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Synthesis and Reactions of 2-Deoxy-β-*D*-ribofuranosyl Derivatives of 3-Aryl-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-imines

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Summary. 3-Aryl-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]-pyrimidin-4-imines (**4**) as well as 4-arylamino-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-2-methyl-5-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidines (**7**) have been synthesized by glycosylation of the sodium salt of the corresponding nucleobases with 2-deoxy-3,5-*di*-O-*p*-toluyl-β-*D*-*erythro*-pentofuranosyl chloride (**2**) followed by subsequent deprotection with sodium methoxide in methanol. The deprotected nucleoside **4** undergoes a *Dimroth* rearrangement on reflux for 24 h in water to furnish the 4-arylamino nucleoside **7**.

Keywords. *Dimroth* rearrangement; Herpes simplex; HIV; Nucleoside synthesis; 4*H*-Pyrrolo[2,3-*d*]pyrimidin-4-imine nucleosides.

Synthese und Reaktionen von 2-Deoxy-β-*D*-ribofuranosylderivaten von 3-Aryl-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-iminen

Zusammenfassung. 3-Aryl-7-(2-deoxy-β-*D*-*erythro*-pentafuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]-pyrimidin-4-imine (**4**) und 4-Arylamino-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-2-methyl-5-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**7**) wurden durch Glycosylierung der Natriumsalze der entsprechenden Nucleosidbasen mit 2-Deoxy-3,5-*di*-O-*p*-toluyl-β-*D*-*erythro*-pentofuranosylchlorid (**2**) und anschließende Entfernung der Schutzgruppe mit Natriummethoxid in Methanol hergestellt. Das entschützte Nucleosid **4** ergibt bei 24-stündigem Erhitzen in Wasser unter Rückfluß über eine *Dimroth*-Umlagerung das 4-Aminonucleosid **7**.

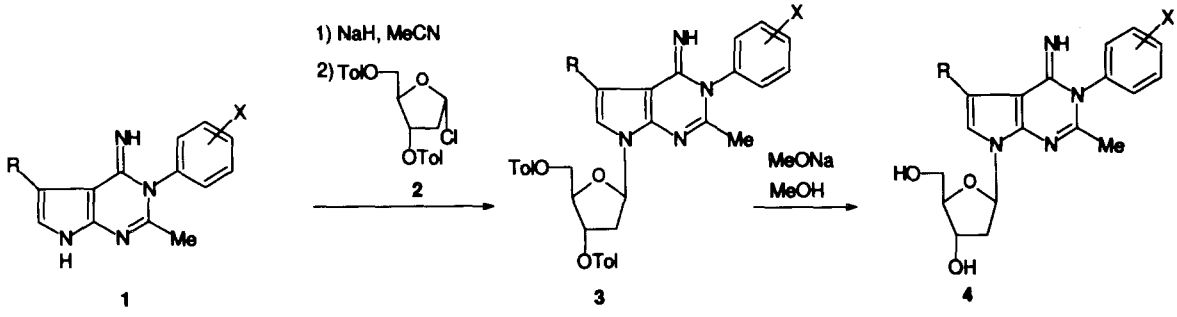
Introduction

The antibiotic pyrrolopyrimidine nucleosides having a wide spectrum of biological activities against viruses, bacterial and tumor cells have been isolated many years ago from bacteria and fungi [1]. A large number of the tubercidin, toyocamycin, and sangivamycin derivatives and analogs have been either isolated from the culture filtrates of streptomyces [2] or synthesized [3–7] in order to study structure-activity relationships in efforts to find compounds having high biological activity. Pyrrolo[2,3-*d*]pyrimidines, often described as 7-deazapurines because of their structural analogy

to purines, have been reported as potential antagonists [8,9]. Pyrrolo[2,3-*d*]pyrimidine antifolates were more growth-inhibitory by about one order of magnitude than methotrexate against carcinoma cells [10]. In the present investigation, we extend this series to the nucleosides of 3-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]-pyrinidin-4-imines (**1**). The corresponding nucleobases have previously been synthesized in our laboratory [11–13].

