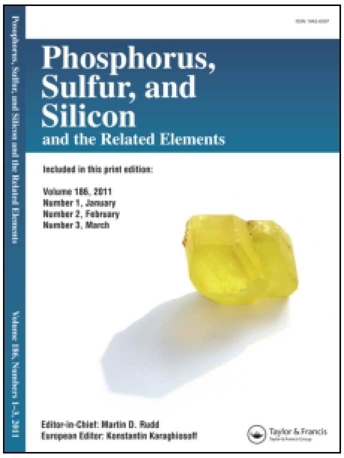

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Synthesis of Some New *S*-Nucleoside Derivatives of 2-Thioxo and (2,4-Dithioxo)-5,6,7,8-Tetrahydrobenzo-Thieno[2,3-*d*]Pyrimidin-4-(3H)Ones

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SYNTHESIS OF SOME NEW *S*-NUCLEOSIDE DERIVATIVES OF 2-THIOXO AND (2,4-DITHIOXO)-5,6,7,8-TETRAHYDROBENZO-THIENO[2,3-*d*]PYRIMIDIN-4-(3H)ONES

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Ribosylation of 2-thioxo-5,6,7,8-tetrahydrobenzo thieno[2,3-d]pyrimidin-4(3H)-one 1a and 2,4-dithioxo-5,6,7,8-tetrahydrobenzo thieno[2,3-*d*]pyrimidine 1b with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose 7 afforded the benzoylated S-nucleoside derivatives 3 and 4, respectively. Debenzoylation of 3 and 4 by using methanolic sodium methoxide yielded the corresponding free S-nucleosides 5 and 6, respectively. Furthermore, the reaction of potassium salt of 2-thioxo-5,6,7,8-tetrahydrobenzo thieno[2,3-*d*]pyrimidin-4(3H)-one 8 with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide 9, afforded 10. Deacetylation of the latter by using methanolic sodium methoxide yielded the corresponding *S*-glycoside, 2-(2′,3′,4′,6′-tetra-hydroxy-β-D-glucopyranosylthio)-5,6,7,8-tetrahydro-benzothieno [2,3-d]pyrimidin-4-one 11. The structural elucidation of the new nucleosides formed was reported.

Keywords 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribo-furanose; 2,4-dithioxo-benzothieno[2,3-*d*]pyrimidine; *S*-glycosides; 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide; 2-thioxo-benzothieno[2,3-*d*]pyrimidin-4(3H)-one

INTRODUCTION

Thieno[2,3-*d*]pyrimidines have a special position among fused pyrimidines because they are structural analogues of biogenic purines and can be considered as potential nucleic acid antimetabolites. Their derivatives have been reported to have remarkable activity, e.g., antifungal, antibacterial, insecticidal, hypnotic, antiallergic, and antiviral activity.[1,2,13–17] In addition, some interesting compounds exhibit moderate anti-HIV-1 potency and antitumor activity when the thiophene moiety is fused to a carbocyclic ring.[3,18]

Derivatives containing the thieno[2,3-*d*]pyrimidine nucleosides have been reported to possess several important pharmacological properties; in particular the biological activity of some thieno[2,3-*d*]pyrimidine nucleosides as antiviral agents against HIV-1 and herpes simplex virus (HSV-1) has been reported.[4,5]

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Other differently substituted thieno[2,3-*d*]pyrimidine nucleosides as antiviral agents against hepatitis-A virus (HAV) have been recently described.[6] In light of these considerations and in continuation of the studies in the chemistry of nucleosides and thieno[2,3-*d*]pyrimidine,[7–12,22–24] we thought it interesting to investigate the synthesis of some new nucleosides of thieno[2,3-*d*]pyrimidine.

RESULTS AND DISCUSSION

The starting compounds, 2-thioxo-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3H)-one (**1a**) and 2,4-dithioxo-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidine (**1b**) were prepared as reported in the literature[19] from the reaction of 2-amino-4,5,6,7-tetrahydrobenzo-thiophene-3-[carbo(thio)oxamide] with carbondisulfide. Ribosylation of **1a**,**b** was achieved by refluxing in hexamethyldisilazane (HMDS) to give the silylated derivatives **2a**,**b**. The latter was stirred with 1-O-acetyl-2,3,5-O-benzoyl-β-D-ribofuranose (**7**) in the presence of 1,2-dichloroethane as solvent using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a catalyst for 24 h (followed by TLC), following the method of Vorbruggen et al.,[20] to give the corresponding β-anomeric protected *S*-nucleoside derivatives **3** and **4**, respectively, in good yields (Scheme 1).

