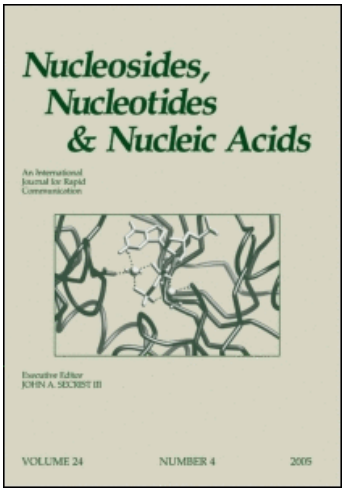

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Thiosugar Nucleosides. Synthesis and Biological Activity of 1,3,4-Thiadiazole, Thiazoline and Thiourea Derivatives of 5-Thio-D-Glucose

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ABSTRACT

New acylated 5-thio-β-D-glucopyranosylimino-disusbstituted 1,3,4-thiadiazols **8**, and **11** were prepared, via spontaneous rearrangements, by cycloaddition of the glycosyl isothiocyanate **2** with the reactive intermediates 1-aza-2-azoniaallene hexachloroantimonates **4** and **6**, respectively. Reaction of **2** with aminoacetone or chloroethylamine afforded the acylated 5-thio-β-D-glucopyranosyl-4-imidazoline-2-thione nucleoside **16** and glucopyranosylamino-2-thiazoline derivative **18**, respectively. Deblocking of **8**, **11**, **17** and **19** furnished the free nucleoside analogues **9**, **12**, **18** and **20**, respectively. Analogously, treatment of **2** with chloroethylamine in the 1:2 ratio afforded the thioureylendisaccharide **21**. No in vitro antiviral activity against HIV-1, HIV-2, human cytomegallovirus (HMCV), has been found for the new synthesized compounds.

Key Words: Antitumor activity; Cumulenes; Glycosylimino-1,3,4-thiadiazoles; Glycosyl isothiocyanates; Glycosylthiourea.

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INTRODUCTION

Because isothiocyanates[1] and glycosylisothiocyanate[2–4] are versatile synthetic synthons in organic chemistry, their stereoselective syntheses of different heterocyclic derivatives, via nucleophilic and cycloadditions, such as *N*-nucleosides,[1,5–7] glycosylamino-heterocycles, glycosyl-thioureas,[8–11] glycosyl-guanidines and glycosyl derivatives of β-cyclodextrines[12–17] with potential pharmacological properties,[18] are of continuing interest. On the other hand, 5-thio-D-glucose is an important synthone in carbohydrate chemistry since exhibited interesting biological activities, such as inhibition of D-glucose transport across membranes (inhibition of spermatogenesis) and of carbohydrate-metabolising enzymes.[19–21]

