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Synthesis and Biological Evaluation of Some Novel 4′-Thio-L-ribonucleosides with Modified Nucleobase Moieties

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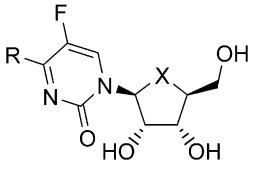
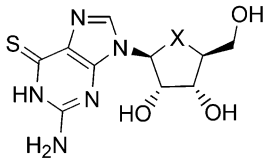
Abstract—1,2,3,5-Tetra-*O*-acetyl-4-thio-β-L-ribofuranose (**13**) was synthesized by an improved five-step sequence starting from methyl α-D-lyxopyranoside. Compound **13** was then converted to the corresponding L-4′-thionucleosides **4**–**6** and **19** by a modified Vorbrüggen procedure. All of these nucleoside analogues were tested for their antitumour activity in vitro.

The discovery that replacement of the furanose ring-oxygen with a sulphur atom leads to promising antiviral or antitumour nucleosides has stimulated the synthesis of this class of compounds.[1] A number of syntheses of β-D-4′-thionucleosides have been reported,[2] along with a limited number of syntheses of their L-enantiomers.[3] Some of these representatives, as for example D-4′-thio-5-fluorouridine[2b,d] and 9-(4′-thio-β-D-ribofuranosyl)-6-mercaptopurine[2g] showed marked cytotoxicity against the leukemia L-1210 and certain human tumours. In contrast to L-4′-thionucleosides, a number of L-ribonucleoside analogues have been synthesized,[4] including the β-L-ribofuranosyl-5-fluorouracil[4a] (**1**), β-L-ribofuranosyl-5-fluorocytosine[4a] (**2**), as well as the 9-(β-L-ribofuranosyl)-6-mercaptoguanine[5] (**3**). However, there has been no report in literature concerning either the synthesis or the biological data of 4′-thio-L-ribonucleosides bearing modified nucleobase moieties. In this paper we wish to report on the synthesis of three novel 4′-thio-L-ribonucleosides of 5-fluorouracil (**4**), 5-fluorocytosine (**5**), and 6-mercaptoguanine (**6**), along with their effects on the proliferation of some malignant and normal cells.



1 R = OH, X = O
2 R = NH_2, X = O
4 R = OH, X = S
5 R = NH_2, X = S



3 X = O
6 X = S

Chemistry

The 1,2,3,5-tetra-*O*-acetyl-4-thio-β-L-ribofuranose (**13**), a key intermediate in the synthesis of the corresponding 4′-thio-L-nucleosides, has been synthesized previously by Reist et al.[6] starting from D-lyxose. This approach afforded the product **13** as a mixture of the corresponding α- and β-anomers in 13.6% overall yield from six synthetic steps. By modifying the original procedure[6] we have prepared pure β-anomer **13** starting from methyl α-D-lyxopyranoside (**7**, Scheme 1), which is readily available from D-lyxose,[6] or D-xylose.[7] The first step of the sequence (**7**→**8**) was carried out as earlier described.[6] However, 4-*S*-acetyl derivative **10** was synthesized from alcohol **8** via the triflic ester **9**. This enabled the usage of milder reaction conditions in the