Debenzoylation of **3** and **4** was performed by using methanolic sodium methoxide solution following Zemplen et al.'s method[21] to afford the free nucleosides **5** and **6**, respectively (Scheme 1).

The chemical structures of nucleoside derivatives **3–6** were established and confirmed on the basis of their elemental analyses and spectral data (IR, ^{1}H and ^{13}C NMR) (see the Experimental section). ^{1}H NMR spectra of **3** and **4** showed in each case a doublet signals at δ 6.5 for compound **3** and at δ 6.3, 6.4 for compound **4** assigned to the anomeric proton of the ribose moiety with spin–spin coupling constant ($J_{1',2'}$) equal to 5.5 Hz, which confirms the β-anomeric configuration. This is in accord with the results for other 2,3,5-tri-O-benzoyl-1-β-D-furanosyl pyrimidine and purine nucleosides.[20,22–24]

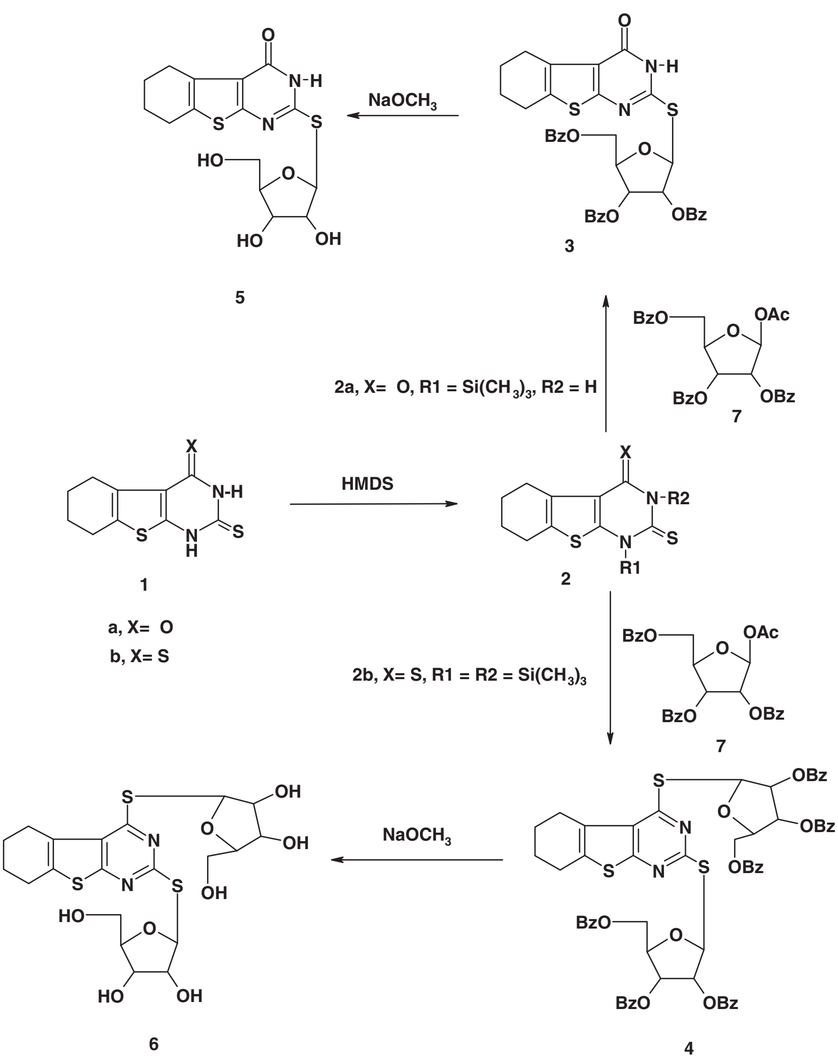
The ^{13}C NMR of nucleoside products revealed the absence of a thione carbon atom at about δ 173.0 for product **3** and at δ 169.0, 181.0 for product **4**. The resonance of the $-N{=}C{=}N-$ carbon atom (C2) of **3** at δ 159.0 was similar to the chemical shift of the corresponding carbon atom of compound **1a**. The signals at δ 163.2, 164.1, 165.2, and 166.4 are due to the four benzoyl carbonyl carbon atoms and the signals at δ 22.0–31.0 are assigned to tetrahydro benzo carbon atoms. The five signals at δ 86.2, 80.8, 77.3, 75.5, and 63.7 were assigned to C-1′, C-2′, C-3′, C-4′, and C-5′ of the sugar moiety, respectively.

