# Synthesis and anti-HBV activity of isocytosine derivatives linked to 5-position of methyl β-D-ribofuranoside

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A series of isocytosine derivatives linked to the 5-position of methyl β-D-ribofuranoside were synthesised. The new compounds were evaluated *in vitro* for cytotoxicity against hepatitis B virus (HBV) and showed moderate activity.

**Keywords:** cytosine, isocytosine, guanine, antiviral activity

Modified nucleosides and nucleic aãd bases have been a subject of many studies due to their potential activity as enzyme inhibitors resulting in antitumor[1] and antiviral activity.[2] 1-(α-D-Arabinofuranosyl)cytosine (ara-C)[3] has been used in treatment of acute myeloblastic leukemia[4] and 2,2'-anhydro-1-(α-D-arabinofuranosyl)cytosine is a highly effective antitumor agent.[5] 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.[6] A variety of 2-amino-4-pyrimidinones display anticancer, antiviral, antibacterial properties,[7] or are valuable agrochemicals.[8] Speãfically, platinum group metal complexes of isocytosine and derivatives attract considerable attention because of their antitumor activity.[9] The isocytosine system has been recently explored, as a versatile, easily accessible, building block for supramolecular synthesis.[10] Consequently, it becomes interesting to synthesise new isocytosine derivatives. In continuation of our work on the synthesis of modified nucleosides with anti-HBV activities we report on the synthesis and anti-HBV activity of methyl 5-deoxy-5-(pyrimidin-2-ylamino)-β-D-ribofuranosides **4a–d** and methyl 5-*O*-(pyrimidin-2-ylaminoethyl)-β-D-ribofuranosides **10a–d** derivatives.

## Results and discussion

*Chemistry*

A solution of D-ribose in acetone/2,2-dimethoxypropane/methanol saturated with hydrogen chloride afforded after stirring methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside.[11]

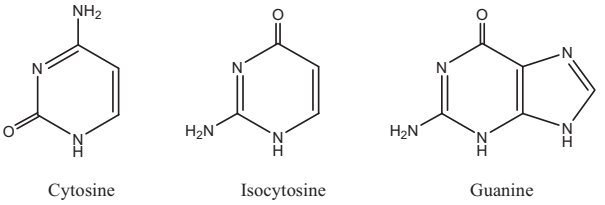
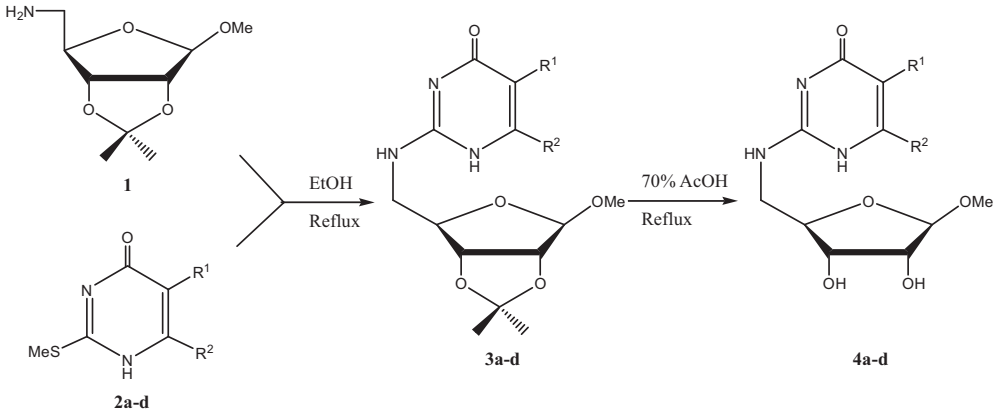



**Fig. 1**

Tosylation and subsequent displacement of the 5-tosyloxy group with potassium phthalimide in the presence of sodium iodide gave methyl 5-deoxy-2,3-*O*-isopropylidene-5-phthalimido-β-D-ribofuranoside.[12] The latter was deprotected with hydrazine hydrate in methanol to afford methyl 5-amino-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside(**1**).[13] 2-Methyl-thiouraãls **2a–d** were prepared according to the method described by Brown *et. al*.[14] When **2a–d** were treated with **1** in ethanol under reflux, nucleophilic substitution reaction was occurred on the pyrimidine ring and the corresponding isocytosine derivatives **3a–d** were produced in 61–70% yield after chromatographic purification. The $^1$H NMR spectra of compounds **3a–d** showed two singlets at δ 1.30–1.45 and 1.50–1.63 corresponding to the isopropylidine group. The methoxy groups appear as singlet in the range δ 3.31–3.37. Deprotection of **3a–d** using 70% AcOH at reflux temperature afforded methyl 5-deoxy-5-(pyrimidin-2-ylamino)-β-D-ribofuranosides **4a–d** in 67–71%. The structures of **4a–d** were confirmed by studying $^1$H NMR spectra, which showed the disappearance of the isopropylidine group.




