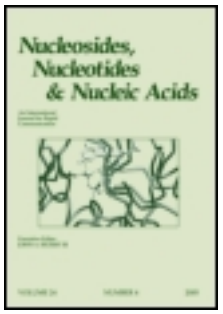

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Microwave-Assisted Synthesis and Anti-HIV Activity of New Acyclic C-Nucleosides of 3-(D-Ribo-Tetritol-1-yl)-5-Mercapto-1,2,4-Triazoles. Part 1

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MICROWAVE-ASSISTED SYNTHESIS AND ANTI-HIV ACTIVITY OF NEW ACYCLIC *C*-NUCLEOSIDES OF 3-(D-*RIBO*-TETRITOL-1-YL)-5-MERCAPTO-1,2,4-TRIAZOLES. PART 1

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□ *Microwave-assisted synthesis of novel acyclic C-nucleosides of 6-alkyl/aryl-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**5–12**) and the 6-aryl-thiomethyl analogues **25–27** has been described. Deblocking of **5–12** and **25–27** afforded the free acyclic C-nucleosides **13–20**, and **28–30**, respectively. All of the synthesized compounds showed no inhibition against HIV-1 and HIV-2 replication in MT-4 cells. However, 6-(3,4-dichlorophenyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (**6**) is a potent inhibitor, in vitro, of the replication of HIV-2. These results suggest that compound **6** should be considered as a new lead in the development of antiviral agent.*

Keywords Anti-HIV activity; acyclic *C*-nucleosides; microwave-assisted synthesis; 6-substituted-3-(D-*ribo*-tetritol-1-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles

INTRODUCTION

Recent work has demonstrated the feasibility of using acyclic nucleoside analogues as antiviral chemotherapeutic agents. The acyclic purine derivatives have been the most widely studied.[1–4] For instance, (*S*)-9-(2,3-dihydroxypropyl)adenine ((*S*)-DHPA) **1**,[5] the potent antiherpetic drug[6a,7] acyclovir (ACV, Zovirax),[8,9] 9-(2-phosphonylmethoxyethyl) adenine (PMEA), (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl) adenine (HPMPA),[10] (*RS*)-9-[4-hydroxy-2-(hydroxymethyl)butyl] guanine (HBG)

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This article is dedicated for Professor W. Pfleiderer on the occasion of his 80th birthday.
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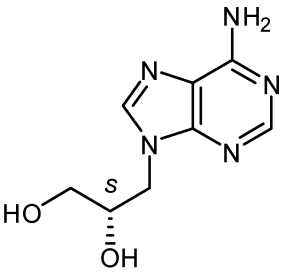
and 9-[(1,3-dihydroxy-2-propoxy)methyl] guanine (DHPG),[11,12] are examples of such potent antiviral agents against a number of DNA and RNA viruses. Structure-activity relationship studies have shown that the side chains of acyclonucleosides play a crucial role in the interaction of the acyclonucleosides with their antiviral target enzymes.[13,14]

In addition, compounds containing five-membered heterocyclic bases are important targets in chemical synthesis because of their pronounced biological activities. Various substituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and their schiff bases are associated with diverse pharmacological activities such as analgesic, antihelmintic, antitubercular, plant growth regulating, antiviral, antifungal, antibacterial, and anticancer properties.[15–19] Recently, Al-Masoudi et al.[20] have reviewed the synthetic approaches of 1,2,4-triazoles and their pharmacological importance.

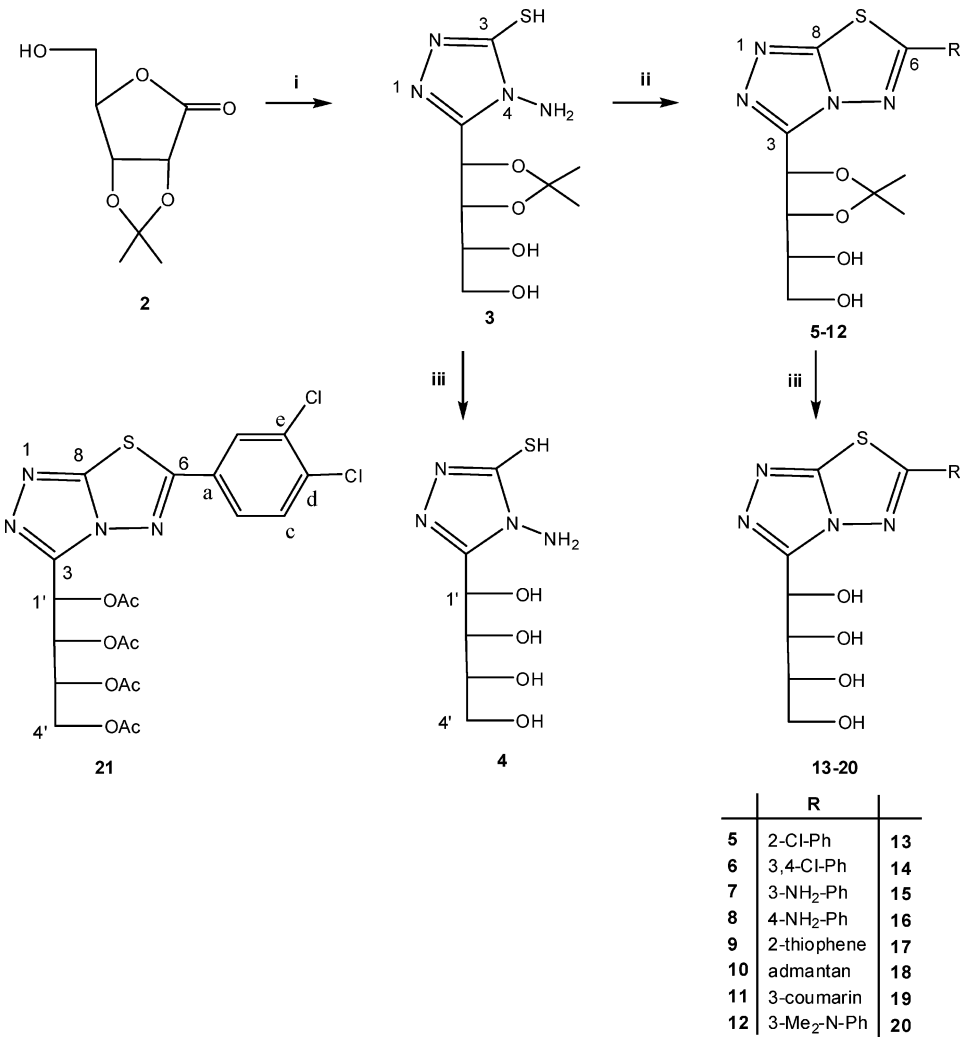
Prompted by the varied biological activities of the acyclic nucleosides with 1,2,4-triazole and 1,3,4-thiadiazole rings, and as a continuation of our recent work on the synthesis of acyclic *N*- and *C*-nucleosides,[25–30] we herein report on the synthesis of novel acyclic 6-alkyl/aryl-and 6-thioarylthiomethyl-3-(1,2-*O*-isopropylidene-D-*ribo*-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles, and their free nucleosides with evaluation of their anti-HIV activity.



