OH–C(3′)); 5.84 (*ddd*, J(2′,3′) = 4, J(2′,F) = 54, H–C (2′)); 4.96 (*br. t*, HO–C(5′)); 4.40 (*m*, H–C(3′)); 4.12 (*s*, MeO); 4.10 (*m*, H–C(4′)); 3.60 (*m*, 2 H–C(5′)). ^{19}F-NMR (DMSO + $CFCl_3$): −193.70 (J(2) = 54.5, J(3) = 16.35, J(3) = 23.98). MS: 285 ([M + H]$^+$). Anal. calc. for $C_{11}H_{13}FN_4O_4$ (284.25): C 46.48, H 4.61, N 19.71; found: C 46.40, H 4.62, N 19.51.

*2-(2-Deoxy-2-fluoro-β-*D-*arabinofuranosyl)-4-methoxy-2*H-*pyrazolo[3,4-*d*]pyrimidine* (**9**). A suspension of **5** (250 mg, 0.51 mmol) in MeOH (6 ml) was treated with 0.50N MeONa in MeOH (3 ml). The mixture became a clear soln. after 5 min and was neutralized with glacial AcOH after 4 h. The soln. was concentrated to a small volume and applied to a prep. TLC plate (*Analtech GF*, 20 × 20 cm, 2,000 μ) that was developed four times in $CHCl_3$/MeOH 9:1. The residue from the MeOH plate extract solidified when triturated with acetone to yield **9** (107 mg, 73%). M.p.: softens at 167°, decomp. at 210°. TLC ($CHCl_3$/MeOH 9:1): R_f 0.38. HPLC: 0.01M $NH_4H_2PO_4$/MeOH 70:30 (pH 5.1). UV (MeOH): 260 (9.64), 285 (sh). ^{1}H-NMR ((D_6)DMSO): 8.92 (*s*, H–C(3)); 8.58 (*s*, H–C(6)); 6.46 (*br. t*, J = 6, H–C(1′)); 6.04 (*s*, HO–C(3′)); 5.36 (*ddd*, J(2′,3′) = 6, J(2′,F) = 54, H–C(2′)); 5.20 (*br. m*, HO–C(5′)); 4.55 (*br. dd*, H–C(3′)); 4.10 (*s*, MeO); 3.96 (*m*, H–C(4′)); 3.76 (*m*,

2 H–C(5′)). ^{19}F-NMR (DMSO + $CFCl_3$): – 202.08 ($J(2) = 52.3$, $J(3) = 6.54$, $J(3) = 18.0$). MS: 285 ($[M+H]^+$). Anal. calc. for $C_{11}H_{13}FN_4O_4 \cdot 0.25H_2O$ (288.75): C 45.76, H 4.71, N 19.40; found: C 45.96, H 4.60, N 19.02.

*2-(2-Deoxy-2-fluoro-α-*D*-arabinofuranosyl)-4-methoxy-2*H*-pyrazolo[3,4-*d*]pyrimidine* (**10**). Compound **6** (50 mg, 0.10 mmol) was reacted with 0.50N MeONa as described for **5**. Purification by prep. TLC (*Analtech GF*, 10 × 20 cm, 1000 μ) was accomplished with one development in $CHCl_3$/MeOH 9 : 1. The MeOH plate extract was solidified by Et_2O trituration to provide **10** (21 mg, 67%). M.p.: softens at 130°, decomp. at 200°; TLC ($CHCl_3$/MeOH 9 : 1): R_f 0.49. HPLC: 0.01M $NH_4H_2PO_4$/MeOH 70 : 30 (pH 5.1). UV (MeOH): 260 (9.49), 285 (sh). ^{1}H-NMR ((D$_6$)DMSO): 8.87 (*s*, H–C(3)); 8.60 (*s*, H–C(6)); 6.44 (*dd*, $J(1',2') = 2$, $J(1',F) = 16$, H–C(1′)); 6.04 (*br. s*, HO–C(3′)); 5.62 (*ddd*, $J(2',3') = 2$, $J(2',F) = 52$, H–C(2′)); 5.10 (*br. s*, HO–C(5′)); 4.35 (*m*, H–C(3′), H–C(4′)); 4.10 (*s*, MeO); 3.60 (*m*, 2 H–C(5′)). ^{19}F-NMR (DMSO + $CFCl_3$): – 188.66 ($J(2) =$ 52.54, $J(3) = 15.3$, $J(3) = 20.71$). MS: 285 ($[M+H]^+$). Anal. calc. for $C_{11}H_{13}FN_4O_4 \cdot 0.30H_2O \cdot 0.30\ CH_3CO_2Na$ (314.26): C 44.33, H 4.65, N 17.83; found: C 44.42; H 4.50, N 17.55.

*4-Amino-1-(2-deoxy-2-fluoro-β-*D*-arabinofuranosyl)-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine* (**11**). A soln. of **7** (38 mg, 0.13 mmol) in conc. NH_4OH (10 ml) was stirred at r.t. for 67 h. The solvent was evaporated, and the residue was purified by prep. TLC (*Analtech GF*, 10 × 20 cm, 1000 μ) with two developments in $CHCl_3$/MeOH 5 : 1 containing 1% conc. NH_4OH. The product isolated from the MeOH extract of the plate band was crystallized from hot MeCN to yield pure **11** (19 mg, 53%). M.p. 208–210°; TLC ($CHCl_3$/MeOH 5 : 1 + 1% NH_4OH): R_f 0.40. HPLC: 0.01M $NH_4H_2PO_4$/MeOH 70 : 30 (pH 5.1). UV (MeOH): 260 (9.59), 275 (11.1). ^{1}H-NMR ((D$_6$)DMSO): 8.20 (*s*, H–C(3), H–C(6)); 7.82 (*br. dd*, NH_2); 6.60 (*dd*, $J = 6$, H–C(1′)); 5.86 (*br. d*, HO–C(3′)); 5.40 (*ddd*, $J(2',3') = 8$, $J(2',F) = 52$, H–C(2′)); 4.84 (*br. t*, HO–C(5′)); 4.74 (*m*, H–C(3′)); 3.80 (*m*, H–C(4′)); 3.65 (*m*, 2 H–C(5′)). MS: 270 ($[M+H]^+$). Anal. calc. for $C_{10}H_{12}FN_5O_3$ (269.24): C 44.61, H 4.49, N 26.01; found: C 44.68, H 4.59, N 26.33.

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