| 2-4 | a | b | c | d |
|---|---|---|---|---|
| $R^1$ | H | Me | H | H |
| $R^2$ | H | H | Me | Pr |

**Scheme 1**

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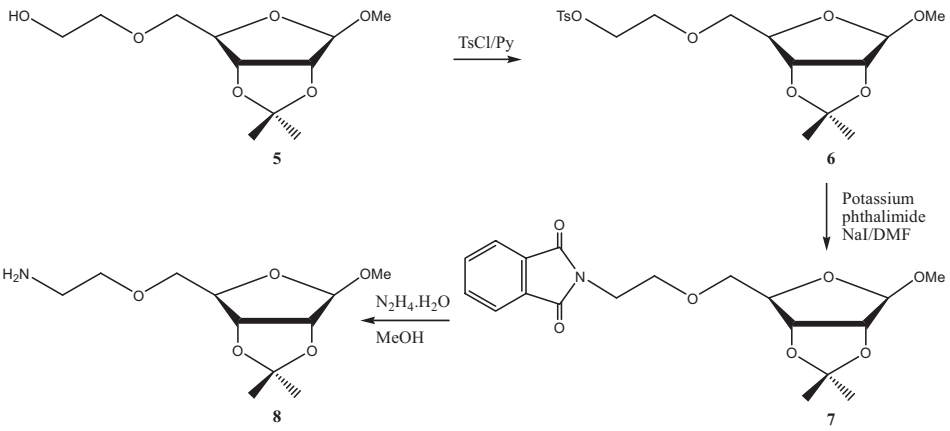



**Scheme 2**

Methyl 5-*O*-(2-hydroxyethyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) was synthesised according to the method described by Coat and David.[15] Tosylation of **5** using *p*-toluenesulfonyl chloride in pyridine afforded **6** in 90% yield. Displacement of the tosyloxy group with potassium phthalimide and sodium iodide in DMF afforded methyl 2,3-*O*-isopropylidene-5-*O*-phthalimidoethyl-β-D-ribofuranoside (**7**) in 93% yield. Phthalimido group was deprotected with hydrazine hydrate in methanol at reflux temperature to afford the corresponding amino derivative **8** in 89% yield.

By the same way when compounds **2a–d** were treated with **8**, the corresponding isocytosine derivatives **9a–d** were produced in 80–88% yield, after purification on silica gel column chromatography. Deprotection of **9a–d** afforded **10a–d** in 74–80%.

*Antiviral screening*

Preliminary viral screening against HBV (Hep G2 2.2.15 cell method)[16-19] indicated that compounds **4b, 4d** and **10b** showed high viral replication inhibition and mild cytotoxiãty with selective indexes 166.6–500.0, while compounds **4a, 4c, 10a, 10c** and **10d** showed high inhibition with moderate cytotoxiãty.

## Experimental

Melting points were determined using a Kofler block instrument. $^1$H NMR spectra were recorded with Bruker AC 250 FT NMR spectrometer at 250 MHz with TMS as an internal standard. EIMS spectra were recorded with a Finnigen MAT 312/AMD. The microanalyses were performed at the microanalytical unit, Universität Konstanz, Germany. Viral screening against HBV was conducted at the National Liver Institute, Menoufia University, Egypt.

*Methyl 5-deoxy-2,3-O-isopropylidene-5-(pyrimidin-2-ylamino)-β-D-ribofuranosides* **3a–d**

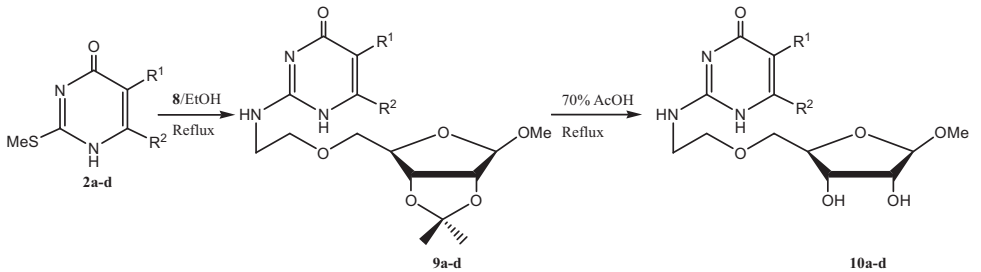
A solution of **2a–d** (5 mmol) and **1** (1.01 g, 5 mmol) in ethanol (20 ml) was stirred under reflux for 3 h. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column with 5% MeOH in $CHCl_3$ to give **3a–d** in 61–70% yields.