1. (*S*)-DHPA

RESULTS AND DISCUSSION

The required N^4-amino-3-(1,2-*O*-isopropylidene-D-*ribo*-tetritol-1-yl)-5-mercapto-1,2,4-triazole (**3**) (87%) was prepared by treatment of the γ-lactone **2** with thiocarbohydrazide in pyridine under microwave irradiation (MWI) for 15 minutes (Scheme 1). Then, **3** was cyclized with the appropriate substituted benzoic acids, 2-chloro-, 3,4-dichloro-, 3-amino- and 4-aminobenzoic acids, thiophene-2-carboxylic acid, adamantan-1-carboxylic acid, coumarin-3-carboxylic acid, and 3-(dimethylamino)benzoic acid, respectively, in DMF at 120°C for 45 minutes furnishing the 6-alkyl/aryl-3-(1,2-*O*-isopropylidene-D-*ribo*-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*]



SCHEME 1 *Reagents and conditions* (i) $(NH_2NH)_2C{=}S$, pyridine, MWI, 15 min; (ii) RCO_2H, DMF, MWI, 45 min, 120°C; (iii) 80% HOAc, 80°C, 12 h

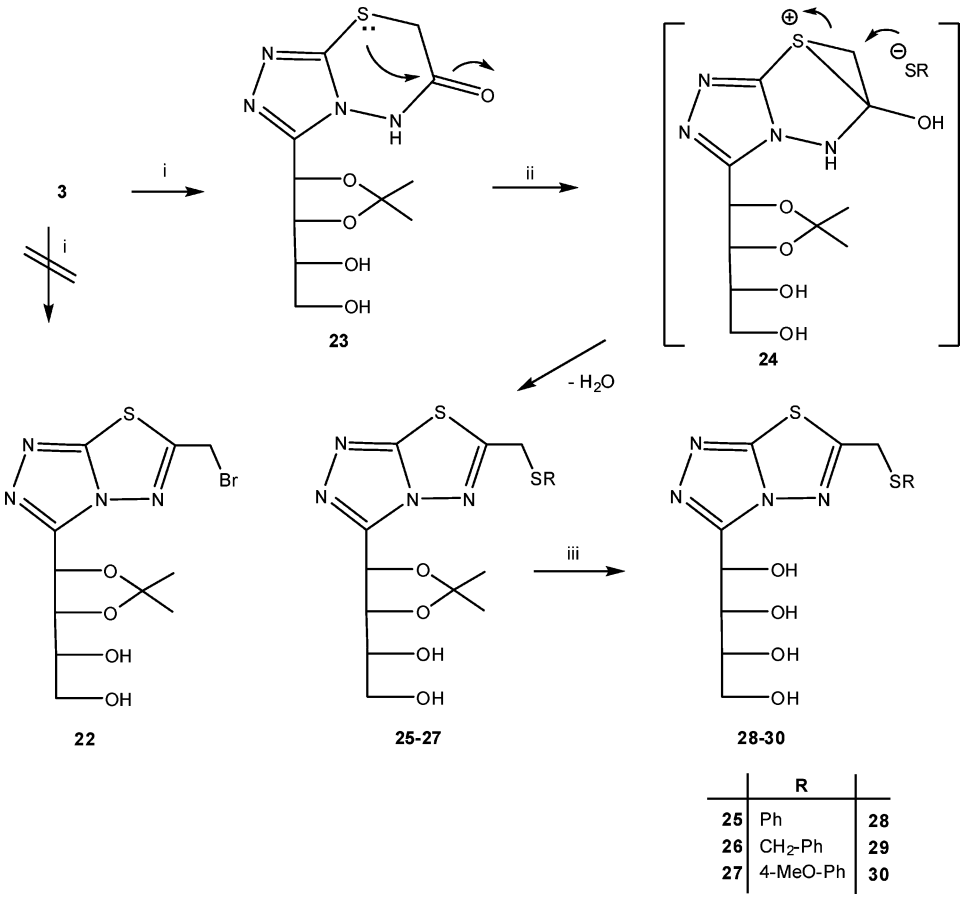
[1,3,4]thiadiazoles (**5–12**) in 56–94% yield. Acid hydrolysis of **3**, and **5–12** with 80% HOAc at 80°C for 12 hours afforded the free nucleosides **4** and **13–20** (73% and 66–83% yield, respectively). Acetylation of **14** with acetic anhydride in pyridine at 23°C gave the crystalline tertaacetate derivative **21** (83%).

The structures of the newly synthesized compounds **3–20** were assigned by the ^1H, ^{13}C NMR and mass spectra. The ^1H NMR spectra of **3** and **5–12** showed rather similar pattern for the 1,2-*O*-isopropylidene-D-ribose protons at ~δ 1.45 and 1.35. Thus, the doublets at δ 4.78–4.84 with $J_{1',2'} \sim 5.5$ Hz were assigned to H-1′, while the doublets of doublets oriented at the region

δ 4.71–4.78 were assigned to H-2′ ($J_{2',3'} \sim 2.3$ Hz). The triplets at δ 4.56–4.63 were assigned to H-3′ ($J_{3',4'a} \sim 2.3$ Hz), while the doublets of doublets at δ 3.92–3.99 and δ 3.74–3.94 arose due to the geminal H-4′a and H-4′b protons, respectively, ($J_{3',4'a} \sim 2.5$ Hz, $J_{3',4'b} \sim 4.5$ Hz, $J_{4'a,4'b} \sim 12.0$ Hz). In the ^{13}C NMR spectra of **3**, the signals at δ 182.0 and 174.2 were assigned to C=S and C=N, while C-6, and C-3 and C-8 of compounds **5–12** appear at δ 174.1–174.9, δ 160.0–171.8 and, δ 141.4–154.1, respectively (except **9**, C-6 and C-3 appeared at δ 183.4 and δ 174.9, respectively). The sugar carbons were fully analysed, where C-1′ appeared at the region δ 78.1–78.3 and C-2′ at the region δ 82.1–82.8. C-3′ and C-4′ resonate at δ 74.9–75.7, and δ 60.0–62.1, respectively. The phenyl, adamantan, coumarin, thiophene, and the isopropylidene carbon atoms were fully assigned (see Experimental section). Similarly, the ^{1}H-, and ^{13}C NMR spectra of the free nucleosides **4** and **13–20** were well established. The tetraacetate **21** was selected for further spectroscopic analysis. From the gradient selected HMBC spectrum[27] of **21**, C-3 at δ_C 169.8 shows a heteronuclear $^{2}J_{C,H}$ correlation to H-1′ at δ_H 5.73, while C-6 at δ_C 170.2 shows $^{3}J_{C,H}$ correlation with the aromatic protons H_b at δ_H 8.10 and H_f at δ_H 7.85, respectively.

