

Synthesis of N^2 -Arylisocytidines and N^2 -Aryl-2'-deoxyisocytidines

Omar M. Ali*

Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt

Received February 20, 2007; accepted February 28, 2007; published online June 29, 2007
© Springer-Verlag 2007

Summary. 2-(Arylamino)pyrimidin-4-ones were synthesized, silylated, and condensed with 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranoside to afford the corresponding N^2 -aryl protected isocytidines. Deprotection of the acetylated isocytidines using saturated NH_3 in *MeOH* solution gave 1-(β -D-ribofuranosyl)-2-(arylamino)-4-pyrimidinones. Methyl 2-deoxy-3,5-di-*O*-toluyl- α/β -D-ribofuranoside was prepared and condensed with the previously silylated bases to afford the anomeric mixture of protected nucleosides. The pure β -anomers were synthesized with better yield by treating the sodium salts of N^2 -arylisocytosine derivatives with 2-deoxy-3,5-di-*O*-toluyl- α -D-ribofuranosyl chloride. Deprotection of the latter anomers afforded the corresponding free hydroxyl derivatives. The synthesized free nucleosides are under antiviral and oligonucleotide investigations.

Keywords. Cytosine; Isocytosine; Guanine; Isocytidine; 2'-Deoxyisocytidine.

Introduction

Isocytosine (2-amino-4-pyrimidinone) designates the pyrimidine part of guanine, and even though it is not involved directly as a carrier of the genetic code, it is of biological significance and its medical applications are numerous [1] (Fig. 1). A variety of 2-amino-4-pyrimidinones display anticancer, antiviral, or antibacterial properties [2–6], or are rendered as valuable agrochemicals [7–9]; specifically, platinum group metal complexes of isocytosine and derivatives attracted considerable attention because of their antitumor activity [10]. In addition, the isocytosine ring system has been explored as a molecular functionality for supramolecular assembly of H-bonded rod

and layered organic materials [11], as a host for guests with suitable H-bonding abilities [12], or as color reagents for metal cations [13]. Nucleoside analogues bearing unnatural hydrogen bonding patterns have been proposed to expand the number of complementary nucleoside pairs available in nucleic acids [14, 15]. Several nucleoside pairs with complementary H-bonding patterns have been introduced into oligonucleotides [16–18]. In this paper we present the synthesis of N^2 -arylisocytidines and N^2 -aryl-2'-deoxyisocytidines.

Results and Discussion

2-(Arylamino)pyrimidin-4-ones **2a–2c** were synthesized by refluxing 2-methylthiouracil (**1**) [19] with arylamines (aniline, *N*-methylaniline, and 4-chloroaniline) in glacial acetic acid. The products were recrystallized from *AcOH*/ H_2O to afford pale yellow powders in 75–90% yields. The ^1H NMR spectra showed H-5 and H-6 as doublet at $\delta = 6.17\text{--}6.37$ and $7.55\text{--}7.85$ ppm. The ^{13}C NMR spectra showed the signals of C-5 and C-6 at $\delta = 109.4\text{--}109.6$ and $158.9\text{--}160.2$ ppm. Silylation of these bases was carried out according to the Wittenburg method [20] by treating the 2-(arylamino)pyrimidin-4-ones **2a–2c** with 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) in presence of $(\text{NH}_4)_2\text{SO}_4$ as a catalyst at reflux temperature.

Condensation of 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranoside (**3**) with silylated bases using the trimethylsilyl trifluoromethanesulfonate (*TMS*-triflate) method of Vorbrüggen *et al.* [21] in dry *MeCN* at -30°C to room temperature for 2 h, gave the corresponding