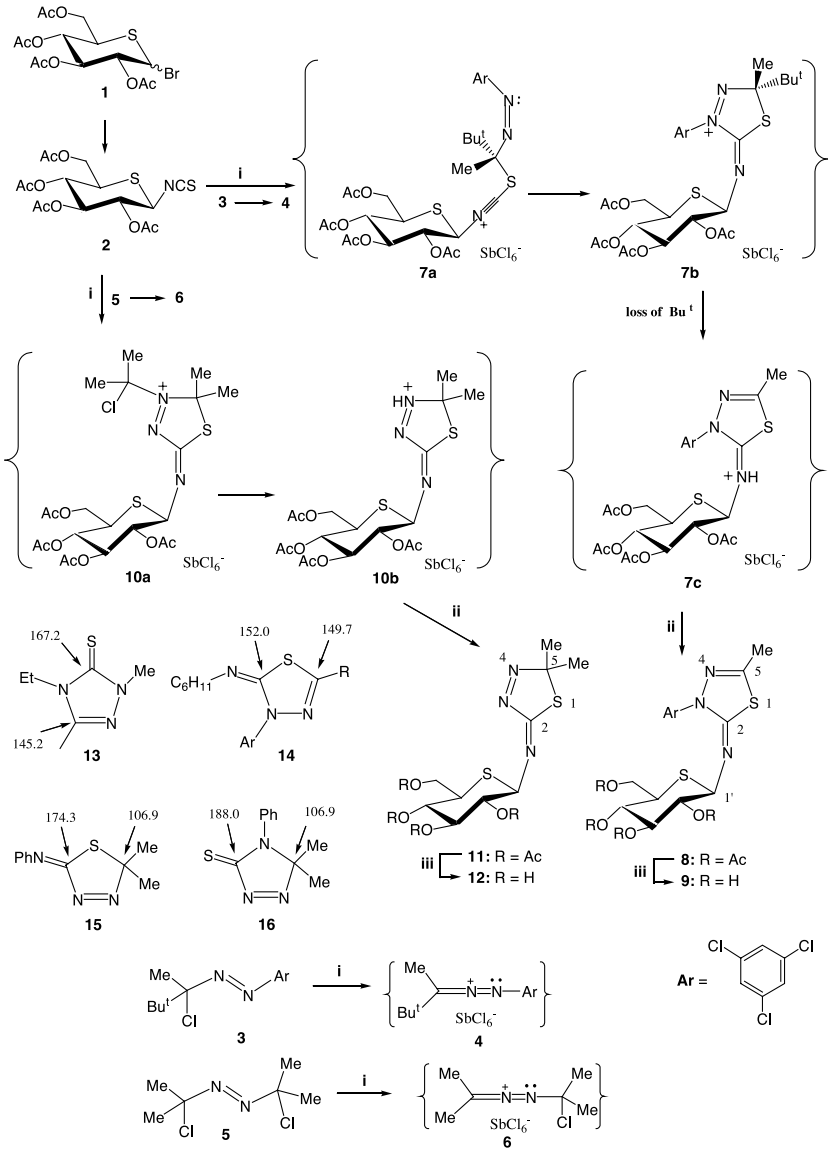
Recently, we reported syntheses of 2,5- and 2,3-dihydro-(glycosylimino)-1,3,4-thiadiazole and 3′-(disubstituted 1,3,4-thiadiazolimino)-2′,3′-dideoxythymidines formed by reaction of a glycosyl and 3′-thymidine isothiocyanate, respectively, with certain cumulene salts.[5,6] We now describe the results of a more investigation of reactive cumulenes, aminoacetone or chloroethylamine with acylated 5-thio-D-glucose isothiocyanate.

RESULTS AND DISCUSSION

In our recent work, some reactive cumulenes have been used in the synthesis of new types of glycosyl 1,2,4-triazole *C*-nucleosides,[6,22–24] and glycosylimino-1,3,4-thiadiazole nucleosides[5,6] from cycloaddition with the glycosyl nitrile and isothiocyanate, respectively. The starting material 2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl isothiocyanate (**2**) was prepared, in 39% yield, by treatment of the corresponding bromo derivative **1**[25] with trimethylsilyl isothiocyanate in the presence of $SnCl_4$ as a Lewis acid. The heteroallene **4** carrying a *tert*-butyl group were used to synthesize electrically neutral 2-substituted 1,2,4-triazoles.[26,27] Compound **4**, which formed at low temperature from **3**[6,24] and $SbCl_5$, reacted with isothiocyanate **2** via C = S cycloaddition to give the nitrilium ion **7a** as an intermediate. The latter is cyclized to the thiadiazolium salt **7b** giving, after the loss of the *tert*-butyl group (as isobutene), the inseparable iminium salt **7c**. The *tert*-butyl group was probably lost during or after the rearrangement. In situ deprotection of **7c** with saturated aqueous $NaHCO_3$ afforded thiadiazole **8** (67%). Deblocking of **8** with NaOMe in MeOH afforded after purification the free glycosylimino derivative **9** (82%). The *concerted* cycloaddition to isothiocyanate could have been occurred across the C = S bond of **2** to give **8** [*cf.* structure **14**, δ_C: C = N (152.0); N = C–S (149.7][28,29] and not the C = N bond, which furnishs an isomeric 4,5-dihydro-1*H*-1,3,4-triazole-5-thione (*cf.* structure **13**). The ^{13}C chemical shift of **8** spectral data indicated the **2** reacts as *S*-nucleophile and not as *N*-nucleophile, from the ^{13}C NMR spectrum data in comparison to those of **14**. Furthermore, L'abbé et al. reported values in the range of δ_C 151–164 ppm for C-2 and of δ_C 149–155 for C-5 for several thiadiazoles of type **14**,[30] which are in agreement with data shown by compound **8** (δ_C: 158.0 for C-5 and 147.2 for C-1).