Results and Discussion

Using the reported stereospecific glycosylation procedure of *Kazimierczuk et al.* [14], we treated the sodium salt of pyrrolo[2,3-*d*]pyrimidines **1**, generated *in situ* by sodium hydride in dry acetonitrile, with 2-deoxy-3,5-*di*-O-*p*-toluyl-α-*D*-*erythro*-pentofuranosyl chloride [15] under nitrogen; thus, we obtained 3-aryl-7-(2-deoxy-3,5-*di*-O-*p*-toluoyl-β-*D*-*erythro*-pentofuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-imines. After chromatographic purification on silica gel, the protected nucleosides **3** obtained in 68–85% yield were treated with sodium methoxide in methanol to afford 3-aryl-7-(2-deoxy-β-*D*-*erythro*-pentofuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-imines. It is worthy to report here that the sodium salt glycosylation method seems to be stereoselective, since the β nucleoside **3**, according to TLC analysis, is the only observed anomer. The structures of the iminopyrrolopyrimidine nucleosides **3** and **4** were assigned on the basis of NMR and mass spectrometry.



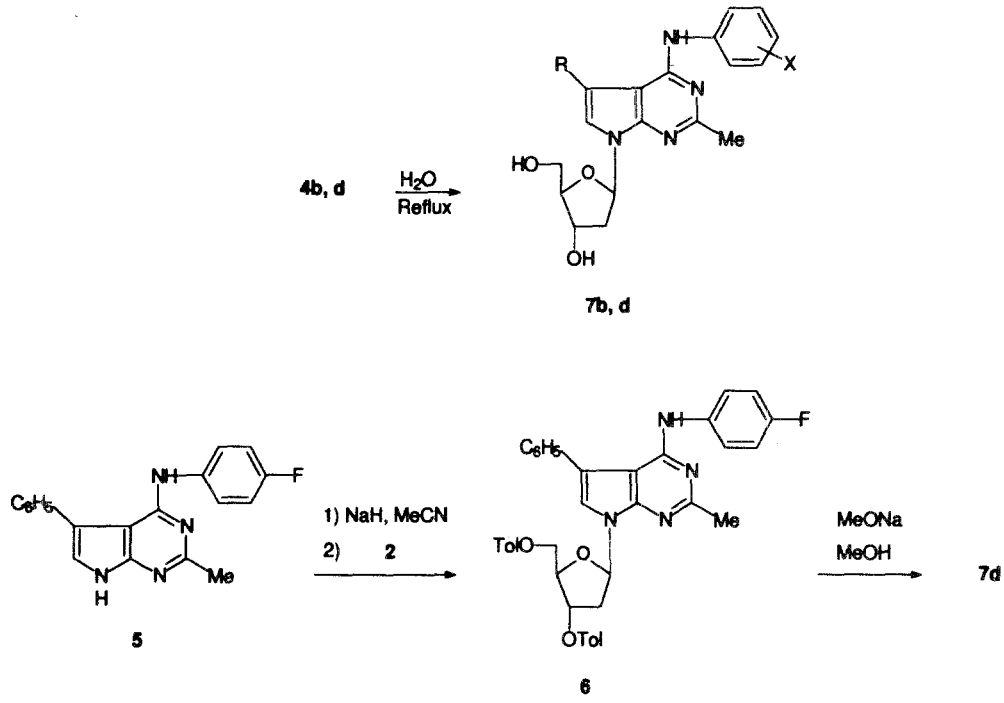
1, 3, 4, 7	a	b	c	d	e
R	Me	Me	Me	C_6H_5	Me
X	4-Cl	2-F	3-F	4-F	2,4-Cl_2

Tol: 4-MeC_6H_4CO

Scheme 1

The structure of **4** was also confirmed by chemical reactions. When the iminopyrrolo-pyrimidine nucleosides **4b** and **4d** were refluxed in water, a *Dimroth* rearrangement took place, and the corresponding 4-arylamino nucleosides **7b** and **7d** were formed, respectively, in accordance with the procedure of *Taylor* and *Hendess* [16] who have shown that 3-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-imines can undergo a *Dimroth* rearrangement reaction in boiling water to give the corresponding 4-arylamino compounds.