*Methyl 5-deoxy-2,3-O-isopropylidene-5-(pyrimidin-2-ylamino)-β-D-ribofuranoside* (**3a**): Yield 67% as a white foam. $^1$H NMR ($CDCl_3$) δ: 1.30 (s, 3 H, $CH_3$), 1.50 (s, 3 H, $CH_3$), 3.35 (s, 3 H, OMe), 4.43–4.55 (m, 3 H, H-4', H-5'), 4.68 (d, 1 H, *J* = 5.9 Hz, H-3'), 4.89 (d, 1 H, *J* = 5.9 Hz, H-2'), 5.03 (s, 1 H, H-1'), 6.48 (d, 1 H, *J* = 5.0 Hz, H-5), 7.00 (t, 1 H, *J* = 4.1 Hz, NH), 8.25 (d, 1 H, *J* = 5.0 Hz, H-6). EI-MS: *m/z* (%): 297 (33). Anal. Calcd. for $C_{13}H_{19}N_3O_5$: C, 52.51; H, 6.44; N, 14.13. Found: C, 52.40; H, 6.33; N, 14.00%.

*Methyl 5-deoxy-2,3-O-isopropylidene-5-(5-methylpyrimidin-2-ylamino)-amino-β-D-ribofuranoside* (**3b**): Yield 70% as a white foam. $^1$H NMR ($CDCl_3$) δ: 1.31 (s, 3 H, $CH_3$), 1.51 (s, 3 H, $CH_3$), 2.05 (s, 3 H, $CH_3$), 3.37 (s, 3 H, OMe), 4.35–4.70 (m, 3 H, H-4', H-5'), 4.81 (d, 1 H, *J* = 5.9 Hz, H-3'), 4.80 (d, 1 H, *J* = 5.9 Hz, H-2'), 5.00 (s, 1 H, H-1'), 7.01 (t, 1 H, *J* = 4.0 Hz, NH), 8.05 (s, 1 H, H-6). EI-MS: *m/z* (%): 311 (39). Anal. Calcd. for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.79; N, 13.49. Found: C, 53.89; H, 6.65; N 13.30%.

*Methyl 5-deoxy-2,3-O-isopropylidene-5-(6-methylpyrimidin-2-ylamino)-β-D-ribofuranoside* (**3c**): Yield 63% as a white foam. $^1$H NMR ($CDCl_3$) δ: 1.33 (s, 3 H, $CH_3$), 1.50 (s, 3 H, $CH_3$), 2.38 (s, 3 H, $CH_3$), 3.33 (s, 3 H, OMe), 4.40–4.54 (m, 3 H, H-4', H-5'), 4.71 (d, 1 H, *J* = 5.8 Hz, H-3'), 4.85 (d, 1 H, *J* = 5.8 Hz, H-2'), 5.05 (s, 1 H, H-1'), 6.30 (s, 1 H, H-5), 6.98 (t, 1 H, *J* = 4.2 Hz, NH). EI-MS: *m/z* (%): 311 (17). Anal. Calcd. for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.79; N, 13.49. Found: C, 53.83; H, 6.66; N, 13.29%.

*Methyl 5-deoxy-2,3-O-isopropylidene-5-(6-propylpyrimidin-2-ylamino)-β-D-ribofuranoside* (**3d**): Yield 61% as a white foam. $^1$H NMR ($CDCl_3$) δ: 0.98 (t, 3 H, *J* = 7.5 Hz, $CH_3$), 1.45 (s, 3 H, $CH_3$), 1.63 (s, 3 H, $CH_3$), 1.81–1.95 (m, 2 H, $CH_2$), 2.55–2.65 (m, 2 H, $CH_2$), 3.31 (s, 3 H, OMe), 4.42–4.53 (m, 3 H, H-4', H-5'), 4.71 (d, 1 H, *J* = 5.9 Hz, H-3'), 4.82 (d, 1 H, *J* = 5.9 Hz, H-2'), 5.04 (s, 1 H, H-1'), 6.25 (s, 1 H, H-5), 6.99 (t, 1 H, *J* = 4.0 Hz, NH). EI-MS: *m/z* (%): 339 (29). Anal. Calcd. for $C_{16}H_{25}N_3O_5$: C, 56.62; H, 7.42; N, 12.38. Found: C, 56.50; H, 7.30; N, 12.20%.




**2a-d** **9a-d** **10a-d**

| 2,9,10 | a | b | c | d |
|---|---|---|---|---|
| $R^1$ | H | Me | H | H |
| $R^2$ | H | H | Me | Pr |

**Scheme 3**

*Methyl 5-deoxy-5-(pyrimidin-2-ylamino)-β-D-ribofuranosides* **4a–d**
Compounds **3a–d** (0.25 g) were refluxed in 80% aqueous acetic aãd (10 ml) for 2 h. The solvents were removed *in vacuo* and the residue coevaporated with water (4 × 5 ml) and finally EtOH (3 × 5 ml). The residue was purified on column chromatography using 10% MeOH in $CHCl_3$ to give **4a–d** in 67–71% yields.