Analogously, the α,α-dichloroazo compound **5**[31] was obtained by chlorination of the bis-hydrazone, and the 1-aza-2-azaniaallene salt **6**[32–34] by treatment of **5** at −60°C with $SbCl_5$. Addition of **2** to the reactive intermediate **6**, by employing the methods of Jochims et al.,[6] lead to a color change of the orange suspension

of **6** between −60°C and +23°C indicating a cycloaddition reaction. The resulting 1,3,4-thiadiazolium hexachloroantimonate **10a** lost its CMe_2Cl group and furnished the protonated salt **10b**. Deprotection afforded 1,3,4-thiadiazole **11** (41%) (Scheme 1). Deblocking of **11** with NaOMe in MeOH afforded **12** in 83% yield. Again, the concerted cycloaddition of **2** with the reactive cumulene **6** would occurred via C = S double bond, as shown from the ^{13}C NMR spectrum [δ_C: C-5 (106.9); C-2 (176.8)] [*cf.* C_5-Me_2 (106.9); C = N (174.3)] and not across the C = N double bond to give an



Scheme 1. Reagent and conditions: (i) $SbCl_5$, CH_2Cl_2, − 60°C to 23°C, 7 h, CH_2Cl_2, 23°C; (ii) aq. $NaHCO_3$, 2 h, 23°C, (iii) NaOMe, MeOH, 16 h, 23°C.

isomeric mixture of 4,5-dihydro-1*H*-1,3,4-triazole-5-thione (*cf.* structure of **15**], while for several triazoles **16** C = S shifts close to δ_C 188 and shifts of the saturated ring carbon (C-5) of δ_C 109–110 were found.[28] Accordingly compound **11** is a thiadiazole. The large coupling constants ($J_{1',2'}$ and $J_{4',5'} \sim 9-10$ Hz) is indicating of the β-configuration, and the $^4C_1$ conformation of the sugar moiety.

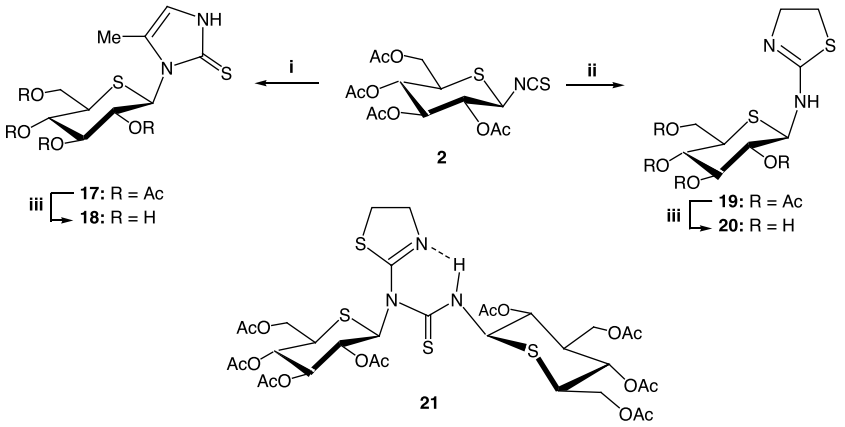
Next, our attempt to synthesize the *N*-nucleoside 5-methyl-1-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)-4-imidazoline-2-thione (**17**), in 51% yield, by cycloaddition reaction of the corresponding glycosyl isothiocyanate **2** with aminoacetone hydrochloride in acetone at 23°C. Deblocking of **17** afforded the free nucleoside **18** (86%). The structures of **17** and **18** were identified by their ^{1}H NMR, ^{13}C NMR, and mass spectrum. The ^{1}H NMR spectrum is characterized by the presence of H-1′ and H-4′ as doublet and triplet at δ_H 5.80 ($J_{1',2'}$ = 9.3 Hz), and δ_H 5.40 ($J_{4',5'}$ = 10.0 Hz), indicating for the β-configuration and $^4C_1$ conformation of the sugar moiety. The rotating nuclear Overhauser effect (ROE)[35–37] between H-1′ and H-5′ is an additional proof for β-configuration. The two singlets at δ_H 2.36 and δ_H 10.69 were attributed to the methyl group at C-5 and NH group of the imidazoline ring. The ribosylation of **17** occurred at the *N*-site of the imidazoline ring, and this was proved by the selected homo- and heteronuclear NMR study. Thus, gradient selected HMBC[38] spectrum allowed via $^2J_{C,H}$ and $^3J_{C,H}$ couplings the assignment of all the carbon atoms. C = S and C-5 groups at δ_C 163.0 and δ_C 34.5, respectively, were identified from their $^2J_{C,H}$ correlations to H-1′ at δ_H 5.80. C-4 at δ_C 127.0 was identified from its $^3J_{C,H}$ correlation with H-1′ as well. Furthermore, these data are in agreement with those of the related nucleosides.[7]

