Fluorinated Pyrrolo[2,3-*d*]pyrimidine Nucleosides: 7- Fluoro-7-deazapurine 2′-Deoxyribofuranosides and 2′-Deoxy-2′-fluoroarabinofuranosyl Derivatives

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Abstract: The syntheses of 7-deaza-7-fluoro-2′-deoxyadenosine (**1a**), 7-deaza-7-fluoro- 2′-deoxyinosine (**3a**) and 7-deaza-7-fluoro-2′-deoxyguanosine (**3c**) as well as of the 2′-deoxy-2′-fluoroarabinofuranosyl derivatives **1b**, **3b** are described. Starting materials were 6-chloro-7-fluoro-7-deazapurine (4-chloro-5-fluoropyrrolo[2,3-*d*]pyrimidine, **4b**) and 2-pivaloylamino-6-chloro-7-fluoro-7-deazapurine (2-pivaloylamino-4-chloro-5-fluoropyrrolo[2,3-*d*]pyrimidine, **6**). Nucleobase anion glycosylation of **4b** or **6** with the halogenoses **7** or **9** furnished the protected β-D-nucleosides **8**, **10** and **11**, which were converted to compounds **1a**, **1b** by ammonolysis and to **2a**–**c** by sodium methoxide treatment. The 2′-deoxyinosine derivatives **3a**, **3b** and the guanosine analogue **3c** were obtained from **2a**–**c**. Conformational analysis of the nucleosides **1a**, **1b** was performed in solution and in the solid state. Single-crystal X-ray analyses showed that the sugar moiety of **1a** exhibits the *S*-conformation (P = 164.8°, τ = 40.1°). In solution the 2′-fluoro substituents shift the sugar conformation slightly towards *N*.

Key words: fluorine, glycosylations, pyrrolo[2,3-*d*]pyrimidines, nucleosides, sugar conformation

Fluorine-substituted analogues of the nucleic acid components have become established as antiviral, antitumor, and antifungal agents. Important compounds of this class of nucleosides contain the fluorine atom at the C-2′ position of the sugar moiety, but the most active compounds such as 5-fluorouridine have the fluorine atom at the base. As pyrrolo[2,3-*d*]pyrimidine nucleosides represent structural mimics of the parent purine compounds, they are useful as structural probes in DNA diagnostics as well as in antisense technology. The 7-position of 7-deazapurine system is supposed to be a matching position to the 5-position of pyrimidines. Recently, the 7-fluoro derivative of tubercidin was prepared which exhibits reduced cytotoxicity compared to the parent tubercidin.[1] Some halogenated 7-deazapurine (pyrrolo[2,3-*d*]pyrimidine) nucleosides have gained attention since some of them, such as 7-iodotubercidin,[2–4] 2′-deoxy-2′-fluoroarabinotubercidin[5] and 2-amino-2′-deoxy-2′-fluoroarabinotubercidin,[6,7] exhibit a broad spectrum of biological activity (purine numbering is used throughout the general section). Furthermore, 7-halogenated 7-deazapurine nucleosides can stabilize the DNA duplex structures.[8–11] We were interested in combining the favorable properties of pyrrolo[2,3-*d*]pyrimidine nucleosides with the well documented pharmaceutical behaviors of fluorine substitution. Thus, fluorine substituents were introduced into 7-deazapurine nucleosides.

From the steric point of view, the presence of a fluorine atom in a nucleoside does not lead to a significant perturbation to the shape of the molecule because of the small van der Waals radius of 1.47 Å.[12] At the same time, the fluorine atom has the highest electronegativity (3.98 vs 3.44 of oxygen). As a result, the incorporation of the fluorine atom in a nucleobase give rise to changes in the electronic state of the heterocyclic moiety, and the presence in the sugar part leads to conformational changes. This paper reports on the stereoselective synthesis and properties of 7-deaza-7-fluoro-2′-deoxyadenosine (7-fluoro-2′-deoxytubercidin, **1a**), 7-deaza-7-fluoro-2′-deoxyinosine (**3a**), and 7-deaza-7-fluoro-2′-deoxyguanosine (**3c**), in addition to 2′-deoxy-2′-fluoroarabinonucleosides **1b**–**3b** with the fluorine atom in the 7-position are described (Figure 1).