* Corresponding author. E-mail: omasaf@hotmail.com

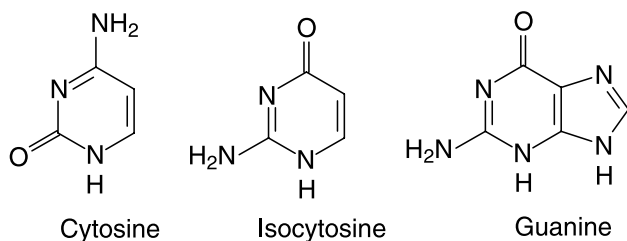
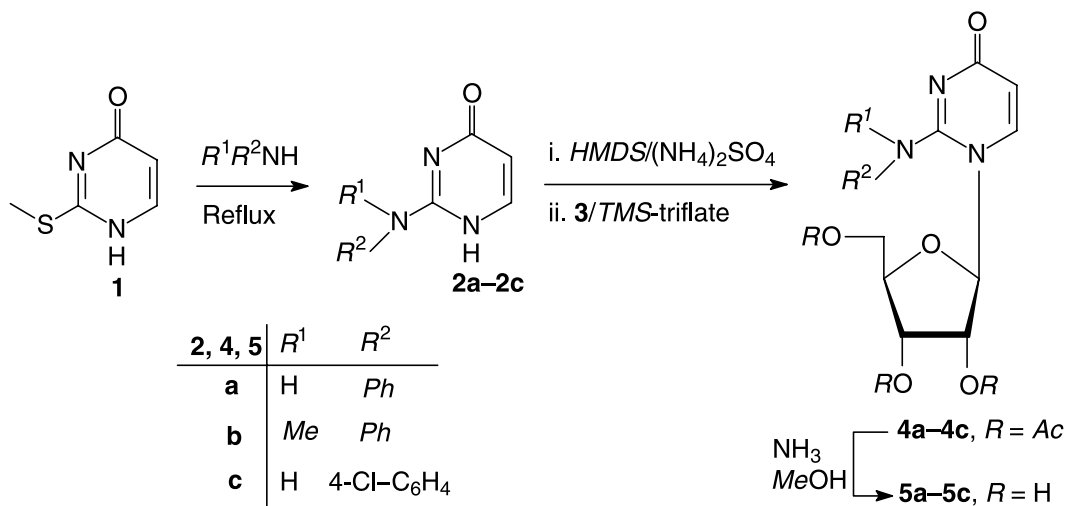
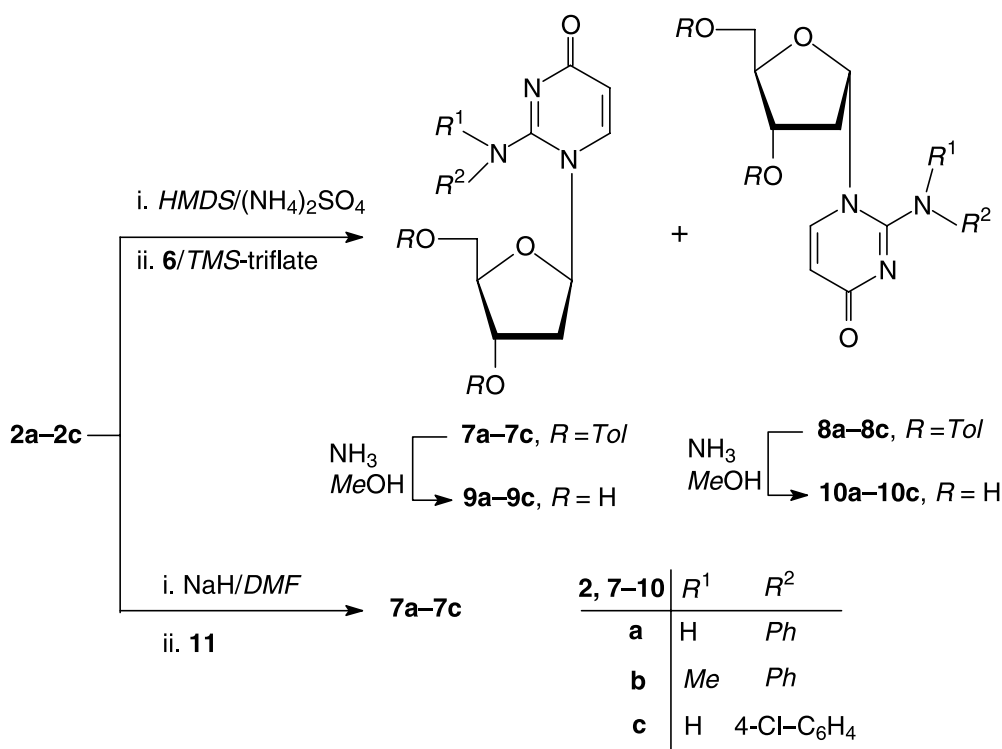


Fig. 1. Structures of cytosine, isocytosine, and guanine

*N*²-aryl protected isocytidines **4a–4c** in 28–35% yields. The ¹H NMR spectra showed three singlets at δ = 2.04–2.09, 2.10–2.12, and 2.16–2.18 ppm corresponding to *Me* of three *Ac* groups, while the anomeric proton appears as doublet at δ = 6.25–6.28 ppm. The ¹³C NMR spectra showed three signals at 20.3, 20.9, and 21.2 corresponding to *Me* of three *Ac* groups, while the three carbonyl groups of



Scheme 1



Scheme 2

Ac appear at $\delta = 169.3$, 169.7 , and 170.1 ppm. Deprotection of **4a–4c** using saturated NH_3 in *MeOH* solution at room temperature gave 1-(β -D-ribofuranosyl)-2-(arylamino)-4-pyrimidinones **5a–5c** in 91–93% yields. ^1H and ^{13}C NMR spectra showed the disappearance of the acetyl groups (Scheme 1).

Methyl 2-deoxy-3,5-di-*O*-toluyl- α/β -D-ribofuranoside (**6**) was prepared from 2-deoxy-D-ribose [22]. Condensation of **6** with silylated bases **2a–2c** as described before afforded the anomeric mixture of protected nucleosides **7a–7c** and **8a–8c**. After separation and purification by silica gel column chromatography using 30% ether in *n*-hexane, the β -anomers **7a–7c** were obtained as the major products in 18–24% yields, while the α -anomers **8a–8c** as the minor products were isolated in 6–8% yields. The ^1H NMR spectra showed the presence of the anomeric proton of β -anomers **7a–7c** as multiplet in the range $\delta = 6.34$ – 6.49 ppm, while for α -anomers **8a–8c** gave multiplet in the range $\delta = 6.14$ – 6.19 ppm. The anomeric protons as well as the rest of sugar protons were identified in comparison to the previously identified protons [23]. In order to synthesize the pure β -anomers **7a–7c** with better yield than the previously mentioned method we treated the N^2 -arylisocytosine derivatives **2a–2c** with NaH in dry *DMF* to form the corresponding sodium salts which were treated directly with 2-deoxy-3,5-di-*O*-toluyl- α -D-ribofuranosyl chloride (**11**) for 2 h to afford **7a–7c** in 29–38%. Deprotection of **7a–7c** and **8a–8c** was carried out with saturated NH_3 in *MeOH* solution at room temperature to afford the corresponding free hydroxyl derivatives **9a–9c** (92–94%) and **10a–10c** (92–93%) (Scheme 2). The synthesized free nucleosides **5a–5c** and **9a–9c** are under antiviral and oligonucleotide investigations.