Next, our efforts have been focused on the synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-6-one derivatives as potential pharmacological compounds. Thus, treatment of **3** with 2-bromoacetic acid in DMF under MWI for 45 minutes afforded a compound tentatively identified as a thiadiazin-6-one derivative **23** (57%) and not 6-(bromomethyl)-3-(1,2-*O*-isopropylidene-D-*ribo*-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**22**) (Scheme 2). The HMBC spectrum of **23** revealed two $^{2}J_{C,H}$ correlations between CH_2S at δ_H 2.81 and C=O at δ_C 175.1, and C-9 at δ_C 149.9, confirming the existence of the thiadiazin-6-one ring. These data are in accordance with the observations of Holla et al.[28] The mass fragmentation pattern was consistent with the suggested structure, however, the FABMAS spectrum showed a protonated molecular ion at *m/z* 317 $(M+H)^+$.

Heating of **23** with aryl mercaptans for 5 h afforded, after purification, products tentatively identified as 6-arylthio-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **25–27** in 72%, 86%, and 90% yield, respectively. The structures of **25–27** were identified from the ^{1}H-, ^{13}C-NMR and mass spectra. The sugar protons and carbons showed rather similar pattern for those of compounds **5–12**. CH_2S protons resonated as singlets at δ_H 4.27, 3.09 and 4.11, respectively, while the carbons appeared at δ_C 40.6, 41.5, and 45.7, respectively. The formation of the thiadiazole derivatives has been identified from the HMBC spectrum of **25**, which showed a $^{2}J_{C,H}$ correlation between *CH*$_2$SPh at δ_H 4.27 and C-6 at δ_C 174.7 in comparison for a $^{2}J_{C,H}$ correlation in **23** between C=O (C-6) and SCH_2. A plausible mechanism for formation of **25–27** likely involves the sulphur participation to form the episulphonium ion **24** (Scheme 2).



SCHEME 2 *Reagents and conditions* (i) $BrCH_2CO_2H$, DMF, 45 min, MWI; (ii) RSNa or RSH, Et_3N, reflux, CH_2Cl_2, (III) 80% HOAc, 80°C, 12 h.

Acid hydrolysis of **25–27** with 80% HOAc at 80°C gave the free nucleosides **28–30** in 85, 83, and 90% yield, respectively. Similary, the structures of **28–30** were assigned from the ^{1}H-, ^{13}C-NMR and mass spectra, which their sugar protons and carbons were almost identical for those of **13–20**.

IN VITRO ANTI-HIV-ASSAY

All the new synthesized compounds were evaluated for their in vitro anti-HIV activity using the MT-4/MTT assay.[29] Of the compounds tested, only compound 6 showed any antiviral activity against *HIV-2*. Compound **6** showed an EC_{50} of 17.30 μg/mL and a CC_{50} of 97.17 ± 18.09 μg/mL, resulting in a selectivity index of 5. Based on the chemical structure and the fact that compound **6** inhibits HIV-2 in comparison to **3–5** and **7–30**, it can

be concluded that the 3,4-dichlorophenyl residue play a major role in the antiviral activity in such molecules.

EXPERIMENTAL

Microwave supported reactions were performed in a SmithSynthesizer (Personal Chemistry AB, monomode microwave cavity at 2.45 GHz, temperature control by automated adjustment of irradiation power in a range from 0 to 300 W) in Biotage microwave reaction vials (2–5 mL) with Teflon septum and an aluminum crimp top. Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). Microanalytical data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). NMR spectra were recorded on 300 and 600 MHz (^{1}H) and at 62.9 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on δ scale in ppm. Heteronuclear assignments were verified by ^{1}H-^{13}C HMBC experiment. Mass spectra were recorded at 70 eV on EI and FAB mass spectra were measured on a MAT 8200 spectrometer (Finnigana MAT, USA) using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrices. Some molecular ions were detected by doping the sample with Na^+ ion.

***4-Amino-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-5-mercapto-1,2,4-triazole* (3).** A mixture of thiocarbohydrazide (94 mg, 0.50 mmol) and **2** (53 mg, 0.50 mmol) in pyridine (5 mL) was sealed with a Teflon septum and an aluminum crimp top in a glass vial (Biotage microwave reaction vial 2–5 mL). The vessel was then heated to 120°C under microwave irradiation using the SmithSynthesizer. After 15 minutes the vial was cooled to rroom temperature by gas jet cooling. The solution was evaporated to dryness and the residue was washed with EtOH (4×15 mL). The white precipitate was recrystallized from EtOH to give **2** (120 mg, 87%), m.p. 121–123°C. ^{1}H NMR ($CDCl_3$): δ 4.83 (d., 1H, $J_{1',2'} = 5.5$ Hz, H-1′); 4.77 (dd, 1H, $J =$ 2.7 Hz, H-2′); 4.62 (t, 1H, $J_{3',4'b} = 2.7$ Hz, H-3′); 3.99 (dd, $J_{3',4'a} = 2.2$ Hz, H-4′a); 3.80 (dd, 1H, $J_{4'a,4'b} = 12.0$ Hz, H-4′b); 2.56 (br s, 2H, OH); 1.47, 1.38 (2 × s, 6H, CMe_2). ^{13}C NMR (DMSO-d_6): δ 182.0 (C=S); 174.2 (C=N); 111.5 (CMe_2); 82.1 (C-2′); 78.0 (C-1′); 74.9 (C-3′); 60.3 (C-4′); 26.4, 25.0 (CMe_2). Anal. calc. for $C_9H_{16}N_4O_4S$ (276.31): C, 39.12; H, 5.84; N, 20.28. Found; C, 38.89; H, 5.73; N, 20.06. MS: *m/z* (FAB) 277 $(M+H)^+$.

