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# 7-Functionalized 7-deazapurine β-D and β-L-ribonucleosides related to tubercidin and 7-deazainosine: glycosylation of pyrrolo[2,3-*d*]pyrimidines with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D or β-L-ribofuranose

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**Abstract**—Several 7-functionalized 7-deazapurine ribonucleosides were prepared. Glycosylation of 7-halogenated 6-chloro-7-deazapurines with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose gave the protected β-D-nucleosides **8c**–**e** (53–62%) and the β-L-nucleosides **9b**–**e** (57–72%), which were transformed to 7-halogenated 7-deazapurine ribonucleosides related to tubercidin and 7-deazainosine. 7-Alkynyl derivatives (**1f**,**g**) and (**2f**,**g**) were obtained from the 7-iodo nucleosides **1e** and **2e** employing the palladium-catalyzed Sonogashira cross-coupling reaction. Within the series of 7-deazaadenosine (tubercidin) analogues and 7-deazainosine derivatives physical data such as p$K_a$ values, chromatographic mobilities, $^{13}$C NMR chemical shifts were determined and correlated to each other.
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## 1. Introduction

Pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) ribonucleosides are naturally occurring. Because of their widespread biological activities they received attention as antiviral and anticancer reagents.[1,2] Among the monomeric molecules are tubercidin (**1a**) and its 7-substituted derivatives, toyocamycin (**1h**) and sangivamycin (**1i**), which were isolated from *Streptomyces* strains (purine numbering is used throughout Section 2) (Fig. 1). 7-Halogenated analogues such as 5′-deoxy-7-iodotubercidin were detected in marine organisms.[3] 7-Deazapurine ribonucleosides were found as constituents of tRNA: queuosine and archaeosine represent 7-substituted 7-deazaguanine ribonucleosides, which are formed by the post-modification of a nucleic acid.[2,4] Other naturally occurring 7-deazapurine nucleoside antibiotics were isolated, including mycalisines A and B,[5] cadeguomycin,[6] the antibiotic AB-116 (kanagawamicin) and dapiramicin.[7–9] 7-Deazainosine has been isolated from the ascidian *Aplidium pantherinum*.[10] As the shape of the 7-deazapurines closely resembles that of purines, they are used as substitutes for the canonical constituents of DNA and RNA.

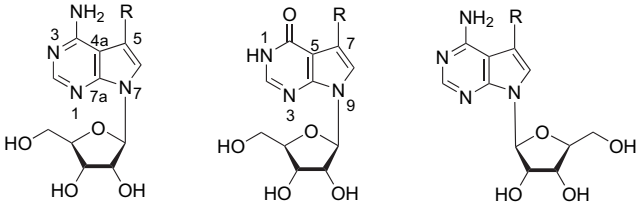


**Figure 1**. Structures of nucleosides **1**–**3**.

Recent developments in RNA chemistry and biology such as the discovery of the catalytic function of RNA or RNA interference have focused the interest of base modified

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ribonucleosides.[11,12] The frequent occurrence and biological properties of this class of compounds have prompted ample studies toward the synthesis, biological activities, and incorporation in oligonucleotides as well as of chemically designed analogues.[13–21] In many cases these 7-deazapurines are functionalized at the 7-position. Halogen-functionalized derivatives can present biological activity or can be used for further manipulations[22–25] such as cross-coupling chemistry.[26–31]

Earlier work demonstrated that 7-deazapurines resist glycosylation when 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose was employed in the glycosylation reaction.[13,32] Thus, an efficient protocol for the synthesis of 7-deazapurine ribonucleosides is indispensable. Recent work on 7-functionalized 7-deazapurine ribonucleosides focused on the preparation of nucleosides related to guanosine, xanthosine, and purine-2,6-diamine.[33] The present manuscript investigates the synthesis of 7-halogenated 7-deazapurine ribonucleosides related to adenosine and inosine. In particular, the synthesis of 7-deazaadenosines **1c–e**, their β-L-enantiomers **3b–e** as well as 7-deazainosines **2b–e** will be described. The work reports on the further functionalization of the 7-iodo derivatives by the Sonogashira cross-coupling reaction (**1f**,**g** and **2f**,**g**) and studies the influence of the 7-substituents on the physical properties.

## 2. Results and discussion

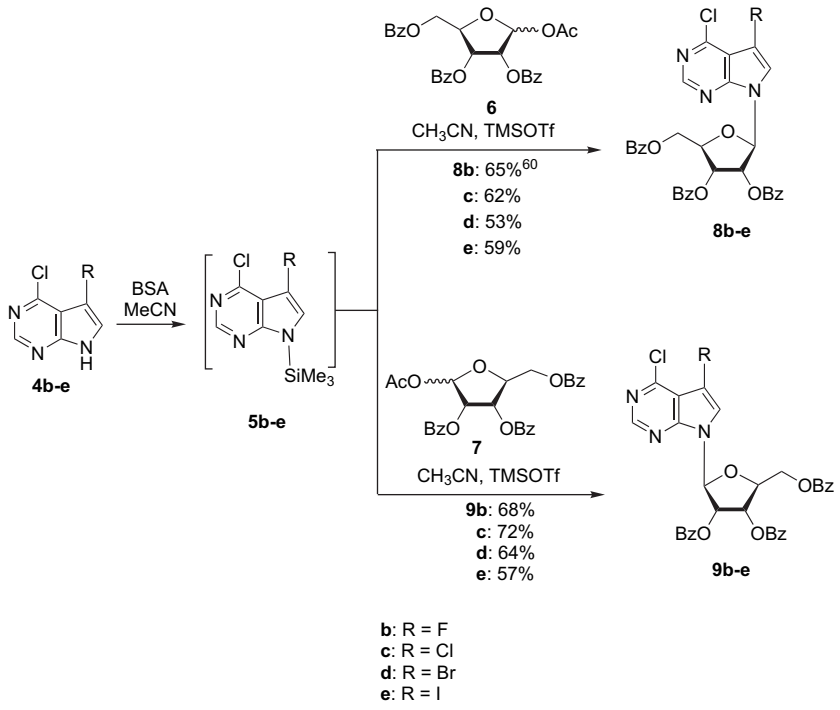
### 2.1. Glycosylation of the 7-deazapurines 4b–e with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (6) or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (7)

Considerable effort has been expended in the development of methods for the synthesis of 7-deazapurine ribonucleosides including tubercidin and 7-deazainosine. Mizuno et al. reported on the 7-deazainosine (**2a**) synthesis using an amino functionalized pyrimidine derivative and a protected sugar aldehyde as starting materials to form a Schiff base as intermediate yielding 7-deazainosine in a multistep procedure.[34] Robins and co-workers synthesized 4-chloro-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine by chlorination of 7-deazainosine which was obtained from the naturally occurring tubercidin by chemical deamination.[35] With this intermediate, halogenated compounds such as **1c–e** and **2d** were prepared in low overall yields.[36] A protocol involving 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose for the glycosylation of a toyocamycin precursor was reported by Townsend, another group employed the fusion reaction which resulted in low yields as well.[37,38] Overall, it was shown that the pyrrole nitrogen is rather inert to glycosylation with the result that the reaction is directed into the pyrimidine moiety,[32] takes place at the more nucleophilic pyrrole carbons[39,40] or results in poor yields.

The development of the stereoselective nucleobase anion glycosylation made 7-deazapurine 2′-deoxyribonucleosides easily accessible.[41–43] Later on, this protocol was applied to 7-deazapurine ribonucleosides' synthesis, using activated ribosugar derivatives (ribofuranosyl halides).[44–52] Unfortunately, *ortho* amides are formed by neighboring group participation when the sugar contains an acyl protecting group at the 2-position with no or little formation of the expected N-9 nucleosides.[45–47] This was circumvented when the nucleobase anion glycosylation of a 7-deazapurine base was performed with a sugar halide protected at the 2′,3′-*cis* diol with benzyl residues or an isopropylidene moiety.[45–52] While benzyl protected sugars lead to anomeric mixture of nucleosides,[17,47] the usage of 1-chloro-2,3-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-D-ribofuranose gives the β-D-anomers exclusively.[45,46,48–52] However, glycosylation of the 7-substituted derivatives did not work satisfactorily.[33] As we wanted to use the commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose as a sugar component for glycosylation, we went back to the silylation of the nucleobase. We and others have already shown that the application of the Wittenburg protocol (silylated base, sugar bromide, and mercuric oxide in benzene or other solvents) results in mixtures of isomeric glycosylation products with very little of the N-7 glycosylated pyrrolo[2,3-*d*]pyrimidine.[32,53] As an alternative the silyl-Hilbert–Johnson reaction[54] was employed. This reaction is usually performed as a two-step protocol (i) silylation of the nucleobase in the presence of ammonium sulfate and (ii) glycosylation with an acylated ribosugar derivative in the presence of a Friedel–Crafts catalyst (Vorbrüggen conditions).[55,56] However, also under these conditions a glycosylation of the pyrrole nitrogen was not observed.[33]

In addition to the above synthetic methods a so called 'one-pot' protocol of the silyl-Hilbert–Johnson reaction was described.[33] This 'one-pot' protocol was used by Wolfe for the synthesis of 2′-*C*-methyl-β-D-ribonucleosides.[57] In this procedure, the nucleobase was silylated with BSA (*N,O*-bis(trimethylsilyl)acetamide) in MeCN and glycosylated with 2′-*C*-methyl-1,2,3,5-tetra-*O*-benzoyl-D-ribofuranose in the presence of $SnCl_4$. Later, Ding employed the same procedure for the synthesis of toyocamycin derivatives and 7-deazainosine derivatives.[58] Here, MeCN was used as a solvent, and TMSOTf (trimethylsilyl trifluoromethanesulfonate) as glycosylation catalyst (Vorbrüggen conditions). The nucleobases were silylated and directly glycosylated in one step. Townsend applied this procedure for the synthesis of toyocamycin.[59]