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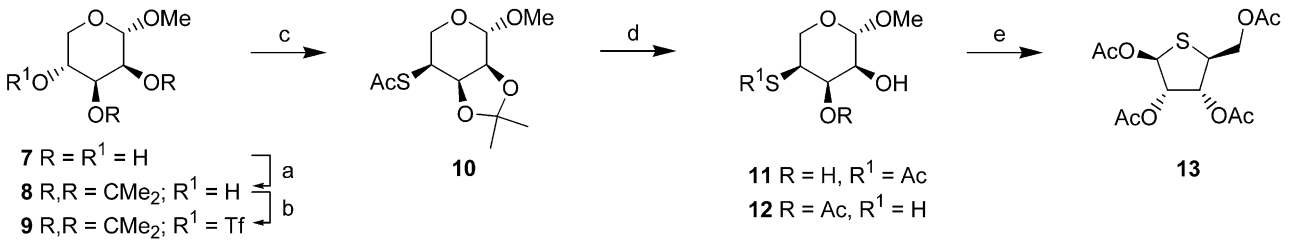
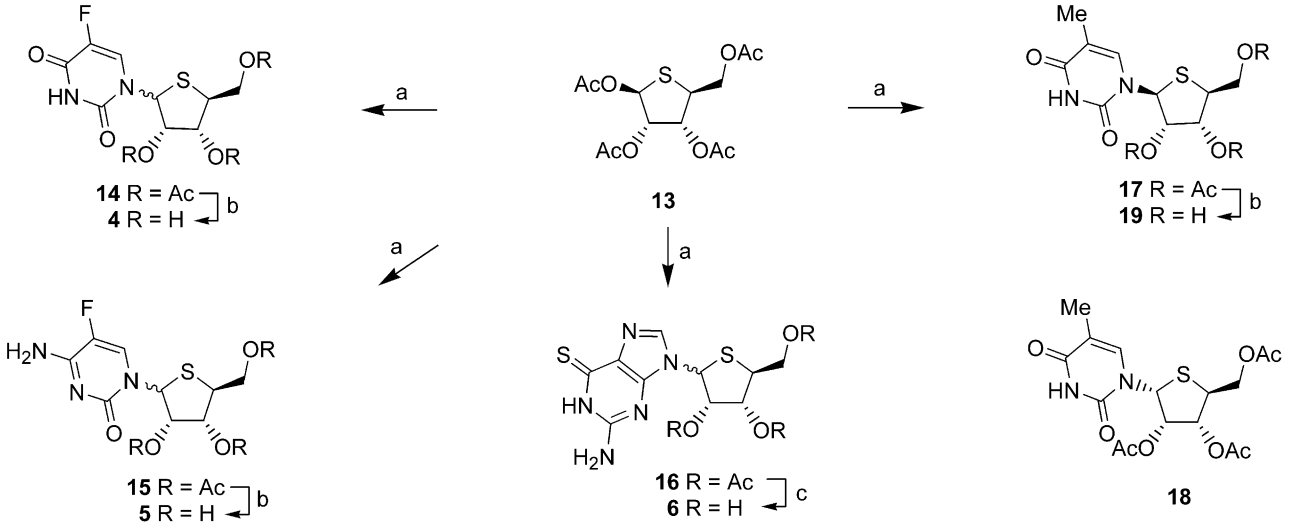


Scheme 1. Conditions: (a) $Me_2C(OMe)_2$, TsOH, Me_2CO, rt, 24 h, 78%; (b) Tf_2O, DMAP, Py, CH_2Cl_2, −15 °C, 0.5 h; (c) KSAc, DMF, rt, 2 h, 47% from **8**; (d) 9:1 TFA–H_2O, rt, 2 h; (e) 15:15:1 AcOH–Ac_2O–H_2SO_4, 0 °C, 48 h, 58% from **10** (21% overall from **7**).



Scheme 2. Conditions: for **14**, (a) (i) 5-fluorouracil, TMSCl, $(NH_4)_2SO_4$, HMDS↑↓, 4 h; (ii) **13**, TMSOTf, MeCN, rt, 6 h; for **15**, (a) (i) 5-fluorocytosine, TMSCl, $(NH_4)_2SO_4$, HMDS↑↓, 3 h; (ii) **13**, TMSOTf, MeCN, 40 °C, 2 h; for **16**; (a) (i) 6-mercaptoguanine, TMSCl, $(NH_4)_2SO_4$, HMDS↑↓, 5 h; (ii) **13**, TMSOTf, MeCN, rt, 2 h; for **17**; (a) (i) Thymine, TMSCl, $(NH_4)_2SO_4$, HMDS↑↓, 5 h; (ii) **13**, TMSOTf, MeCN, rt, 6 h, 48% of **17** and 1.5% of **18**; (b) NaOMe, MeOH, rt, 2 h for **14**, 1 h for **15**, 20 min for **17**, 49% of **4**, 67% of **5**, 90% of **19**; (c) NH_3/MeOH, 0 °C, 24 h, 46%.