Experimental

Melting points were determined using a Kofler block instrument. TLC was performed on plastic plates Silica Gel 60 F₂₅₄ (E. Merck, layer thickness 0.2 mm). The detection was achieved by treatment with a solution of 15% H_2SO_4 in methanol, and heating at 150°C . NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for ^1H NMR and 62.9 MHz for ^{13}C NMR with TMS as an internal standard. MALDI-MS were measured with a KRATOS Analytical Compact, using 2,5-dihydroxybenzoic acid (DHB) as matrix. The $(\text{M} + \text{Na})^+$ ion was peak matched using ions derived from the 2,5-dihydroxybenzoic acid matrix. The microanalyses were performed at the microanalytical unit, Odense University, Denmark, and were found to agree favourably with the calculated values.

General Procedure for the Synthesis of 2-(Arylamino)pyrimidin-4-ones **2a–2c**

A mixture of 2.84 g **1** (20 mmol) and arylamines (30 mmol) in 60 cm^3 glacial acetic acid was refluxed for 10 h (TLC). The solvent was removed under reduced pressure and the residue was recrystallized from $\text{AcOH}/\text{H}_2\text{O}$ to afford **2a–2c** as pale yellow powders in 75–90% yield.

2-(Phenylamino)pyrimidin-4-one (**2a**, $\text{C}_{10}\text{H}_9\text{N}_3\text{O}$)

Yield 3.20 g (85%); Mp 217 – 219°C ; ^1H NMR (*DMSO*- d_6 , 250 MHz): $\delta = 6.37$ (d, $J = 3.7$ Hz, H-5), 7.19 – 7.43 (m, *Ph*-H, NH), 7.68 (d, $J = 6.8$ Hz, H-6), 8.55 (br s, NH) ppm; ^{13}C NMR (*DMSO*- d_6 , 62.5 MHz): $\delta = 109.4$ (C-5), 122.8 , 122.9 , 130.2 , 147.2 (*Ph*-C), 152.6 (C-2), 160.0 (C-6), 164.3 (C-4) ppm; MS: m/z (%) = 188 [$\text{M}^+ + 1$], 12.7].

2-[Methyl(phenyl)amino]pyrimidin-4-one (**2b**, $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$)

Yield 3.01 g (75%); Mp 207 – 209°C ; ^1H NMR (*DMSO*- d_6 , 250 MHz): $\delta = 3.45$ (s, CH_3), 6.17 (d, $J = 3.0$ Hz, H-5), 7.34 – 7.68 (m, *Ph*-R, NH), 7.85 (d, $J = 6.1$ Hz, H-6) ppm; ^{13}C NMR (*DMSO*- d_6 , 62.5 MHz): $\delta = 31.9$ (CH_3), 109.6 (C-5), 122.9 , 125.9 , 129.6 , 141.8 (*Ph*-C), 153.9 (C-2), 158.9 (C-6), 163.8 (C-4) ppm; MS: m/z (%) = 202 [$\text{M}^+ + 1$], 13.2].

2-(4-Chlorophenylamino)pyrimidin-4-one (**2c**, $\text{C}_{10}\text{H}_8\text{ClN}_3\text{O}$)

Yield 3.96 g (90%); Mp 248 – 250°C ; ^1H NMR (*DMSO*- d_6 , 250 MHz): $\delta = 6.35$ (d, $J = 3.8$ Hz, H-5), 7.05 – 7.55 (m, *Ph*-H, H-6, NH), 8.55 (br s, NH) ppm; ^{13}C NMR (*DMSO*- d_6 , 62.5 MHz): $\delta = 109.4$ (C-5), 116.5 , 125.6 , 128.7 , 141.5 (*Ph*-C), 152.6 (C-2), 160.2 (C-6), 164.3 (C-4) ppm; MS: m/z (%) = 222 [$\text{M}^+ + 1$], 12.8].

1-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-2-(arylamino)-4-pyrimidinones **4a–4c**

A mixture of 3 mmol **2a–2c**, 30 cm^3 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*), and 40 mg $(\text{NH}_4)_2\text{SO}_4$ (0.22 mmol) was heated under reflux overnight. The solvent was removed *in vacuo* to afford the silylated base which was dissolved in 20 cm^3 dry *MeCN*. **3** (0.95 g, 3 mmol) in 20 cm^3 dry *MeCN* were added and the mixture was cooled to -30°C . A solution of 0.25 cm^3 trimethylsilyl trifluoromethanesulfonate (1.24 mmol) in 5 cm^3 dry *MeCN* was added dropwise over 25 min to the reaction mixture with stirring. The reaction mixture was stirred at room temperature for 2 h until the total consuming of sugar (TLC). The solvent was removed under reduced pressure and the residue was dissolved in 100 cm^3 CH_2Cl_2 and washed with $3 \times 50\text{ cm}^3$ saturated aqueous solution of NaHCO_3 and $3 \times 50\text{ cm}^3$ H_2O . The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give a crude dark brown product which was purified by silica gel column chromatography using ether/*pet. ether* (1/1, *v/v*).

1-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-2-(phenylamino)-4-pyrimidinone (**4a**, $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_8$)

White foam (0.45 g, 34%); ^1H NMR (CDCl_3 , 250 MHz): $\delta = 2.09$, 2.12 , 2.17 (3s, $3\text{CH}_3\text{CO}$), 4.09 – 4.34 (m, H-5'), 4.43 (m, H-4'), 5.71 (dd, $J = 5.0$, 6.0 Hz, H-3'), 5.91 (m, H-2'), 5.99 (d, $J = 4.0$ Hz, H-5), 6.25 (d, $J = 6.0$ Hz, H-1'),

7.22–7.40 (m, *Ph*-H), 7.53 (d, $J = 6.8$ Hz, H-6) ppm; ^{13}C NMR (CDCl_3 , 250 MHz): $\delta = 20.3$, 20.9, 21.2 ($3\text{CH}_3\text{CO}$), 63.0 (C-5'), 70.6 (C-3'), 73.2 (C-2'), 80.4 (C-4'), 85.4 (C-1'), 105.8 (C-5), 121.9, 122.6, 129.9, 144.2 (*Ph*-C), 131.6 (C-6) 148.3 (C-2), 164.3 (C-4), 169.3, 169.7, 170.1 ($3\text{CH}_3\text{CO}$) ppm; MS: m/z (%) = 468 [$(\text{M}^+ + \text{Na})$, 24.6].