We used the 'one-pot' method for the synthesis of the 7-deazaadenosine analogues **1c–e**, and the 7-deazainosine nucleosides **2b–e** as well as the β-L-nucleosides **3b–e**. The nucleobases **4b–e**[60,61] were silylated with 1.2 equiv of BSA in anhydrous MeCN at room temperature and then reacted with 1.2 equiv of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**6**) or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (**7**) in the presence of TMSOTf (trimethylsilyl trifluoromethanesulfonate) at 80 °C (Scheme 1). This afforded the glycosylated intermediates **8b–e** and **9b–e** in the β-D and the β-L series. It was found that 1.2 equiv of TMSOTf led to completion of the reaction within 1 h resulting in 53–72% yields of the glycosylation products **8b–e** and **9b–e**. This is different from the reaction conditions applied for the more sensitive 7-halogenated 2-amino-6-chloro-7-deazapurines, which required 40–50 °C, with 24 h reaction time.[33] We were not able to perform the glycosylation under the same reaction conditions with the same protected ribofuranoses **6** and **7** using the non-fuctionalized **4a** which is




**Scheme 1**. Glycosylation performed on compounds **4** with the sugar derivatives **6** and **7**.

not bearing an electron-withdrawing substituent at the 7-position. Bio and co-workers reported a similar observation for **4a** employing 2′-*C*-methyl-1,2,3,5-tetra-*O*-benzoyl-D-ribofuranose in the glycosylation reaction.[62] It is obvious that the electron-withdrawing character of the 7-halogeno substituents is a prerequisite for a successful glycosylation employing the common sugar derivative, most probably such conditions are already required for a successful silylation. In the case of nucleobases not functionalized at the 7-position the isopropylidene protected sugar has to be used.[45,46,48–52] The other option would be the synthesis of bromo or iodo compounds followed by reductive removal of halogen.

Regarding the characteristics of the nucleoside structures we performed a single crystal X-ray analysis on 7-fluorotubercidin (**1b**), which was synthesized by Wang and co-workers.[60] Both, the glycosylation position (N-9) and the anomeric configuration (β-D) were confirmed.[63] The $^{13}$C NMR chemical shifts of the synthesized nucleosides will be discussed later. The enantiomeric character of the β-L-nucleosides was deduced from their identical $^{1}$H and $^{13}$C NMR spectra; the assignment to the L-series is deduced from the L-sugar used for the glycosylation. The CD spectra and the spatial mirror images are diagnostic for the enantiomeric character (Fig. 2).

## 2.2. Synthesis of the 7-halogenated 7-deazaadenosines 1b–e and 7-deazainosines 2b–e

The ribonucleosides **2b–e** were prepared from the intermediates **8b–e**. Deprotection of **8b–e** in 0.5 M NaOMe/MeOH at room temperature afforded the deblocked nucleosides **10b–e** under simultaneous displacement of the 6-chloro substituent to a 6-methoxy group (Cl→$OCH_3$). Two protocols were employed for the substitution of the 6-methoxy group to an oxo group: $Me_3SiCl$/NaI in $CH_3CN$ or aq NaOH solution (Scheme 2).[33,64] Compounds **10b–d** were demethylated with $Me_3SiCl$/NaI/$CH_3CN$, while demethylation of **10e** with $Me_3SiCl$/NaI/$CH_3CN$ resulted in partial deiodination thereby forming a mixture of **2a** and **2e**, which was confirmed by NMR spectra. Both the $^{1}$H and $^{13}$C NMR spectra of the reaction product show two sets of nucleoside signals which correspond to the signals of **2a** and **2e**, respectively. When compounds **10b–d** were treated with $Me_3SiCl$/NaI/$CH_3CN$, the 7-fluoro, 7-chloro, and 7-bromo substituents were not affected, which was different from the corresponding 7-deazaxanthosine derivatives.[33,64] In the case of 7-halogenated 7-deazaxanthosines, the 7-chloro and the 7-bromo substituents were partially displaced by an iodo substituent.

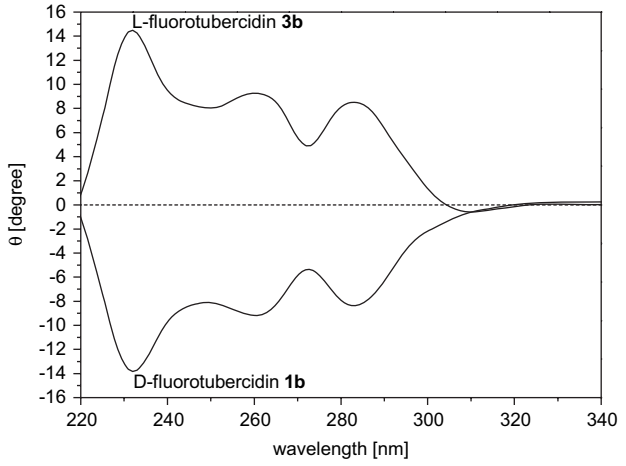
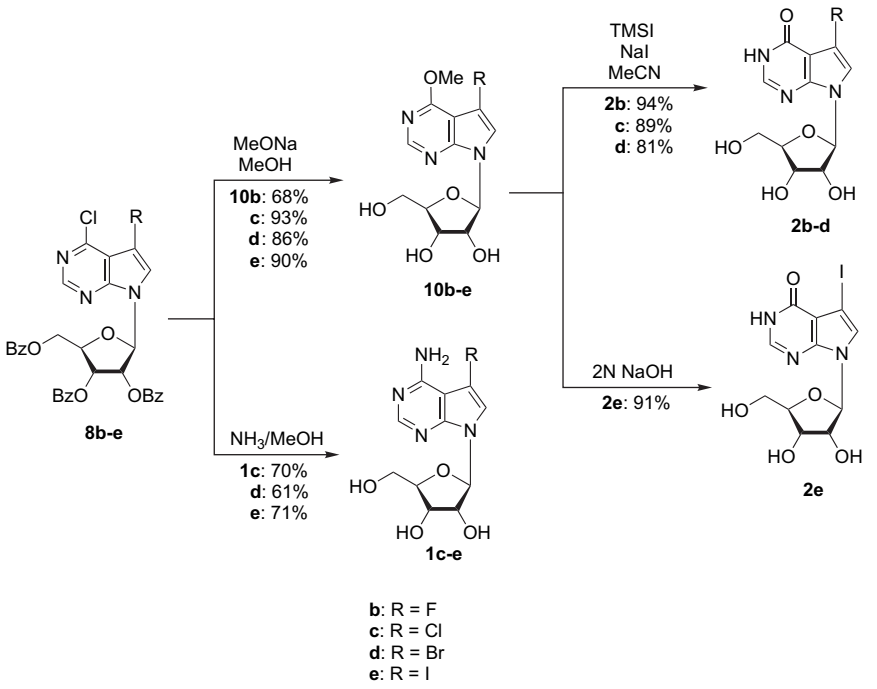


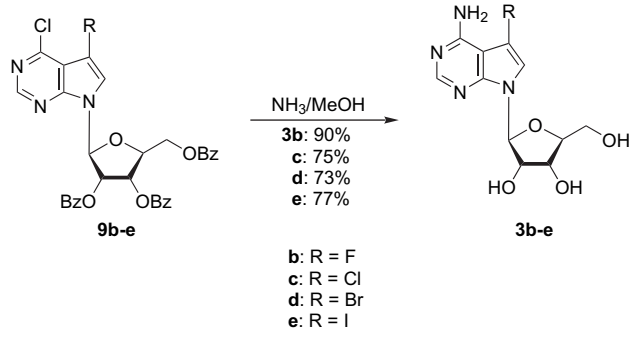

**Figure 2**. The CD spectra of nucleosides **1b** and **3b** measured in MeOH ($c$=4×10$^{-4}$ M).



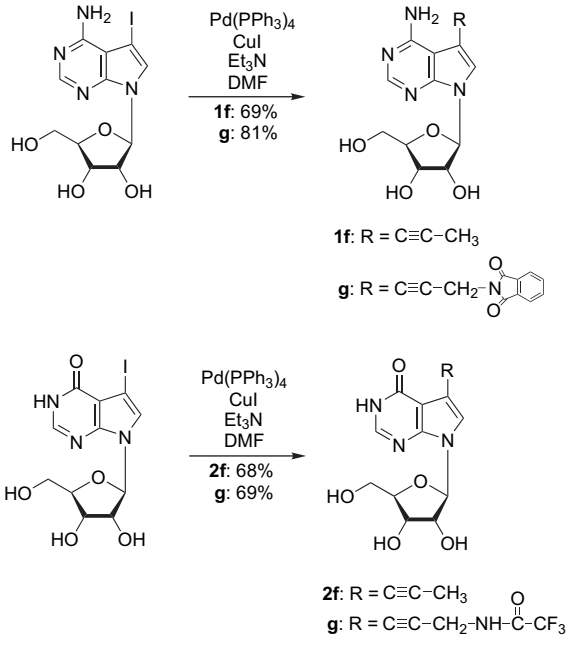

**Scheme 2**. Transformation of the intermediates **8b–e** to the nucleosides **1c–e** and **2b–e**.

To avoid the unwanted side reaction occurring on **10e**, the nucleophilic OMe/OH displacement was performed under alkaline conditions (2 N aq NaOH, reflux 1.5 h). This resulted in a clean exchange of the methoxy group under formation of **2e** (91% yield). In another series of experiments, compounds **8c–e** were converted into the 7-halogenated tubercidin derivatives **1c–e**, employing methanolic ammonia in an autoclave (120 °C, overnight). The corresponding β-L enantiomers **9b–e** were converted by the same procedure as described for the β-D nucleosides **8b–e**, yielding the 7-halogenated β-L-tubercidin derivatives **3b–e** (Scheme 3).