The question of amino *versus* imino isomers prompted us to synthesize the 4-arylamino nucleoside **6** according to the sodium salt glycosylation procedure. The



Scheme 2

sodium salt of the 4-(arylamino)-pyrrolo[2,3-*d*]pyrimidine **5**, generated *in situ* by sodium hydride in dry acetonitrile, reacted with the pentofuranosyl chloride **2** to afford-after chromatographic purification – the protected nucleoside **6** which, upon treatment with sodium methoxide in methanol, gave the 4-(arylamino)-pyrrolo[2,3-*d*]- pyrimidine nucleoside **7d**. NMR and mass spectra of this compound were in all respects the same as those obtained for the compound prepared *via Dimroth* rearrangement reaction by refluxing the nucleoside **4d** in water.

The nucleosides **4a**, **b**, **e** and **7b** did not show any significant activity against HIV-1 in MT-4 cells at 100 μM. Compound **7d** showed toxicity against the MT-4 cells at 100 μM, but no activity was observed against HIV-1 at lower concentrations. Expression of HIV in culture medium was quantified by the HIV antigen detection method ELISA. The same compounds were also devoid of any activity at 100 μM against herpes simplex virus, type 1 (HSV-1), strain *McIntyre*, when tested in African green monkey kidney cell line *Vero*. Only compound **7d** showed toxicity against *Vero* cells at 100 μM, but without showing any activity against HSV-1 at lower concentrations.

Experimental

Thin layer chromatography was performed on Merck precoated 60 F_{254} plates. Column chromatographic separations were done using silica gel 60 (230–400 mesh, E. Merck). NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 Hz for ^1H and 62.9 MHz for ^{13}C. FAB mass spectra were recorded on a Varian MAT 311A instrument. Anhydrous MeCN was distilled from P_2O_5 followed by distillation from CaH_2. All other solvents for chromatographic separation were used after distillation and normal drying.

3-Arylpyrrolo[2,3-d]pyrimidin-4-imine Nucleosides (**3**) and *4-(Arylamino)-pyrrolo[2,3-d]-pyrimidine Nucleoside* (**6**), *general procedure*

To a solution of 3-arylpyrrolo[2,3-*d*]pyrimidin-4-imines [9] (**1**, 3.5 mmol) or 4-(arylamino)-pyrrolo-[2,3-*d*]pyrimidine (**5**, 3.5 mmol) in dry MeCN (25 ml), sodium hydride (55–65% oil dispersed, 159 mg, 6.65 mmol) was added under nitrogen. The mixture was stirred for 2 h before 2-deoxy-3,5-*di*-O-*p*-tolyl-α-*D-erythro*-pentofuranosyl chloride [15] (**2**, 1.40 g, 3.6 mmol) was added in one portion. The mixture was stirred at room temperature for 3 h. A few drops of MeOH were then added, followed by evaporation of the mixture till dryness. TLC analysis of the residue indicated only one nucleoside anomer. The residue was purified on a silica gel column using MeOH:$CHCl_3$ (2:98–4:96, v/v) as the eluent.