Sainsbury[39] had reported that reaction of β-haloalkylamines with alkyl(aryl)-isothiocyanate furnished 2-alkyl(alkyl)aminothiazolines. Therefore, reaction of **2** with an excess of chloroethylamine for 12 h at 23°C, followed by treatment with aqueous solution of $NaHCO_3$ gave after chromatographic purification an a foam, tentatively identified as 2-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)amino-2-thiazoline (**19**) (82%). Deblocking of **19** with NaOMe in MeOH afforded the free aminoglycoside (**20**) (82%). The structures of **19** and **20** were assigned from their ^{1}H NMR, which showed similar pattern, and mass spectra. H-1′ and H-4′ of **19** were appeared as doublet of doublets at δ_H 4.97 ($J_{1',2'}$ = 8.8 Hz, $J_{NH,H\text{-}1'}$ = 5.5 Hz) and δ_H 5.30 ($J_{4',5'}$ = 9.2 Hz), respectively, giving an proof for the β-configuration and $^4C_1$-conformation of the sugar moiety. The doublet at δ_H 8.20 were attributed to $C_{1'}$-NH, while the triplets at δ_H 3.60 and 3.20 (J = 7.2 Hz) were assigned to CH_2-5 and CH_2-4, respectively. These data are in agreement with those of the related oxygen analogue prepared previously.[7]

Under the above condition, by using chloroethylamine and **2** in the 1:2 ratio the thioureylendisaccharide **21** was obtained (71%). The structure of **21** was based on analytical UV and ^{1}H NMR data. The shift at lower wave number of NH ($\Delta\nu$ = 252 cm^{-1}) and C = N ($\Delta\nu$ = 20–40 cm^{-1}), with respect to other non-bonded thiazolines, 2-amino-2-thiazolines and 2-amino-2-oxazolines,[40] indicates a strong intramolecular hydrogen bond is present in compound **21**. Furthermore, these data is coincident with those reported for *N*-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)-*N*′-(2-thiazolin-2-yl)thiourea[41] (Scheme 2).

Biological Activity

Compounds **9**, **12**, **20** and **21** were evaluated for their anti-HIV activity in vitro using the IIIB strain for HIV-1 and the ROD strain for HIV-2, and monitored by the



Scheme 2. Reagents and conditions: (i) $NH_2CH_2COMe.HCl/NaHCO_3$, Me_2CO, 30 min, 23°C; (ii) $ClC_2H_4NH_2.HCl/H_2O$/ether, M NaOH, 15 h, 23°C.

inhibition of the virus-induced cytopathic effect in human MT-4 lymphocyte cells at non-toxic concentrations, as well as for the human anti-cytomegallovirus (HMCV, causing pneumonia and CNS diseases) in human embryonic lung (HEL) cells with AD-169 and Davis strain and were found to be inactive in comparison to the anti-HIV activity of Delviridine.[42] In conclusion, the 4-thio-glycofuranosyl moiety carrying the similar heterocycles might optimize the antiviral activity and then could balance both the hydrophobic and hydrophilic requirements of our target molecules.

Experimental

General Procedure

See Refs. [6,22–24].

2,3,4,6-Tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl isothiocyanate (2). A solution of **1**[25] (4.27 g, 10 mmol), trimethylsilyl isothiocyanate (1.31 g, 10 mmol) and distilled $SnCl_4$ (2.61 g, 10 mmol) in CH_2Cl_2 (60 mL) was boiled under reflux for 13 h. After addition of further trimethylsilyl isothiocyanate (0.66 g, 5.0 mmol) and $SnCl_4$ (2.61 g, 10 mmol), the mixture was boiled for another 12 h. After cooling, the mixture was neutralized by shaking with water (50 mL) and excess of $NaHCO_3$, followed by filtration and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic extracts were dried (Na_2SO_4), treated with charcoal, filtered (*celite*) and evaporated to dryness to give an anomeric mixture of the glycosyl isothiocyanate **2** as a dark orange syrup. The crude product was poured onto a column of silica gel (40 g) using toluene-ethyl acetate (3:1) as eluent. Eluted first was a syrup, as an unidentified product, while further elution yielded a syrup which crystallized at 5°C. Recrystallization twice from EtOH yielded the pure β-isomer (1.58 g, 39%); m.p. 96–99°C; $[\alpha]_D$ + 6° (*c* 1.2, $CHCl_3$); ν_{max} (CCl_4) 2019 cm^{-1} (NCS); δ_H ($CDCl_3$): 5.18 (dd, 1H, $J_{4,5}$ = 10.5 Hz, H-4); 5.10 (t, 1H, H-2); 4.98 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3); 4.42 (d, 1H, $J_{1,2}$ = 10.6 Hz, H-1); 4.22 (dd, 1H, $J_{6,6'}$ = 12.0 Hz,