1-(2,3,5-Tri-O-acetyl- β -D-ribofuranosyl)-2-(methyl(phenyl)amino)-4-pyrimidinone (4b, $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_8$)

White foam (0.38 g, 28%); ^1H NMR (CDCl_3 , 250 MHz): $\delta = 2.08$, 2.12, 2.18, (3s, $3\text{CH}_3\text{CO}$), 3.44 (CH_3), 4.10–4.32 (m, H-5'), 4.42 (m, H-1'), 5.74 (dd, $J = 4.6$, 6.1 Hz, H-3'), 5.89 (m, H-2'), 5.97 (d, $J = 4.0$ Hz, H-5), 6.28 (d, $J = 6.0$ Hz, H-1'), 7.20–7.44 (m, *Ph*-H), 7.58 (d, $J = 6.5$ Hz, H-6) ppm; ^{13}C NMR (CDCl_3 , 62.5 MHz): $\delta = 20.3$, 20.9, 21.2 ($3\text{CH}_3\text{CO}$), 34.2 (CH_3), 63.1 (C-5'), 70.6 (C-3'), 73.4 (C-2'), 80.5 (C-4'), 89.1 (C-1'), 106.0 (C-5), 124.7, 125.2, 129.6, 131.5, 142.1 (*Ph*-C), 131.5 (C-6), 147.6 (C-2), 163.5 (C-4), 169.3, 169.7, 170.1 ($3\text{CH}_3\text{CO}$) ppm; MS: m/z (%) = 482 [$(\text{M}^+ + \text{Na})$, 25.9].

1-(2,3,5-Tri-O-acetyl- β -D-ribofuranosyl)-2-(4-chlorophenylamino)-4-pyrimidinone (4c, $\text{C}_{21}\text{H}_{22}\text{ClN}_3\text{O}_8$)

White foam (0.50 g, 35%); ^1H NMR (CDCl_3 , 250 MHz): $\delta = 2.04$, 2.10, 2.16 (3s, $3\text{CH}_3\text{CO}$), 4.11–4.33 (m, H-5'), 4.42 (m, H-1'), 5.71 (dd, $J = 4.3$, 5.8 Hz, H-3'), 5.94 (m, H-2'), 6.09 (d, $J = 3.8$ Hz, H-5), 6.26 (d, $J = 6.0$ Hz, H-1'), 7.22–7.67 (m, *Ph*-H, H-6) ppm; ^{13}C NMR (CDCl_3 , 62.5 MHz): $\delta = 20.3$, 20.9, 21.2 ($3\text{CH}_3\text{CO}$), 63.2 (C-5'), 70.9 (C-3'), 73.2 (C-2'), 80.6 (C-4'), 85.4 (C-1'), 105.9 (C-5), 118.8, 124.9, 128.7, 144.1 (*Ph*-C), 131.6 (C-6) 146.2 (C-2), 163.3 (C-4), 169.3, 169.7, 170.1 ($3\text{CH}_3\text{CO}$) ppm; MS: m/z (%) = 502 [$(\text{M}^+ + \text{Na})$, 24.6].

1-(β -D-Ribofuranosyl)-2-(arylamino)-4-pyrimidinones 5a–5c

A solution of **4a–4c** (0.6 mmol) in 30 cm^3 saturated NH_3/MeOH was allowed to stir overnight at room temperature. The mixture was concentrated and purified by column chromatography using 12% *MeOH* in CH_2Cl_2 .

1-(β -D-Ribofuranosyl)-2-(phenylamino)-4-pyrimidinone (5a, $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_5$)

White foam (0.18 g, 93%); ^1H NMR ($\text{DMSO}-d_6$, 250 MHz): $\delta = 3.45$ –3.71 (m, H-5'), 3.98 (m, H-4'), 4.25 (m, H-3'), 4.60 (m, H-2'), 4.99 (br s, HO-5'), 5.18 (br s, HO-3'), 5.41 (br s, HO-2'), 6.05 (d, $J = 3.5$ Hz, H-5), 6.12 (d, $J = 5.0$ Hz, H-1'), 7.32–7.45 (m, *Ph*-H), 7.55 (d, $J = 7.0$ Hz, H-6) ppm; ^{13}C NMR ($\text{DMSO}-d_6$, 62.5 MHz): $\delta = 62.1$ (C-5'), 71.9 (C-3'), 73.9 (C-2'), 85.8 (C-4'), 87.9 (C-1'), 105.8 (C-5), 121.6, 122.5, 129.7, 143.4 (*Ph*-C), 133.2 (C-6) 147.2 (C-2), 164.6 (C-4) ppm; MS: m/z (%) = 320 [$(\text{M}^+ + 1)$, 18.5].

1-(β -D-Ribofuranosyl)-2-[methyl(phenyl)amino]-4-pyrimidinone (5b, $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_5$)

White foam (0.19 g, 91%); ^1H NMR ($\text{DMSO}-d_6$, 250 MHz): $\delta = 3.34$ (m, H-5'), 3.49 (s, CH_3), 3.51 (m, H-5'), 3.88 (m, H-4'), 4.45 (m, H-3'), 4.64 (m, H-2'), 5.09 (br s, HO-5'), 5.16 (br s, HO-3'), 5.39 (br s, HO-2'), 5.92 (d, $J = 3.6$ Hz,

H-5), 6.15 (d, $J = 5.2$ Hz, H-1'), 7.28–7.51 (m, *Ph*-H), 7.58 (d, $J = 6.8$ Hz, H-6) ppm; ^{13}C NMR ($\text{DMSO}-d_6$, 62.5 MHz): $\delta = 34.2$ (CH_3), 62.1 (C-5'), 71.9 (C-3'), 72.2 (C-2'), 86.7 (C-4'), 88.4 (C-1'), 106.0 (C-5), 124.7, 125.1, 129.5, 144.7 (*Ph*-C), 133.0 (C-6) 146.7 (C-2), 163.6 (C-4) ppm; MS: m/z (%) = 334 [$(\text{M}^+ + 1)$, 18.8].