The ^{1}H NMR of **5** and **6** showed the expected base moiety protons in addition to the sugar moiety protons (see the Experimental section).

The IR spectrum of compound **3** did not show the signal of a thione group but showed signals at 1670 cm^{-1} for the C=O group. Stretching vibration frequencies of the benzoyl carbonyl groups appeared at 1740 cm^{-1}.

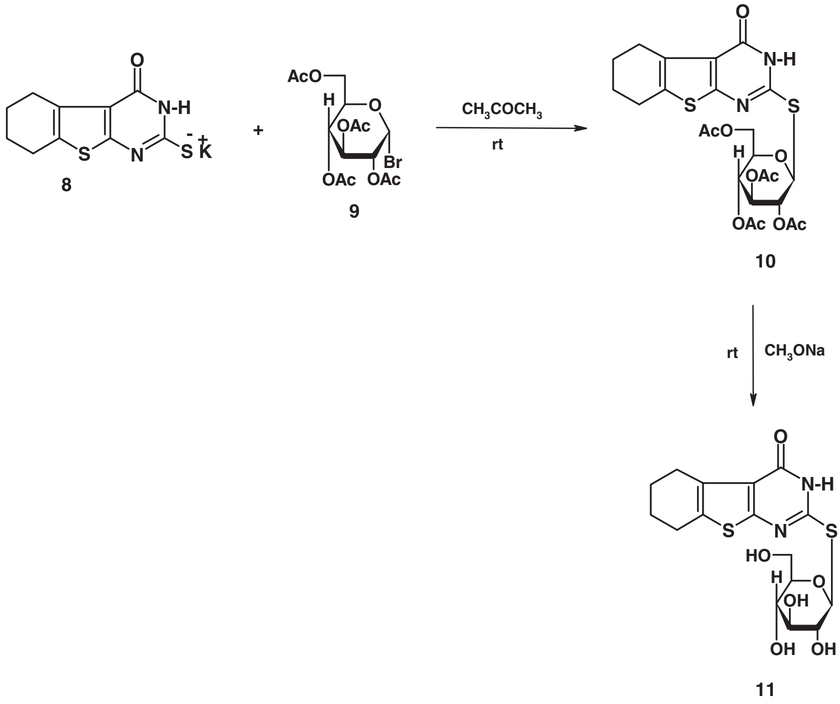
IR spectra of compounds **5** and **6** showed absorptions around 3400 cm^{-1} for (OH).

Furthermore, the potassium salt of the starting material 2-thioxo-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4(3H)-one (**8**) was treated with 2,3,4,6-tetracetyl-*O*-acetyl-α-D-glucopyranosyl bromide (**9**) in dry acetone to give the corresponding *S*-glycoside **10** (Scheme 2). Thin layer chromatography showed the formation of a single unique compound. The structure of the product **10** was established and confirmed by elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR) (see the Experimental



Scheme 1

section). The ^{1}H NMR spectrum of 2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-gluco-pyranosylthio)-5,6,7,8-tetrahydro-benzothieno[2,3-*d*]pyrimidin-4-one **10** showed the anomeric proton of the glucose moiety as a doublet at δ 5.98 with a coupling constant ($J_{1',2'}$) = 5.1 Hz, indicating *β*-configuration of the anomeric center. The other protons of the glucopyranose ring resonated at δ 3.90–5.50, while the four acetoxy groups appeared as four singlets at δ 2.10–2.20. The ^{13}C NMR revealed the absence of a thione carbon atom at about δ 173.0. The signals at δ 168.0, 169.0, 169.5, and 170.3 are due to the four acetoxy carbonyl carbon atoms, and the signals at δ 21.0–22.0 are assigned to the acetate methyl carbon atoms. The five signals at δ 62.0, 68.0, 69.0, 74.1, and 82.5 were assigned to C-6′, C-4′, C-2′, C-3′, and C-5′, respectively. The IR spectrum of compound **10** did not show the signal of a thione group, but showed signals at 1675 cm^{-1} for the C=O group. Stretching vibration frequencies of the acetate carbonyl groups appeared at 1745 cm^{-1}.