H-6′); 4.07 (dd, 1H, Hz, H-6); 3.25 (ddd, 1H, $J_{5,6}$ = 5.5 Hz, $J_{5,6'}$ = 3.4 Hz, H-5); 2.09, 2.00, 1.96, 1.87 (4xs, 12H, 4xOAc). Anal Calc. for $C_{15}H_{19}N_2S_2O_8$ (405.4): C, 44.44; H, 4.72; N., 3.45. Found: C, 44.18; H, 4.61; N., 3.19. MS: m/z (FAB) 406 $(M + H)^+$.

General procedure for the preparation of the acylated 5-thio-β-D-glucopyranosylimino-disusbstituted 1,3,4-thiadiazols 8, and 11. A solution of $SbCl_5$ (0.90 g, 3.0 mmol) was added dropwise to a stirred, cooled (−60°C) solution of **2** (0.41 g, 1.0 mmol) and **3** or **5** (3.0 mmol) in CH_2Cl_2 (15 mL). After stirring the mixture at −60°C for 1 h, then at 0°C for 1 h, and finally at 23°C for 10 min, the solvent was evaporated to dryness. The brown residue was dissolved in MeCN (15 mL). After cooling the mixture to 0°C, an aqueous solution of $NaHCO_3$ [2.52 g (30 mmol) in (H_2O (10 mL)] was added slowly. The mixture was stirred at 23°C for 30 min and filtered. The organic solvent was evaporated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (3 × 10 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. The amorphous residue was purified on a column of SiO_2 (20 g) using first CH_2Cl_2 and then CH_2Cl_2–MeOH (99:1) as eluents.

2,3-Dihydro-5-methyl-2-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosylimino)-3-(2,4,6-trichlorophenyl)-1,3,4-thiadiazole (8). From **3** (0.98 g). Yield: 0.43 g, (67%). δ_H ($CDCl_3$): 7.41 (dd, J = 2.2 Hz, ArH); 5.43 (t, 1H, $J_{4',5'}$ = 9.0 Hz, H-4′); 5.25 (t, 1H, $J_{2',3'}$ = 9.0 Hz, H-2′); 5.17 (t, 1H, $J_{3',4'}$ = 9.0 Hz, H-3′); 4.40 (d, 1H, $J_{1',2'}$ = 8.9 Hz, H-1′); 4.26 (dd, 1H, $J_{6',6''}$ = 11.5 Hz, H-6″); 4.10 (dd, 1H, $J_{5',6'}$ = 4.9 Hz, H-6′); 3.47 (ddd, 1H, $J_{5',6''}$ = 3.5 Hz, H-5′); 2.42 (s, 3H, C_5-Me); 2.03, 1.99, 1.96, 1.88 (4xs, 12H, 4xOAc). δ_C ($CDCl_3$): 170.4, 170.1, 169.1, 168.9 (C = O); 158.0 (C_5 = N); 147.2 (C_1 = N); 136.4, 136.0, 135.7, 133.0, 128.8, 128.5 (Ar-*C*); 74.2 (C-2′); 73.6 (C-3′); 72.0 (C-4′); 64.5 [$^1J(^{13}C\text{-}^1H)$ = 152.0 Hz, (C-1′)]; 61.4 (C-6′); 42.2 (C-5′); 20.6–20.3 (4xCO*Me*). Anal Calc. for $C_{23}H_{24}Cl_3N_3S_2O_8$ (640.9): C, 43.10; H, 3.77; N., 6.56. Found: C, 42.78; H, 3.62; N., 6.32. MS: m/z (FAB) 663/665 $(M + Na)^+$.