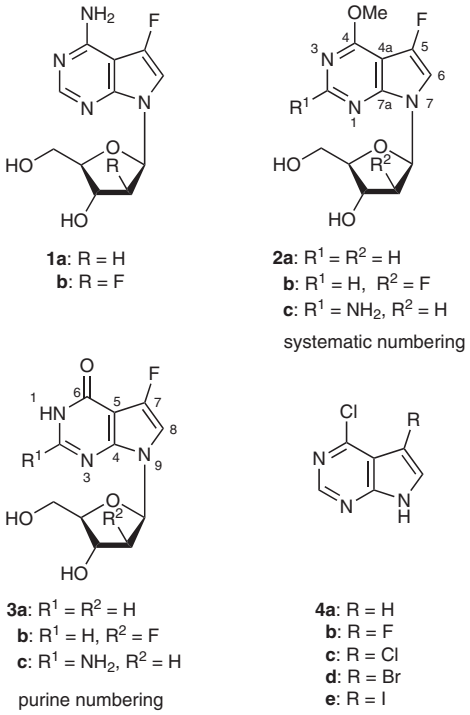

Figure 1 Compounds **1**–**4**

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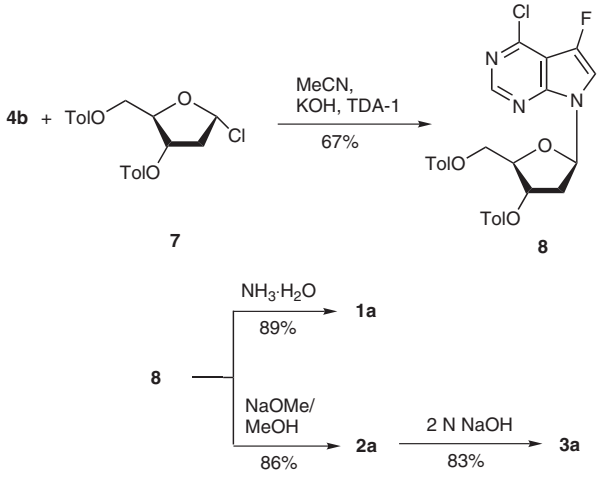
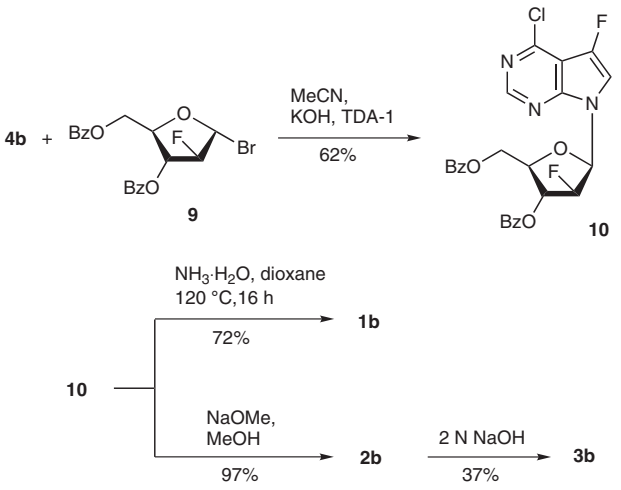
7-Halogenated 7-deazapurine nucleosides can be prepared by the halogenation of an appropriately protected nucleoside or the nucleobase which is glycosylated afterwards.[13,14] The electrophilic fluorination of heterocycles is usually carried out with fluorine gas or acetyl hypofluorites.[15] However, milder conditions were expected to work on the electron-rich 7-position of 7-deazpurines. In the case of 7-deazapurine nucleosides the fluorination resulted in decomposition by using various electrophilic fluorinating conditions.[1] Thus, the fluorination was performed on the base level. Among the different fluorination reagents Selectfluor[16] proved to be the most promising reagent as 6-chloro-7-fluoro-7-deazapurine (**4b**) was already prepared by this way.[1]

Next, compound **4b** was employed in the stereoselective nucleobase-anion glycosylation[17,18] using 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**7**).[19] The reaction was performed in acetonitrile with powdered KOH and TDA-1 {tris[2-(2-methoxyethoxy)ethyl]amine}as catalyst. The protected nucleoside **8** was isolated in 67% yield without formation of the α-D-anomer (Scheme 1). Deprotection of compound **8** with 25% aqueous ammonia (120 °C) resulted in the removal of the toluoyl groups and a simultaneous conversion of the 6-chloro substituent to an amino group resulting in **1a**. When the deprotection was performed in NaOMe/MeOH, it resulted in the formation of the methoxy nucleoside **2a**. Treatment of **2a** with 2 N aqueous NaOH yielded the 2′-deoxyinosine analogue **3a** (83% yield). In all cases the fluorine substituent was not displaced. A selective removal of the sugar protecting groups without displacement of the 6-chloro substituent was not successful.



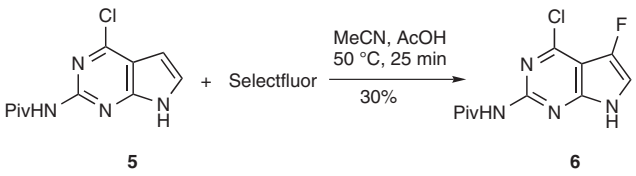
Scheme 1

In a similar way as described above, the 2-deoxy-2-fluoro-β-D-arabinonucleosides **1b**, **2b**, **3b**, were prepared (Scheme 2). 3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**9**) which was employed in the glycosylation reaction was obtained from 1-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose by a three-step procedure as described in the literature.[20–22] Stereochemical control of the 2′-deoxy-2′-arabinofluoronucleoside synthesis proceeds in a similar way to that of 2′-deoxyribonucleosides. Glycosylation of **4b** with bromosugar **9** resulted in the exclusive formation of the protected β-D-nucleoside **10**. Treatment with aqueous ammonia removed the protecting groups and displaced the 6-chloro substituent to an amino group to form nucleoside **1b**. With sodium methoxide treatment **10** was converted to the 6-methoxy compound **2b**. Usually, the conversion of methoxy derivatives to the corresponding inosine analogues is performed in refluxing aqueous 2 N NaOH at elevated temperature. However, in the case of **2b**, decomposition took place after prolonged treatment. Thus, the reaction time was limited to one hour to give compound **3b** (Scheme 2).



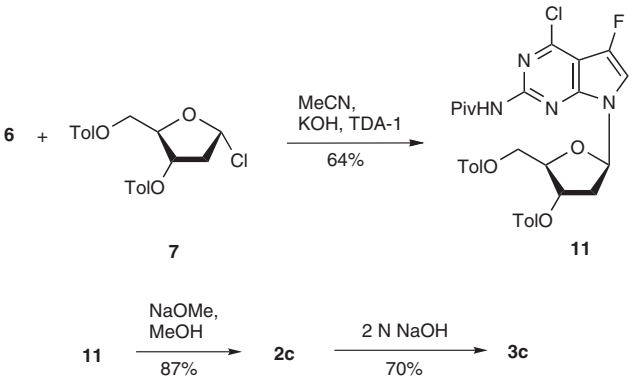
Scheme 2

For the synthesis of the related nucleosides with a 2-amino function, the preparation started from 2-amino-6-chloro-7-deazapurine. Compound **5** with a bulky pivaloyl protecting group was selected to direct the electrophilic fluorination to the 7-position as it was observed for other halogenation reactions.[9,14,23–25] Selectfluor was chosen as a fluorination reagent. However, only traces of the desired product were formed under condition used for compound **4b**. Consequently, the reaction temperature was decreased from 80 to 50 °C and the concentration of acetic acid as well as the reaction time was reduced. Under these optimized conditions (50–60 °C, 25 min and 10% acetic acid) compound **6** was obtained in 30% yield (Scheme 3).