subsequent nucleophilic displacement process with thioacetate anion. Thus, the reaction of **9** with potassium thioacetate in *N,N*-dimethylformamide was completed in 2 h at room temperature, in contrast to the reaction of the corresponding tosyl derivative with potassium thiobenzoate,[6] which required 24 h at 105 °C to be completed. Hydrolytic removal of the isopropylidene protective group in **10** gave a 2:1 mixture of the expected diol **11** and the 4-*O*-acetyl derivative **12**.[8] As the compounds **11** and **12** could not be separated by column chromatography, their mixture was subjected to acetolysis under the Whistler reaction conditions,[9] to afford the crystalline β-anomer **13** in 58% yield with respect to **10**. Thus obtained sample **13**, was for the first time fully characterized by the corresponding physical and spectral data.[10]

The coupling reactions of **13** with 5-fluorouracil, 5-fluorocytosine and 6-mercaptoguanine were performed by applying a modified Vorbrüggen method.[11] Thus, the nucleobases were refluxed in hexamethyldisilazane, and the resulting silylated bases were reacted with **13**, in the presence of trimethylsilyl triflate as a catalyst in dry acetonitrile as a solvent at room temperature, to afford the corresponding protected nucleosides **14**–**16** (Scheme 2). The results are summarized in Table 1.

The chemical yields of the obtained protected nucleosides **14**–**16** were fair, and the ratio of the β- and α-anomers was variable. As expected, the β-anomers were the major components in the mixtures owing to 2-*O*-acetyl participation. The presence of a considerable amount of α-anomer **16** is not entirely unexpected since it is well known that the Vorbrüggen method[11] shows a lower selectivity with purine nucleobases. The structural elucidation and assignment of α- and β-anomers of **14** was achieved by NMR spectroscopy, in particular by virtue of the observed NOE after irradiation of multiplets at 3.69 (H-4′, major isomer) and 3.96 ppm (H-4′, minor isomer). Only the minor isomer clearly exhibited NOE between H-6 of the nucleobase and H-4′, thus implying a spatial vicinity of these protons. Such an arrangement is only possible if the minor isomer **14** represents an α-anomer, as confirmed by molecular

Table 1. Coupling reactions of modified nucleobases with **13**

Silylated base	Product	Yield[a] (%)	β/α Ratio[b]
5-Fluorouracil	**14**	79	5.5:1
5-Fluorocytosine	**15**	59	10:1
6-Mercaptoguanine	**16**	54	2.5:1

[a]Isolated yields.
[b]The ratios of the α- and β-anomers were determined by ^1H NMR.

modeling (HyperChem Molecular Modeling Package, release 6.03; Hypercube Inc., Gainesville, FL). The conformational search was performed by varying sugar endocyclic torsion angles in α-**14** by the usage directed method. The conformations obtained were geometry optimized by AMBER 94 force field to reach rms gradients of <0.01 kcal/(Å mol). The structures having energies of 6 kcal/mol higher than the lowest energy conformation, as well as those with relative energy differences within 0.05 kcal/mol were discarded in the post-optimization runs. At least four low-energy conformations were found that have the H-4′/H-6 distance in the range of 2.70–3.18 Å. These findings are consistent with the NOE results.