1-(β -D-Ribofuranosyl)-2-(4-chlorophenylamino)-4-pyrimidinone (5c, $\text{C}_{15}\text{H}_{16}\text{ClN}_3\text{O}_5$)

White foam (0.19 g, 92.5%); ^1H NMR ($\text{DMSO}-d_6$, 250 MHz): 3.35–3.60 (m, H-5'), 3.86 (m, H-4'), 4.24 (m, H-3'), 4.56 (m, H-2'), 5.05 (br s, HO-5'), 5.16 (br s, HO-3'), 5.38 (br s, HO-2'), 5.95 (d, $J = 3.6$ Hz, H-5), 6.10 (d, $J = 5.0$ Hz, H-1'), 7.12–7.34 (dd, $J = 4.0$, 8.0 Hz, *Ph*-H), 7.58 (d, $J = 6.8$ Hz, H-6) ppm; ^{13}C NMR ($\text{DMSO}-d_6$, 62.5 MHz): $\delta = 62.1$ (C-5'), 72.0 (C-3'), 73.6 (C-2'), 84.9 (C-4'), 87.3 (C-1'), 105.8 (C-5), 118.7, 124.9, 128.6, 144.2 (*Ph*-C), 133.2 (C-6) 146.4 (C-2), 162.8 (C-4) ppm; MS: m/z (%) = 354 [$(\text{M}^+ + 1)$, 32.9].

1-(2-Deoxy-3,5-di-O,O-(4-methylbenzoyl)- α/β -D-ribofuranosyl)-2-(arylamino)-4-pyrimidinones 7a–7c and 8a–8c

Method A: The appropriate base **2a–2c** (3 mmol) was treated with 30 cm^3 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) and 40 mg $(\text{NH}_4)_2\text{SO}_4$ (0.22 mmol) at 130°C for 20 h. The silylated compound was concentrated and used, without further purification, for *Vorbruggen* coupling. The silylated base was redissolved in 20 cm^3 *MeCN*, 1.15 g **6** (3 mmol) in 20 cm^3 dry *MeCN* were added, and the mixture was cooled to -30°C . Trimethylsilyl trifluoromethanesulfonate (0.25 cm^3 , 1.24 mmol) in 5 cm^3 dry *MeCN* was added dropwise over 25 min to the reaction mixture with stirring overnight. After concentration, the residue was diluted with CH_2Cl_2 . It was extracted with $3 \times 50\text{ cm}^3$ saturated NaHCO_3 and $3 \times 50\text{ cm}^3$ H_2O . The organic layer was dried over anhydrous Na_2SO_4 and purified by column chromatography using 30% ether in *n*-hexane to give α - and β -derivatives.

Method B: A solution of **2a–2c** (3 mmol) in 30 cm^3 *DMF* was treated with 127 mg NaH (60% in mineral oil, 3.2 mmol). The solution was heated to 80°C for 1 h. After cooling to room temperature, 1.17 g **11** (3 mmol) were added portionwise, and the reaction was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with $3 \times 50\text{ cm}^3$ NaHCO_3 and $3 \times 50\text{ cm}^3$ H_2O . The organic layer was dried over anhydrous Na_2SO_4 and purified by column chromatography using 50% ether in *n*-hexane to give the β -derivative only.

1-(2-Deoxy-3,5-di-O,O-(4-methylbenzoyl)- β -D-ribofuranosyl)-2-(phenylamino)-4-pyrimidinone (7a, $\text{C}_{31}\text{H}_{29}\text{N}_3\text{O}_6$)

White foam (0.39 g, 24%, method A; 0.61 g, 38%, method B); ^1H NMR (CDCl_3 , 250 MHz): $\delta = 2.38$, 2.46 (2s, 2CH_3), 2.88–3.14 (m, H-2'), 4.48 (m, H-5'), 4.53 (m, H-4'), 4.71 (m, H-5'), 5.67 (m, H-3'), 5.94 (d, $J = 3.2$ Hz, H-5), 6.49 (m, H-1'), 7.10–8.04 (m, *Ph*-H, H-6) ppm; ^{13}C NMR (CDCl_3 , 62.5 MHz): $\delta = 20.9$, 21.5 (2CH_3), 39.9 (C-2'), 64.1 (C-5'), 75.0 (C-3'), 81.7 (C-4'), 83.6 (C-1'), 105.8 (C-5), 121.8, 122.5, 129.8, 130.8, 132.4, 133.6, 135.5, 138.3, 143.5 (*Ph*-C, C-6), 146.3 (C-2), 164.82 (C-4), 165.2, 165.8 (2CO) ppm; MS: m/z (%) = 562 [$(\text{M}^+ + \text{Na})$, 35.6].