The introduction of alkynyl or aminoalkynyl side chains to purine constituents of DNA or RNA has a major impact on the oligonucleotide structure and stability,[65–69] e.g., resistance against enzymatic degradation,[70] or an increased sensitivity of oligonucleotide detection by MALDI-TOF spectrometry.[71,72] The 7-iodo-substituted derivatives **1e** and **2e** are particularly valuable intermediates for introducing alkynyl or aminoalkynyl side chains since they can be used as starting materials in Pd-catalyzed cross-coupling reactions.[31] Thus, they were employed as precursors in this type of reaction yielding the 7-alkynyl and aminoalkynyl 7-deazapurine ribonucleosides **1f**,**g** and **2f**,**g**. The reaction was performed in anhydrous DMF with tetrakis(triphenylphosphine)palladium(0), copper(I)iodide, and triethylamine under nitrogen and resulted in 68–81% yields of the alkynyl derivatives (Scheme 4).




**Scheme 3**. Transformation of the intermediates **9b–e** to the β-L-nucleosides **3b–e**.




**Scheme 4**. Synthesis of 7-alkynyl-7-deazapurine nucleosides.

## 2.3. Physical properties of the 7-functionalized 7-deazapurine nucleosides

All compounds were characterized by UV–vis spectra (Table 1 and Section 4). The UV spectra of compounds

**Table 1**. UV data of 7-substituted 7-deazapurine ribonucleosides[a]

| Compound | $\lambda_{max}$ (nm) | $\varepsilon$ | Compound | $\lambda_{max}$ (nm) | $\varepsilon$ |
|---|---|---|---|---|---|
| **1a**[44] | 270 | 11,900 | | | |
| **1b** | 281 | 9700 | **3b** | 279 | 10,200 |
| **1c** | 281 | 9900 | **3c** | 280 | 9500 |
| **1d** | 281 | 9600 | **3d** | 281 | 9200 |
| **1e** | 284 | 8000 | **3e** | 284 | 7900 |
| **1f** | 237 | 12,500 | | | |
| | 280 | 8800 | | | |
| **1g** | 280 | 10,700 | | | |
| **2a** | 259 | 9100 | **2e** | 266 | 7500 |
| **2b** | 264 | 7500 | **2f** | 271 | 9800 |
| **2c** | 264 | 8100 | **2g** | 270 | 12,000 |
| **2d** | 265 | 8400 | | | |

[a] Measured in MeOH.

**1a–g**, **2a–g**, and **3b–e** were measured in methanol. Table 1 indicates that the 7-halogeno and 7-alkynyl substituents induce a bathochromic shift compared to the corresponding non-functionalized nucleosides **1a** and **2a**. In the series of the 7-substituted tubercidin derivatives **1**, the wavelength maximum was shifted 11 nm in the case of the fluoro, chloro, and bromo derivatives **1b–d** and 14 nm for the iodo derivative **1e**, while in the case of the alkynyl side chains, the shift is about 10 nm for **1f** and **1g**. For the iodo derivative of nucleoside **1e** a stronger shift is found. In the 7-deazainosine series **2**, the UV bathochromic shift is only 5 nm for the fluoro and chloro derivatives, 6 nm for the bromo derivative, and 7 nm for the iodo compound. In contrast to the halogeno compounds the alkynyl side chains induce a bathochromic shift of about 12 nm. Here, the wavelength shift for the halogeno compounds is moderate compared to the series of compounds **1**, while the bathochromic shifts for alkynyl substituted compounds are almost the same as for the halogeno series **1**. For the series of β-L compounds **3b–e**, the shifts are comparable to their β-D counterparts.

The p$K_a$ values of the nucleosides can strongly affect the base pairing properties and duplex stability of oligonucleotides.[73] Therefore, the p$K_a$ values of nucleosides **1a–f** and **2a–e** were measured by spectrophotometric titration[74] (pH 1.5–13.5) at 200–350 nm. As shown in Table 2, the p$K_a$ values of the 7-halogenated compounds **1b–e**, **2b–e** as well as the 7-alkynyl nucleoside **1f** are lower than those of the corresponding non-functionalized nucleosides **1a** and **2a** (Fig. 3). These p$K_a$ changes result from the electron-withdrawing character of the 7-substituents including halogens as well as alkynyl groups making deprotonation more favorable and protonation more difficult.

**Table 2**. p$K_a$ Values of the 7-deazapurine ribonucleosides[a]

| Compound | Wavelength (nm) | p$K_a$ | Compound | Wavelength (nm) | p$K_a$ |
|---|---|---|---|---|---|
| **1a** | 226 | 5.33 | **2a** | 226 | 10.21 |
| **1b** | 226 | 4.42 | **2b** | 220 | 9.73 |
| **1c** | 232 | 4.24 | **2c** | 220 | 9.33 |
| **1d** | 234 | 4.29 | **2d** | 223 | 9.41 |
| **1e** | 239 | 4.42 | **2e** | 226 | 9.93 |
| **1f** | 241 | 4.50 | | | |

[a] Determination according to the spectrophotometric titration at indicated wavelength.

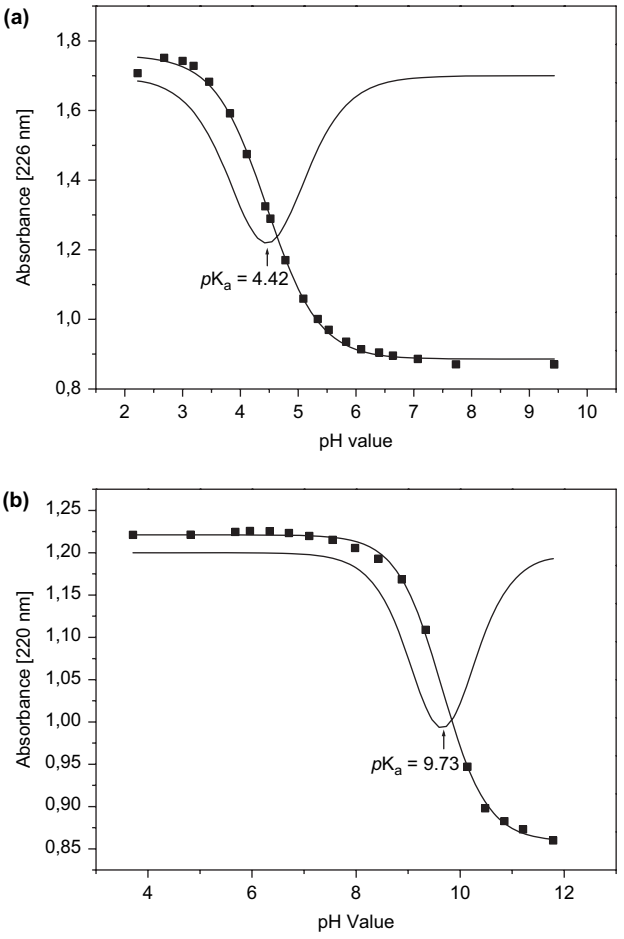



**Figure 3**. Absorbance change of compounds **1b** (a) and **2b** (b) as a function of pH values measured at 226 nm.

Earlier, a series of 7-deaza-2′-deoxyadenosine derivatives were reported showing fluorescence.[75] Therefore, it was of interest to investigate this matter on 7-(alkynyl)-7-deazaadenosine and 7-(alkynyl)-7-deazainosine. Only the 7-propynyl-7-deazaadenosine exhibited significant fluorescence (Fig. 4). The same large *Stokes* shift (90 nm) with an emission at 370 nm was observed when the compound was

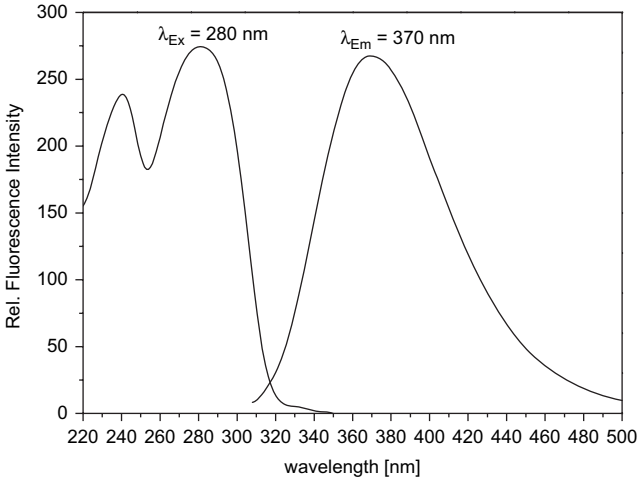



**Figure 4**. Fluorescence spectrum of the 7-propynyl-7-deazaadenosine **1f** in MeOH ($c$=10$^{-5}$ M).

irradiated at 280 nm for **1f** as observed for its 2′-deoxyribo derivative.[75a] None of the 7-deazainosine derivatives were fluorescent.