Due to their similar chromatographic properties, the α- and β-anomers **14**–**16** could not be separated by silica gel column chromatography, but were in the mixtures further converted to the corresponding deprotected nucleosides **4**–**6**. As shown in Scheme 2, deacetylation of **14**, **15** and **16** gave the corresponding 4′-thio-L-ribonucleosides **4** (49%), **5** (67%) and **6** (46%), in β/α ratios of 6:1, 10:1 and 2.5:1, respectively. Similarly to their synthetic precursors, the α- and β-anomers of **4**–**6** could not be separated by column chromatography. However, even in the mixture their structure, including their stereochemistry at the anomeric positions was successfully resolved by ^{1}H NMR spectroscopy.[12–14] The most reliable method for assignment of anomeric configuration of free *N*- and *C*-nucleosides is the usage of differences in H-1′ chemical shifts. Namely, the H-1′ proton of β-anomers appears at higher field than those of α-anomers due to the shielding effects of a *cis* hydroxyl group at C-2′.[16] It appears that this rule is also valid for the 4′-thioribonucleosides, since NMR peak analysis revealed a high-field chemical shift for H-1′ of the β-anomer with respect to H-1′ of the corresponding α-anomer for each of the synthesized compounds **4**–**6**.

Since 4′-thio-β-D-ribofuranosylthymine demonstrated a moderate in vitro cytotoxicity against certain human tumours,[2b] its L-configuration counterpart **19** was also prepared for comparison (Scheme 2). Condensation of **13** with silylated thymine, in presence of trimethylsilyl triflate, gave the corresponding β- **17** and α-anomer **18** in an approximate ratio of 30:1. After chromatographic purification on a column of silica gel (1:1 hexane–EtOAc), pure β-anomer **17** was isolated in 48% yield, along with a small amount of **18** (1.5%). The major product **17** was deprotected with sodium methoxide in methanol to afford the corresponding nucleoside **19**[15] (90%) after silica gel column chromatography.

Biological Evaluation

Compounds **4**–**6** and **19** were evaluated for their in vitro cytotoxicity[17] to C6 rat glioma, HTB14 human glioma, HeLa human cervical carcinoma, NB4 leukemia, T47D breast cancer, as well as to normal human dermal fibroblast (NHDF) cell lines. The results are shown in Table 2.

Table 2. In vitro cytotoxicity of synthesized compounds

Compd	IC_{50} μM[a]					
	C6	HTB14	HeLa	NB4	T47D	NHDF
4	>100	41.5	>100	>100	>100	>100
5	>100	83.3	95.9	GSA[b]	GSA[b]	>100
6	>100	62.1	>100	>100	GSA[b]	>100
19	>100	67.8	100	>100	>100	>100

[a]IC_{50} is a compound concentration required to inhibit the cell growth by 50% compared to an untreated control.
[b]GSA – Growth-stimulatory activity.

All tested compounds showed a moderate growth inhibitory activity only against HTB14 human glioma cells, while on C6 rat glioma and HeLa cells the highest compound concentration tested (100 μM) caused inhibition of cell proliferation from 15 to 50%. These compounds had no growth inhibitory effect on NHDF cell line at any concentration tested. Such a result is consistent with earlier findings that most of L-nucleoside analogues are not recognized by normal cellular enzymes and are less toxic to normal cells.[18] However, compounds **5** and **6** exhibited a significant growth stimulatory activity towards NB4 and T47D cells at concentrations 0.78–1.56 μM. Compound 5 enhanced the growth of both NB4 and T47D cell lines by 63 and 86%, respectively, while compound **6** stimulated the cell proliferation of T47D by 89% with respect to an untreated control. To the best of our knowledge compounds **5** and **6** represent the first nucleoside analogues with growth stimulatory activity towards NB4 and T47D cells.

In summary we have developed an improved five-step route to 1,2,3,5-tetra-*O*-acetyl-4-thio-β-L-ribofuranose (**13**), a key intermediate in the synthesis of several new L-4′-thioribonucleosides (**4**–**6**, and **19**). The products obtained were evaluated for their cytotoxicity profile to certain malignant and normal cell lines. Further work directed to syntheses of novel L-4′-thioribonucleosides with modified base moieties is currently underway.