Scheme 2

Deacetylation of the blocked nucleoside **10** was achieved in methanolic sodium methoxide to afford the corresponding deprotected *S*-nucleoside **11** (Scheme 2). IR spectra of the latter compound showed absorption around 3420 cm^{-1} for (OH). The ^1H NMR of **11** showed the expected base moiety protons in addition to the sugar moiety protons (see the Experimental section).

A distinction between the *O*-, *N*-, and *S*-glycosides was possible by comparison of the ^1H NMR and ^{13}C NMR spectra with those of literature data of similar compounds.[25–30] $^{13}C{=}S$ Chemical shifts of δ 172.0 were reported for cycloalkyl[4,5]thieno[2,3-*d*]pyrimidin-4-one-2-thione, while 2-alkylthio-cycloalkyl[4,5]thieno[2,3-*d*]pyrimidin-4-one showed chemical shifts of C-2 around δ 159 ppm. Some literature data of *N*- and *S*-glycosides are shown in Chart 1.

EXPERIMENTAL

Melting points were determined on an Electrothermal apparatus. IR spectra were recorded in potassium bromide using a PU 9712 spectrophotometer. Elemental analyses were carried out at the Microanalytical Laboratory in the National Research Center, Giza, Egypt. ^1H and ^{13}C NMR spectra were recorded in the appropriate deuterated solvents using a Jeol 400 MHz apparatus with tetramethylsilane as an internal standard. IR spectra were recorded for KBr discs on Testscan Shimadzu FTIR 8000 Series and Bruker IFS 113V spectrophotometers. 2-Thioxo-5,6,7,8-tetrahydrobenzo-thieno[2,3-*d*]pyrimidin-4(3H)-one **1a** and 2,4-dithioxo-5,6,7,8-tetrahydrobenzo-thieno[2,3-*d*]pyrimidine **1b** were prepared according to the procedures reported in the literature.[19]