Scheme 3

Compound **6** was converted to the nucleoside **11** by nucleobase-anion glycosylation with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**7**), similar to that of compound **4b**. The protected nucleoside **11** which was obtained in 64% yield was treated with 0.5 N NaOMe in MeOH (2 h) under reflux resulting in the removal of both the toluoyl and pivaloyl groups; also the 6-chloro group was displaced by the methoxy function to give compound **2c**. Next, the methoxy compound **2c** was converted to the 7-fluorinated 2′-deoxyguanosine derivative **3c** in aqueous 2 N NaOH at elevated temperature (Scheme 4).



Scheme 4

The nucleosides and the intermediates were characterized by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy as well as by elemental analysis or mass spectra. To confirm the anomeric configuration of **1a–c**, ^{1}H-NOE spectra was measured for compound **1a**. Irradiation of H-8 resulted in NOE effects at H-1′ (1.7%) and $H_β$-2′ (4.4%); no NOE was observed for $H_α$-2′, which proved the β-D conformation. The ^{13}C NMR data are summarized in Table 1. Assignments of the ^{13}C NMR chemical shifts are made according to the gate-decoupled ^{13}C NMR spectra and referring to the earlier literature.[26,27] Table 1 also shows that the halogens at the 7 position change the chemical shift of the C-7 in 6-chloro-7-deazapurine. Compared to the non-functionalized 6-chloro-7-deazapurine **4a** the C-7 signal of the 7-fluoro derivative **4b** is shifted downfield (40 ppm) while the 7-chloro[25] base **4c** shows a downfield shift of only 3 ppm. The other halogens induce an upfield shift (**4d**[26], Δδ = ca. 13 ppm; **4e**[28] Δδ = ca. 50 ppm). This trend is also observed in other ring systems such as 5-halogenated uracil derivatives.[29]

The fluorine position 7 or 8 was assigned from the coupling constants (Table 2) as well as on the basis of the crystal structure. $J_{F,C-7}$ has a value of about 250 Hz, showing a ^1J coupling, whereas $J_{F,C-8}$ and $J_{F,C-5}$ have values of about 25 and 15 Hz, respectively, as ^2J coupling constants (Table 2). Gated-decoupled ^{13}C NMR for **4b** showed $^1J_{H,C-2}$ = 209.3 Hz, $^1J_{H,C-8}$ = 192.2 Hz and $^2J_{H,C-7}$ = 6.8 Hz.

The pK_a values of the various nucleosides are summarized in Table 3. For the protonation of the nucleoside, the pK_a value of 7-deaza-2′-deoxyadenosine (2′-deoxytubercidin) is 1.43 higher than that of 2-halogenated derivatives. This results from the electron-withdrawing effect of the 7-halogen substituents reducing the basicity of 7-deaza-2′-deoxyadenosine. However, the differences among the halogenated derivatives are small. The situation is different for the deprotonation of the corresponding inosine derivatives. Here, an increasing electronegativity of the halogen substituents increases the acidity of the nucleobase.

In nucleosides, the most populated conformations of the furanose ring are *N*(C-3′-*endo*) and *S*(C-2′-*endo*). These conformations depend on the various gauche and anomeric effects.[31] In 2'-deoxyribonucleosides, the 5′-OH and the 3′-OH groups prefer a gauche orientation resulting in an *S*-sugar pucker. In the case of the 2′-deoxy-2′-fluoro-β-D-arabinonucleosides containing a modified nucleobase the situation is more complex due to the strong gauche effect of the highly electronegative F-atom and the anomeric-effect induced by the modified base. In order to study the effect of the fluorine substitution on the base and the sugar moiety the conformational analysis of the nucleosides **1a**, **1b**, **3a**, and **3b** was performed using the PSEUROT program (version 6.3)[32] and employing updated values for the substituent electronegativity constants.[33] In this program, a minimization of the difference between the experimental and calculated couplings are accomplished by a nonlinear Newton–Raphson minimization; the quality of the fit is expressed by the root-mean-square (rms) difference. This procedure presupposes the existence of a two-state *N*/*S* equilibrium in the solution. The program calculates the best fits of the $^3J_{H,H}$ and $^3J_{F,H}$ experimental coupling constants to the five conformational parameters: the phase angles (P_S and P_N) and puckering amplitudes ($Ψ_S$ and $Ψ_N$) of the *S*- and *N*-conformers, and the population of the *S*-type conformer (X_S; $X_S + X_N = 1$).

The input contained the following ^{1}H NMR coupling constants: $J_{H-1′,H-2′}$, $J_{H-1′,H-2″}$, $J_{H-2′,H-3′}$, $J_{H-2″,H-3′}$, $J_{H-3′,H-4′}$, $J_{H-1′,F-2′}$, $J_{H-3′,F-2′}$. They were taken from well-resolved ^{1}H NMR spectra measured in D_2O. The use of the both $^3J_{H,H}$ and $^3J_{H,F}$ coupling constants permits a detailed conformational analysis of the pentofuranose ring (Table 4).