***N*^{4}*-Amino-5-(D-ribo-tetritol-1-yl)-1,2,4-triazole-3-thiol* (4).** A solution of **3** (0.25 mmol) in 80% HOAc (10 mL) was stirred at 80°C for 12 hours. The solution was evaporated to dryness and the residue was co-evaporated with EtOH (4×20 mL) and the residue was extracted between water (15 mL) and diethyl ether (3×15 mL). The aq. layer was evaporated to dryness to give **4** (110 mg, 73%); m.p. 121–123°C. ^{1}H NMR (DMSO-d_6): δ 12.89 (s, 1H, SH); 5.82 (s, 2H, NH_2); 5.60 (br s, 4H, OH); 4.40 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′);

4.22 (dd, 1H, $J_{2',3'} = 2.7$ Hz, H-2′); 4.12 (t, 1H, $J_{3',4'b} = 2.7$ Hz, H-3′); 3.56 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.3 (C-SH); 174.2 (C=N); 85.3 (C-2′); 69.3 (C-3′); 68.6 (C-1′); 60.4 (C-4′). Anal. calc. for $C_6H_{12}N_4O_4S$ (236.25): C, 30.50; H, 5.12; N, 23.72. Found; C, 30.30; H, 5.01; N, 23.48. MS: *m/z* (FAB) 237 $(M+H)^+$.

***6-Alkyl/aryl-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-b][1,3,4]thia-diazoles* (5–12).** A mixture of **3** (100 mg, 0.36 mmol) and the appropriate aryl or alkyl benzoic acid (0.40 mmol) in DMF (5 mL) was sealed with a Teflon septum and an aluminum crimp top in a glass vial (Biotage microwave reaction vial 2–5 mL). The vessel was then heated to 120°C under microwave irradiation using the SmithSynthesizer. After 45 minutes, the vial was cooled to room temperature by gas jet cooling. The solution was evaporated to dryness and the residue was partitioned between water (15 mL) and EtOAc (15 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness to give a white precipitate, which recrystallized from EtOH or EtOAc to give the desired product.

***6-(4-Chlorophenyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)[1,2,4]triazolo [3,4-b][1,3,4] thiadiazole* (5).** From 2-chlorobenzoic acid (62 mg). Yield: 80 mg (56%); m.p. 121–123°C. ^{1}H NMR ($CDCl_3$): δ 7.99 (dd, 1H, $J =$ 6.8 Hz, 1.6 Hz, ArH); 7.49–7.34 (m, 3H, ArH); 4.84 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1′); 4.78 (dd, 1H, $J_{2',3'} = 2.2$ Hz, H-2′); 4.63 (t, 1H, $J_{3',4'b} = 2.2$ Hz, H-3′); 3.99 (dd, 1H, $J_{3',4'a} = 4.8$ Hz, H-4′a); 3.81 (dd, 1H, $J_{4'a,4'b} = 12.1$ Hz, H-4′b); 1.48, 1.38 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.2 (C-6); 163.4 (C-3); 141.4 (C-8); 133.3, 132.3, 131.4, 126.4 (Ar-C); 113.2 (CMe_2); 82.7 (C-2′); 78.0 (C-1′); 75.7 (C-3′); 62.0 (C-4′); 26.7, 25.5 (CMe_2). Anal. calc. for $C_{16}H_{17}ClN_4O_4S$ (396.85): C, 48.42; H, 4.32; N, 14.12. Found; C, 48.59; H, 4.25; N, 14.06. MS: *m/z* (FAB) 396/398 $(M+2)^+$.

***6-(3,4-Dichlorophenyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-7H-1,2,4-triazolo [3,4-b][1,3,4] thiadiazole* (6).** From 3,4-dichlorobenzoic acid (48 mg). Yield: 96 mg (88%); m.p. 116–119°C. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 1H, $J = 2.0$ Hz, ArH); 7.93 (dd, 1H, $J = 6.3$ Hz, 2.0 Hz, ArH); 7.56 (d, 1H, $J =$ 6.3 Hz, ArH); 4.81 (d., 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.77 (dd, 1H, $J_{2',3'} = 2.3$ Hz, H-2′); 4.63 (t, 1H, $J_{3',4'b} = 2.3$ Hz, H-3′); 3.99 (dd, 1H, $J_{3',4'a} = 4.6$ Hz, H-4′a); 3.81 (dd, 1H, $J_{4'a,4'b} = 12.2$ Hz, H-4′b); 1.47, 1.38 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.2 (C-6); 163.5 (C-3); 141.5 (C-8); 132.1, 130.7, 129.1 (Ar-C); 113.2 (CMe_2); 82.6 (C-2′); 78.2 (C-1′); 75.7 (C-3′); 62.1 (C-4′); 26.7, 25.5 (CMe_2). Anal. calc. for $C_{16}H_{16}Cl_2N_4O_4S$ (431.29): C, 44.56; H, 3.74; N, 12.99. Found; C, 44.32; H, 3.59; N, 12.71. MS: *m/z* (FAB) 431/433 $(M+2)^+$.

***6-(3-Aminophenyl)-3-(1′,2′-O-isopropylidene-D-ribo-tetritol-1-yl)-7H-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole* (7).** From 3-aminobenzoic acid (34 mg). Yield: 84 mg (88%); m.p. 106–108°C. ^{1}H NMR ($CDCl_3$): δ 8.07 (br s, 2H, NH_2); 7.41, 7.34, 7.18, 6.86 (m, 4H, ArH); 4.78 (d., 1H, $J_{1',2'} = 5.6$ Hz, H-1′); 4.71 (dd, 1H, $J_{2',3'} = 2.3$ Hz, H-2′); 4.56 (t, 1H, $J_{3',4'b} = 2.3$ Hz, H-3′);

3.93 (dd, 1H, $J_{3',4'a} = 4.6$ Hz, H-4′a); 3.74 (dd, 1H, $J_{4'a,4'b} = 12.3$ Hz, H-4′b); 1.41, 1.31 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.8 (C-6); 170.1 (C-3); 146.4 (C-8); 136.4, 130.6, 130.3, 120.4, 116.2 (Ar-C); 113.2 (CMe_2); 82.7 (C-2′); 78.2 (C-1′); 75.6 (C-3′); 62.0 (C-4′); 26.7, 25.5 (CMe_2). Anal. calc. for $C_{16}H_{19}N_5O_4S$ (377.42): C, 50.92; H, 5.07; N, 18.56. Found; C, 50.71; H, 4.94; N, 18.37. MS: *m/z* (FAB) 378 $(M+H)^+$.