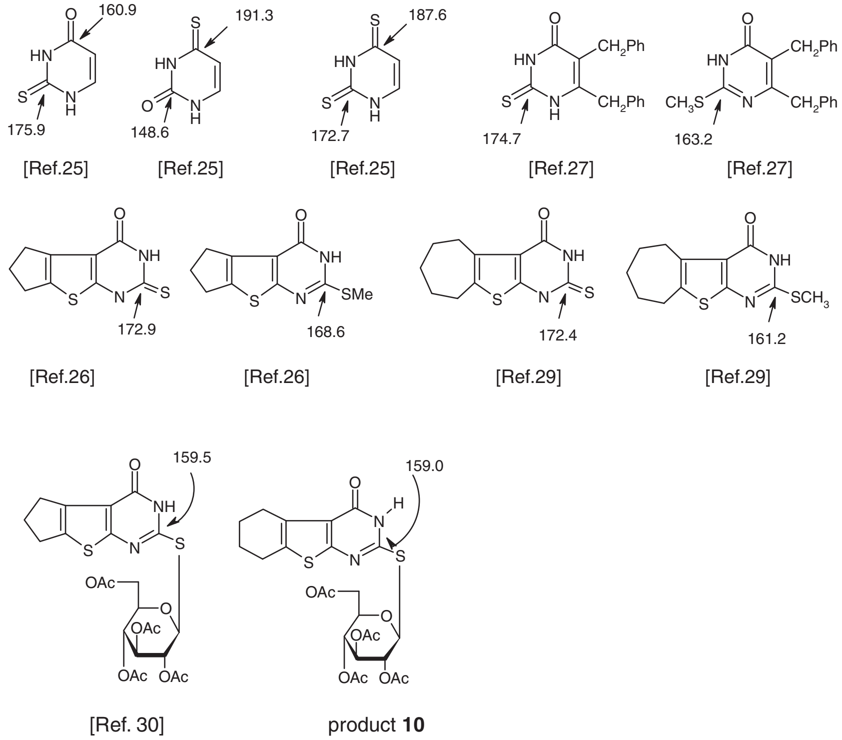


Chart 1

Preparation of 2-(2′,3′,5′-Tri-*O*-benzoyl-*β*-D-ribofuranosylthio)-5,6,7,8-tetrahydrobenzo-thieno[2,3-*d*]pyrimidin-4(3H)-one (3) and 2,4-Di(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosylthio)-5,6,7,8-tetrahydrobenzo-thieno [2,3-*d*]pyrimidine (4)

A mixture of **1a** or **1b** (20 mmol) and dry hexamethyldisilazane (100 mL) was heated under reflux for 4 h with a catalytic amount of ammonium sulfate (100 mg). After the clear solution was cooled, it was evaporated to dryness under anhydrous condition to give the silylated derivative **2a** or **2b**, respectively, which was directly dissolved in 50 mL of dry 1,2-dichloroethane. To this, a solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β -D-ribofuranose (**7**) (9.6 g, 19.6 mmol) in dry 1,2-dichloroethane (50 mL) was then added. The mixture was cooled in an ice bath, and a solution of trimethylsilyl trifluoromethanesulfonate (4 mL, 20 mmol) in dry 1,2-dichloroethane (20 mL) was added dropwise. It was stirred at room temperature for 24 h, and then diluted with chloroform (500 mL), washed with a saturated solution of aqueous sodium bicarbonate (200 mL) and water (3 × 150 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was washed with petroleum ether 60–80 to afford a white solid, which was crystallized from ethanol to yield colorless crystals of the corresponding nucleoside derivative **3** or **4**.

Compound 3. Yield (60%); mp 100–102°C (ethanol); ν (cm^{-1}) (KBr) 1740, 1670 (CO); ^{1}H NMR (CDCl$_3$): δ_{H} 1.30 (m, 2H, CH$_2$), 2.03 (m, 4H, 2CH$_2$), 3.03 (s, 2H, CH$_2$), 4.40 (m,1H, H-5′), 4.73 (d, 1H, H-4′, $J_{4',3'} = 4.3$ Hz), 4.70 (d, 1H, H-3′, $J_{3',4'} = 4.4$ Hz), 6.09 (t, 1H, H-2′, J = 5.9 Hz), 6.50 (d, 1H, H-1′, $J_{1',2'} = 5.5$ Hz), 7.30–8.09 (m, 15H, Ar-H), 11.7

(s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ_C 22.0, 22.9, 25.0, 31.0 (4 C's of tetrahydrobenzo), 63.7, 75.5, 77.3, 80.8, 86.2, (sugar carbons), 120.0, 122.0, 125.0, 128.2., 128.5, 129.0, 131.0, 132.0, 133.0, 150.0 (Ar. C's and 4 C's of thiophene), 159.0 (N=C), 163.2, 164.1, 165.2, 166.4 (4 CO); Anal. Found/ Calcd.: C, 63.50; H, 4.60; N, 4.12; S, 9.40%; $C_{36}H_{30}N_2O_8S_2$ (682.78); C, 63.33; H, 4.43; N, 4.10; S, 9.39%.