From Table 4 it is apparent that all nucleosides are in the *N* ⇆ *S* equilibrium in solution showing a preferred *S* population. The values of the 7-fluorinated 2′-deoxytubercidin (**1a**) show a population of 70% *S* and 30% *N*, which is almost the same as the other halogenated 2′-deoxytubercidin derivatives (30% *N* for chloro, 29% *N* for bromo and 29% *N* for iodo).[34] Furthermore, no change was observed when the nucleoside was changed from adenosine analogue **1a** (30% *N*) to the inosine derivative **3a** (30% *N*). However, in the case of the 2′-fluoroarabino nucleosides the *N*-population is increased from 33% in **1b** to 40% in **3b**. These values are similar to what were observed in 7-halogenated 2-amino-7-deazapurine 2′-fluoroarabino nucleosides (34–37% *N*).[35] Moreover, it can be seen that the presence of a fluorine atom on 2′-arabino position of the 7-deazapurine nucleosides **1b**, **3b** does not change the sugar conformation strongly compared to the 2′-deoxynucleosides **1a**, **3a**. This is different to the pyrazolo[3,4-

Table 1 ^{13}C NMR Chemical Shifts (δ) of Nucleosides and Precursors[a]

Product[b,c]	C-2 C-2	C-4 C-6	C-4a C-5	C-5 C-7	C-6 C-8	C-7a C-4	C-1′	C-2′)	C-3′	C-4′	C-5′
4a	150.0	150.4	116.6	98.9	128.3	151.8	–	–	–	–	–
4b	151.1	148.5	105.4	139.7	111.2	146.8	–	–	–	–	–
4c	151.1	149.9	112.6	101.6	126.1	150.5	–	–	–	–	–
4d	150.9	150.2	113.6	85.8	128.6	151.5	–	–	–	–	–
4e	150.4	150.7	115.7	51.5	133.8	151.4	–	–	–	–	–
6	147.9[e]	152.0[e]	102.2	140.2	109.7	148.5[e]	–	–	–	–	–
8	151.5	149.1	106.7	140.4	111.3	146.5	83.5	36.1	74.7	81.4	64.0
10	151.8	149.2	106.6	140.5	112.5	146.6	81.7	93.3	76.1	78.0	63.7
1a	152.7	155.8	92.3	142.6	103.9	145.8	82.4	–[d]	70.9	87.2	61.9
1b	152.9	155.8	92.1	140.6	105.3	146.0	80.4	95.8	72.5	82.7	60.3
2a	151.6	161.4	95.0	141.4	107.2	147.0	82.7	–[d]	70.8	87.4	61.8
2b	151.7	161.4	94.7	142.1	108.2	147.0	80.8	95.7	72.2	82.8	60.2
3a	144.8	156.3	97.3	144.9	103.4	143.1	82.6	–[d]	70.8	87.4	61.8
3b	145.0	156.2	97.3	144.7	105.0	143.1	80.9	95.6	72.2	82.8	60.1
11[f]	152.0[e]	147.8[e]	104.4	142.2	107.9	150.9[e]	84.0	37.8	74.8	82.3	64.0
2c	160.0[e]	162.1[e]	87.5	142.9	101.2	150.3[e]	81.8	–[d]	70.9	86.9	62.0
3c	153.0[e]	156.9[e]	89.9	145.6	99.5	147.6[e]	81.8	–[d]	70.9	87.0	61.9

[a] Measured in DMSO-d_6.
[b] Systematic numbering.
[c] Purine numbering.
[d] Superimposed by DMSO.
[e] Tentative.
[f] Measured in $CDCl_3$.

d]pyrimidine 2′-fluoroarabinonucleosides showing a predominant *N*-conformer population.[36] It is the result of the combined influence of the gauche effect of the 2′-fluoro atom and the anomeric effect of the nucleobase with the N atom next to the glycosylation site.[36]

The single crystal X-ray analysis of compound **1a** confirms the β-D configuration of the nucleoside.[37] Furthermore, the crystal structures for **1a** is characterized by the *anti* orientation of the glycosylic bond with a O4′–C1′–N9–C4 torsion angle of $\chi = -101.1°$. The sugar ring has the C(2′)-*endo*-C(3′)-*exo* ($^2T_3$) conformation, *S*-type with $P = 164.8°$, $\tau = 40.1°$. The preferred population in the solution is also *S* (30% *N* and 70% *S*).

All chemicals were purchased from ACROS, Fluka, or Sigma-Aldrich. Solvents were distilled from technical grade. Petroleum ether (PE) used had bp 40–60 °C. TLC: aluminum sheets, silica gel 60 F_{254} (0.2 mm, VWR International). Flash chromatography (FC): 0.4 bar, silica gel 60 (VWR International, Darmstadt, Germany). Mp: Linström apparatus, not corrected. UV spectra: U-3200 UV/Vis spectrometer (Hitachi, Japan). NMR spectra: Avance DPX 250 or AMX-500 spectrometers (Bruker); δ values in ppm relative to Me_4Si as internal standard. *J* values are in Hz. Elemental analyses were performed by the Mikroanalytisches Laboratorium Beller, Göttingen, Germany. ESI-TOF mass spectra were performed on a micrOTOF Bruker Daltonics spectrometer in electropositive mode.

4-Chloro-5-fluoro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (6)

4-Chloro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (**5**;[14] 1.01 g, 4 mmol) and Selectfluor (2.13 g, 6.0 mmol) were placed in a round-bottom flask, followed by the addition of anhyd MeCN (40 mL) and AcOH (4 mL). The mixture was then heated at 50 °C for 25 min under N_2. The mixture was cooled by ice-water and diluted with CH_2Cl_2 (120 mL). The organic layer was washed with 5% aq $NaHCO_3$. The inorganic layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was evaporated; the residue was adsorbed on silica gel and applied on the top of a silica gel column (4 × 12 cm). Elution with CH_2Cl_2–MeOH (200:1) afforded **6** as colorless foam (0.32 g, 30%); $R_f = 0.11$ (CH_2Cl_2–MeOH, 40:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.22 (s, 9 H, 3 CH_3), 7.52 (m, 1 H, H-6), 10.13 (br s, 1 H, CONH), 12.21 (br s, 1 H, H-7).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –167.07 (F-5).