The nucleosides and the intermediates were characterized by $^{1}H$ and $^{13}C$ NMR spectra. The $^{13}C$ NMR data are summarized in Table 3. Assignments of the $^{13}C$ NMR chemical shifts were made according to the gated-decoupled $^{13}C$ NMR spectra and referring to the earlier literature.[76,77] Table 3 shows that the 7-substituted compounds exhibited a characteristic shift of C-7 induced by the various substituents. Compared to the non-functionalized nucleosides **1a** and **2a**, the C-7 signals are downfield shifted about 43 ppm for the fluoro derivatives **1b** and **2b**, while the chloro derivatives **1c** and **2c** show a downfield shift of only about 3 ppm. On the other hand, the bromo and iodo substituents induce an upfield shift of 12 ppm for **1d** and **2d** and 48 ppm for **1e** and **2e**. This trend is also observed for the bases **4a**–**e**[78] and other heterocycle ring systems such as 5-halogenated uracil derivatives.[79] The alkynyl side chains also induce an upfield shift, but the effects are weaker than for the bromo and iodo derivatives. It is in the range of 5 ppm for **1f**,**g** and **2f**,**g**. In Figure 5, the chemical shifts observed for the 7-deaza-7-haloinosine at C-7 and C-8 carbon position are plotted against the substituent electronegativity (Ex) values of Shoolery and Dailey.[80] $\delta$ ($^{13}C$) of C-7 is increasing, with increasing electronegativity of the substituents. At position C-8, two bonds away from the substituent, the substituent effect is lower relative to that of C-7. Additionally, $\delta$ ($^{13}C$) signals are observed to decrease linearly with increasing electronegativity (Ex) (Fig. 5).

Due to the introduction of various substituents into the 7-position of the 7-deazapurine moiety, the lipophilic character of the nucleosides is changed. The differences in lipophilicity were evaluated by HPLC experiments performed on a hydrophobic column (RP-18 (250×10 mm)) (Fig. 6) and were compared with the calculated log *P* values (Table 4). According to Table 4 and compared to non-functionalized nucleoside **1a**, the log *P* values are increased for the halogenated derivatives and an even stronger increase is found for the alkynyl modified derivatives **1f**,**g**. For **1f**,**g**, the log *P* values increase from −0.36±0.46 for **1a** to 0.98±0.60 and 2.51±0.65, respectively. These values are closely matched to the retention times (Fig. 6) attained from the reversed-phase HPLC experiments. The retention times of nucleosides are 8.8 min for the non-functionalized nucleoside **1a**, 13.5 min for the fluoro derivative **1b**, 34.9 min for the alkynyl modified derivative **1g**.

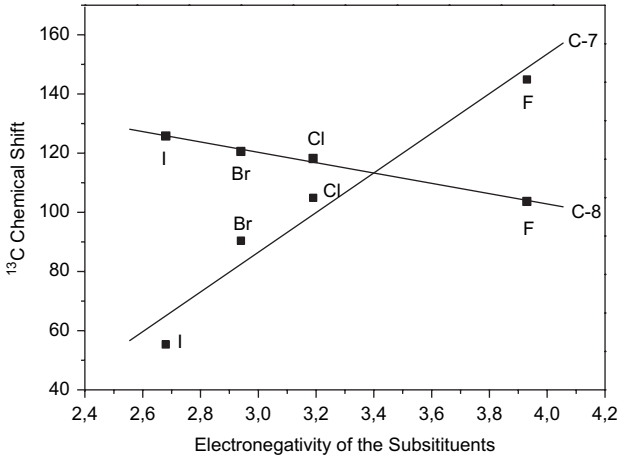



**Figure 5**. Plot of the $^{13}C$ chemical shift at the indicated carbon position versus substituent electronegativity (Ex), for 7-halogenated 7-deazainosines.

**Table 3**. $^{13}C$ NMR chemical shifts of 7-deazapurine ribonucleosides[a]

| Compound | C(2)[b] / C(2)[c] | C(4)[b] / C(7a)[c] | C(5)[b] / C(4a)[c] | C(6)[b] / C(4)[c] | C(7)[b] / C(5)[c] | C(8)[b] / C(6)[c] | C(1′) | C(2′) | C(3′) | C(4′) | C(5′) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a**[51] | 151.5 | 149.9 | 103.1 | 157.5 | 99.5 | 122.3 | 87.6 | 73.7 | 70.8 | 85.1 | 61.9 |
| **1b** | 152.8 | 146.3 | 92.5 | 155.9 | 142.6 | 104.4 | 86.5 | 73.9 | 70.6 | 85.0 | 61.7 |
| **1c** | 152.7 | 149.2 | 99.9 | 156.8 | 102.7 | 119.3 | 86.8 | 74.0 | 70.5 | 85.2 | 61.6 |
| **1d** | 152.4 | 149.6 | 101.1 | 156.9 | 86.8[d] | 121.8 | 86.7[d] | 73.9 | 70.5 | 85.2 | 61.5 |
| **1e** | 152.0 | 150.2 | 103.3 | 157.2 | 51.9 | 127.2 | 86.9 | 73.9 | 70.5 | 85.2 | 61.6 |
| **1f** | 152.5 | 149.4 | 102.4 | 157.6 | 95.6 | 125.9 | 87.2 | 73.9 | 70.6 | 85.2 | 61.6 |
| **1g** | 153.1 | 150.0 | 102.7 | 157.8 | 94.3 | 123.7 | 86.4 | 74.3 | 70.6 | 85.6 | 61.9 |
| **2a** | 147.8 | 143.8 | 108.4 | 158.2 | 102.5 | 121.1 | 87.0 | 74.3 | 70.6 | 85.1 | 61.6 |
| **2b** | 144.8 | 143.7 | 97.4 | 156.3 | 144.9 | 103.7 | 86.5 | 74.3 | 70.4 | 85.3 | 61.4 |
| **2c** | 145.1 | 146.9 | 106.5 | 157.1 | 104.9 | 118.2 | 86.7 | 74.4 | 70.5 | 85.3 | 61.4 |
| **2d** | 144.9 | 147.3 | 106.0 | 157.2 | 90.4 | 120.6 | 86.7 | 74.4 | 70.4 | 85.3 | 61.4 |
| **2e** | 144.7 | 147.8 | 108.1 | 157.8 | 55.4 | 125.8 | 86.8 | 74.4 | 70.5 | 85.3 | 61.4 |
| **2f** | 144.8 | 147.2 | 107.6 | 157.5 | 99.8 | 124.7 | 86.9 | 74.4 | 70.5 | 85.2 | 61.4 |
| **2g** | 145.1 | 147.5 | 107.6 | 157.4 | 98.2 | 118.1 | 86.9 | 74.5 | 70.4 | 85.2 | 61.3 |
| **3b** | 153.0 | 146.4 | 92.8 | 156.0 | 142.8 | 104.7 | 86.7 | 74.1 | 70.8 | 85.2 | 61.8 |
| **3c** | 152.7 | 149.2 | 99.9 | 156.8 | 102.6 | 119.2 | 86.7 | 73.9 | 70.5 | 85.2 | 61.5 |
| **3d** | 152.4 | 149.6 | 101.1 | 157.0 | 86.8[d] | 121.8 | 86.7[d] | 73.9 | 70.5 | 85.2 | 61.5 |
| **3e** | 151.9 | 150.2 | 103.2 | 157.2 | 51.9 | 127.2 | 86.8 | 73.9 | 70.5 | 85.2 | 61.6 |
| **10b** | 151.6 | 147.5 | 95.0 | 161.5 | 141.4 | 107.2 | 86.5 | 74.1 | 70.5 | 85.2 | 61.5 |
| **10c** | 151.6 | 150.6 | 102.7 | 162.1 | 102.7 | 121.8 | 86.8 | 74.2 | 70.4 | 85.3 | 61.4 |
| **10d** | 151.5[d] | 151.1[d] | 104.1 | 162.2 | 86.6 | 124.2 | 86.8 | 74.2 | 70.4 | 85.3 | 61.4 |
| **10e** | 151.1[d] | 151.8[d] | 106.7 | 162.3 | 51.4 | 129.4 | 86.8 | 74.1 | 70.5 | 85.3 | 61.4 |

[a] Measured in DMSO-$d_6$.
[b] Purine numbering.
[c] Systematic numbering.
[d] Tentative.

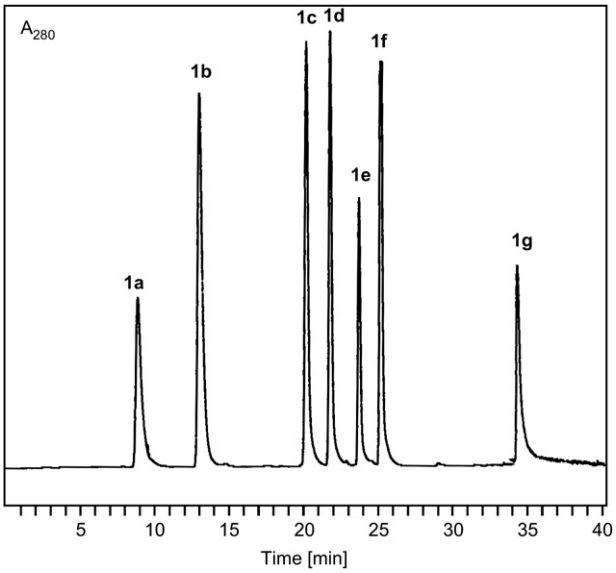



**Figure 6**. Reversed-phase HPLC profile of an artificial mixture of the nucleosides **1a–g**. Column, RP-18 (250×10 mm); gradient: 0 min 100% B, after 10 min 5% A, after 20 min 15% A, after 25 min 20% A, after 30 min 30% A, after 35 min 15% A in B; A=MeCN, B=0.1 M $(Et_3NH)OAc$ buffer, pH=7.0.