2,3-Dihydro-5-methyl-2-(5-thio-β-D-gluopyranosylimino)-3-(2,4,6-trichlorophenyl)-1,3,4-thiadiazole (9). A solution of **8** (0.30 g, 0.47 mmol) in 0.3 M NaOMe solution (10 mL) was stirred at 23°C for 9 h. The solution was neutralized with AcOH to pH 5 and then evaporated to dryness. The residue was partitioned between water (10 mL) and ether (10 mL) and the aqueous layer was evaporated to dryness and the residue was co-evaporated with EtOH (4 × 10 mL). The residue was purified by column chromatography on (5 g) using, in gradient, MeOH (0–10%) and CH_2Cl_2 to give **9** (0.18 g, 82%), m.p. 149–152°C. δ_H (DMSO-d_6/D_2O): 7.84 (dd, J = 2.2 Hz, ArH); 3.97 (d, 1H, $J_{1',2'}$ = 9.6 Hz, H-1′); 3.89 (dd, 1H, $J_{6',6''}$ = 12.0 Hz, H-6″); 3.80 (dd, 1H, $J_{5',6'}$ = 3.5 Hz, H-6′); 3.54 (dd, 1H, $J_{4',5'}$ = 10.4 Hz, H-4′); 3.49 (dd, 1H, $J_{2',3'}$ = 9.2 Hz, H-2′); 3.27 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3′); 3.01 (ddd, 1H, $J_{5',6''}$ = 6.0 Hz, H-5′); 2.40 (s, 3H, C_5-Me). Anal Calc. for $C_{15}H_{16}Cl_3N_3S_2O_4$ (472.8): C, 38.11; H, 3.41; N., 8.89. Found: C, 37.76; H, 3.32; N., 8.. MS: m/z (FAB) 663/665 $(M + Na)^+$.

2,5-Dihydro-5,5-dimethyl-2-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-gluopyranosylimino)-1,3,4-thiadiazole (11). From **5** (0.55 g). Yield: 0.58 g, (41%). δ_H ($CDCl_3$): 5.56 (t, 1H, $J_{4',5'}$ = 9.5 Hz, H-4′); 5.47 (t, 1H, $J_{2',3'}$ = 9.5 Hz, H-2′); 5.33 (t, 1H,

$J_{3',4'}$ = 9.5 Hz, H-3′); 4.81 (d, 1H, $J_{1',2'}$ = 9.2 Hz, H-1′); 4.27 (dd, 1H, $J_{6',6''}$ = 12.0 Hz, H-6″); 4.16 (dd, 1H, $J_{5',6'}$ = 5.0 Hz, H-6′); 3.56 (ddd, 1H, $J_{5',6''}$ = 3.5 Hz, H-5′); 2.08, 2.50 [2xs, 6H, C_5-(Me_2)]; 2.00, 1.97, 1.92, 1.84 (4xs, 12H, 4xOAc). δ_C ($CDCl_3$): 176.8 (C-2); 170.3, 170.1, 169.0, 168.7 (C = O); 106.9 (C-5); 74.4 (C-2′); 73.9 (C-3′); 72.2 (C-4′); 64.8 [$^1J(^{13}C-^1H)$ = 153.0 Hz, (C-1′)]; 61.6 (C-6′); 42.6 (C-5′); 27.8, 27.1 [C_5-(*Me_2*)]; 20.5–20.3 (4xCO*Me*). Anal Calc. for $C_{18}H_{25}N_3S_2O_8$ (475.5): C, 45.46; H, 5.03; N., 8.84. Found: C, 45.49; H, 4.94; N., 8.61. MS: m/z (FAB) 476 $(M + H)^+$.

2,5-Dihydro-5,5-dimethyl-2-(5-thio-β-D-gluopyranosylimino)-1,3,4-thiadiazole (11). From tetracatate **11** (0.40 g, 0.84 mmol) as described for analogue **9**. The oily product was purified on a SiO_2 column, using in gradient MeOH (0–10%) and CH_2Cl_2 to give **15** (0.21 g, 83%), as a foam. δ_H (DMSO-d_6/D_2O): 4.01 (d, 1H, $J_{1',2'}$ = 9.5 Hz, H-1′); 3.85 (dd, 1H, $J_{6',6''}$ = 12.0 Hz, H-6″); 3.82 (dd, 1H, $J_{5',6'}$ = 3.7 Hz, H-6′); 3.60 (dd, 1H, $J_{4',5'}$ = 10.0 Hz, H-4′); 3.54 (dd, 1H, $J_{2',3'}$ = 9.0 Hz, H-2′); 3.29 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3′); 3.11 (ddd, 1H, $J_{5',6''}$ = 5.5 Hz, H-5′); 2.11, 2.52 [2xs, 6H, C_5-(Me_2)]. Anal Calc. for $C_{10}H_{17}N_3S_2O_4$ (307.4): C, 39.07; H, 5.57; N., 13.67. Found: C, 38.72; H, 5.48; N., 13.47. MS: m/z (FAB) 330 $(M + Na)^+$.