3-(4-Chlorophenyl)-7-(2-deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranosyl)-3,7-dihydro-2,5-dimethyl-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**3a**)

Yield: 1.87 g (85%); ^{1}H NMR ($CDCl_3$): $\delta = 2.06$ (s, 3H, 2-CH_3), 2.24 (s, 3H, 5-CH_3), 2.41 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.65 (m, 1H, 2′-H), 2.84 (m, 1H, 2′-H), 4.54 (m, 2H, 4′-H, 5′-H), 4.71 (dd, $J = 4.1$ Hz, 11.6 Hz, 1H, 5′-H), 5.74 (m, 1H, 3′-H), 6.60 (s, 1H, 6-H), 6.60 (t, $J = 5.5$ Hz, 1H, 1′-H), 7.17–7.99 (m, 12H, H_{atom}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.64$ (5-CH_3), 21.46 (CH_3), 21.48 (CH_3), 24.33 (2-CH_3), 37.39 (C-2′), 63.99 (C-5′), 75.02 (C-3′), 81.60 (C-4′), 83.01 (C-1′), 104.14 (C-4a), 115.37, 126.38, 126.75, 129.00, 129.47, 129.57, 129.99, 130.05, 130.27, 130.34, 134.76, 137.25, 142.12, 143.79, 144.08 (C_{arom}, C-7a, C-6), 152.24 (C-2), 157.57 (C-4), 165.78 (C=O), 165.97 (C=O) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 625$ ($M + H^+$, 100).

7-(2-Deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranosyl)-3,7-dihydro-2,5-dimethyl-3-(2-fluorophenyl)-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**3b**)

Yield: 1.46 g (68%); ^{1}H NMR ($CDCl_3$): $\delta = 2.11$ (s, 3H, 2-CH_3), 2.24 (s, 3H, 5-CH_3), 2.42, 2.43 (s, 6H, 2 × CH_3), 2.65–2.81 (m, 2H, 2′-H), 4.53–4.57 (m, 2H, 4′-H, 5′-H), 4.68 (dd, $J = 4.1$ Hz, 11.8 Hz, 1H, 5′-H), 5.73 (m, 1H, 3′-H), 6.60 (m, 2H, 6-H, 1′-H), 7.26–7,99 (m, 12H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.83$ (5-CH_3), 21.67, 21.69 (2 × CH_3), 23.73 (2-CH_3), 37.68 (C-2′), 64.22 (C-5′), 75.25 (C-3′), 81.85 (C-4′), 83.03 (C-1′), 104.08 (C-4a), 115.54, 115.85, 117.27, 125.53, 126.58, 126.94, 129.20, 129.49, 130.64, 142.43, 144.04 (C_{arom}, C-7a, C-6), 152.72 (C-2), 157.33 (C-4), 157.97 (d, $J = 250.9$ Hz, C-2″), 166.03 (C=O), 166.22 (C=O) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 609$ ($M + H^+$).

7-(2-Deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranosyl)-3,7-dihydro-2,5-dimethyl-3-(3-fluorophenyl)-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**3c**)

Yield: 1.63 g (76%); ^{1}H NMR ($CDCl_3$): $\delta = 2.08$ (s, 3H, 2-Ch_3), 2.25 (s, 3H, 5-CH_3), 2.42 (s, 6H, 2 × CH_3), 2.59–2.88 (m, 2H, 2′-H), 4.61 (m, 3H, 5′-H, 4′-H), 5.74 (m, 1H, 3′-H), 6.60 (s, 1H, 6-H), 6.63 (m, 1H, 1′-H), 6.98–7.99 (m, 12H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.66$ (2-CH_3), 21.50 (2 × CH_3), 24.19 (5-CH_3) 37.42 (C-2′), 64.03 (C-5′), 75.05 (C-3′), 81.63 (C-4′), 83.02 (C-1′), 104.20 (C-4a), 115.45, 115.58, 116.25, 124.59, 126.78, 129.02, 129.50, 129.60, 131.17, 131.25, 140.10, 142.11, 143.82 (C_{arom}, C-7a, C-6), 152.16 (C-2), 157.42 (C-4), 163.25 (d, $J = 249.6$ Hz, 3″-C), 166.01 (2 C=O) ppm.