Table 2 $^{13}C,^{19}F$ Coupling Constants of the Fluorinated Compounds[a,b]

Compound	C-5,F-7	C-7,F-7	C-8,F-7	C-1′,F-2′	C-2′,F-2′	C-3′,F-2′	C-4′,F-2′
4b	13.8	246.1	25.6	–	–	–	–
6	14.6	245.6	25.8	–	–	–	–
8	14.3	249.6	26.9	–	–	–	–
10	14.5	249.3	25.1	16.4	191.8	28.3	5.4
1a	15.8	248.1	28.4	–	–	–	–
1b	15.7	245.3	30.2	16.9	191.8	22.6	5.3
2a	15.5	246.5	26.7	–	–	–	–
2b	15.3	246.7	27.6	17.0	192.2	22.9	5.8
3a	12.4	247.8	27.1	–	–	–	–
3b	10.1	247.5	30.0	16.7	192.3	23.0	5.6
11[c]	14.9	247.3	26.6	–	–	–	–
2c	16.7	246.5	27.2	–	–	–	–
3c	14.3	246.1	27.2	–	–	–	–

[a] Measured in DMSO-d_6.
[b] Purine numbering.
[c] Measured in $CDCl_3$.

Table 3 pK_a Values of the Nucleosides[a]

Nucleoside	pK_a[b]	Nucleoside	pK_a[c]
2′-deoxyadenosine	3.65	2′-deoxyinosine	9.07
7-deaza-2′-deoxyadenosine	5.08	7-deaza-2′-deoxyinosine	9.84
7-deaza-7-fluoro-2′-deoxyadenosine (**1a**)	4.43	7-deaza-7-fluoro-2′-deoxyinosine (**3a**)	9.22
7-bromo-7-deaza-2′-deoxyadenosine	4.16	7-deaza-7-chloro-2′-deoxyinosine	9.52
7-chloro-7-deaza-2′- deoxyadenosine	4.18	7-deaza-7-bromo-2′-deoxyinosine	9.64
7-deaza-7-iodo-2′- deoxyadenosine	4.23	7-deaza-7-iodo-2′-deoxyinosine	9.81
7-deaza-2′,7-difluoro-2′-deoxyarabinoadenosine (**1b**)	4.30	7-deaza-2′,7-difluoro-2′-deoxyarabinoinosine (**3b**)	9.30
7-deaza-2′-deoxyguanosine	1.70	7-deaza-2′-deoxyguanosine	10.2
7-deaza-7-fluoro-2′-deoxyguanosine (**3c**)	1.89	7-deaza-7-fluoro-2′-deoxyguanosine (**3c**)	9.9

[a] Measured by spectrophotometric titration (pH 1.5–12.5) at 220–350 nm.[30,]
[b] Protonation.
[c] Deprotonation.

MS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{13}ClFN_4O$ [M + 1]$^+$: 271.08; found: 271.08; *m*/*z* calcd for $C_{11}H_{12}ClFN_4O$ + Na [M + Na]$^+$: 293.06; found: 293.06.

UV (MeOH): λ_{max} (ε) = 244 (29300), 282 (5200), 302 nm (4900).

Anal. Calcd for $C_{11}H_{12}ClFN_4O$ (270.69): C, 48.81; H, 4.47. Found: C, 50.16; H, 4.62.

4-Chloro-7-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine (8)

To a suspension of powdered KOH (85%, 0.94 g, 14.3 mmol) in MeCN (50 mL), were added TDA-1 (0.18 mL, 0.57 mmol) and compound **4b**[1] (700 mg, 4.08 mmol). After the mixture was kept stirring for 5 min, compound **7**[19] (2.07 g, 5.32 mmol) was added in 15 min, and the stirring was continued for 20 min. Insoluble material was filtered off, the precipitate was washed with MeCN, and the filtrate was evaporated to dryness. The residue was applied to FC

Table 4 $^3J_{H,H}$ Coupling Constant of the Sugar Moiety and Conformer Population of Nucleosides[a]

Product	$^3J_{H,H}$ (Hz)					$^3J_{H,F}$ (Hz)			Pseudorotational Parameters			
	1′,2′	1′,2″	2′,3	2″,3′	3′,4′	1′F	3′F	2′F	%*N*	%*S*	P_s (°)	ψ_s (°)
1a	7.30	6.55	6.30	3.15	3.50	–	–	–	30	70	150.7	33.0
1b	3.02	–	3.26	–	4.76	17.1	18.9	51.7	33	67	127.8	43.0
3a	6.82	6.49	6.65	3.39	3.61	–	–	–	30	70	152.5	27.8
3b	3.92	–	3.54	–	5.13	16.2	18.8	51.7	40	60	131.1	41.0

[a] Measured in D_2O.

(silica gel, column 4 × 10 cm), and eluted with PE–EtOAc (8:1). The main zone was collected and condensed to a colorless solid, which was crystallized from MeOH to give colorless crystals of **8** (1.43 g, 67%); mp 114 °C; R_f = 0.2 (PE–EtOAc, 6:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.73–2.80 (m, 1 H, H-2′), 2.01–3.12 (m, 1 H, H-2′), 4.48–4.63 (m, 3 H, H-4′, H-5′), 5.75 (m, 1 H, H-3′), 6.80 (t, 1 H, *J* = 6.9 Hz, H-1′), 7.28–7.96 (m, 8 H, 2 C_6H_4), 8.01 (s, 1 H, H-6), 8.69 (s, 1 H, H-2).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –169.38 (F-5).