*Methyl 5-deoxy-5-(pyrimidin-2-ylamino)*-β-*D-ribofuranoside* (**4a**): Yield 70% as a white foam. $^1$H NMR (DMSO-$d_6$) δ: 3.35 (s, 3 H, OMe), 4.41–4.55 (m, 3 H, H-4', H-5'), 4.70–4.81 (m, 2 H, H-2', H-3'), 5.01 (s, 1 H, H-1'), 5.25 (d, 1 H, *J* = 5.9 Hz, 3'-OH), 5.56 (d, 1 H, *J* = 5.9 Hz, 2'-OH), 6.50 (d, 1 H, *J* = 5.0 Hz, H-5), 7.00 (t, 1 H, *J* = 4.1 Hz, NH), 8.20 (d, 1 H, *J* = 5.0 Hz, H-6). EI-MS: *m/z* (%): 257 (51). Anal. Calcd. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.87; N, 16.33. Found: C, 46.53; H, 5.66; N, 16.16%.

*Methyl 5-deoxy-5-(5-methylpyrimidin-2-ylamino)*-β-*D-ribofuranoside* (**4b**): Yield 71%. M.p. 116–117°C. $^1$H NMR (DMSO-$d_6$) δ: 2.10 (s, 3 H, $CH_3$), 3.35 (s, 3 H, OMe), 4.48–4.58 (m, 3 H, H-4', H-5'), 4.78 (d, 1 H, *J* = 5.9 Hz, H-3'), 4.88 (d, 1 H, *J* = 5.9 Hz, H-2'), 5.01 (s, 1 H, H-1'), 5.31 (d, 1 H, *J* = 5.9 Hz, 3'-OH), 5.61 (d, 1 H, *J* = 5.9 Hz, 2'-OH), 7.05 (t, 1 H, *J* = 4.2 Hz, NH), 8.02 (s, 1 H, H-6). EI-MS: *m/z* (%): 271 (67). Anal. Calcd. for $C_{11}H_{17}N_3O_5$ C, 48.70; H, 6.31; N, 15.48. Found: C, 48.60; H, 6.21; N, 15.37%.

*Methyl 5-deoxy-5-(6-methylpyrimidin-2-ylamino)*-β-*D-ribofuranoside* (**4c**): Yield 69%. M.p. 134–135°C. $^1$H NMR (DMSO-$d_6$) δ: 2.35 (s, 3 H, $CH_3$), 3.35 (s, 3 H, OMe), 4.45–4.55 (m, 3 H, H-4', H-5'), 4.61 (d, 1 H, *J* = 5.8 Hz, H-3'), 4.75 (d, 1 H, *J* = 5.8 Hz, H-2'), 5.02 (s, 1 H, H-1'), 5.30 (d, 1 H, *J* = 5.9 Hz, 3'-OH), 5.60 (d, 1 H, *J* = 5.9 Hz, 2'-OH), 6.28 (s, 1 H, H-5), 7.02 (t, 1 H, *J* = 4.0 Hz, NH). EI-MS: *m/z* (%): 271 (54). Anal. Calcd. for $C_{11}H_{17}N_3O_5$: C, 48.70; H, 6.31; N, 15.48. Found: C, 48.63; H, 6.36; N, 15.50%.

*Methyl 5-deoxy-5-(6-propylpyrimidin-2-ylamino)*-β-*D-ribofuranoside* (**4d**): Yield 67%. M.p. 154–156°C. $^1$H NMR (DMSO-$d_6$) δ: 0.95 (t, 3 H, *J* = 7.2 Hz, $CH_3$), 1.60–1.75 (m, 2 H, $CH_2$), 2.50–2.65 (m, 2 H, $CH_2$), 3.35 (s, 3 H, OMe), 4.45–4.55 (m, 3 H, H-4', H-5'), 4.62 (d, 1 H, *J* = 5.9 Hz, H-3'), 4.73 (d, 1 H, *J* = 5.9 Hz, H-2'), 5.01 (s, 1 H, H-1'), 5.30 (d, 1 H, *J* = 5.9 Hz, 3'-OH), 5.60 (d, 1 H, *J* = 5.9 Hz, 2'-OH), 6.28 (s, 1 H, H-5), 7.01 (t, 1 H, *J* = 4.0 Hz, NH). EI-MS: *m/z* (%): 299 (44). Anal. Calcd. for $C_{13}H_{21}N_3O_5$: C, 52.16; H, 7.07; N, 14.03. Found: C, 52.23; H, 7.17; N, 14.20%.