1-(2-Deoxy-3,5-di-O,O-(4-methylbenzoyl)-β-D-ribofuranosyl)-2-[methyl(phenyl)amino]-4-pyrimidinone (7b, C₃₂H₃₁N₃O₆)

White foam (0.30 g, 18%, method A; 0.48 g, 29%, method B); ¹H NMR (CDCl₃, 250 MHz): δ = 2.36, 2.44 (2s, 2CH₃), 2.86–3.20 (m, H-2'), 3.50 (s, CH₃), 4.48 (m, H-5'), 4.52 (m, H-4'), 4.74 (m, H-5'), 5.65 (m, H-3'), 5.88 (d, *J* = 3.2 Hz, H-5), 6.34 (m, H-1'), 7.10–7.96 (m, *Ph*-H, H-6) ppm; ¹³C NMR (CDCl₃, 62.5 MHz): δ = 20.9, 21.5 (2CH₃), 34.2 (CH₃), 39.1 (C-2'), 64.0 (C-5'), 74.8 (C-3'), 81.6 (C-4'), 85.1 (C-1'), 106.0 (C-5), 124.7, 125.1, 126.1, 129.0, 129.5, 132.1, 143.5 (*Ph*-C, C-6), 146.8 (C-2), 165.5 (C-4), 165.3, 165.8 (2CO) ppm; MS: *m/z* (%) = 576 [(M⁺ + Na), 36.3].

1-(2-Deoxy-3,5-di-O,O-(4-methylbenzoyl)-β-D-ribofuranosyl)-2-(4-chlorophenylamino)-4-pyrimidinone (7c, C₃₁H₂₈ClN₃O₆)

White foam (0.32 g, 22%, method A; 0.50 g, 37%, method B); ¹H NMR (CDCl₃, 250 MHz): δ = 2.39, 2.44 (2s, 2CH₃), 2.92–3.20 (m, H-2'), 4.46 (m, H-5'), 4.51 (m, H-4'), 4.68 (m, H-5'), 5.70 (m, H-3'), 6.00 (d, *J* = 3.4 Hz, H-5), 6.44 (m, H-1'), 7.00–7.94 (m, *Ph*-H, H-6) ppm; ¹³C NMR (CDCl₃, 62.5 MHz): δ = 20.9, 21.5 (2CH₃), 39.9 (C-2'), 64.2 (C-5'), 75.1 (C-3'), 81.8 (C-4'), 84.4 (C-1'), 105.6 (C-5), 118.7, 124.9, 126.8, 128.6, 129.0, 132.2, 138.9, 143.5 (*Ph*-C, C-6), 146.5 (C-2), 164.7 (C-4), 165.34, 165.9 (2CO) ppm; MS: *m/z* (%) = 596 [(M⁺ + Na), 35.3].

1-(2-Deoxy-3,5-di-O,O-(4-methylbenzoyl)-α-D-ribofuranosyl)-2-(phenylamino)-4-pyrimidinone (8a, C₃₁H₂₉N₃O₆)

White foam (0.13 g, 8%); ¹H NMR (CDCl₃, 250 MHz): δ = 2.30 (m, H-2'), 2.40, 2.49 (2s, 2CH₃), 2.62 (m, H-2'), 3.54–3.76 (m, H-5'), 4.50 (m, H-4'), 5.26 (m, H-3'), 5.95 (d, *J* = 3.4 Hz, H-5), 6.18 (m, H-1'), 7.14–7.96 (m, *Ph*-H, H-6) ppm; ¹³C NMR (CDCl₃, 62.5 MHz): δ = 21.1, 21.5 (2CH₃), 39.7 (C-2'), 63.9 (C-5'), 74.3 (C-3'), 86.2 (C-1'), 88.0 (C-4'), 105.7 (C-5), 122.0, 122.8, 129.1, 132.6, 138.4, 143.7 (*Ph*-C, C-6), 146.3 (C-2), 163.9 (C-4), 166.1, 166.8 (2CO) ppm; MS: *m/z* (%) = 562 [(M⁺ + Na), 35.5].

1-(2-Deoxy-3,5-di-O,O-(4-methylbenzoyl)-α-D-ribofuranosyl)-2-[methyl(phenyl)amino]-4-pyrimidinone (8b, C₃₂H₃₁N₃O₆)

White foam (0.10 g, 6%); ¹H NMR (CDCl₃, 250 MHz): δ = 2.33 (m, H-2'), 2.41, 2.46 (2s, 2CH₃), 2.59 (m, H-2'), 3.46 (s, CH₃), 3.50–3.75 (m, H-5'), 4.55 (m, H-4'), 5.29 (m, H-3'), 5.90 (d, *J* = 3.1 Hz, H-5), 6.14 (m, H-1'), 7.14–7.90 (m, *Ph*-H, H-6) ppm; ¹³C NMR (CDCl₃, 62.5 MHz): δ = 20.9, 21.4 (2CH₃), 34.3 (CH₃), 39.8 (C-2'), 64.1 (C-5'), 74.3 (C-3'), 86.5 (C-1'), 87.9 (C-4'), 106.1 (C-5), 124.3, 125.4, 127.1, 129.1, 130.4, 133.7, 144.2 (*Ph*-C, C-6), 146.9 (C-2), 163.5 (C-4), 165.3, 165.8 (2CO) ppm; MS: *m/z* (%) = 576 [(M⁺ + Na), 36.7].

1-(2-Deoxy-3,5-di-O,O-(4-methylbenzoyl)-α-D-ribofuranosyl)-2-(4-chlorophenylamino)-4-pyrimidinone (8c, C₃₁H₂₈ClN₃O₆)

White foam (0.10 g, 7%); ¹H NMR (CDCl₃, 250 MHz): δ = 2.34 (m, H-2'), 2.39, 2.48 (2s, 2CH₃), 2.65 (m, H-2'), 3.52–3.74 (m, H-5'), 4.53 (m, H-4'), 5.22 (m, H-3'), 6.01 (d, *J* = 3.3 Hz, H-5), 6.19 (m, H-1'), 7.05–7.96 (m, *Ph*-H, H-6)

ppm; ¹³C NMR (CDCl₃, 62.5 MHz): δ = 20.9, 21.7 (2CH₃), 39.7 (C-2'), 63.8 (C-5'), 74.3 (C-3'), 86.5 (C-1'), 87.8 (C-4'), 105.4 (C-5), 119.0, 124.7, 129.1, 132.4, 138.8, 143.4 (*Ph*-C, C-6), 163.7 (C-4), 165.4, 165.9 (2CO) ppm; MS: *m/z* (%) = 596 [M⁺ + Na], 35.4].