**Table 4**. log *P* Values and retention times of 7-functionalized tubercidin derivatives

| Compound | log *P* Value | Retention time (min) |
|---|---|---|
| **1a** | −0.36±0.46 | 8.8 |
| **1b** | −0.30±0.55 | 13.5 |
| **1c** | 0.24±0.49 | 20.4 |
| **1d** | 0.42±0.55 | 21.7 |
| **1e** | 0.68±0.55 | 24.0 |
| **1f** | 0.98±0.60 | 25.6 |
| **1g** | 2.51±0.65 | 34.9 |

## 3. Conclusion

Although a number of methods have been developed for the-synthesis of the 7-deazapurine ribonucleosides using activated sugar halides, the outcome of the products of the fusion reaction, nucleobase anion glycosylation, and other procedures is disappointing. The glycosylation is directed into the pyrimidine moiety,[32] takes place at the more nucleophilic pyrrole carbons,[39,40] or results in poor yields. The present investigation shows that the TMSOTf-catalyzed 'one-pot' glycosylation reaction is an efficient method for the synthesis of 7-functionalized-7-deazapurines. Electron-withdrawing substituents (such as halogens) on the 7-deazapurine moiety facilitate the glycosylation reaction. 7-Deazapurines without 7-substituents resist glycosylation.

The glycosylation products **8c–e** and their β-L-enantiomers **9b–e** were obtained in yields of 53–72%. From the intermediates, the tubercidin analogues **1b–e**, the β-L-enantiomers **3b–e**, and 7-deazainosine analogues **2b–e** were obtained. The palladium-catalyzed cross-coupling chemistry afforded 7-alkynyl or 7-aminoalkynyl derivatives. They can be used for reporter group attachment in protocols of RNA-sequencing and detection within single or double-stranded oligoribonucleotides. Apart from these synthetic aspects, physical data were determined which shed light into the behavior of tubercidin and 7-deazainosine analogues.

## 4. Experimental part

### 4.1. General

All chemicals were purchased from ACROS, Fluka or Sigma–Aldrich (Sigma–Aldrich Chemie GmbH, Deisenhofen, Germany). Solvents were of laboratory grade. TLC: aluminum sheets, silica gel 60 $F_{254}$ (0.2 mm, VWR International, Darmstadt, Germany); flash column chromatography (FC): silica gel 60 (VWR International, Darmstadt, Germany) at 0.4 bar; solvent systems for TLC and FC: cyclohexane/ethyl acetate 10:1 (A), cyclohexane/ethyl acetate 3:1 (B), $CH_2Cl_2$/MeOH 20:1 (C), $CH_2Cl_2$/MeOH 9:1 (D), $CH_2Cl_2$/MeOH 6:1 (E); sample collection with a MultiRac fraction collector (LKB Instruments Sweden). Reverse-phase HPLC was carried out on a 250×10 mm RP-18 LiChrosorb column (Merck) with a Merck–Hitachi HPLC pump (model 655 A-12) connected with a variable wavelength monitor (model 655-A), a controller (model L-5000), and an integrator (model D-2000). UV spectra: U-3200 UV–vis spectrophotometer (Hitachi, Japan); CD spectra: Jasco J-600A spectropolarimeter (Jasco, Japan). NMR spectra: Avance-DPX-250 or AMX–500 spectrometer (Bruker, Rheinstetten, Germany); $\delta$ values in parts per million relative to $Me_4Si$ as internal standard ($^1H$ and $^{13}C$), *J* values in hertz. Melting points were determined by a Linström apparatus and are not corrected. Element analyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen, Germany.

**4.1.1. 4,5-Dichloro-7-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (8c).** *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.55 mL, 2.2 mmol) was added to a stirred suspension of 4,5-dichloro-7*H*-pyrrolo[2,3-*d*]-pyrimidine[61] (376 mg, 2.0 mmol) in dry acetonitrile (15 mL). After stirring at rt for 10 min, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1.13 g, 2.24 mmol) was added, followed by the addition of trimethylsilyl trifluoromethanesulfonate (0.42 mL, 2.17 mmol). The reaction mixture was stirred at rt for 15 min after which the flask was transferred to a preheated oil bath at 80 °C. After stirring for 1 h at 80 °C, the reaction mixture was cooled to rt and diluted with EtOAc (75 mL). The organic phase was sequentially washed with aq satd $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated to provide the crude nucleoside. Purification by flash column chromatography (FC) (column 10×5 cm, A) provided **8c** as a colorless foam (780 mg, 62%). TLC (silica gel, B): $R_f$ 0.46. UV (MeOH): $\lambda_{max}$ 228 (68,100), 274 (6100). $^1H$ NMR (DMSO-$d_6$) $\delta$: 8.63 (s, H–C(2)); 8.29 (s, H–C(6)); 8.00–7.84 (m, arom, H); 7.65 (m, arom, H); 7.54–7.40 (m, arom, H); 6.72 (d, *J*=4.90 Hz, H–C(1′)); 6.30 (t, *J*=5.74 Hz, *J*=5.29 Hz, H–C(2′)); 6.13 (t, *J*=5.55 Hz, *J*=5.76 Hz, H–C(3′)); 4.88–4.64 (m, H–C(4′), H–C(5′)). Anal. Calcd for $C_{32}H_{23}Cl_2N_3O_7$ (632.45): C 60.77, H 3.67, N 6.64; found: C 60.65, H 3.58, N 6.60.

**4.1.2. 4,5-Dichloro-7-[(2,3,5-tri-*O*-benzoyl)-β-L-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (9c).** As described for **8c** with *N,O*-bis(trimethylsilyl)acetamide (BSA,

0.67 mL, 2.70 mmol), 4,5-dichloropyrrolo[2,3-*d*]pyrimidine[61] (461 mg, 2.45 mmol), dry acetonitrile (12 mL), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (1.40 g, 2.78 mmol), and trimethylsilyl trifluoromethanesulfonate (0.50 mL, 2.59 mmol) yielding **9c** as colorless foam (1.12 g, 72%). TLC (silica gel, B): $R_f$ 0.46. UV (MeOH): $\lambda_{max}$ 228 (65,200), 273 (6400). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.63 (s, H–C(2)); 8.30 (s, H–C(6)); 8.00–7.84 (m, arom, H); 7.63 (m, arom, H); 7.54–7.40 (m, arom, H); 6.73 (d, $J$=4.49 Hz, H–C(1′)); 6.30 (t, $J$=5.13 Hz, $J$=5.00 Hz, H–C(2′)); 6.13 (t, $J$=5.24 Hz, $J$=5.58 Hz, H–C(3′)); 4.87–4.65 (m, H–C(4′), H–C(5′)). Anal. Calcd for $C_{32}H_{23}Cl_2N_3O_7$ (632.45): C 60.77, H 3.67, N 6.64; found: C 60.95, H 3.75, N 6.53.

**4.1.3. 4-Chloro-5-fluoro-7-[(2,3,5-tri-*O*-benzoyl)-β-L-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine (9b).** As described for **8c** with *N,O*-bis(trimethylsilyl)acetamide (BSA, 0.68 mL, 2.74 mmol), 4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine[60] (390 mg, 2.27 mmol), dry acetonitrile (12 mL), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (1.40 g, 2.78 mmol), and trimethylsilyl trifluoromethanesulfonate (0.53 mL, 2.74 mmol) yielding **9b** as colorless foam (950 mg, 68%). TLC (silica gel, B): $R_f$ 0.46. UV (MeOH): $\lambda_{max}$ 227 (62,000), 273 (6500). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.63 (s, H–C(2)); 8.12 (s, H–C(6)); 8.00–7.84 (m, arom, H); 7.65 (m, arom, H); 7.54–7.40 (m, arom, H); 6.73 (m, H–C(1′)); 6.29 (d, $J$=3.25 Hz, H–C(2′)); 6.12 (d, $J$=3.64 Hz, H–C(3′)); 4.87–4.62 (m, H–C(4′), H–C(5′)). Anal. Calcd for $C_{32}H_{23}ClFN_3O_7$ (615.99): C 62.39, H 3.76, N 6.82; found: C 62.51, H 3.86, N 6.72.

**4.1.4. 5-Bromo-4-chloro-7-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (8d).** As described for **8c** with *N,O*-bis(trimethylsilyl)acetamide (BSA, 0.55 mL, 2.22 mmol), 4-bromo-5-chloro-7*H*-pyrrolo-[2,3-*d*]pyrimidine[61] (465 mg, 2.00 mmol), dry acetonitrile (12 mL), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1.13 g, 2.24 mmol), and trimethylsilyl trifluoromethanesulfonate (0.40 mL, 2.07 mmol) yielding **8d** as colorless foam (723 mg, 53%). TLC (silica gel, B): $R_f$ 0.46. UV (MeOH): $\lambda_{max}$ 230 (59,800), 273 (6000). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.62 (s, H–C(2)); 8.32 (s, H–C(6)); 8.00–7.84 (m, arom, H); 7.65 (m, arom, H); 7.54–7.40 (m, arom, H); 6.72 (d, $J$=4.83 Hz, H–C(1′)); 6.30 (t, $J$=4.50 Hz, $J$=6.72 Hz, H–C(2′)); 6.13 (t, $J$=5.80 Hz, $J$=5.69 Hz, H–C(3′)); 4.88–4.66 (m, H–C(4′), H–C(5′)). Anal. Calcd for $C_{32}H_{23}BrClN_3O_7$ (676.90): C 56.78, H 3.42, N 6.21; found: C 56.70, H 3.30, N 6.24.