*Methyl 2,3-O-isopropylidene-5-O-[2-(p-toluenesulfonyloxyethyl)]*-β-*D-ribofuranoside* (**6**): *p*-Toluenesulfonyl chloride (9.52 g, 50 mmol) was added in a small portions to a stirred cold solution of **5** (12.15 g, 49 mmol) in dry pyridine (100 ml). The reaction mixture was stirred overnight at room temperature. The solvent was evaporated and coevaporated with toluene. The residue was dissolved in water (100 ml) and extracted with dichloromethane (3×50 ml). The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure to give **6** (17.72 g, 90%). M.p. 91–93°C. $^1$H NMR ($CDCl_3$) δ: 1.28 (s, 3 H, $CH_3$), 1.44 (s, 3 H, $CH_3$), 2.42 (s, 3 H, $CH_3$), 3.29 (s, 3 H, OMe), 3.67 (d, 2 H, *J* = 6.5 Hz, H-5), 3.88–4.00 (m, 4 H, 2xOCH$_2$), 4.31 (t, 1 H, *J* = 6.5 Hz, H-4), 4.52 (d, 1 H, *J* = 5.9 Hz, H-3), 4.61 (d, 1 H, *J* = 5.9 Hz, H-2), 4.99 (s, 1 H, H-1), 7.35 (d, 2 H, *J* = 7.9 Hz, Ar-H), 7.70 (d, 2 H, *J* = 8.0 Hz, Ar-H). EI-MS: *m/z* (%): 402 (19). Anal. Calcd. for $C_{18}H_{26}O_8S$: C, 53.72; H, 6.51. Found: C, 53.60; H, 6.31%.

*Methyl 2,3-O-isopropylidene-5-O-phthalimidoethyl-β-D-ribofuranoside* (**7**): A suspension of **6** (11.25 g, 28 mmol), potassium phthalimide (6.7 g, 36 mmol) and sodium iodide (8 g) in dry DMF (100 ml) was heated at about 150°C for 20 min. The resulting solution was cooled and poured into 1l of ice water. The colourless crystals which formed were collected by filtration and washed with water to yield 9.81 g (93%). M.p. 145–147°C. $^1$H NMR ($CDCl_3$) δ: 1.30 (s, 3 H, $CH_3$), 1.43 (s, 3 H, $CH_3$), 3.32 (s, 3 H, OMe), 3.60 (d, 2 H, *J* = 6.5 Hz, H-5), 3.68 (m, 2 H, $OCH_2$), 4.08 (m, 2 H, $NCH_2$), 4.37 (t, 1 H, *J* = 6.5 Hz, H-4), 4.49 (d, 1 H, *J* = 5.9 Hz, H-3), 4.58 (d, 1 H, *J* = 5.9 Hz, H-2), 5.09 (s, 1 H, H-1), 7.95 (m, 2 H, Ar–H), 8.09 (m, 2 H, Ar–H). EI-MS: *m/z* (%): 377 (15). Anal. Calcd. for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.34; H, 6.05; N, 3.49%.

*Methyl 5-O-(2-aminoethyl)-2,3-O-isopropylidene*-β-*D-ribofuranoside* (**8**): A solution of **7** (2.82 g, 7.5 mmol) and 80% hydrazine hydrate (2 ml) in methanol (20 ml) was heated under reflux for 2 h. The methanol was removed *in vacuo* from the resulting suspension, and the white solid residue was dissolved in 40 ml of water and aãdified to pH 1. The preãpitate of phthalhydrazine was removed by filtration, and the colourless filtrate was brought to pH > 12. The basic solution was extracted three times with 30 ml of dichloromethane and the extracts were dried. Evaporation of the solvent gave 1.64 g (89%) of the colourless liquid amine. $^1$H NMR ($CDCl_3$) δ: 1.33 (s, 3 H, $CH_3$), 1.44 (s, 3 H, $CH_3$), 2.12 (brs, 2 H, $NH_2$), 2.59 (m, 2 H, $NCH_2$), 3.34 (s, 3 H, OMe), 3.48 (m, 2 H, $OCH_2$), 3.58 (d, 2 H, *J* = 6.5 Hz, H-5), 4.39 (t, 1 H, *J* = 6.5 Hz, H-4), 4.50 (d, 1 H, *J* = 5.9 Hz, H-3), 4.59 (d, 1 H, *J* = 5.9 Hz, H-2), 5.07 (s, 1 H, H-1). EI-MS: *m/z* (%): 247 (67). Anal. Calcd. for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.23; H, 8.29; N, 5.39%.