Compound 4. Yield (55%); mp 109–112°C (EtOH); ν (cm^{-1}) (KBr) 1740 (CO); ^{1}H NMR ($CDCl_3$): δ_H 1.90 (m, 2H, CH_2), 2.40 (m, 4H, $2CH_2$), 3.30 (s, 2H, CH_2), 4.30 (m,1H, H-5′), 4.40 (m,1H, H-5″), 4.50 (d, 1H, H-4′, $J_{4',3'} = 4.3$ Hz), 4.70 (d, 1H, H-4″, $J_{4',3'} = 4.3$ Hz), 4.85 (d, 1H, H-3′, $J_{3',4'} = 4.4$ Hz), 4.90 (d, 1H, H-3″, $J_{3'',4'} = 4.4$ Hz), 5.80 (t, 1H, H-2′, J = 5.8 Hz)), 5.90 (t, 1H, H-2″, J = 5.8 Hz)), 6.30 (d, 1H, H-1′, $J_{1',2'} = 5.5$ Hz), 6.40 (d, 1H, H-1″, $J_{1',2'} = 5.5$ Hz), 7.50–8.04 (m, 30H, Ar-H); ^{13}C NMR ($CDCl_3$): δ_C 22, 22.9, 25, 31 (4 C's of tetrahydrobenzo), 63.8, 63.9, 71.4, 71.9, 75.3, 75.9, 80.0, 84.0, 84.5, 93.0 (sugar carbons), 129.0, 129.5, 129.8, 130, 131, 132, 133, 134, 150 (Ar. C's and 4 C's of thiophene), 158, 159 (N=C),164,165,169 (3 CO); Anal. Found/Calcd.: C, 65.00; H, 4.50; N, 2.12; S, 8.50%; $C_{62}H_{50}N_2O_{14}S_3$ (1143.29); C, 65.14; H, 4.41; N, 2.45; S, 8.41%.

Preparation of 2-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl thio)-5,6,7,8-tetrahydrobenzo-thieno[2,3-*d*]pyrimidin-4(3H)-one (10)

To a solution of **1a** (5 mmol) in aqueous potassium hydroxide [(0.28 g, 5 mmol) in distilled H_2O (4 mL)], a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **9** (2.06 g, 5 mmol) in acetone (20 mL) was added. The reaction mixture was stirred at room temperature overnight (12 h) and judged to be complete by TLC ($CHCl_3$/MeOH, 9:1). The solvent was evaporated under reduced pressure at 40°C, and the crude product was filtered off and washed with distilled H_2O (3 × 4 mL) to remove the potassium bromide that formed. The product was dried and crystallized from the proper solvent to afford the desired product **10**.

Compound 10. Pale white powder, yield (70%), mp 180–182°C (ethanol); IR (KBr) ν cm^{-1}: 1745, 1675, 1520; ^{1}H NMR (DMSO): δ_H 1.80 (m, 2H, CH_2), 2.10–2.20 (4s, 12H, $4CH_3$), 2.35(m, 4H, $2CH_2$), 3.21(t, 2H, CH_2, J = 7.1 Hz), 3.90 (m, 1H, H-5′), 4.00–4.25 (d, 2H, H-6′, J = 5.1 Hz), 5.20 (t, 1H, H-3′, J = 5.0 Hz), 5.50 (t, 1H, H-2′, J = 5.0 Hz), 5.98 (d, 1H, H-1′, $J_{1',2'} = 5.1$ Hz), 11.5 (s, 1H, NH); ^{13}C NMR (DMSO): δ_C 21.0, 21.5, 21.7, 22.0, 27.0, 27.5, 27.7, 29.0, 30.0, 33.0, 62.0, 68.0, 69.0, 74.1, 82.5, 120.0, 136.4, 137.0, 152.0, 158.5, 159.8, 168.0, 169.0, 169.5, 170.3; Anal. Found/Calcd.: C, 51.00; H, 4.90; N, 4.70; S, 11.50%; $C_{24}H_{28}N_2O_{10}S_2$ (568.63); C, 50.70; H, 4.96; N, 4.93; S, 11.28%.

Deprotection of 3, 4, and 10: Synthesis of 2-(β-D-Ribofuranosylthio)-5,6,7,8-tetrahydrobenzo-thieno[2,3-*d*]pyrimidin-4(3H)-one (5), 2,4-Di(β-D-ribofuranosylthio)-5,6,7,8-tetrahydrobenzo-thieno[2,3-*d*]-pyrimidine (6), and 2-(2′,3′,4′,6′-Tetrahydroxy-β-D-glucopyranosylthio)-5,6,7,8-tetrahydrobenzo-thieno[2,3-*d*]pyrimidin-4(3H)-one (11)

A mixture each of the protected nucleosides **3**, **4**, and **10** (2 mmol), absolute methanol (40 mL), and sodium methoxide (120 mg, 2.2 mol) was stirred at room temperature for 24 h. Evaporation of the solvent under vacuum gave a colorless solid, which was dissolved in hot water and neutralized with acetic acid. The precipitate was filtered off and afforded, upon crystallization from water, the free nucleosides **5**, **6**, and **11**, respectively as colorless crystals.