5-Methyl-1-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)-4-imidazoline-2-thione (17). A solution of aminoacetone hydrochloride (0.30 g, 2.13 mmol) in water (15 mL) was neutralized with $NaHCO_3$ (0.17 g, 2.13 mmol) and added to a solution of **2** (0.82 g, 2.0 mmol) in acetone (30 mL) under nitrogen. The reaction mixture was stirred at 23°C for 30 min, the evaporated to dryness. The residue was partitioned between CH_2Cl_2 (3 × 30 mL) and water (30 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The crude foam was purified on a SiO_2 column (15 g) using, in gradient, MeOH (0–0.1%) and CH_2Cl_2 to give **17** (0.47 g, 51%) as a foam. δ_H ($CDCl_3$): 10.69 (s, 1H, NH); 6.13 (s, 1H, H-4); 5.80 (d, 1H, $J_{1',2'}$ = 9.3 Hz, H-1′); 5.73 (t, 1H, $J_{2',3'}$ = 9.5 Hz, H-2′); 5.40 (t, 1H, $J_{4',5'}$ = 10.0 Hz, H-4′); 5.23 (t, 1H, $J_{3',4'}$ = 9.2 Hz, H-3′); 4.26 (dd, 1H, $J_{6',6''}$ = 12.0 Hz, H-6″); 4.07 (dd, 1H, $J_{5',6'}$ = 5.0 Hz, H-6′); 3.46 (ddd, 1H, $J_{5',6''}$ = 3.7 Hz, H-5′); 2.36 (s, 3H, C_5-Me); 2.01, 1.98, 1.94, 1.86 (4xs, 12H, 4xOAc). δ_C ($CDCl_3$): 170.4, 169.6, 169.3, 169.2 (C = O); 163.0 (C = S); 127.0 (C-4); 112.2 (C-5); 74.4 (C-2′); 73.6 (C-3′); 72.3 (C-4′); 63.0 (C-1′); 61.8 (C-6′); 42.2 (C-5′); 34.5 (C_5-*Me*); 20.6, 20.5, 20.4, 20.4 (4xCO*Me*). Anal Calc. for $C_{18}H_{24}N_2S_2O_8$ (460.5): C, 46.95; H, 5.25; N., 6.08. Found: C, 46.76; H, 5.16; N., 5.86. MS: m/z (FAB) 461 $(M + H)^+$.

5-Methyl-1-(5-Thio-β-D-glucopyranosyl)-4-imidazoline-2-thione (18). From **17** (0.20 g, 0.43 mmol) as described for analogue **9**. Yield: 0.05 g, (86%), m.p. 146–150°C (from EtOH). δ_H (DMSO-d_6/D_2O): 6.17 (s, 1H, H-4); 5.31 (d, 1H, $J_{1',2'}$ = 9.0 Hz, H-1′); 3.98 (t, 1H, $J_{2',3'}$ = 9.0 Hz, H-2′); 3.88 (dd, 1H, $J_{5',6'}$ = 10.0 Hz, H-4′); 3.52 (dd, 1H, $J_{3',4'}$ = 9.2 Hz, H-3′); 3.23 (dd, 1H; $J_{6',6''}$ = 12.0 Ht, H-6″); 3.14 (dd, 1H, $J_{5',6'}$ = 5.5 Hz, H-6′); 3.09 (ddd, 1H, $J_{5',6''}$ = 3.5 Hz, H-5′); 2.38 (s, 3H, C_5-Me). Anal Calc. for $C_{10}H_{16}N_2S_2O_4$ (292.4): C, 41.08; H, 5.52; N., 9.58. Found: C, 40.81; H, 5.40; N., 9.29. MS: m/z (FAB) 315 $(M + Na)^+$.

2-(2,3,4,6-Tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)amino-2-thiazoline (19). To a solution of chloroethylamine hydrochloride (0.20 g, 1.72 mmol) in water (3 mL),