*Methyl 2,3-O-isopropylidene-5-(pyrimidin-2-ylaminoethyl)-β-D-ribofuranosides* **9a–d**
A solution of **2a–d** (5 mmol) and **8** (1.23 g, 5 mmol) in ethanol (20 ml) was stirred under reflux for 3–5 h (TLC). The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column using 5% MeOH in $CHCl_3$ to give **9a–d** in 80–88% yields.

*Methyl 2,3-O-isopropylidene-5-(pyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**9a**): Yield 85% as a white foam. $^1$H NMR ($CDCl_3$) δ: 1.33 (s, 3H, $CH_3$), 1.44 (s, 3H, $CH_3$), 3.34 (s, 3H, OMe), 4.38–4.82 (m, 9H, H-2', H-3', H-4', H-5', $OCH_2$, $NCH_2$), 5.08 (s, 1H, H-1'), 6.78 (d, 1H, *J* = 5.0 Hz, H-5), 7.08 (t, 1H, *J* = 4.1 Hz, NH), 7.17 (d, 1H, *J* = 5.0 Hz, H-6), 10.01 (brs, 1H, NH). EI-MS: *m/z* (%): 341 (15). Anal. Calcd. for $C_{15}H_{23}N_3O_6$: C, 52.78; H, 6.79; N, 12.31. Found: C, 52.70; H, 6.66; N, 12.23%.

*Methyl 2,3-O-isopropylidene-5-(5-methylpyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**9b**): Yield 88% as a white foam. $^1$H NMR ($CDCl_3$) δ: 1.31 (s, 3H, $CH_3$), 1.47 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 3.38 (s, 3H, OMe), 4.35–4.80 (m, 9H, H-2', H-3', H-4', H-5', $OCH_2$, $NCH_2$), 5.02 (s, 1H, H-1'), 7.00 (t, 1H, *J* = 4.0 Hz, NH), 8.09 (s, 1H, H-6), 10.01 (brs, 1H, NH). EI-MS: *m/z* (%): 355 (17). Anal. Calcd. for $C_{16}H_{25}N_3O_6$: C, 54.07; H, 7.09; N, 11.82. Found: C, 54.00; H, 6.97; N, 11.62%.

*Methyl 2,3-O-isopropylidene-5-(6-methylpyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**9c**): Yield 83% as a white foam. $^1$H NMR ($CDCl_3$) δ: 1.33 (s, 3H, $CH_3$), 1.48 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 3.35 (s, 3H, OMe), 4.30–4.79 (m, 9H, H-2', H-3', H-4', H-5', $OCH_2$, $NCH_2$), 5.00 (s, 1H, H-1'), 6.32 (s, 1H, H-5), 6.99 (t, 1H, *J* = 4.2 Hz, NH), 9.95 (brs, 1H, NH). EI-MS: *m/z* (%): 355 (14). Anal. Calcd. for $C_{16}H_{25}N_3O_6$: C, 54.07; H, 7.09; N, 11.82. Found: C, 53.93; H, 7.01; N, 11.77%.

*Methyl 2,3-O-isopropylidene-5-(6-propylpyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**9d**): Yield 80% as a white foam. $^1$H NMR ($CDCl_3$) δ: 0.99 (t, 3H, *J* = 7.5 Hz, $CH_3$), 1.42 (s, 3H, $CH_3$), 1.60 (s, 3H, $CH_3$), 1.80–1.99 (m, 2H, $CH_2$), 2.57–2.69 (m, 2H, $CH_2$), 3.35 (s, 3H, OMe), 4.33–4.84 (m, 9H, H-2', H-3', H-4', H-5', $OCH_2$, $NCH_2$), 5.01 (s, 1H, H-1'), 6.29 (s, 1H, H-5), 6.96 (t, 1H, *J* = 4.0 Hz, NH), 9.99 (brs, 1H, NH). EI-MS: *m/z* (%): 383 (13). Anal. Calcd. for $C_{18}H_{29}N_3O_6$: C, 56.38; H, 7.62; N, 10.96. Found: C, 56.31; H, 7.53; N, 10.82%.

*Methyl 5-(pyrimidin-2-ylaminoethyl)-β-D-ribofuranosides* **10a–d**
Compounds **9a–d** (0.25 g) were refluxed in 70% aqueous acetic aãd (10 ml) for 2 h. The solvents were removed *in vacuo* and the residue was coevaporated with water (4×5 ml) and finally EtOH (3×5 ml). The residue was purified on column chromatography using 10% MeOH in $CHCl_3$ to afford **10a–d** in 70–80% yields.