**4.1.5. 5-Bromo-4-chloro-7-[(2,3,5-tri-*O*-benzoyl)-β-L-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (9d).** As described for **8c** with *N,O*-bis(trimethylsilyl)acetamide (BSA, 0.55 mL, 2.2 mmol), 4-bromo-5-chloro-7*H*-pyrrolo[2,3-*d*]-pyrimidine[61] (465 mg, 2.00 mmol), dry acetonitrile (12 mL), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (1.13 g, 2.24 mmol), and trimethylsilyl trifluoromethanesulfonate (0.40 mL, 2.07 mmol) affording **9d** as colorless foam (866 mg, 64%). TLC (silica gel, B): $R_f$ 0.46. UV (MeOH): $\lambda_{max}$ 228 (61,600), 273 (5900). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.62 (s, H–C(2)); 8.31 (s, H–C(6)); 8.00–7.84 (m, arom, H); 7.63 (m, arom, H); 7.54–7.40 (m, arom, H); 6.72 (d, $J$=4.90 Hz, H–C(1′)); 6.30 (t, $J$=5.41 Hz, $J$=5.71 Hz, H–C(2′)); 6.13 (t, $J$=5.47 Hz, $J$=5.78 Hz, H–C(3′)); 4.88–4.66 (m, H–C(4′), H–C(5′)). Anal. Calcd for $C_{32}H_{23}BrClN_3O_7$ (676.90): C 56.78, H 3.42, N 6.21; found: C 56.98, H 3.50, N 5.99.

**4.1.6. 4-Chloro-5-iodo-7-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (8e).** As described for **8c** with *N,O*-bis(trimethylsilyl)acetamide (BSA, 0.11 mL, 0.44 mmol), 5-chloro-4-iodo-7*H*-pyrrolo[2,3-*d*]-pyrimidine[61] (112 mg, 0.40 mmol), dry acetonitrile (5 mL), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (222 mg, 0.44 mmol), and trimethylsilyl trifluoromethanesulfonate (0.081 mL, 0.42 mmol) affording **8e** as colorless foam (171 mg, 59%). TLC (silica gel, B): $R_f$ 0.46. UV (MeOH): $\lambda_{max}$ 230 (61,000), 272 (5800). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.60 (s, H–C(2)); 8.30 (s, H–C(6)); 8.00–7.83 (m, arom, H); 7.65 (m, arom, H); 7.52–7.43 (m, arom, H); 6.71 (d, $J$=4.87 Hz, H–C(1′)); 6.29 (t, $J$=5.81 Hz, $J$=5.19 Hz, H–C(2′)); 6.14 (t, $J$=5.54 Hz, $J$=5.85 Hz, H–C(3′)); 4.87–4.64 (m, H–C(4′), H–C(5′)). Anal. Calcd for $C_{32}H_{23}ClIN_3O_7$ (723.90): C 53.09, H 3.20, N 5.80; found: C 53.13, H 3.16, N 5.85.

**4.1.7. 4-Chloro-5-iodo-7-[(2,3,5-tri-*O*-benzoyl)-β-L-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine (9e).** As described for **8c** with *N,O*-bis(trimethylsilyl)acetamide (BSA, 0.55 mL, 2.22 mmol), 5-chloro-4-iodo-7*H*-pyrrolo[2,3-*d*]-pyrimidine[61] (559 mg, 2.00 mmol), dry acetonitrile (15 mL), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (1.13 g, 2.24 mmol), and trimethylsilyl trifluoromethanesulfonate (0.45 mL, 2.33 mmol) affording **9e** as colorless foam (830 mg, 57%). TLC (silica gel, B): $R_f$ 0.46. UV (MeOH): $\lambda_{max}$ 230 (60,000), 274 (5700). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.60 (s, H–C(2)); 8.30 (s, H–C(6)); 8.00–7.84 (m, arom, H); 7.63 (m, arom, H); 7.55–7.40 (m, arom, H); 6.71 (d, $J$=4.61 Hz, H–C(1′)); 6.29 (t, $J$=5.53 Hz, $J$=5.09 Hz, H–C(2′)); 6.14 (t, $J$=5.39 Hz, $J$=5.45 Hz, H–C(3′)); 4.86–4.64 (m, H–C(4′), H–C(5′)). Anal. Calcd for $C_{32}H_{23}ClIN_3O_7$ (723.90): C 53.09, H 3.20, N 5.80; found: C 52.88, H 3.28, N 5.95.

**4.1.8. 5-Fluoro-4-methoxy-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (10b).** Compound **8b**[60] (643 mg, 1.04 mmol) was dissolved in 0.5 M $NaOCH_3$ (20 mL). The solution was stirred overnight and then evaporated, the residue was applied to FC (column 10×5 cm, C), yielding **10b** as colorless solid (213 mg, 68%). TLC (silica gel, D): $R_f$ 0.39. UV (MeOH): $\lambda_{max}$ 220 (17,600), 278 (5400). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.47 (s, H–C(2)); 7.67 (s, H–C(6)); 6.21 (d, $J$=5.50 Hz, H–C(1″)); 5.52 (d, $J$=1.14 Hz, OH–C(2′)); 5.40 (d, $J$=3.90 Hz, OH–C(3′)); 5.20 (m, OH–C(5′)); 4.33 (d, $J$=3.24 Hz, H–C(2′)); 4.08 (m, $OCH_3$–C(4), H–C(3′)); 3.91 (d, $J$=2.34 Hz, H–C(4′)); 3.59 (m, H–C(5′)). Anal. Calcd for $C_{12}H_{14}FN_3O_5$ (299.26): C 48.16, H 4.72, N 14.04; found: C 48.27, H 4.61, N 13.98.

**4.1.9. 5-Chloro-4-methoxy-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (10c).** Compound **8c** (700 mg, 1.11 mmol) was dissolved in 0.5 M $NaOCH_3$ (20 mL). The solution was stirred overnight and evaporated. The residue was applied to FC (column 20×5 cm, C), yielding **10c** as colorless solid (325 mg, 93%). TLC (silica gel, D): $R_f$ 0.42. UV (MeOH): $\lambda_{max}$ 222 (22,700), 279 (6700).

$^1$H NMR (DMSO-$d_6$) $\delta$: 8.47 (s, H–C(2)); 7.86 (s, H–C(6)); 6.16 (d, $J$=5.64 Hz, H–C(1′)); 5.40 (d, $J$=5.90 Hz, OH–C(2′)); 5.19 (d, $J$=4.40 Hz, OH–C(3′)); 5.10 (m, OH–C(5′)); 4.35 (m, H–C(2′)); 4.06 (m, $OCH_3$–C(4), H–C(3′)); 3.91 (m, H–C(4′)); 3.61 (m, H–C(5′)). Anal. Calcd for $C_{12}H_{14}ClN_3O_5$ (315.71): C 45.65, H 4.47, N 13.31; found: C 45.78, H 4.56, N 13.19.

**4.1.10. 5-Bromo-4-methoxy-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (10d).** As described for **10b** with **8d** (672 mg, 0.99 mmol) and 0.5 M $NaOCH_3$ (20 mL); **10d** was obtained as colorless solid (307 mg, 86%). TLC (silica gel, D): $R_f$ 0.42. UV (MeOH): $\lambda_{max}$ 223 (19,900), 280 (5900). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.46 (s, H–C(2)); 7.89 (s, H–C(6)); 6.15 (d, $J$=5.93 Hz, H–C(1′)); 5.40 (d, $J$=6.26 Hz, OH–C(2′)); 5.19 (d, $J$=4.64 Hz, OH–C(3′)); 5.10 (t, $J$=5.25 Hz, $J$=4.92 Hz, OH–C(5′)); 4.35 (m, H–C(2′)); 4.06 (m, $OCH_3$–C(4), H–C(3′)); 3.91 (m, H–C(4′)); 3.61 (m, H–C(5′)). Anal. Calcd for $C_{12}H_{14}BrN_3O_5$ (360.16): C 40.02, H 3.92, N 11.67; found: C 39.89, H 3.84, N 11.75.

**4.1.11. 5-Iodo-4-methoxy-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (10e).** As described for **10b** with **8e** (713 mg, 0.98 mmol) and 0.5 M $NaOCH_3$ (20 mL) affording **10e** as colorless solid (359 mg, 90%). Crystallization from MeOH gave colorless needles of **10e**. Mp 211–212 °C (dec) (lit. 212–213 °C).[46] TLC (silica gel, D): $R_f$ 0.45. UV (MeOH): 226 (21,200), 282.5 (5540). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.44 (s, H–C(2)); 7.88 (s, H–C(6)); 6.13 (d, $J$=6.16 Hz, H–C(1′)); 5.38 (d, $J$=6.29 Hz, OH–C(2′)); 5.17 (d, $J$=4.66 Hz, OH–C(3′)); 5.10 (t, $J$=5.37 Hz, $J$=5.25 Hz, OH–C(5′)); 4.37 (m, H–C(2′)); 4.07 (m, $OCH_3$–C(4), H–C(3′)); 3.90 (d, $J$=3.12 Hz, H–C(4′)); 3.63 (m, H–C(5′)).

**4.1.12. 4-Amino-5-chloro-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (1c).** Compound **8c** (900 mg, 1.42 mmol) was dissolved in methanolic ammonia (saturated with $NH_3$ at 0 °C, 100 mL) and placed in an autoclave. The reaction mixture was heated at 120–130 °C overnight. The mixture was then cooled and the solvent was evaporated to provide the crude nucleoside. Purification by FC (silica gel, D) provided **1c** as colorless solid. Crystallization from MeOH gave colorless needles of **1c** (299 mg, 70%). Mp 226 °C (lit. 226–228 °C).[36] TLC (silica gel, E) $R_f$ 0.34. UV (MeOH): 281 (9800). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.09 (s, H–C(2)); 7.67 (s, H–C(6)); 6.69 (s, $NH_2$–C(4)); 6.02 (d, $J$=6.07 Hz, H–C(1′)); 5.33 (d, $J$=6.24 Hz, OH–C(2′)); 5.17 (m, OH–C(3′)); 5.13 (d, $J$=4.48 Hz, OH–C(5′)); 4.35 (m, H–C(2′)); 4.05 (m, H–C(3′)); 3.88 (m, H–C(4′)); 3.57 (m, H–C(5′)).