7-(2-Deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranosyl)-3,7-dihydro-2-methyl-5-phenyl-3-(4-fluorophenyl)-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**3d**)

Yield: 1.89 g (80%); ^{1}H NMR ($CDCl_3$): $\delta = 2.20$ (s, 3H, CH_3), 2.36 (s, 6H, 2 × CH_3), 2.43 (s, 3H, CH, CH_3), 2.68–2.86 (m, 2H, 2″-H), 4.58–4.78 (m, 3H, 5′-H, 4′-H), 5.75–5.77 (m, 1H, 3′-H), 6.69 (t, $J = 7.60$ Hz, 1H, 1′-H), 7.10–8.00 (m, 14H, H_{arom}, 6-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.43$, 21.52 (2 × CH_3), 24.21 (2-CH_3), 38.23 (C-2′), 63.93 (C-5′), 75.01 (C-3′), 82.38 (C-4′), 83.76 (C-5′), 100.59 (C-4a), 107.04 (C-5), 117.46, 118.64, 121.38, 127.65, 128.55, 128.90, 129.35, 129.71, 132.46, 142.38, 144.01 (C_{arom}, C-7a, C-6), 153.15 (C-2), 156.15 (C-4), 165.91 (C=O), 166.05 (C=O) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 671$ ($M + H^+$, 100%).

7-(2-Deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranosyl)-3-(2,4-dichlorophenyl)-3,7-dihydro-2,5-dimethyl-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**3e**)

Yield: 1.80 g (78%); ^{1}H NMR ($CDCl_3$): $\delta = 2.16$ (s, 6H, $2 \times CH_3$), 2.34 (s, 6H, $2 \times CH_3$), 2.62–2.77 (m, 2H, 2′-H), 4.56–4.75 (m, 3H, 5′-H, 4′-H), 5.71–5.73 (m, 1H, 3′-H), 6.58 (t, $J = 7.65$ Hz, 1H, 1′H), 7.12–8.48 (m, 12H, H_{arom}, 6-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.58$ (5-CH_3), 21.40, 21.57 ($2 \times CH_3$), 23.25 (2-CH_3), 38.03 (C-2′), 63.97 (C-5′), 74.98 (C-3′), 82.11 (C-4′), 83.27 (C-1′), 102.23 (C-4a), 115.62 (C-5), 126.41, 128.50, 129.19, 129.54, 129.69, 131.36, 133.40, 143.76, 144.32 (C_{arom}, C-7a, C-6), 151.77 (C-2), 155.36 (C-4), 165.89 (C=O), 166.07 (C=O) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 659$ ($M + H^+$).

7-(2-Deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranosyl)-4-(4-fluorophenylamino)-2-methyl-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine (**6**)

Yield: 1.65 g (70%); ^{1}H NMR ($CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.73–2.95 (m, 2H, 2′-H), 4.59–4.79 (m, 4H, 5′-H, 3′-H, 4′-H), 5.79 (m, 1H, 1′-H), 6.88–8.01 (m, 18H, H_{arom}, 6-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.45$ (CH_3), 21.52 (CH_3), 25.88 (2-CH_3), 37.90 (C-2′), 64.10 (C-5′), 75.19 (C-3′), 82.02 (C-4′), 83.25 (C-1′), 99.94 (C-4a), 114.99, 115.35, 116.99, 118.56, 120.79, 120.91, 126.48, 126.76, 127.47, 128.79, 128.90, 129.07, 129.45, 129.69, 135.37, 143.77 (C_{arom}, C-5, C-6), 151.73 (C-7a), 153.59 (C-2), 161.28 (C-4), 165.94 (C=O), 166.00 (C=O) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 671$ ($M + H^+$, 100).

3-Aryl-7-(2-deoxy-β-D-erythro-pentofuranosyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-imines (**4**) *and 4-(Arylamino)-7-(2-deoxy-β-D-erythro-pentofuranosyl)-pyrrolo[2,3-d]pyrimidine* (**7**)
general procedure

To a stirred solution of **3** or **6** (2.5 mmol) in dry methanol (30 ml), 1 *M* sodium methoxide in MeOH (2.5 ml) was added and the mixture was stirred overnight at room temperature. The mixture was neutralized with Dowex-50$^+$ resin and filtered. The filtrate was evaporated till dryness. The residual semisolid material was purified on a silica gel column with methanol:chloroform (5:95–8:92 v/v).