*Methyl 5-(pyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**10a**): Yield 78%. M.p. 133–135°C. $^1$H NMR (DMSO-$d_6$) δ: 3.36 (s, 3H, OMe), 4.43–4.90 (m, 9H, H-2', H-3', H-4', H-5', $OCH_2$, $NCH_2$), 5.01 (s, 1H, H-1'), 5.29 (d, 1H, *J* = 5.9 Hz, 3'-OH), 5.59 (d, 1H, *J* = 5.9 Hz, 2'-OH), 6.48 (d, 1H, *J* = 5.0 Hz, H-5), 7.03 (t, 1H, *J* = 4.1 Hz, NH), 8.18 (d, 1H, *J* = 5.0 Hz, H-6), 9.98 (brs, 1H, NH). EI-MS: *m/z* (%): 301 (34). Anal. Calcd. for $C_{12}H_{19}N_3O_6$: C, 47.84; H, 6.36; N, 13.95. Found: C, 47.77; H, 6.23; N, 13.79%.

*Methyl 5-(5-methylpyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**10b**): Yield 80%. M.p. 139–141°C. $^1$H NMR (DMSO-$d_6$) δ: 2.13 (s, 3H, $CH_3$), 3.39 (s, 3H, OMe), 4.45–4.98 (m, 9H, H-2', H-3', H-4', H-5', $OCH_2$, $NCH_2$), 5.04 (s, 1H, H-1'), 5.37 (d, 1H, *J* = 5.9 Hz, 3'-OH), 5.67 (d, 1H, *J* = 5.9 Hz, 2'-OH), 7.04 (t, 1H, *J* = 4.2 Hz, NH), 8.00 (s, 1H, H-6), 9.97 (brs, 1H, NH). EI-MS: *m/z* (%): 315 (29). Anal. Calcd. for $C_{13}H_{21}N_3O_6$: C, 49.52; H, 6.71; N, 13.33. Found: C, 49.43; H, 6.54; N, 13.19%.

*Methyl 5-(6-methylpyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**10c**): Yield 75%. M.p. 176–177°C. $^1$H NMR (DMSO-$d_6$) δ: 2.33 (s, 3H, $CH_3$), 3.38 (s, 3H, OMe), 4.45–4.98 (m, 9H, H-2', H-3', H-4', H-5', $OCH_2$, $NCH_2$), 5.02 (s, 1H, H-1'), 5.33 (d, 1H, *J* = 5.9 Hz, 3'-OH), 5.67 (d, 1H, *J* = 5.9 Hz, 2'-OH), 6.33 (s, 1H, H-5), 7.05 (t, 1H, *J* = 4.0 Hz, NH), 9.96 (brs, 1H, NH). EI-MS: *m/z* (%): 315 (26). Anal. Calcd. for $C_{13}H_{21}N_3O_6$: C, 49.52; H, 6.71; N, 13.33. Found: C, 49.47; H, 6.66; N, 13.21%.

*Methyl 5-(6-propylpyrimidin-2-ylaminoethyl)-β-D-ribofuranoside* (**10d**): Yield 70%. M.p. 199–201°C. $^1$H NMR (DMSO-$d_6$) δ: 0.94 (t, 3H, *J* = 7.2 Hz, $CH_3$), 1.63–1.79 (m, 2H, $CH_2$), 2.50–2.69 (m, 2H, $CH_2$), 3.38 (s, 3H, OMe), 4.45–4.98 (m, 9H, H-2', H-3', H-4', H-5',

$OCH_2$, $NCH_2$), 5.02 (s, 1H, H-1'), 5.33 (d, 1H, $J$ = 5.9 Hz, 3'-OH), 5.65 (d, 1H, $J$ = 5.9 Hz, 2'-OH), 6.31 (s, 1H, H-5), 7.04 (t, 1H, $J$ = 4.0 Hz, NH), 9.99 (brs, 1H, NH). EI-MS: *m/z* (%): 343 (21). Anal. Calcd. for $C_{15}H_{25}N_3O_6$: C, 52.47; H, 7.34; N, 12.24. Found: C, 52.33; H, 7.20; N, 12.09%.