Acknowledgements

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10. Selected data for **13**: mp 64–65 °C (from MeOH), $[\alpha]_D$ +106 (*c* 0.1 in $CHCl_3$); ref 12 (for D-enantiomer): mp 64–65 °C, $[\alpha]_D$ −102 (*c* 2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.07, 2.08, 2.11 and 2.14 (4×s, 3H each, 4×MeCO), 3.80 (ddd, 1H, $J_{4,5a}=6.8$, $J_{4,5b}=5.5$, $J_{3,4}=8.5$ Hz, H-4), 4.14 (dd, 1H, $J_{5a,5b}=11.4$ Hz, H-5a), 4.37 (dd, 1H, H-5b), 5.36 (dd, 1H, $J_{2,3}=3.7$ Hz, H-3), 5.56 (dd, 1H, $J_{1,2}=2$ Hz, H-2), 5.81 (d, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 20.23, 20.25, 20.31 and 20.52 (4×*Me*CO), 45.23 (C-4), 64.36 (C-5), 73.55 (C-3), 75.50 (C-2), 79.08 (C-1), 168.95, 169.10, 169.37 and 169.93 (4×Me*C*O); CI MS: *m*/*z* 335 ($M^+ + H$).

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12. Selected data for **4** (6:1 mixture of β- and α-anomer): ^{1}H NMR (DMSO-d_6): β-anomer: δ 3.2 (m, 1H, $J_{4',5'}=5.2$ and 5.5, $J_{3',4'}=2.1$ Hz, H-4′), 3.50–3.80 (several signals, 2H, 2×H-5′), 4.00 (dd, 1H, $J_{2',3'}=3.4$ Hz, H-3′), 4.14 (dd, 1H, $J_{1',2'}=6$ Hz, H-2′), 5.00–5.75 (several signals, 3H, 3×OH), 5.83 (d, 1H, H-1′), 8.32 (d, 1H, $J_{6,F}=7$ Hz, H-6); α-anomer: δ 3.38 (m, 1H, H-4′), 3.50–3.80 (several signals, 4H, H-2′, H-3′ and 2×H-5′), 5.00–5.75 (several signals, 3H, 3×OH), 6.03 (d, $J_{1',2'}=5.2$ Hz, H-1′), 8.26 (d, $J_{6,F}=7.3$ Hz, H-6); ^{13}C NMR (DMSO-d_6): β-anomer: δ 53.13 (C-4′), 62.71 (C-5′), 63.26 (C-1′), 73.07 (C-3′), 76.54 (C-2′), 125.96 (d, $J_{6,F}=34.3$ Hz, C-6), 139.97 (d, $J_{5,F}=$ 230.8 Hz, C-5), 149.92 (C-2), 157.04 (d, $J_{4,F}=26.2$ Hz, C-4); α-anomer: δ 53.80 (C-4′), 60.03 (C-5′), 63.49 (C-1′), 73.84 and 74.72 (C-2′ and C-3′), 129.31 (d, $J_{6,F}=35.3$ Hz, C-6), 138.14 (d, $J_{5,F}=230$ Hz, C-5), 149.92 (C-2), 160.13 (d, $J_{4,F}=33.9$ Hz, C-4).