3-(4-Chlorophenyl)-7-(2-deoxy-β-D-erythro-pentofuranosyl)-3,7-dihydro-2,5-dimethyl-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**4a**)

Yield: 730 mg (75%); ^{1}H NMR (*DMSO*-d_6): δ=2.12 (s, 3H, CH_3). 2.23–2.25 (m, 1H, 2′-H), 2.41 (s, 3H, CH_3), 2.49–2.50 (m, 1H, 2′-H), 3.13–3.36 (broad s, 1H, NH), 3.54 (m, 1H, 5′-H), 3.87 (m, 1H, 3′-H), 4.39 (m, 1H, 4′-H), 5.09 (broad s, 1H, OH), 5.47 (broad s, 1H, OH), 6.50 (t, $J = 7.5$ Hz, 1H, 1′-H), 7.38 (s, 1H, 6-H), 7.65–7.77 (m, 4H, H_{arom}) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 11.80$ (2-CH_3), 23.89 (5-CH_3), 39.53 (C-2′), 61.75 (C-5′), 70.94 (C-3′), 82.54 (C-4′), 87.49 (C-1′), 100.60 (C-4a), 113.42 (C-5), 120.60 (C-6), 130.35, 130.40, 130.94, 134.59, 135.31 (C_{arom}), 144.77 (C-7a), 152.36 (C-2), 153.40 (C-4) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 389$ ($M + H^+$, 100%).

7-(2-Deoxy-β-D-erythro-pentofuranosyl)-3,7-dihydro-2,5-dimethyl-3-(2-fluorophenyl)-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**4b**)

Yield: 640 mg (69%); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.10$ (s, 3H, 5-CH_3), 2.21 (dd, $J = 5.0$ Hz, 7.5 Hz, 1H, 2′-H), 2.38 (s, 3H, 2-CH_3), 2.41–2,51 (m, 1H, 2′-H), 3.24–3.36 (broad s, 1H, NH), 3.54 (m, 2H, 5′-H), 3.85 (m, 1H, 3′-H), 4.37 (m, 1H, 4′-H), 5.02 (broad s, 1H, OH), 5.40 (broad s, 1H, OH), 6.46 (dd, $J = 6.3$ Hz, 7.8 Hz, 1H, 1′-H), 7.27 (s, 1H, 6-H), 7.46–7.92 (m, 4H, H_{arom}) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 11.69$ (5-CH_3), 23.13 (2-CH_3), 39.53 (C-2′), 61.83 (C-5′), 70.95 (C-3′), 82.52 (C-4′), 87.41 (C-1′), 101.06 (C-4a), 113.67 (C-5), 117.22, 119.75, 123.67, 126.37, 130.71, 132.87 (C_{arom}, C-6), 143.73 (C-7a), 152.09 (C-2), 153.79 (C-4), 157.00 (d, $J = 250.6$ Hz, C-2″) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 373$ ($M + H^+$).

7-(2-Deoxy-β-D-erythro-pentofuranosyl)-3,7-dihydro-2,5-dimethyl-3-(3-fluorophenyl)-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**4c**)

Yield: 0.58 g (62%); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.15$ (s, 3H, 2-CH_3), 2.20–2.25 (m, 1H, 2′-H), 2.43 (s, 3H, 5-CH_3), 2.51 (m, 1H, 2′-H), 3.40–3.49 (broad s, 1H, NH), 3.55 (m, 2H, 5′-H), 3.87 (m, 1H, 3′-H), 4.40 (s, br, 1H, 4′-H), 5.13 (broad s, 1H, OH), 5.52 (broad s, 1H, OH), 6.51 (t, $J = 7.5$ Hz, 1H, 1′-H), 7.41–7.80 (m, 5H, 6-H, H_{arom}) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 11.87$ (2-CH_3), 23.75 (5-CH_3), 39.52 (C-2′), 61.76 (C-5′), 70.98 (C-3′), 82.59 (C-4′), 87.54 (C-1′), 100.52 (C-4a), 113.49 (C-5), 116.19, 117.95, 120.83, 124.76, 132.51, 136.91 (C_{arom}, C-6), 144.89 (C-7a), 152.29 (C-2), 153.25 (C-4), 162.93 (d, $J = 246.5$ Hz, C-3″) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 373$ ($M + H^+$).