**4.1.13. 4-Amino-5-bromo-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (1d).** As described for **1c** with **8d** (756 mg, 1.12 mmol), methanolic ammonia (saturated with $NH_3$ at 0 °C, 100 mL) affording **1d** as colorless solid. Crystallization from MeOH gave colorless needles of **1d** (237 mg, 61%). Mp 232 °C (lit. 231–232 °C).[36] TLC (silica gel, E) $R_f$ 0.38. UV (MeOH): $\lambda_{max}$ 281 (9200). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.10 (s, H–C(2)); 7.65 (s, H–C(6)); 6.79 (s, $NH_2$–C(4)); 6.05 (d, $J$=6.01 Hz, H–C(1′)); 5.32 (d, $J$=6.22 Hz, OH–C(2′)); 5.15 (d, $J$=5.42 Hz, OH-(3′)); 5.11 (d, $J$=4.72 Hz, OH-(5′)); 4.35 (m, H–C(2′)); 4.06 (m, H–C(3′)); 3.88 (m, H–C(4′)); 3.58 (m, H–C(5′)).

**4.1.14. 4-Amino-5-iodo-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (1e).** As described for **1c** with **8e** (830 mg, 1.15 mmol), methanolic ammonia (70 mL) affording **1e** as brown solid. Crystallization from MeOH gave brownish needles of **1e** (320 mg, 71%). Mp 215 °C (lit. 216–217 °C).[36] TLC (silica gel, E) $R_f$ 0.41. UV (MeOH): $\lambda_{max}$ 284 (8000). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.10 (s, H–C(2)); 7.67 (s, H–C(6)); 6.68 (s, $NH_2$–C(4)); 6.02 (d, $J$=6.19 Hz, H–C(1′)); 5.33 (d, $J$=6.20 Hz, OH–C(2′)); 5.19 (d, $J$=5.30 Hz, OH–C(3′)); 5.14 (d, $J$=4.60 Hz, OH–C(5′)); 4.35 (m, H–C(2′)); 4.06 (m, H–C(3′)); 3.88 (m, H–C(4′)); 3.59 (m, H–C(5′)).

**4.1.15. 5-Fluoro-3,7-dihydro-7-(β-D-ribofuranosyl)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2b).** To a suspension of **10b** (145 mg, 0.48 mmol) and NaI (374 mg, 2.49 mmol) in MeCN (15 mL), chlorotrimethylsilane (0.32 mL, 2.49 mmol) was added. The suspension was stirred at rt for 3 h, evaporated to dryness, and the residue was applied to FC (column 20×5 cm, E), yielding **2b** as colorless solid (130 mg, 94%). TLC (silica gel, E) $R_f$ 0.27. UV (0.1 M $NaH_2PO_4$ buffer): $\lambda_{max}$ 217 (17,000), 265 (6600). $^1$H NMR (DMSO-$d_6$) $\delta$: 12.12 (s, H–N(3)); 7.92 (s, H–C(2)); 7.34 (s, H–C(6)); 6.05 (d, $J$=5.65 Hz, H–C(1′)); 5.37 (d, $J$=5.92 Hz, OH–C(2′)); 5.15 (d, $J$=4.3 Hz, OH–C(3′)); 5.04 (t, $J$=5.32 Hz, $J$=4.92 Hz, OH–C(5′)); 4.23 (m, H–C(2′)); 4.05 (m, H–C(3′)); 3.87 (m, H–C(4′)); 3.56 (m, H–C(5′)). Anal. Calcd for $C_{11}H_{12}FN_3O_5$ (285.23): C 46.32, H 4.24, N 14.73; found: C 46.06, H 4.13, N 14.56.

**4.1.16. 5-Chloro-3,7-dihydro-7-(β-D-ribofuranosyl)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2c).** As described for **2b** with **10c** (161 mg, 0.51 mmol), NaI (229 mg, 1.53 mmol), chlorotrimethylsilane (0.20 mL, 1.53 mmol), and MeCN (10 mL) affording **2c** as colorless solid (137 mg, 89%). TLC (silica gel, E) $R_f$ 0.33. UV (0.1 M $NaH_2PO_4$): $\lambda_{max}$ 220 (16,800), 266 (7600). $^1$H NMR (DMSO-$d_6$) $\delta$: 12.14 (s, NH–C(3)); 7.95 (s, H–C(2)); 7.54 (s, H–C(6)); 6.02 (d, $J$=5.32 Hz, H–C(1′)); 5.38 (m, OH–C(2′)); 5.16 (m, OH–C(3′)); 5.06 (m, OH–C(5′)); 4.27 (m, H–C(2′)); 4.06 (m, H–C(3′)); 3.88 (m, H–C(4′)); 3.57 (m, H–C(5′)). Anal. Calcd for $C_{11}H_{12}ClN_3O_5$ (301.68): C 43.79, H 4.01, N 13.93; found: C 43.90, H 4.05, N 13.99.

**4.1.17. 5-Bromo-3,7-dihydro-7-(β-D-ribofuranosyl)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2d).** As described for **2b** with **10d** (130 mg, 0.36 mmol), NaI (162 mg, 1.08 mmol), chlorotrimethylsilane (0.15 mL, 1.17 mmol), and MeCN (10 mL) affording **2d** as colorless solid (101 mg, 81%). Recrystallization from MeOH gave **2d** as colorless needles. Mp 225–226 °C (dec) (lit. 254.5–255 °C, from water).[36] TLC (silica gel, E) $R_f$ 0.36. UV (0.1 M $NaH_2PO_4$): $\lambda_{max}$ 222 (16,200), 267 (7700). $^1$H NMR (DMSO-$d_6$) $\delta$: 12.13 (s, NH–C(3)); 7.95 (s, H–C(2)); 7.57 (s, H–C(6)); 6.01 (d, $J$=5.95 Hz, H–C(1′)); 5.38 (d, $J$=4.95 Hz, OH–C(2′)); 5.15 (m, OH–C(3′)); 5.06 (m, OH–C(5′)); 4.28 (m, H–C(2′)); 4.05 (m, H–C(3′)); 3.87 (m, H–C(4′)); 3.57 (m, H–C(5′)).

**4.1.18. 3,7-Dihydro-5-iodo-7-(β-D-ribofuranosyl)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2e).** Compound **10e**

(260 mg, 0.64 mmol) was dissolved in 2 N NaOH (20 mL). The solution was refluxed for 1.5 h, and then neutralized with diluted HCl. Purification by FC (silica gel, D) provided **2e** as colorless solid (230 mg, 91%). Recrystallization from MeOH gave **2e** as colorless needles. Mp 224–225 °C (dec). TLC (silica gel, E) $R_f$ 0.36. UV (0.1 M $NaH_2PO_4$): $\lambda_{max}$ 226 (14,300), 274 (7200). $^1$H NMR (DMSO-$d_6$) $\delta$: 12.13 (s, NH–C(3)); 7.94 (s, H–C(2)); 7.57 (s, H–C(6)); 5.98 (d, $J$=6.07 Hz, H–C(1′)); 5.37 (m, OH–C(2′)); 5.09 (m, OH–C(3′)); 4.28 (m, H–C(2′)); 4.04 (m, H–C(3′)); 3.87 (m, H–C(4′)); 3.55 (m, H–C(5′)). Anal. Calcd for $C_{11}H_{12}IN_3O_5$ (393.13): C 33.61, H 3.08, N 10.69; found: C 33.52, H 3.01, N 10.62.

**4.1.19. 4-Amino-5-fluoro-7-(β-L-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3b).** Compound **9b** (480 mg, 0.78 mmol) was dissolved in methanolic ammonia (saturated with $NH_3$ at 0 °C, 70 mL), placed in autoclave, and stirred at 120–130 °C overnight. The reaction mixture was then cooled and the solvent evaporated to provide the crude nucleoside. FC (silica gel, D) provided **3b** as colorless solid (200 mg, 90%). Recrystallization from MeOH gave **3b** as colorless needles. Mp 220–221 °C (dec). TLC (silica gel, E) $R_f$ 0.25. UV (MeOH): $\lambda_{max}$ 279 (10,200). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.07 (s, H–C(2)); 7.36 (s, H–C(6)); 7.03 (s, $NH_2$–C(4)); 6.07 (d, $J$=5.9 Hz, H–C(1′)); 5.32 (d, $J$=6.32 Hz, OH–C(2′)); 5.14 (m, OH–C(3′), OH–C(5′)); 4.30 (m, H–C(2′)); 4.06 (m, H–C(3′)); 3.86 (m, H–C(4′)); 3.59 (m, H–C(5′)). Anal. Calcd for $C_{11}H_{13}FN_4O_4$ (284.24): C 46.48, H 4.61, N 19.71; found: C 46.60, H 4.53, N 19.63.

**4.1.20. 4-Amino-5-chloro-7-(β-L-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3c).** As described for **3b** with **9c** (566 mg, 0.89 mmol), methanolic ammonia (saturated with $NH_3$ at 0 °C, 100 mL) yielding **3c** as colorless solid (201 mg, 75%). Recrystallization from MeOH gave **3c** as colorless needles. Mp 228–230 °C (dec). TLC (silica gel, E) $R_f$ 0.34. UV (MeOH): $\lambda_{max}$ 280 (9500). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.09 (s, H–C(2)); 7.59 (s, H–C(6)); 6.90 (s, $NH_2$–C(4)); 6.04 (d, $J$=5.9 Hz, H–C(1′)); 5.34 (d, $J$=6.17 Hz, OH–C(2′)); 5.17 (d, $J$=4.72 Hz, OH–C(3′)); 5.13 (d, $J$=3.99 Hz, OH–C(5′)); 4.32 (m, H–C(2′)); 4.06 (m, H–C(3′)); 3.87 (m, H–C(4′)); 3.56 (m, H–C(5′)). Anal. Calcd for $C_{11}H_{13}ClN_4O_4$ (300.70): C 43.94, H 4.36, N 18.63; found: C 43.73, H 4.40, N 18.69.