13. Selected data for **5** (10:1 mixture of β- and α-anomer): ^{1}H NMR (methanol-d_6): β-anomer: δ 3.42 (m, 1H, $J_{3',4'}=5.2$, $J_{4',5'a}=4.3$, $J_{4',5'b}=4.4$ Hz, H-4′), 3.79 (dd, 1H, $J_{5'a,5'b}=11.8$ Hz, H-5′a), 3.87 (dd, 1H, H-5′b), 4.12 (dd, 1H, $J_{2',3'}=3.8$ Hz, H-3′), 4.22 (dd, 1H, $J_{1',2'}=4.9$ Hz, H-2′), 5.98 (dd, 1H, $J_{1',F}=1.8$ Hz, H-1′), 8.51 (d, 1H, $J_{6,F}=7.1$ Hz, H-6,); α-anomer: δ 6.29 (dd, 1H, $J_{1',F}=1.9$ Hz, $J_{1',2'}=4.8$ Hz, H-1′), 8.29 (d, 1H, $J_{6,F}=7.3$ Hz, H-6); ^{13}C NMR (methanol-d_6): β-anomer: δ 53.83 (C-4′), 62.97 (C-5′), 66.70 (C-1′), 74.66 (C-3′), 79.74 (C-2′), 128.13 (d, $J_{6,F}=33.9$ Hz, C-6), 138.28 (d, $J_{5,F}=243.2$ Hz, C-5), 157.30 (C-2), 159.30 (d, $J_{4,F}=14.3$ Hz, C-4); α-anomer: δ 54.41 (C-4′), 62.19 (C-1′), 64.56 (C-5′), 75.37 (C-2′), 76.8 (C-3′); HR MS: *m*/*z* 278.0611 ($M^+ + H$); calcd for $C_9H_{13}FN_3O_4S$: 278.0611.

14. Selected data for **6** (2.5:1 mixture of β- and α-anomer): ^{1}H NMR (dMSO-d_6): β-anomer: δ 3.30–3.45 (m, 3H, $J_{5'a,5'b}=11$, $J_{4',5'}=4.4$ and 7 Hz, 2×H-5′ and H-4′), 3.96 (dd, 1H, $J_{2',3'}=3.4$, $J_{3',4'}=7.1$ Hz, H-3′), 4.15 (t, 1H, $J_{1',2'}=3$ Hz, H-2′), 5.14 (d, 1H, H-1′), 6.38 and 6.40 (2×bs, 2H, NH_2), 7.90 (s, 1H, H-8), 12.60 (bs, 1H, NH); α-anomer: δ 3.30–3.45 (overlapped m, 2H, 2×H-5′), 3.49 (m, 1H, $J_{4',5'}=7.6$ and 3.7, $J_{3',4'}=7.6$ Hz, H-4′), 3.84 (dd, 1H, $J_{2',3'}=3.4$ Hz, H-3′), 4.23 (dd, 1H, $J_{1',2'}=4.5$, H-2′), 5.89 (d, 1H, H-1′); ^{13}C NMR (dMSO-d_6): β-anomer: δ 50.23 (C-1′), 52.34 (C-4′), 64.03 (C-5′), 74.28 (C-3′), 79.22 (C-2′), 123.25, 151.97 and 158.28 (C-2, C-4 and C-5), 139.05 (C-8) 159.58 (C-6); α-anomer: δ 49.06 (C-1′), 52.86 (C-4′), 63.43 (C-5′), 75.05 and 76.03 (C-2′ and (C-3′); FAB MS: *m*/*z* 338 ($M^+ + Na$), 316 ($M^+ + 1$).

15. Selected data for **19**: mp 171–177 °C; $[\alpha]_D$ +47 (*c* 1 in MeOH); ^{1}H NMR (methanol-d_6): δ 1.90 (bs, 3H, 5-Me), 3.39 (m, 1H, $J_{3',4'}=3.6$, $J_{4',5'a}=5.1$, $J_{4',5'b}=4.7$ Hz, H-4′), 3.77 (dd, 1H, $J_{5'a,5'b}=11.7$ Hz, H-5′a), 3.84 (dd, 1H, H-5′b), 4.19 (t, 1H, $J_{2',3'}=3.7$ Hz, H-3′), 4.30 (dd, 1H, $J_{1',2'}=6.5$ Hz, H-2′), 6.06 (d, 1H, H-1′), 8.04 (bs, 1H, H-6); ^{13}C NMR (methanol-d_6): δ 12.50 (5-Me), 54.11 (C-4′), 63.86 (C-5′), 64.87 (C-1′), 75.14 (C-3′), 78.98 (C-2′), 111.88 (C-5), 138.91 (C-6), 153.16 (C-2), 163.78 (C-4); FAB MS: *m*/*z* 297 ($M^+ + Na$), 275 ($M^+ + 1$).

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