7-(2-Deoxy-β-D-erythro-pentofuranosyl)-3,7-dihydro-3-(4-fluorophenyl)-2-methyl-5-phenyl-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**4d**)

Yield: 0.74 g (68%); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.07$ (s, 3H, 2-CH_3), 2.25–2.59 (m, 2H, 2′-H), 3.55–3.61 (m, 3H, NH, 5′-H), 3.91 (m, 1H, 3′-H), 4.43 (m, 1H, 4′-H), 5.20 (broad s, 2H, 2 × OH), 6.55–6.58 (m, 1H, 1′-H), 7.21–7.90 (m, 10H, H_{arom}, 6-H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 24.06$ (2-CH_3), 39.52 (C-2′), 61.98 (C-5′), 71.11 (C-3′), 83.05 (C-4′), 87.55 (C-1′), 100.61 (C-4a), 118.77 (C-5), 119.89, 126.80, 128.45, 129.34, 131.02, 133.89, 134.43 (C_{arom}, C-6), 142.78 (C-7a), 153.11 (C-2), 155.65 (C-4) 161.93 (d, $J = 245.9$ Hz, C-4″) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 435$ ($M + H^+$).

7-(2-Deoxy-β-D-erythro-pentofuranosyl)-3-(2,4-dichlorophenyl)-3,7-dihydro-2,5-dimethyl-4H-pyrrolo[2,3-d]pyrimidin-4-imine (**4e**)

Yield: 0.63 g (60%); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.03$ (s, 3H, 2-CH_3), 2.17–2.22 (m, 1H, 2′-H), 2.34 (s, 3H, 5-CH_3), 2.37–2.52 (m, 1H, 2′-H), 3.53 (m, 2H, 5′-H), 3.84 (m, 1H, 3-H), 4.35–4.37 (m, 1H, 4′-H), 5.04–5.40 (broad s, 2H, 2 × OH), 6.43 (t, $J = 7.5$ Hz, 1H, 1′-H), 7.15 (s, 1H, 6-H), 7.70 (m, 2H, H_{arom}), 7.96 (s, 1H, H_{arom}) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 11.67$ (CH_3), 23.10 (CH_3), 39.47 (C-2′), 61.91 (C-5′), 71.01 (C-3′), 82.43 (C-4′), 87.31 (C-1′), 101.70 (C-4a), 113.74 (C-5), 129.49, 130.38, 132.37, 132.96, 133.84, 133.86, 135.26 (C_{arom}, C-6), 142.81 (C-7a), 151.60 (C-2), 154.14 (C-4) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 423$ ($M + H^+$).

7-(2-Deoxy-β-D-erythro-pentofuranosyl)-4-(4-fluorophenylamino)-2-methyl-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine (**7d**)

Yield: 0.66 g (61%); m.p.: 118–121 °C; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.23$–2.30 (m, 1H, 2′-H), 2.52–2.69 (m, 4H, CH_3, 2′-H), 3.36–3.39 (broad s, 1H, NH), 3.63 (m, 2H, 5′-H), 3.92 (m, 1H, 3′-H), 4.44 (m, 1H, 4′-H), 5.12 (broad s, 1H, OH), 5.31 (broad s, 1H, OH), 6.68 (t, $J = 7.5$ Hz, 1H, 1′H), 7.07–7.60 (m, 10H, H_{arom}, 6-H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 25.47$ (CH_3), 39.62 (C-2′), 62.00 (C-5′), 71.10 (C-3′), 83.00 (C-4′), 87.40 (C-1′), 99.44 (C-4a), 115.73 (C-5), 115.19, 121.06, 127.02, 128.47, 128.90, 134.36, 135.83, (C_{arom}, C-6), 151.28 (C-7a), 153.25 (C-2), 159.64 (C-4) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 435$ ($M + H^+$).