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## References

1 M. MacCoss and M.J. Robins, In *Chemistry of Antitumor Agents* (D.E.V. Wilman (ed.)), Blackie UK 1990, p. 261; R. K. Robins and G. D. Kinin, In *Chemistry of Antitumor Agents,* (D.E.V. Wilman (ed.)), Blackie UK 1990, p. 299.
2 R.K. Robins and G.R. Revankar, In *Antiviral Drug Development* (E. De Clercq and R.T. Walker (eds.)), Plenum, New York 1988, p. 11.
3 W.K. Roberts and C.A. Dekker, *J. Org. Chem.*, 1967, **32**, 816; I.L. Doerr and J.J. Fox, *J. Org. Chem.*, 1967, **32**, 1462.
4 J.A. Montogomery, In *Cancer Chemotherapeutic Agents* (W.O. Foye (ed.)), American Chemical Soãety, DC Washington 1995, p. 47.
5 A. Rossi, In *Nucleoside Analogues. Chemistry, Biology, and Medical Application* (R.T. Walker, E. De Clercq and F. Eckstein (ed.)), Plenum, New York 1998, p. 59.
6 A. Les and L. Adamowicz, *J. Phys. Chem.*, 1990, **94**, 7021; A.V; Erkin and V.I. Krutikov, *Zh. Obshch. Kim.*, 2005, **75**, 677; 2005, **75**, 1898; 2006, **76**, 501.
7 T. Matsukawa, S. Ban, K. Shirakawa and M. Yoneda, *Yakugaku Zasshi*, 1953, **73**, 159; O. WJr Lever, L.N. Bell, C. Hyman, H.M. McGuire and R. Ferone, *J. Med. Chem.*, 1986, **29**, 665; G. Biswas, I. Litaka, D. Shugar and A. Banerjee, *Nucleosides & Nucleotides*, 1989, **8**, 1335; D.G. Cooper, G.J. Durant, C.R. Ganellin, R.J. Ife, M.L. Meeson and G.S. Sach, *Il Farmaco*, 1991, **46**, 3; E.C. Taylor and W.B. Young, *J. Org. Chem.*, 1995, **60**, 7947.
8 S. Mager, M. Diudea, F. Jugrestan, I. Cristea and I. Panea, *Romanian Patent*, 1981, 76712, *Chem. Abstr.*, 1983, **99**, 158454e; I. Panea, S. Mager, V. Farcasan, I. Hopartean, F. Paiu, I. Cristea and V. Popa, *Romanian Patent*, 1981, 77114, *Chem. Abstr.*, 1985, **102**, 62259z; E.C. Taylor and P. Zhou, *Tetrahedron Lett.*, 1997, **38**, 4339.
9 K.L. Yakovlev, A.I. Stetsenko and A.A. Tulub, *5th Int. Symp. Platinum and Other Coordination Compounds in Cancer Chemotherapy* 1987, p. 361.
10 R.-F. Liao, J.W. Lauher and F.W. Fowler, *Tetrahedron*, 1996, **52**, 3153; L.M. Toledo, K. Musa, J.W. Lauher and F.W. Fowler, *Chem. Mater.*, 1995, **7**, 1639; F.H. Beijer, R.P. Sijbesma, H. Kooijman, A.L. Speck and F.W. Meijer, *J. Am. Chem. Soc.*, 1998, **120**, 6761; B.D. Sharma and J.F. McConnell, *Acta Cryst.*, 1965, **19**, 797; R. Custelcean and L. Craãum, *Tetrahedron*, 2000, **56**, 5067; I. Krizmanić, A. Višnjevac, M. Luić, L. Glavaš, G.-O. Zinić and B. Zinić, *Tetrahedron*, 2003, **59**, 4047; H.M. Keizer, R.P. Sijbesma and E.W. Meijer, *Eur. J. Org. Chem.*, 2004, 2553.
11 E.J. Reist, R.R. Spencer, M.E. Wain, I.G. Junga, L. Goodman and B.R. Baker, *J. Org. Chem.*, 1961, **26**, 2821; R. Baker and H.G. Fletcher, *J. Org. Chem.*, 1961, **26**, 4605; J.A. Montogomery and K. Hewson, *J. Org. Chem.*, 1964, **29**, 3436; A.A.-H. Abdel-Rahman, A.E.-S. Abdel-Megied, A.E.-S. Goda, I.F. Zeid and E.S.H.El Ashry, *Nucleosides, Nucleotides, Nucleic Aãds*, 2003, **22**, 2027.
12 P.A. Levene and E.T. Sitlier, *J. Biol. Chem.*, 1934, **104**, 299.
13 N.J. Leonard and K.L. Carraway, *J. Heterocycl. Chem.*, 1966, **3**, 485.
14 T.H. Brown, R.C. Blakemore, G.J. Emmett, G.C. Robin, M.E. Parsons, D.A. Anthony and T.F. Walker, *Eur. J. Med. Chem.*, 1988, **23**, 53.
15 J.P. Coat and S. David, *Carbohydr. Res*., 1970, **12**, 335.
16 M.A. Sells, A.Z. Zelent, M. Shvartsman and G. Acs, *J. Virol.*, 1988, **62**, 2836.
17 M.A. Sells, M.L. Chen and G. Acs, *Proc. Nat. Acad. Sã. USA*, 1987, **84**, 1005.
18 B.E. Korba and J.L. Gerin, *Antiviral Res.*, 1992, **19**, 55.
19 T. Fouad, C. Nielsen, L. Brunn and E.B. Pederson, *J. Az. Med. Fac. (GIRLS)*, 1998, **19**, 1173.