***6-(4-Aminophenyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-7H-1,2,4-triazolo [3,4-b][1,3,4] thiadiazole* (8).** From 4-aminobenzoic acid (34 mg). Yield: 80 mg (84%); m.p. 155–158°C. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 2H, $J =$ 14.1 Hz, NH_2); 7.84 (dd, 2H, $J = 8.8$ Hz, 2.2 Hz, ArH); 6.59 (dd, 2H, $J =$ 8.8 Hz, 2.2 Hz, ArH); 4.79 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1′); 4.72 (dd, 1H, $J_{2',3'}$ = 1.8 Hz, H-2′); 4.56 (t, 1H, $J_{3',4'b} = 1.8$ Hz, H-3′); 3.90 (dd, 1H, $J_{3',4'a} = 4.2$ Hz, H-4′a); 3.74 (dd, 1H, $J_{4'a,4'b} = 12.3$ Hz, H-4′b); 1.41, 1.31 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.9 (C-6); 162.8 (C-3); 141.4 (C-8); 132.2, 118.7, 113.7 (Ar-C); 113.0 (CMe_2); 82.7 (C-2′); 78.3 (C-1′); 75.6 (C-3′); 61.8 (C-4′); 26.7, 25.4 (CMe_2). Anal. calc. for $C_{16}H_{19}N_5O_4S$ (377.42): C, 50.92; H, 5.07; N, 18.56. Found; C, 50.68; H, 4.97; N, 18.54. MS: *m/z* (FAB) 378 $(M+H)^+$.

***3-(1,2-O-Isopropylidene-D-ribo-tetritol-1-yl)-6-(thiophen-2-yl)-7H-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole* (9).** From thiophene-2-carboxylic acid (32 mg). Yield: 90 mg (93%); m.p. 102–104°C. ^{1}H NMR ($CDCl_3$): δ 7.81 (dd, 1H, $J = 3.6$ Hz, 1.8 Hz, thiophen-H); 7.56 (dd, 1H, $J = 4.8$ Hz, 1.8 Hz, thiophen-H); 7.06 (dd, 1H, $J = 3.6$ Hz, 4.8 Hz, thiophen-H); 4.78 (d., 1H, $J_{1',2'} = 5.5$ Hz, H-1′); 4.72 (dd, 1H, $J_{2',3'} = 2.3$ Hz, H-2′); 4.57 (t, 1H, $J_{3',4'b}$ = 2.3 Hz, H-3′); 3.92 (dd, 1H, $J_{3',4'a} = 4.5$ Hz, H-4′a); 3.74 (dd, 1H, $J_{4'a,4'b}$ = 12.2 Hz, H-4′b); 2.56 (br s, 2H, OH); 1.40, 1.31 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.9 (C-6); 166.5 (C-3); 141.4 (C-8); 134.4, 133.6, 133.1, 127.9 (thiophen-C); 113.1 (CMe_2); 82.8 (C-2′); 78.3 (C-1′); 75.6 (C-3′); 61.9 (C-4′); 26.8, 25.4 (CMe_2). Anal. calc. for $C_{14}H_{16}N_4O_4S_2$ (368.43): C, 45.64; H, 4.38; N, 15.21. Found; C, 45.39; H, 4.21; N, 14.98. MS: *m/z* (FAB) 369 $(M+H)^+$.

***6-(Adamantan-1-yl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole* (10).** From 1-adamantan-carboxylic acid (45 mg). Yield: 100 mg (94%); semi-solid. ^{1}H NMR ($CDCl_3$): δ 4.83 (d, 1H, $J_{1',2'} = 5.7$ Hz, H-1′); 4.78 (dd, 1H, $J_{2',3'} = 2.0$ Hz, H-2′); 4.63 (t, 1H, $J_{3',4'b}$ = 2.0 Hz, H-3′); 3.99 (dd, 1H, $J_{3',4'a} = 4.4$ Hz, H-4′a); 3.81 (dd, 1H, $J_{4'a,4'b}$ = 12.3 Hz, H-4′b); 2.02 (m, 2H, adamant-H), 1.90 (m, 4H, adamant-H); 1.71 (m, 4H, adamant-H); 1.47, 1.38 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 183.4 (C-6); 174.9 (C-3); 151.2 (C-8); 113.1 (CMe_2); 82.7 (C-2′); 78.2 (C-1′); 75.6 (C-3′); 61.9 (C-4′); 40.4, 38.6, 36.4, 27.8 (adamant-C), 26.7, 25.4 (CMe_2). Anal. calc. for $C_{20}H_{28}N_4O_4S$ (420.53): C, 57.12; H, 6.71; N, 13.32. Found; C, 56.89; H, 6.58; N, 13.19. MS: *m/z* (FAB) 421 $(M+H)^+$.

***6-(Coumarin-3-yl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole* (11).** From coumarin-3-carboxylic acid (47

mg). Yield: 94 mg (83%); m.p. 101–105°C. ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H, coumar-H-4); 7.71 (d, 1H, J = 7.6 Hz, coumar-H-5); 7.50 (t, 1H, J = 7.6 Hz, coumar-H-7); 7.35 (d, 1H, J = 7.7 Hz, coumar-H-8); 7.27 (t, 1H, J = 7.6 Hz, coumar-H-6); 4.82 (d, 1H, $J_{1',2'}$ = 5.6 Hz, H-1′); 4.78 (dd, 1H, $J_{2',3'}$ = 2.2 Hz, H-2′); 4.61 (t, 1H, $J_{3',4'b}$ = 2.2 Hz, H-3′); 3.98 (dd, 1H, $J_{3',4'a}$ = 4.2 Hz, H-4′a); 3.79 (dd, 1H, $J_{4'a,4'b}$ = 12.0 Hz, H-4′b); 1.47, 1.38 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.7 (C-6); 162.7 (coumar-C-2); 160.0 (C-3); 154.1 (C-8); 150.1 (coumar-C-8a); 143.4 (coumar-C-4); 131.8 (coumar-C-3); 129.8 (coumar-C-7); 127.8 (coumar-C-5); 124.4 (coumar-C-6); 120.2 (coumar-C-8); 118.8 (coumar-C-4a); 113.1 (CMe_2); 82.6 (C-2′); 78.3 (C-1′); 75.6 (C-3′); 62.0 (C-4′); 26.7, 25.5 (CMe_2). Anal. calc. for $C_{19}H_{20}N_4O_6S$ (432.45): C, 52.77; H, 4.66; N, 12.96. Found; C, 52.53; H, 4.54; N, 12.72. MS: *m/z* (FAB) 433 $(M+H)^+$.