1-(2-Deoxy-α/β-D-ribofuranosyl)-2-(arylamino)-4-pyrimidinones 9a–9c, and 10a–10c

Compounds **7a–7c** and **8a–8c** (0.2 mmol) in 10 cm³ saturated NH₃/MeOH were stirred at room temperature for 16 h. The resulting solution was evaporated till dryness under reduced pressure. The residue was chromatographed on a silica gel column with 8% MeOH in CH₂Cl₂ to give **9a–9c** in 92–94% and **10a–10c** in 92–93% yields.

1-(2-Deoxy-β-D-ribofuranosyl)-2-(phenylamino)-4-pyrimidinone (9a, C₁₅H₁₇N₃O₄)

White foam (0.06 g, 94%); ¹H NMR (DMSO-d₆, 250 MHz): δ = 2.55–2.65 (m, H-2'), 3.49–3.75 (m, H-5'), 4.24 (m, H-4'), 4.48 (m, H-3'), 5.08, 5.22 (2s, 2OH), 5.98 (d, *J* = 3.7 Hz, H-5), 6.19 (dd, *J* = 6.7, 4.7 Hz, H-1'), 7.22–7.48 (m, *Ph*-H), 7.58 (d, *J* = 6.8 Hz, H-6) ppm; ¹³C NMR (DMSO-d₆, 62.5 MHz): δ = 39.6 (C-2'), 61.6 (C-5'), 70.8 (C-3'), 84.8 (C-4'), 87.6 (C-1'), 105.8 (C-5), 121.6, 122.4, 130.1, 132.2, 137.8, 143.5 (*Ph*-C, C-6), 147.2 (C-2), 163.2 (C-4) ppm; MS: *m/z* (%) = 304 [(M⁺ + 1), 17.7].

1-(2-Deoxy-β-D-ribofuranosyl)-2-[methyl(phenyl)amino]-4-pyrimidinone (9b, C₁₆H₁₉N₃O₄)

White foam (0.06 g, 92%); ¹H NMR (DMSO-d₆, 250 MHz): δ = 2.38–2.54 (m, H-2'), 3.48 (s, CH₃), 3.49–3.72 (m, H-5'), 4.14 (m, H-4'), 4.42 (m, H-3'), 5.16, 5.25 (2br s, 2OH), 6.08 (d, *J* = 3.7 Hz, H-5), 6.27 (dd, *J* = 6.6, 4.5 Hz, H-1'), 7.28–7.53 (m, *Ph*-H), 7.64 (d, *J* = 6.4 Hz, H-6) ppm; ¹³C NMR (DMSO-d₆, 62.5 MHz): δ = 34.2 (CH₃), 38.8 (C-2'), 61.6 (C-5'), 70.8 (C-3'), 85.6 (C-4'), 87.9 (C-1'), 106.1 (C-5), 125.6, 129.5, 132.6, 144.8 (*Ph*-C, C-6), 147.0 (C-2), 164.7 (C-4) ppm; MS: *m/z* (%) = 318 [(M⁺ + 1), 18.7].

1-(2-Deoxy-β-D-ribofuranosyl)-2-(4-chlorophenylamino)-4-pyrimidinone (9c, C₁₅H₁₆ClN₃O₄)

White foam (0.06 g, 94%); ¹H NMR (DMSO-d₆, 250 MHz): δ = 2.52–2.64 (m, H-2'), 3.46–3.70 (m, H-5'), 4.20 (m, H-4'), 4.42 (m, H-3'), 5.10, 5.19 (2br s, 2OH), 5.99 (d, *J* = 3.8 Hz, H-5), 6.26 (dd, *J* = 6.4, 4.8 Hz, H-1'), 7.06–7.51 (dd, *J* = 8.2, 4.3 Hz, *Ph*-H), 7.62 (d, *J* = 7.0 Hz, H-6) ppm; ¹³C NMR (DMSO-d₆, 62.5 MHz): δ = 39.6 (C-2'), 62.0 (C-5'), 71.1 (C-3'), 84.8 (C-4'), 87.4 (C-1'), 105.8 (C-5), 118.7, 125.1, 128.6, 132.5, 137.8, 143.4 (*Ph*-C, C-6), 147.4 (C-2), 163.8 (C-4) ppm; MS: *m/z* (%) = 338 [(M⁺ + 1), 23.1].

1-(2-Deoxy-α-D-ribofuranosyl)-2-(phenylamino)-4-pyrimidinone (10a, C₁₅H₁₇N₃O₄)

White foam (0.06 g, 93%); ¹H NMR (DMSO-d₆, 250 MHz): δ = 2.17, 2.89 (m, H-2'), 3.11–3.29 (m, H-5'), 3.79 (m, H-4'), 4.42 (m, H-3'), 5.98 (d, *J* = 3.5 Hz, H-5), 6.24 (m, H-1'), 7.20–7.49 (m, *Ph*-H), 7.62 (d, *J* = 6.7 Hz, H-6) ppm; ¹³C NMR

(DMSO-*d*₆, 62.5 MHz): δ = 40.7 (C-2'), 62.8 (C-5'), 74.6 (C-3'), 87.8 (C-1'), 88.2 (C-4'), 105.5 (C-5), 122.9, 131.1, 133.2, 137.2, 143.7 (*Ph*-C, C-6), 147.3 (C-2), 163.8 (C-4) ppm; MS: m/z (%) = 304 [(M⁺ + 1), 17.7].