UV (MeOH): λ_{max} (ε) = 230 (55900), 276 nm (8100).

Anal. Calcd for $C_{27}H_{23}ClFN_3O_5$ (523.94): C, 61.89; H, 4.42; N, 8.02. Found: C, 61.72; H, 4.36; N, 8.00.

4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine (1a)

A suspension of compound **8** (1.43 g, 2.73 mmol) in 25% aq NH_4OH (100 mL) was introduced into an autoclave and stirred at 120 °C for 24 h. The clear solution was evaporated and the residue was subjected to FC (silica gel, column 5 × 10 cm), and eluted with CH_2Cl_2–MeOH (10:1). The main zone was collected and condensed to a colorless solid, which was crystallized from MeOH–CH_2Cl_2 to yield colorless crystals of **1a** (654 mg, 89%); mp 165 °C; R_f = 0.17 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.13–2.17 (m, 1 H, H-2′), 2.38–2.44 (m, 1 H, H-2′), 3.47–3.57 (m, 2 H, H-5′), 3.79–3.80 (m, 1 H, H-4′), 4.32 (m, 1 H, H-3′), 5.01 (t, 1 H, *J* = 5.3 Hz, 5′-OH), 5.26 (d, 1 H, *J* = 3.9 Hz, 3′-OH), 6.55 (t, 1 H, *J* = 6.6 Hz, H-1′), 7.00 (br s, 2 H, NH_2), 7.34 (s, 1 H, H-6), 8.07 (s, 1 H, H-2).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –167.95 (F-5).

UV (MeOH): λ_{max} (ε) = 276 nm (10700).

Anal. Calcd for $C_{11}H_{13}FN_4O_3$ (268.24): C, 49.25; H, 4.88; N, 20.89. Found: C, 49.19; H, 4.87; N, 20.76.

7-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-fluoro-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (2a)

Compound **8** (220 mg, 0.42 mmol) was suspended in 0.2 N NaOMe in MeOH (50 mL). The mixture was kept stirring at r.t. for 12 h. The mixture was evaporated and applied to FC (silica gel, column 2 × 10 cm), and eluted with CH_2Cl_2–MeOH (20:1). The main zone was collected and condensed to a colorless solid, which was recrystallized from MeOH to give **2a** as colorless crystals (102 mg, 86%); mp 112 °C; R_f = 0.67 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.17–2.24 (m, 1 H, H-2′), 2.39–2.44 (m, 1 H, H-2′), 3.45–3.59 (m, 2 H, H-5′), 3.81–3.82 (m, 1 H, H-4′), 4.05 (s, 3 H, OCH_3), 4.34 (m, 1 H, H-3′), 4.97 (t, 1 H, *J* = 5.4 Hz, 5′-OH), 5.30 (d, 1 H, *J* = 3.8 Hz, 3′-OH), 6.65 (t, 1 H, *J* = 6.2 Hz, H-1′), 7.63 (s, 1 H, H-6), 8.43 (s, 1 H, H-2).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –167.68 (F-5).

UV (MeOH): λ_{max} (ε) = 277 nm (6500).

Anal. Calcd for $C_{12}H_{14}FN_3O_4$ (283.26): C, 50.88; H, 4.98; N, 14.83. Found: C, 50.78; H, 5.06; N, 14.80.

7-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-3,7-dihydro-5-fluoro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (3a)

A solution of **2a** (140 mg, 0.49 mmol) in aq 2 N NaOH (2.5 mL) was refluxed for 3 h. After cooling to r.t., the mixture was neutralized with 1 N AcOH. The mixture was evaporated to dryness which was applied to FC (silica gel, column 2 × 10 cm) and eluted with CH_2Cl_2–MeOH (15:1) to yield a colorless solid. Recrystallization from MeOH afforded **3a** as colorless crystals (110 mg, 83%); mp 211 °C; R_f = 0.33 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.14–2.19 (m, 1 H, H-2′), 2.30–2.41 (m, 1 H, H-2′), 3.50–3.52 (m, 2 H, H-5′), 3.67–3.70 (m, 1 H, H-4′), 4.29 (m, 1 H, H-3′), 4.94 (m, 1 H, 5′-OH), 5.29 (m, 1 H, 3′-OH), 6.52 (t, 1 H, *J* = 6.5 Hz, H-1′), 7.30 (s, 1 H, H-6), 7.91 (s, 1 H, H-2), 12.11 (br s, 1 H, NH).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –166.07 (F-5).

UV (MeOH): λ_{max} (ε) = 263 (7400), 275 nm (7200).

Anal. Calcd for $C_{11}H_{12}FN_3O_4$ (269.23): C, 49.07; H, 4.49; N, 15.61. Found: C, 48.89; H, 4.59; N, 15.35.

4-Chloro-7-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-fluoro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*]pyrimidine (11)

To a suspension of powdered KOH (85%, 105 mg, 1.6 mmol) in MeCN (10 mL), were added TDA-1 (0.02 mL, 0.05 mmol) and compound **6** (135.5 mg, 0.5 mmol). After stirring the mixture for 5 min, compound **7**[19] (252.5 mg, 0.65 mmol) was added within 5 min and the stirring was continued for 20 min. Insoluble material was filtered off, the precipitate was washed with MeCN, and the filtrate was evaporated to dryness. The residue was applied to FC (silica gel, column 2 × 10 cm) and eluted with PE–EtOAc (4:1). The combined fractions were evaporated to give **11** as colorless solid (200 mg, 64%); R_f = 0.25 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, 3 CH_3), 2.42 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 2.78–2.82 (m, 1 H, H-2′), 2.91–2.97 (m, 1 H, H-2′), 4.54–4.70 (m, 3 H, H-5′, H-4′), 5.74–5.77 (m, 1 H, H-3′), 6.77 (t, 1 H, *J* = 6.8 Hz, H-1′), 6.99 (d, *J* = 2.4 Hz, 1 H, H-6), 7.18–7.99 (m, 8 H, 2 C_6H_4), 8.17 (s, 1 H, NHPiv).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –166.85 (F-5).