***6-(3-Dimethylaminophenyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole* (12).** From 3-(dimethylamino) benzoic acid (41 mg). Yield: 83 mg (81%); m.p. 110–112°C. ^{1}H NMR ($CDCl_3$): δ 7.42–7.39 (m, 2H, ArH); 7.26 (t, 1H, J = 8.1 Hz, ArH); 6.91 (ddd, 1H, J = 8.3 Hz, 2.7 Hz, 1.0 Hz, ArH); 4.78 (d, 1H, $J_{1',2'}$ = 5.8 Hz, H-1′); 4.72 (dd, 1H, $J_{2',3'}$ = 2.1 Hz, H-2′); 4.57 (t, 1H, $J_{3',4'b}$ = 2.1 Hz, H-3′); 3.94 (dd, 1H, $J_{3',4'a}$ = 4.1 Hz, H-4′a); 3.94 (dd, 1H, $J_{4'a,4'b}$ = 12.2 Hz, H-4′b); 2.95 (2 × s, 6H, NMe_2); 1.421, 1.33 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.1 (C-6); 171.8 (C-3); 150.5 (C-8); 130.0, 129.1, 118.3, 117.6 (Ar-C); 113.2 (CMe_2); 82.6 (C-2′); 78.2 (C-1′); 75.7 (C-3′); 62.1 (C-4′); 52.1 (NMe_2), 26.7, 25.5 (CMe_2). Anal. calc. for $C_{18}H_{23}N_5O_4S$ (405.47): C, 53.32; H, 5.72; N, 17.27. Found; C, 53.01; H, 5.59; N, 16.95. MS: *m/z* (FAB) 406 $(M+H)^+$.

6-Alkyl/aryl-3-(D-*ribo*-tetritol-1-yl)-7*H*-1,2,4-triazolo[3,4-b][1,3,4] thiadiazoles (13–20)

These compounds were prepared from **5–12** (0.25 mmol), as oily or solid product, by following the procedure used for the preparation of **4**.

***6-(2-Chlorophenyl)-3-(D-ribo-tetritol-1-yl)-[1,2,4-triazolo][3,4-b][1,3,4] thiadiazole* (13).** From **5** (75 mg). Yield: 50 mg (74%); m.p. 122–124°C. ^{1}H NMR (DMSO-d_6): δ 7.97 (dd, 1H, J = 7.3 Hz, 1,7 Hz, ArH); 7.61–7.20 (m, 3H, Ar-H); 4.64 (br s, 4H, OH); 4.39 (d, 1H, $J_{1',2'}$ = 5.0 Hz, H-1′); 4.21 (t, 1H, $J_{2',3'}$ = 5.0 Hz, H-2′); 4.12 (m, 1H, H-3′); 3.57 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.2 (C-6); 166.4 (C-3); 143.7 (C-8); 132.2, 131.6, 131.3, 130.4, 126.4 (Ar-C); 85.2 (C-2′); 69.2 (C-3′); 68.5 (C-1′). Anal. calc. for $C_{13}H_{13}ClN_4O_4S$ (356.78): C, 43.76; H, 3.67; N, 15.70. Found; C, 43.48; H, 3.56; N, 15.51. MS: *m/z* (FAB) 356/358 $(M+2)^+$.

***6-(3,4-Dichlorophenyl)-3-(D-ribo-tetritol-1-yl)-[1,2,4-triazolo][3,4-b][1,3,4] thiadiazole* (14).** From **6** (75 mg). Yield: 80 mg (73%); m.p. 91–94°C. ^{1}H NMR (DMSO-d_6): δ 8.05 (d, 1H, J = 2.0 Hz, ArH); 7.86 (dd, 1H, J = 6.5 Hz, 2.0 Hz, Ar-H); 7.76 (d, 1H, J = 6.5 Hz, Ar-H); 5.95 (br s, 4H, OH); 4.41

(d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.21 (t, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.12 (m, 1H, H-3′); 3.56 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.5 (C-6); 165.3 (C-3); 156.1 (C-8); 131.4, 131.0, 130.8, 129.2 (Ar-C); 85.3 (C-2′); 69.3 (C-3′); 68.6 (C-1′); 60.4 (C-4′). Anal. calc. for $C_{13}H_{12}Cl_2N_4O_4S$ (391.23): C, 39.91; H, 3.09; N, 14.32. Found; C, 39.68; H, 2.98; N, 14.05. MS: *m/z* (FAB) 413/415 $(M+Na)^+/M+Na+2)^+$.

***6-(3-Aminophenyl)-3-(D-ribo-tetritol-1-yl)-[1,2,4-triazolo][3,4-b][1,3,4] thiadiazole* (15).** From **7** (94 mg). Yield: 72 mg (85%); semi-solid. ^{1}H NMR (DMSO-d_6): δ 7.93 (m, 2H, ArH); 7.61 (m, 2H, Ar-H); 5.52 (br s, 4H, OH); 4.42 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.23 (t, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.13 (m, 1H, H-3′); 3.18 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.2 (C-6); 166.1 (C-3); 158.0 (C-8); 133.4, 132.0, 129.9, 127.7, 126.8, 123.2 (Ar-C); 85.2 (C-2′); 69.2 (C-3′); 68.4 (C-1′); 60.3 (C-4′). Anal. calc. for $C_{13}H_{15}N_5O_4S$ (337.35): C, 46.28; H, 4.48; N, 20.76. Found; C, 45.96; H, 4.39; N, 20.54. MS: *m/z* (FAB) 338 $(M+H)^+$.

***6-(4-Aminophenyl)-3-(D-ribo-tetritol-1-yl)-[1,2,4-triazolo][3,4-b][1,3,4] thiadiazole* (16).** From **8** (94 mg). Yield: 66 mg (78%); m.p. 155–158°C. ^{1}H NMR (DMSO-d_6): δ 8.96 (br s, 2H, NH_2); 7.95 (dd, 2H, $J = 7.0$ Hz, 1.3 Hz, ArH); 7.32 (dd, 2H, $J = 7.0$ Hz, 1.3 Hz, Ar-H), 5.30 (br s, 4H, OH); 4.44 (d, 1H, $J_{1',2'} = 5.3$ Hz, H-1′); 4.34 (t, 1H, $J_{2',3'} = 5.3$ Hz, H-2′); 4.15 (d, 1H, $J = 5.3$ Hz, H-3′); 3.17 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.6 (C-6); 166.7 (C-3); 142.7 (C-8); 130.9, 127.5, 124.2, 121.3 (Ar-C); 85.4 (C-2′); 69.4 (C-3′); 68.7 (C-1′); 60.5 (C-4′). Anal. calc. for $C_{13}H_{15}N_5O_4S$ (337.35): C, 46.28; H, 4.48; N, 20.76. Found; C, 46.02; H, 4.37; N, 20.50. MS: *m/z* (FAB) 338 $(M+H)^+$.