Compound 5. Yield (45%); mp 177–179°C (H_2O), ν (cm^{-1}) (KBr) 3400 (OH); ^1H NMR (DMSO-d_6): δ_H 1.80 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 3.30 (s, 2H, CH_2), 3.70–3.85(m, 2H, H-5′), 4.00 (m, 1H, H-4′), 4.20 (m, 1H, H-3′), 4.35–4.40 (m, 1H, H-2′), 4.7–4.8 (t, 1H, OH-5′, J = 5.8 Hz), 5.1–5.2 (d, 1H, OH-3′, J = 5.8 Hz), 5.4–5.5 (d, 1H, OH-2′, J = 5.5 Hz), 6.1–6.2 (d, 1H, $J_{1',2'}$ = 5.5 Hz, H-1′), 11.7 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_C 22.0, 22.7, 24.1, 25.0 (4 C's of tetrahydrobenzo), 61.7, 70.8, 75.8, 85.3, 87.8, (sugar carbons), 128.0, 129.0, 130.0, 132.0 (4 C's of thiophene), 158.0 (N=C) 165.0 (CO); Anal. Found/ Calcd.: C, 48.50; H, 4.60; N, 7.42; S, 17.40%; $C_{15}H_{18}N_2O_5S_2$ (370.45); C, 48.63; H,4 .90; N, 7.56; S, 17.31%.

Compound 6. Yield (40%); mp 203–204°C (H_2O/EtOH, 1:1); ν (cm^{-1}) (KBr) 3400 (OH); ^1H NMR (DMSO-d_6): δ_H 2.00 (m, 2H, CH_2), 2.40 (m, 4H, $2CH_2$), 3.30 (s, 2H, CH_2), 3.85 (m, 2H, H-5′), 3.95 (m,1H, H-5″), 4.10 (m, 1H, H-4′), 4.20 (d, 1H, H-4″, J = 5.5 Hz), 4.30 (m, 1H, H-3′), 4.35 (d, 1H, H-3″, J = 5.5 Hz), 4.40 (m, 1H, H-2′), 4.50 (m, 1H, H-2″), 4.7 (t, 1H, OH-5′, J = 6.8 Hz), 5.1 (d, 1H, OH-3′, J = 5.5 Hz), 5.30 (d, 1H, OH-2′, J = 5.5 Hz), 6.00 (d,1H, $J_{1',2'}$ = 5.5 Hz, H-1′), 6.10 (d, 1H, H-1″, $J_{1',2'}$ = 5.4 Hz); ^{13}C NMR ($CDCl_3$): δ_C 22.0, 23.0, 25.0, 31.0 (4 C's of tetrahydrobenzo), 61.4, 64.6, 71.5, 72.6, 75.5, 75.9, 80.0, 83.0, 93.0, 94.8 (sugar carbons), 128.0, 129.0, 130.0, 131.0 (4 C's of thiophene), 158.0, 159.0 (N=C); Anal. Found/Calcd.: C, 46.10; H, 5.20; N, 5.42; S, 18.50%; $C_{20}H_{26}N_2O_8S_3$ (518.63); C, 46.32; H, 5.05; N, 5.40; S, 18.55%.

Compound 11. White powder, yield (40%), mp 222–223°C (ethanol; IR (KBr) ν cm^{-1}: 3420 (OH); ^1H NMR (DMSO-d_6): δ_H 1.10 (t, 2H, OH-2′ + OH-3′, J = 5.0 Hz), 1.40(m, 2H, OH-4′ + OH-5′), 1.90 (m, 2H, CH_2), 2.20 (m, 4H, $2CH_2$), 3.12 (t, 2H, CH_2, J = 6.9 Hz), 3.45 (s, 1H, H-2′), 3.90 (s, 2H, H-3′ + H-4′), 4.20 (d, 3H, H-5′ + H-6′, J = 5.2 Hz), 6.50 (t, 1H, H-1′, $J_{1',2'}$ = 5.0), 11.2 (s, 1H, NH); Anal. Found/Calcd.: C, 47.99; H, 5.03; N, 7.00; S, 16.01%; $C_{16}H_{20}N_2O_6S_2$ (400.48); C, 47.80; H, 5.25; N, 6.94; S, 15.97%%.

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