4-(Arylamino)-7-(2-deoxy-β-D-erythro-pentofuranosyl)-7H-pyrrolo[2,3-d]-pyrimidine (**7b** *and* **7d**)

4b or **4d** (1.47 mmol) were refluxed overnight in distilled water (5 ml) with stirring. The reaction mixture was cooled and the colourless needles were filtered off. Yield: 0.38 g (59%) of **7d**.

7-(2-Deoxy-β-D-erythro-pentofuranosyl)-2,5-dimethyl-4-(2-fluorophenylamino)-7H-pyrrolo-[2,3-d]pyrimidine (**7b**)

Yield: 0.225 g (41%); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.09$–2.14 (m, 1H, 2′-H), 2.41 (s, 3H, CH_3), 2.43 (m, 4H, CH_3, 2′-H), 3.29 (s, 1H, NH), 3.49–3.58 (m, 2H, 5′-H), 3.80 (m, 1H, 3′-H), 4.32 (m, 1H, 4′-H), 6.50 (t, $J = 8$ Hz,

1H, 1′-H), 7.17–8.13 (m, 5H, H_{arom}, 6-H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 11.77$ (CH_3), 25.43 (CH_3), 39.77 (C-2′), 62.08 (C-5′), 71.07 (C-3′), 82.50 (C-4′), 87.06 (C-1′), 102.04 (C-4a), 108.96 (C-5), 114.89, 119.97, 124.13, 124.64, 127.84 (C_{arom}, C-6), 151.34 (C-7a), 154.16 (C-2), 154.56 (d, $J = 244.1$ Hz, C-2″), 159.22 (C-4) ppm; FAB MS (3-nitrobenzyl alcohol): $m/z = 373$ ($M + H^+$).

References

[1] Suhadolnik RJ (1970) Nucleoside antibiotics. Wiley-Interscience, New York, p 450
[2] Tolman RL, Robins RK, Townsend LB (1968) J Am Chem Soc **90**: 524
[3] Pike JE, Slechta L, Wiley PF (1964) J Heterocycl Chem **1**: 159
[4] Wiley PF, US Pat. (Jan. 16, 1968) 3,364,198; CA **68**: P 76941g
[5] Upjohn Co., Neth. Pat. Appl. (April 13, 1966) 6,513,129; CA **65**: 20206d
[6] Gerster JF, Carpenter B, Robins RK, Townsend LB (1967) J Med Chem **10**: 326
[7] Krawczyk SH, Bernier-Rodriguex M, Nassiri MR, Kern ER, Wotring LL, Drach JC, Townsend LB (1990) J Med Chem **33**: 3160
[8] Welcome Foundation Ltd., Brit. Pat. (April 22, 1957) 812,366; Chem Abstr **54**: 592
[9] Davoll J (1960) J Chem Soc 131
[10] Miwa T, Hitaka T, Akimoto H, Nomura H (1991) J Med Chem **34**: 555
[11] Girgis NS, Jørgensen A, Pedersen EB (1983) Liebigs Ann Chem 2066
[12] Hilmy KMH, Morgensen J, Jørgensen A, Pedersen EB (1990) Heterocycles **31**: 367
[13] Jørgensen A (1986) Heterocycles **24**: 997
[14] Kazimierczuk Z, Cottam HB, Revankar RG, Robins RK (1984) J Am Chem Soc **106**: 6379
[15] Hoffer M (1960) Chem Ber **93**: 2777
[16] Taylor EC, Hendess RW (1965) J Am Chem Soc **87**: 1995

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