***3-(D-Ribo-tetritol-1-yl)-6-(thiophen-2-yl)-[1,2,4-triazolo][3,4-b][1,3,4] thiadiazole* (17).** From **9** (92 mg). Yield: 59 mg (72%); semi-solid. ^{1}H NMR (DMSO-d_6): δ 7.89 (dd, 1H, $J = 3.5$ Hz, 1.7 Hz, thiophene-H); 7.73 (dd, 1H, $J = 4.5$ Hz, 1.7 Hz, thiophene-H), 7.19 (dd, 1H, $J = 3.5$ Hz, 4.8 Hz, thiophene-H); 4.89 (br s., 4H, OH); 4.20 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.22 (d, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.12 (t, 1H, $J = 3.1$ Hz, H-3′); 3.57 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.5 (C-6); 162.8 (C-3; 148.5 (C-8); 128.3, 127.5, 125.3 (Ar-C); 85.4 (C-2′); 68.7 (C-3′); 69.4 (C-1′); 60.5 (C-4′). Anal. calc. for $C_{11}H_{12}N_4O_4S_2$ (328.37): C, 40.23; H, 3.68; N, 17.06. Found; C, 39. 94; H, 3.58; N, 16.86. MS: *m/z* (FAB) 329 $(M+H)^+$.

***6-(Adamantan-2-yl)-3-(D-ribo-tetritol-1-yl)-[1,2,4-triazolo][3,4-b][1,3,4] thiadiazole* (18).** From **10** (105 mg). Yield: 63 mg (66%); m.p. 75–77°C. ^{1}H NMR (DMSO-d_6): δ 5.21 (br s, 4H, OH); 4.97 (d, 1H, $J_{1',2'} = 5.5$ Hz, H-1′); 4.78 (t, 1H, $J_{2',3'} = 3.2$ Hz, H-2′); 4.63 (t, 1H, $J_{3',4'b} = 5.4$ Hz, H-3′); 4.12 (m, 2H, H-4′a, H-4′b); 2.33 (m, 2H, adamant-H), 2.20 (m, 4H, adamant-H); 1.80 (m, 4H, adamant-H). ^{13}C NMR (DMSO-d_6): δ 167.2 (C-6); 163.5 (C-3); 154.2 (C-8); 85.2 (C-2′); 69.3 (C-3′); 68.4 (C-1′); 60.4 (C-4′); 37.9, 36.0, 31.2,

27.4 (adamant-C). Anal. calc. for $C_{17}H_{24}N_4O_4S$ (380.46): C, 53.67; H, 6.36; N, 14.73. Found; C, 53.43; H, 6.29; N, 14.52. MS: *m/z* (FAB) 381 $(M+H)^+$.

***6-(Coumarin-3-yl)-3-(D-ribo-tetritol-1-yl)-[1,2,4-triazolo][3,4-b][1,3,4] thiadiazole* (19).** From **11** (108 mg). Yield: 80 mg (82%); semi-solid. ^{1}H NMR (DMSO-d_6): δ 8.10 (s, 1H, coumarin-H-4); 7.74 (d, 1H, $J = 7.2$ Hz, coumarin-H-5); 7.59 (t, 1H, $J = 7.1$ Hz, coumarin-H-7); 7.40 (d, 1H, $J = 7.8$ Hz, coumarin-H-8); 7.35 (t, 1H, $J = 7.1$ Hz, coumarin-H-6); 4.43 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.78 (d, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.61 (t, 1H, $J_{3',4'b} = 2.7$ Hz, H-3′); 3.57 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.2 (C-6); 161.5 (coumarin-C-2); 158.0 (C-3); 148.2 (C-8); 150.0 (coumarin-C-8a); 145.6 (coumarin-C-4); 131.8 (coumarin-C-3); 128.1 (coumarin-C-7); 126.4 (coumarin-C-5); 125.0 (coumarin-C-6); 121.9 (coumarin-C-8, C-4a); 85.2 (C-2′); 69.1 (C-1′); 68.5 (C-3′); 60.3 (C-4′). Anal. calc. for $C_{16}H_{14}N_4O_6S$ (390.37): C, 49.23; H, 3.61; N, 14.35. Found; C, 48.97; H, 3.50; N, 14.07. MS: *m/z* (FAB) 412/414 $(M+Na)^+$.

***6-(3-Dimethylaminophenyl)-3-(D-ribo-tetritol-1-yl)[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole* (20).** From **12** (101 mg). Yield: 76 mg (83%); oil. ^{1}H NMR (DMSO-d_6): δ 8.10–7.57 (m, 4H, ArH); 5.82 (br s, 4H, OH); 4.41 (d., 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.22 (d, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.12 (t, 1H, $J_{3',4'b} = 3.3$ Hz, H-3′); 3.46 (m, 2H, H-4′a, H-4′b); 3.09, 3.07 (2 × s, 6H, NMe_2). ^{13}C NMR (DMSO-d_6): δ 176.4 (C-6); 166.4 (C-3); 151.9 (C-8); 132.2, 130.8, 130.0 (Ar-C); 85.3 (C-2′); 69.3 (C-3′); 68.6 (C-1′); 60.4 (C-4′); 52.3 (NMe_2). MS: *m/z* (FAB) 366 $(M+H)^+$.

1′,2′,3′,4′-Tetra-O-acetyl-1-(6-(3,4-dichlorophenyl)-3-(D-ribo-tetritol-1-yl)[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole (21)