**4.1.21. 4-Amino-5-bromo-7-(β-L-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3d).** As described for **3b** with **9d** (815 mg, 1.20 mmol), methanolic ammonia (saturated with $NH_3$ at 0 °C, 100 mL) affording **3d** as colorless solid (304 mg, 73%). Recrystallization from MeOH gave colorless needles. Mp 224–225 °C (dec). TLC (silica gel, E) $R_f$ 0.38. UV (MeOH): $\lambda_{max}$ 281 (9200). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.10 (s, H–C(2)); 7.65 (s, H–C(6)); 6.80 (s, $NH_2$–C(4)); 6.04 (d, $J$=6.0 Hz, H–C(1′)); 5.32 (d, $J$=6.16 Hz, OH–C(2′)); 5.14 (d, $J$=5.78 Hz, OH–C(3′)); 5.11 (d, $J$=4.67 Hz, OH–C(5′)); 4.35 (m, H–C(2′)); 4.06 (m, H–C(3′)); 3.88 (m, H–C(4′)); 3.60 (m, H–C(5′)). Anal. Calcd for $C_{11}H_{13}BrN_4O_4$ (345.15): C 38.28, H 3.80, N 16.23; found: C 37.99, H 3.83, N 16.24.

**4.1.22. 4-Amino-5-iodo-7-(β-L-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3e).** As described for **3b** with **9e** (800 mg, 1.11 mmol), methanolic ammonia (saturated with $NH_3$ at 0 °C, 100 mL) yielding **3e** as brownish solid (333 mg, 77%). Recrystallization from MeOH gave brownish needles. Mp 221–223 °C (dec). TLC (silica gel, E) $R_f$ 0.41. Mp UV (MeOH): $\lambda_{max}$ 284 (7900). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.10 (s, H–C(2)); 7.67 (s, H–C(6)); 6.69 (s, $NH_2$–C(4)); 6.02 (d, $J$=5.8 Hz, H–C(1′)); 5.32 (d, $J$=6.13 Hz, OH–C(2′)); 5.17 (m, OH–C(3′)); 5.14 (m, OH–C(5′)); 4.36 (m, H–C(2′)); 4.06 (m, H–C(3′)); 3.88 (m, H–C(4′)); 3.59 (m, H–C(5′)). Anal. Calcd for $C_{11}H_{13}IN_4O_4$ (392.15): C 33.69, H 3.34, N 14.29; found: C 34.01, H 3.23, N 14.49.

**4.1.23. 4-Amino-5-propynyl-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (1f).** A suspension of 4-amino-5-iodo-7-β-D-ribofuranosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1e**, 300 mg, 0.77 mmol),[36] Pd(O)$(PPh_3)_4$ (251 mg, 0.22 mmol), and CuI (80.6 mg, 0.42 mmol) were thoroughly purged with $N_2$. DMF (2 mL) was added, the solution was purged with $N_2$ for another 10 min. $Et_3N$ (0.46 mL, 3.3 mmol) was added, followed by propyne gas cooled in ice bath for 20 min. The solution was sealed and stirred at rt for 18 h. After evaporation, the residue was purified by FC (silica gel, C) to give **1f** as yellowish solid (160 mg, 69%). TLC (silica gel, E) $R_f$ 0.38. UV (MeOH): $\lambda_{max}$ 237 (12,500), 280 (8800). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.09 (s, H–C(2)); 7.65 (s, H–C(6)); 6.67 (s, $NH_2$–C(4)); 6.00 (d, $J$=6.00 Hz, H–C(1′)); 5.31 (d, $J$=5.95 Hz, OH–C(2′)); 5.21 (m, OH–C(3′)); 5.11 (d, $J$=3.14 Hz, OH–C(5′)); 4.36 (m, H–C(2′)); 4.07 (m, H-(3′)); 3.89 (m, H-(4′)); 3.63 (m, H–C(5′)); 2.08 (s, $CH_3$–C(5)). Anal. Calcd for $C_{14}H_{16}N_4O_4$ (304.30): C 55.26, H 5.30, N 18.41; found: C 55.12, H 5.31, N 18.38.

**4.1.24. 4-Amino-5-(phthalimido-1-propynyl)-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (1g).** A suspension of 4-amino-5-iodo-7-β-D-ribofuranosyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine (**1e**, 588 mg, 1.50 mmol),[36] Pd(O)$(PPh_3)_4$ (472 mg, 0.41 mmol), CuI (158 mg, 0.83 mmol), $Et_3N$ (0.90 mL, 6.46 mmol), and 4-phthalimido-1-propyne (1.23 g, 6.5 mmol) in anhydrous DMF (5 mL) was stirred under $N_2$ at rt for 3 h. After evaporation, the residue was purified by FC (silica gel, C) to give **1g** as yellowish solid (546 mg, 81%). Mp 217–220 °C (MeOH) (dec). TLC (silica gel, D) $R_f$ 0.42. UV (MeOH): $\lambda_{max}$ 217 (40,800), 280 (10,700). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.10 (s, H–C(2)); 7.90 (m, arom, H); 7.76 (s, H–C(6)); 6.83 (s, $NH_2$–C(4)); 6.00 (d, $J$=5.99 Hz, H–C(1′)); 5.31 (d, $J$=6.21 Hz, OH–C(2′)); 5.17 (t, $J$=5.34 Hz, $J$=5.01 Hz, OH–C(3′)); 5.09 (d, $J$=4.42 Hz, OH–C(5′)); 4.69 (s, $CH_2$–C(5)); 4.33 (m, H–C(2′)); 4.05 (m, H-(3′)); 3.87 (m, H-(4′)); 3.52 (m, H–C(5′)). Anal. Calcd for $C_{22}H_{19}N_5O_6$ (449.42): C 58.80, H 4.26, N 15.58; found: C 58.69, H 4.66, N 15.28.

**4.1.25. 3,7-Dihydro-5-propynyl-7-(β-D-ribofuranosyl)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2f).** 3,7-Dihydro-5-iodo-7-β-D-ribofuranosyl-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**2e**, 195 mg, 0.49 mmol), Pd(O)$(PPh_3)_4$ (162 mg, 0.14 mmol), CuI (52.1 mg, 0.27 mmol) were thoroughly purged with $N_2$. DMF (2 mL) was added, the solution was purged with $N_2$ for 10 min. $Et_3N$ (0.3 mL, 2.13 mmol) was added, followed by condensed propyne gas cooled in ice for 20 min. The solution was sealed and stirred at rt for 18 h. After evaporation, the residue was purified by FC

(silica gel, D), yielding **2f** as colorless solid (101 mg, 68%). TLC (silica gel, E) $R_f$ 0.38. UV (MeOH): $\lambda_{max}$ 227 (17,700), 271 (9800). $^1$H NMR (DMSO-$d_6$) $\delta$: 12.07 (s, NH–C(3)); 7.91 (s, H–C(2)); 7.58 (s, H–C(6)); 5.99 (d, $J$=5.42 Hz, H–C(1′)); 5.36 (d, $J$=5.82 Hz, OH–C(2′)); 5.15 (d, $J$=3.85 Hz, OH–C(3′)); 5.06 (m, OH–C(5′)); 4.27 (m, H–C(2′)); 4.07 (m, H–C(3′)); 3.87 (m, H–C(4′)); 3.58 (m, H–C(5′)); 2.01 (s, $CH_3$–C(5)). Anal. Calcd for $C_{14}H_{15}N_3O_5$ (305.29): C 55.08, H 4.95, N 13.76; found: C 54.81, H 5.05, N 13.70.

**4.1.26. 3,7-Dihydro-7-(β-D-ribofuranosyl)-5-[3-(trifluoroacetamido)propynyl]-4*H*-pyrrolo [2,3-*d*]pyrimidin-4-one (2g).** 3,7-Dihydro-5-iodo-7-β-D-ribofuranosyl-4*H*-pyrrolo[2,3-*d*] pyrimidin-4-one (**2e**, 200 mg, 0.51 mmol), Pd(O)($PPh_3$)$_4$ (68 mg, 0.058 mmol), CuI (26.4 mg, 0.14 mmol) were thoroughly purged with $N_2$. DMF (2 mL) was added, the solution was purged with $N_2$ for 10 min. $Et_3N$ (0.15 mL, 1.06 mmol) was added, followed by 2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide (0.90 g, 5.92 mmol).[81] The solution was sealed and stirred at rt for 20 h. After evaporation, the residue was purified by FC (silica gel, C) to give **2g** as yellow solid (146 mg, 69%). TLC (silica gel, E) $R_f$ 0.38. UV (MeOH): $\lambda_{max}$ 227 (18,100), 270 (12,000). $^1$H NMR (DMSO-$d_6$) $\delta$: 12.31 (s, NH–C(3)); 10.12 (s, NH–C(5)); 7.97 (s, H–C(2)); 7.73 (s, H–C(6)); 6.03 (m, H–C(1′)); 5.39 (d, $J$=3.35 Hz, OH–C(2′)); 5.18 (m, OH–C(3′)); 5.09 (m, OH–C(5′)); 4.29 (m, $CH_2$–C(5), H–C(2′)); 4.08 (m, H–C(3′)); 3.90 (m, H–C(4′)); 3.79 (m, H–C(5′)). Anal. Calcd for $C_{16}H_{15}F_3N_4O_6$ (416.31): C 46.16, H 3.63, N 13.46; found: C 45.86, H 3.75, N 13.30.

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