1-(2-Deoxy- α -D-ribofuranosyl)-2-[methyl(phenyl)amino]-4-pyrimidinone (**10b**, C₁₆H₁₉N₃O₄)

White foam (0.06 g, 93%); ¹H NMR (DMSO-*d*₆, 250 MHz): δ = 2.24, 2.84 (m, H-2'), 3.18–3.36 (m, H-5'), 3.52 (s, CH₃), 3.84 (m, H-4'), 4.39 (m, H-3'), 6.04 (d, J = 3.4 Hz, H-5), 6.21 (m, H-1'), 7.16–7.46 (m, *Ph*-H), 7.59 (d, J = 6.6 Hz, H-6) ppm; ¹³C NMR (DMSO-*d*₆, 62.5 MHz): δ = 34.6 (CH₃), 40.6 (C-2'), 63.2 (C-5'), 74.7 (C-3'), 87.5 (C-1'), 87.9 (C-4'), 106.5 (C-5), 125.7, 128.9, 133.3, 144.4 (*Ph*-C, C-6), 146.9 (C-2), 163.8 (C-4) ppm; MS: m/z (%) = 318 [(M⁺ + 1), 18.8].

1-(2-Deoxy- α -D-ribofuranosyl)-2-(4-chlorophenylamino)-4-pyrimidinone (**10c**, C₁₅H₁₆ClN₃O₄)

White foam (0.06 g, 92%); ¹H NMR (DMSO-*d*₆, 250 MHz): δ = 2.26, 2.84 (m, H-2'), 3.18–3.30 (m, H-5'), 3.82 (m, H-4'), 4.39 (m, H-3'), 5.95 (d, J = 3.5 Hz, H-5), 6.22 (m, H-1'), 7.10–7.54 (dd, J = 8.3, 4.4 Hz, *Ph*-H), 7.64 (d, J = 6.8 Hz, H-6) ppm; ¹³C NMR (DMSO-*d*₆, 62.5 MHz): δ = 40.4 (C-2'), 62.6 (C-5'), 73.7 (C-3'), 87.5 (C-1'), 87.9 (C-4'), 105.6 (C-5), 119.4, 124.9, 129.1, 133.3, 137.7, 143.8 (*Ph*-C, C-6), 147.5 (C-2), 163.9 (C-4) ppm; MS: m/z (%) = 338 [(M⁺ + 1), 32.1].

References

- [1] Les A, Adamowicz L (1990) *J Phys Chem* **94**: 7021
- [2] Matsukawa T, Ban S, Shirakawa K, Yoneda M (1953) *Yakugaku Zasshi* **73**: 159
- [3] Lever OW Jr, Bell LN, Hyman C, McGuire HM, Ferone R (1986) *J Med Chem* **29**: 665
- [4] Biswas G, Litaka I, Shugar D, Banerjee A (1989) *Nucleos Nucleot* **8**: 1335
- [5] Cooper DG, Durant GJ, Ganellin CR, Ife RJ, Meeson ML, Sach GS (1991) *Il Farmaco* **46**: 3
- [6] Taylor EC, Young WB (1995) *J Org Chem* **60**: 7947
- [7] Mager S, Diudea M, Jugrestan F, Cristea I, Panea I (1981) Romanian Patent 76712, (1983) *Chem Abstr* **99**: 158454e
- [8] Panea I, Mager S, Farcasan V, Hopartean I, Paiu F, Cristea I, Popa V (1981) Romanian Patent 77114 (1985) *Chem Abstr* **102**: 62259z
- [9] Taylor EC, Zhou P (1997) *Tetrahedron Lett* **38**: 4339
- [10] Yakovlev KL, Stetsenko AI, Tulub AA (1987) 5th Int. Symp. on Platinum and Other Coordination Compounds in Cancer Chemotherapy. Padua, p 361
- [11] Toledo LM, Musa K, Lauher JW, Fowler FW (1995) *Chem Mater* **7**: 1639
- [12] Buhlman P, Simon W (1993) *Tetrahedron* **49**: 7627
- [13] Shiho D, Takabayashi N (1955) *Nippon Kagaku Zasshi* **76**: 877
- [14] Rich A (1962) On the Problems of Evolution and Biochemical Information Transfer. In: *Horizons in Biochemistry*, Academic Press, New York, p 103
- [15] Benner SA, Alleman RK, Ellington AD, Ge L, Glasfeld A, Leanz GF, Krauch T, MacPherson LJ, Moroney SE, Piccirilli AJ, Weinhold E (1987) *Cold Spring Harb Symp Quant Biol* **52**: 53
- [16] Switzer C, Moroney SE, Benner SA (1989) *J Am Chem Soc* **111**: 8322
- [17] Piccirilli JA, Krauch T, Moroney SE, Benner SA (1990) *Nature* **343**: 33
- [18] Voegel JJ, Benner SA (1996) *Helv Chim Acta* **79**: 1863
- [19] Brown TH, Blakemore RC, Emmett GJ, Robin GC, Parsons ME, Anthony DA, Walker TF (1988) *Eur J Med Chem* **23**: 53
- [20] Wittenburg EZ (1964) *Chemistry* **4**: 303
- [21] Vorbrüggen H, Krolikiewicz K, Bennua B (1981) *Chem Ber* **114**: 1234
- [22] a) Hansen P, Pedersen EB (1990) *Acta Chem Scand* **44**: 522; b) Motawia MS, Pedersen EB (1990) *Liebigs Ann Chem* **599**
- [23] a) Abdel Magied AE-S, Ali OM, Kofoed K, Pedersen EB (2001) *Nucleos Nucleot Nucl* **20**: 1; b) Jin S, Miduturu CV, McKinney DC, Silverman SK (2005) *J Org Chem* **70**: 4284; c) Kosiova I, Kovackova S, Kois P (2007) *Tetrahedron* **63**: 312