ether (4 mL) and M NaOH (4 mL) were added. The organic layer was decanted and the aqueous solution was extracted with ether (4 × 4 mL). The combined extracts were dried ($MgSO_4$) and then **2** (1.86 g, 4.58 mmol) was added. After stirring for 12 h at 23°C, the solvent was evaporated to dryness to give **19** as a crude hydrochloride. The residue was stirred for 2 h at 23°C in CH_2Cl_2 (50 mL) and aqueous solution of $NaHCO_3$ [3.78 g, 45.0 mmol, in water (50 mL)]. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The residue was poured onto a SiO_2 column (25 g) using, in gradient, MeOH (0–0.1%) in CH_2Cl_2 to give **19** as a foam (1.68 g, 82%). δ_H ($CDCl_3$): 8.20 (d, 1H, $J_{NH,H\text{-}1'}$ = 5.5 Hz, NH); 5.64 (t, 1H, $J_{2',3'}$ = 9.2 Hz, H-2′); 5.37 (t, 1H, $J_{3',4'}$ = 9.2 Hz, H-3′); 5.30 (t, 1H, $J_{4',5'}$ = 9.2 Hz, H-4′); 4.97 (d, 1H, $J_{1',2'}$ = 8.8 Hz, H-1′); 4.28 (dd, 1H, $J_{5',6'}$ = 4.7 Hz, H-6′); 4.16 (dd, 1H, $J_{6',6''}$ = 12.0 Hz, H-6″); 3.56 (ddd, 1H, $J_{5',6''}$ = 3.5 Hz, H-5′); 3.60 (t, 2H, J = 7.2 Hz, CH_2-5); 3.20 (t, 2H, J = 7.2 Hz, CH_2-4); 2.02, 1.99, 1.96, 1.88 (4xs, 12H, 4xOAc). Anal Calc. for $C_{17}H_{24}N_2S_2O_4$ (448.5): C, 45.52; H, 5.39; N., 6.25. Found: C, 45.21; H, 5.30; N., 6.01. MS: m/z (FAB) 449 $(M + H)^+$.

2-(5-Thio-β-D-glucopyranosyl)amino-2-thiazoline (20). From tetracetate **20** (0.35 g, 0.78 mmol) as described for analogue **11**. Yield: 0.18 g, 82%), m.p. 151–154°C. δ_H (DMSO-d_6/D_2O): 4.30 (d, 1H, $J_{1',2'}$ = 10.0 Hz, H-1′); 3. 76 (dd, 1H, $J_{5',6'}$ = 6.0 Hz, H-6′); 3.70 (t, 1H, $J_{2',3'}$ = 9.0 Hz, H-2′); 3.59 (t, 2H, J = 7.1 Hz, CH_2-5); 3.55 (dd, 1H, $J_{6',6''}$ = 12.0 Hz, H-6″); 3.25 (pt, 1H, $J_{4',5'}$ = 10.0 Hz, H-4′); 3.19 (t, 2H, J = 7.1 Hz, CH_2-4); 3.07 (pt, 1H, $J_{3',4'}$ = 8.5 Hz, H-3′); 2.78 (m, 1H, $J_{5',6'}$ = 3.5 Hz, H-5′). Anal Calc. for $C_9H_{16}N_2S_2O_4$ (280.4): C, 38.56; H, 5.75; N., 9.99. Found: C, 38.24; H, 5.66; N., 9.70. MS: m/z (FAB) 281 $(M + H)^+$.

***N,N′*-Bis(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)-*N*-(2-thiazolin-2-yl)thiourea (21).** To a solution of 2-chloroethylamine hydrochloride (0.06 g, 0.52 mmol) in pyridine (2 mL) was added **2** (0.42 g, 1.04 mmol). The mixture was kept at 23°C for 2 h, and then poured into ice–water. The solid product was poured onto column of silica gel (25 g), using, in gradient, ether (0–50%) and hexane to afford a white foam (0.63 g, 71%), tentatively identified as **21**. δ_H ($CDCl_3$): 13.0 (d, 1H, $J_{N'H,H\text{-}1'}$ = 7.8 Hz, N′H); [5.68–5.40 (m, 2H, H-2′, H-3′)]$_{A,B}$; [5.33–5.29 (m, 1H, H-4′)]$_{A,B}$; [5.00 (dd, 1H, $J_{1',2'}$ = 10.5 Hz, H-1′)]$_A$; [4.95 (m, 2H, H-5′)]$_{A,B}$; 4.62 (dt, 1H, = NCH*H*′); 4.48 (dt, 1H, J = 11.0 Hz, = N*CH*H′); [4.27 (m, 2H, H-6″)]$_{A,B}$; 4.21 (m, 1H, H-1′)]$_B$; [4.15–401 (m, 2H, H-6′)]$_{A,B}$; 3.60 (t, 2H, J = 7.2 Hz, CH_2-5); 3.55 [(m, 2H, H-5′]$_{A,B}$; 3.01 (t, 2H, J = 7.0 Hz, S-CH_2); [2,04, 2.02, 2.00, 1.99, 1.96, 1.92, 1.90, 1.87, 1.85 (9xs, 24H, 8xOAc)]$_{A,B}$. Anal Calc. for $C_{32}H_{43}N_3S_4O_{16}$ (854.0): C, 45.01; H, 5.08; N., 4.92. Found: C, 44.72; H, 4.92; N., 4.56. MS: m/z (FAB) 855 $(M + H)^+$.

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