UV (MeOH): λ_{max} (ε) = 243 (58800), 274 nm (7500).

Anal. Calcd for $C_{32}H_{32}ClFN_4O_6$ (623.07): C, 61.69; H, 5.18; N, 8.99. Found: C, 61.66; H, 5.10; N, 9.03.

2-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluoro-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (2c)

Compound **11** (140 mg, 0.22 mmol) was dissolved in 0.5 N NaOMe in MeOH (4 mL), and the mixture was stirred under reflux for 2 h. TLC monitoring showed completion of the reaction. The mixture was evaporated and applied to a silica gel column, eluted with CH_2Cl_2–MeOH (30:1–20:1) to form **2c** as a colorless solid (50 mg, 87%); R_f = 0.34 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.03–2.09 (m, 1 H, H-2′), 2.23–2.30 (m, 1 H, H-2′), 3.45–3.50 (m, 2 H, H-5′), 3.74 (m, 1 H, H-4′), 4.27 (m, 1 H, H-3′), 4.91 (t, J = 5.5 Hz, 5′-OH), 5.22 (d, J = 1.80 Hz, 1 H, 3′-OH), 6.42 (m, 3 H, H-1′, NH_2), 7.00 (br s, 1 H, H-6).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –167.94 (F-5).

UV (MeOH): λ_{max} (ε) = 264 (8900), 287 nm (6100).

Anal. Calcd for $C_{12}H_{15}FN_4O_4$ (298.27): C, 48.32; H, 5.07; N, 18.78. Found: C, 48.46; H, 5.05; N, 18.62.

2-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,7-dihydro-5-fluoro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (3c)

Compound **2c** (60 mg, 0.20 mmol) was dissolved in aq 2 N NaOH (5 mL) and refluxed for 2 h. The mixture was cooled and neutralized with 1 N AcOH and evaporated to dryness. The residue was applied to a silica gel column and eluted with CH_2Cl_2–MeOH (10:1) to obtain the desired product **3c** as a colorless solid (40 mg, 70.5%); R_f = 0.12 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.00–2.07 (m, 1 H, H-2′), 2.19–2.30 (m, 1 H, H-2′), 3.45–3.47 (m, 2 H, H-5′), 3.73 (m, 1 H, H-4′), 4.25 (m, 1 H, H-3′), 4.91 (m, 1 H, 5′-OH), 5.22 (m, 1 H, 3′-OH), 6.32 (m, 1 H, H-1′), 6.43 (s, 2 H, NH_2), 6.81 (s, 1 H, H-6), 10.60 (br s, 1 H, NH).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –167.89 (F-5).

UV (MeOH): λ_{max} (ε) = 261 nm (10700).

MS (ESI-TOF): m/z calcd for $C_{11}H_{14}FN_4O_4$ [M + 1]$^+$: 285.10; found: 285.10; m/z calcd for $C_{11}H_{13}FN_4O_4$ + Na [M + Na]$^+$: 307.08; found: 307.08.

Anal. Calcd for $C_{11}H_{13}FN_4O_4$ (284.24): C, 46.48; H, 4.61; N, 19.71. Found: C, 46.59; H, 4.51; N, 19.41.

1-Bromo-2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranose (9)[20]

To a solution of 1,3,5-tri-*O*-benzoyl-2-fluoro-α-D-arabinofuranose (1.0 g, 2.15 mmol) in CH_2Cl_2 (5 mL), was added a 30% HBr solution in AcOH (1.2 mL). The mixture was stirred at r.t. for 16 h and evaporated to dryness. The oily residue was redissolved in CH_2Cl_2 (20 mL), the solution washed with H_2O (5 mL) and aq sat. $NaHCO_3$ solution (5 mL), and dried (Na_2SO_4). Concentration gave a viscous syrup which was further dried under high vacuum for 18 h at r.t. The colorless syrup **9** (840 mg, 92%) was used in the next step without purification.

4-Chloro-7-(2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-β-D-arabinofuranosyl)-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine (10)

To a stirred suspension of 4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4b**; 0.4 g, 2.33 mmol) in anhyd MeCN (17 mL), powdered KOH (85%, 0.61 g, 9.24 mmol) was added. After the mixture was stirred for 10 min at r.t., the phase-transfer catalyst TDA-1 (0.12 mL, 0.38 mmol) was added. The stirring was continued for another 15 min, and then a solution of bromo sugar **9** (1.38 g, 3.26 mmol) in MeCN (20 mL) was added in portions. After stirring for another 10 min, the mixture was filtered. The filtrate was concentrated and applied to FC (silica gel, column 4 × 10 cm), eluted with PE–EtOAc (7:1). The main zone was collected and condensed to a colorless solid, which was crystallized from MeOH to give colorless crystals of **10** (0.74 g, 61.7%); mp 144 °C; R_f = 0.55 (PE–EtOAc, 3:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.67–4.78 (m, 3 H, H-4′, H-5′), 5.76 (m, 1 H, H-2′), 5.87 (m, 1 H, H-3′), 6.95 (d, J = 14.89 Hz, 1 H, H-1′), 7.85 (s, 1 H, H-6), 7.47–7.75, 7.97–8.10 (m, 10 H, 2 C_6H_5), 8.76 (s, 1 H, H-2).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –169.61 (F-5), –199.11 (dt, $^2J_{F,H-2'}$ = 49.4 Hz, $^3J_{F,H-3'}$ = 21.17, $^3J_{F,H-1'}$ = 18.82 Hz, F-2′).

UV (MeOH): λ_{max} (ε) = 228 (48200), 276 nm (8200).

Anal. Calcd for $C_{25}H_{18}ClF_2N_3O_5$ (513.88): C, 58.43; H, 3.53; N, 8.18. Found: C, 58.58; H, 3.67; N, 8.05.

4-Amino-7-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluoro-7*H*-pyrrolo[2,3-*d*] pyrimidine (1b)

A suspension of compound **10** (2.2 g, 4.28 mmol) in a mixture of 25% aq NH_4OH (150 mL) and dioxane (20 mL) was heated at 120 °C for 16 h in an autoclave. The mixture was then cooled and evaporated to dryness. The residue was subjected to FC (silica gel, column 5 × 15 cm), and eluted with CH_2Cl_2–MeOH (9:1) to yield colorless solid. Crystallization from MeOH afforded **1b** as colorless crystals (0.88 g, 72%); mp 200 °C; R_f = 0.18 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.56–3.68 (m, 2 H, H-5′), 3.75 (m, 1 H, H-4′), 4.34 (m, 1 H, H-3′), 5.00 (t, J = 5.55 Hz, 1 H, 5′-OH), 5.10 (dt, $J_{F,2'}$ = 52.85 Hz, 1 H, H-2′), 5.89 (d, 1 H, J = 4.35 Hz, 3′-OH), 6.56 (d, J = 3.37 Hz, 1 H, H-1′), 7.04 (br s, 2 H, NH_2), 7.23 (s, 1 H, H-6), 8.08 (s, 1 H, H-2).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –168.30 (F-5), –199.68 (dd, $^2J_{F,H-2'}$ = 52.9 Hz, $^3J_{F,H-3'}$ = 21.7, $^3J_{F,H-1'}$ = 16.13 Hz, F-2′).

UV (MeOH): λ_{max} (ε) = 278 nm (10000).

Anal. Calcd for $C_{11}H_{12}F_2N_4O_3$ (286.23): C, 46.16; H, 4.23; N, 19.57. Found: C, 46.00; H, 4.31; N, 19.51.

7-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluoro-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (2b)

Compound **10** (0.3 g, 0.58 mmol) was suspended in 0.2 N NaOMe in MeOH (35 mL), the suspension was stirred at r.t. for 12 h, and the formed solution was neutralized with AcOH. The mixture was evaporated and applied to FC (silica gel, column 2 × 10 cm) and eluted with CH_2Cl_2–MeOH (12:1) to yield **2b** as colorless solid (0.17 g, 97%); R_f = 0.53 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.58–3.66 (m, 2 H, H-5′), 3.79 (m, 1 H, H-4′), 4.07 (s, 3 H, OCH_3), 4.34 (m, $J_{3',F}$ = 20.01 Hz, 1 H, H-3′), 5.06 (t, J = 5.00 Hz, 1 H, 5′-OH), 5.29 (dt, $J_{F,2'}$ = 50.02 Hz, 1 H, H-2′), 5.92 (d, 1 H, J = 5.00 Hz, 3′-OH), 6.67 (dd, $J_{1',2'}$ = 3.9 Hz, 1 H, H-1′), 7.54 (s, 1 H, H-6), 8.46 (s, 1 H, H-2).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –168.11 (F-5), –199.93 (dt, $^2J_{F,H-2'}$ = 52.9, $^3J_{F,H-3'}$ = 21.7, $^3J_{F,H-1'}$ = 16.13 Hz, F-2′).

UV (MeOH): λ_{max} (ε) = 276 nm (6700).

Anal. Calcd for $C_{12}H_{13}F_2N_3O_4$ (301.25): C, 47.84; H, 4.35; N, 13.95. Found: C, 48.00; H, 4.46; N, 13.85.

7-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-3,7-dihydro-5-fluoro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (3b)

A solution of **2b** (140 mg, 0.46 mmol) in aq 2 N NaOH (2.8 mL) was refluxed for 1 h. After cooling to r.t., the mixture was neutralized with 1 N AcOH. The mixture was evaporated to dryness and applied to a silica gel column, elution with CH_2Cl_2–MeOH (15:1) gave a colorless solid which was recrystallized from MeOH to give colorless crystals of **3b** (50 mg, 37%); R_f = 0.34 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.36–3.62 (m, 2 H, H-5′), 3.78 (m, 1 H, H-4′), 4.37 (m, 1 H, H-3′), 5.01 (t, 1 H, 5′-OH), 5.23, 5.02 (dt, $J_{F,2'}$ = 52.95 Hz, 1 H, H-2′), 5.91 (d, 1 H, 3′-OH), 6.50 (dd, $J_{1',F}$ = 16.93 Hz, $J_{1',2'}$ = 3.42 Hz, 1 H, H-1′), 7.36 (s, 1 H, H-6), 7.93 (s, 1 H, H-2), 12.13 (br s, 1 H, NH).

^{19}F NMR (235 MHz, DMSO-d_6): δ = –166.67 (F-5), –200.10 (dt, $^2J_{F,H-2'}$ = 52.94 Hz, $^3J_{F,H-3'}$ = 21.17, $^3J_{F,H-1'}$ = 16.17 Hz, F-2′).

UV (MeOH): λ_{max} (ε) = 263 (6000), 275 nm (5900).

Anal. Calcd for $C_{11}H_{11}F_2N_3O_4$ (287.22): C, 46.00; H, 3.86; N, 14.63. Found: C, 45.88; H, 3.95; N, 14.58.

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