To a solution of **14** (60 mg, 0.15 mmol) in pyridine (5.0 mL) was added acetic anhydride (2.0 mL) and kept for 18 h at 23°C. The mixture was evaporated to dryness and the residue was co-evaporated with EtOH (4 × 15 mL). The residue was purified on a short column of silica gel (using $CHCl_3$-MeOH 95:5, as eluent) to give **21** (70 mg, 83%); m.p. 71–74°C ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (br s, 1H, ArH_f); 7.85 (d, 1H, $J = 8.2$ Hz, Ar-H_b); 7.47 (d, 1H, $J = 8.2$ Hz, Ar-H_c); 5.73 (d, 1H, $J_{1',2'} = 6.0$ Hz, H-1′); 5.46 (d, 1H, $J_{2',3'} = 6.0$ Hz, H-2′); 4.73 (t, 1H, $J_{2',3'} = 3.0$ Hz, H-3′); 4.37 (dd, 1H, $J_{3',4'a} = 3.1$ Hz, H-4′a); 4.33 (dd, 1H, $J_{3',4'a} = 3.0$ Hz, $J_{4'a,4'b} = 12.2$ Hz, H-4′b); 2.25, 2.13, 2.12, 2.10 (4xs, 12H, 4 x OAc). ^{13}C NMR (DMSO-d_6): δ 170.7 (C=O); 170.2 (C-6); 169.8 (C-3); 156.7 (C-8); 134.1 (Ar-C_d); 133.1 (Ar-C_e),; 132.9 (Ar-C_b); 130.6 (Ar-C_f); 129.0 (Ar-C_c, Ar-C_a); 79.9 (C-2′); 69.9 (C-1′); 67.3 (C-3′); 63.8 (C-4′). Anal. calc. for $C_{21}H_{20}Cl_2N_4O_8S$ (559.38): C, 45.09; H, 3.60; N, 10.02. Found; C, 44.81; H, 3.51; N, 9.78. MS: *m/z* (FAB) 558/560 $M^+/(M+2)^+$.

3-(1,2-O-Ispropylidene-D-ribo-tetritol-1-yl)-5H-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazin-6-one (23)

This compound was prepared from compound **3** (70 mg, 0.25 mmmol) and 2-bromoacetic acid (35 mg, 0.25 mmol), by the procedure of preparation of **5–12**. Yield: 54 mg (57%); m.p. 115–116°C. ^{1}H NMR ($CDCl_3$): δ 4.78 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1′); 4.72 (d, 1H, $J_{2',3'} = 5.6$ Hz, H-2′); 4.56 (t, 1H, $J_{3',4'b} = 2.0$ Hz, H-3′); 3.90 (dd, 1H, $J_{3',4'a} = 2.3$ Hz, H-4′a); 3.73 (dd, 1H, $J_{4'a,4'b} = 12.3$ Hz, H-4′b); 2.81 (s., 2H, SCH_2); 1.40, 1.31 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 175.1 (C=O); 163.0 (C-3); 149.9 (C-9); 113.0 (CMe_2); 82.8 (C-2′); 78.3 (C-1′); 75.7 (C-3′); 61.7

(C-4′); 36.7 (SCH_2); 26.6, 25.4 (CMe_2). Anal. calc. for $C_{11}H_{16}N_4O_5S$ (316.33): C, 41.77; H, 5.10; N, 17.71. Found; C, 41.52; H, 5.01; N, 17.50. MS: *m/z* (FAB) 317 $(M+H)^+$.

6-(Alkyl/aryl-thiomethyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)[1,2,4]triazolo [3,4-b][1,3,4]thiadiazoles (25–27)

To a stirred solution of **23** (95 mg, 0.25 mmol) in CH_2Cl_2 were added aryl mercaptans (0.25 mmol) and refluxed for 5 hours. After cooling, the solution was evaporated to dryness and the residue was purified on short SiO_2 column, using CH_2Cl_2-MeOH (95:5) as eluent, giving **25–27**.

***3-(1,2-O-Isopropylidene-D-ribo-tetritol-1-yl)-6-(phenylthiomethyl)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole* (25).** From sodium phenylthiolate (33 mg). Yield: 73 mg (72%); oil. ^{1}H NMR ($CDCl_3$): δ 7.37 (m, 5H, ArH); 4.77 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1′); 4.71 (d, 1H, $J_{2',3'} = 5.6$ Hz, H-2′); 4.56 (t, 1H, $J_{3',4'b} = 2.3$ Hz, H-3′); 4.27 (s, 2H, CH_2S); 3.92 (dd, 1H, $J_{3',4'a} = 2.3$ Hz,

H-4′a); 3.73 (dd, 1H, $J_{4'a,4'b} = 12.2$ Hz, H-4′b); 1.40, 1.31 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.7 (C-6); 167.0 (C-3); 141.8 (C-8); 135.0, 130.7, 131.4, 129.0, 127.1 (Ar-C); 113.1 (CMe_2); 82.6 (C-2′); 78.2 (C-1′); 75.6 (C-3′); 62.0 (C-4′); 40.6 (CH_2S); 26.6, 25.5 (CMe_2). MS: *m/z* (FAB) 431 $(M+Na)^+$.

***6-(Benzylthiomethyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole* (26).** From benzyl mercaptan (31 mg) and Et_3N (25 mg, 0.25 mmol). Yield: 88 mg (86%); m.p. 82–85°C. ^{1}H NMR ($CDCl_3$): δ 7.32–7.24 (m, 5H, ArH); 4.83 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1′); 4.78 (d, 1H, $J_{2',3'} = 5.6$ Hz, H-2′); 4.62 (t, 1H, $J_{3',4'b} = 2.0$ Hz, H-3′); 3.99 (dd, 1H, $J_{3',4'a} = 2.3$ Hz, H-4′a); 3.80 (dd, 1H, $J_{4'a,4'b} = 12.0$ Hz, H-4′b); 3.09 (br s., 4H, CH_2SCH_2Ph); 1.46, 1.37 (2 × s, 6H, CMe_2). ^{13}C NMR (DMSO-d_6): δ 175.0 (C-6); 160.1 (C-3); 151.6 (C-8); 129.4, 128.7, 128.4, 127.4 (Ar-C); 113.0 (CMe_2); 83.7 (C-2′); 78.3 (C-1′); 75.5 (C-3′); 61.7 (C-4′); 45.7 (CH_2SCH_2Ph); 41.5 (CH_2SCH_2Ph); 26.7, 25.4 (CMe_2). Anal. calc. for

$C_{18}H_{22}N_4O_4S_2$ (422.52): C, 51.17; H, 5.25; N, 13.26. Found; C, 50.95; H, 5.19; N, 13.03. MS: *m/z* (FAB) 423 $(M+H)^+$.

***3-(1,2-O-Isopropylidene-D-ribo-tetritol-1-yl)-6-((4-methoxyphenylthio)methyl)-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazole* (27).** From 4-methoxybenzenethiol (35 mg) and Et_3N (25 mg, 0.25 mmol). Yield: 93 mg (90%); m.p. 76–78°C. ^1H NMR ($CDCl_3$): δ 7.36 (d, 2H, $J = 9.0$ Hz, Ar-H); 6.82 (d, 2H, $J = 9.0$ Hz, ArH); 4.81 (br s, 2H, H-1′, H-2′); 4.57 (t, 1H, $J_{3',4'b} = 2.3$ Hz, H-3′); 4.11 (s, 2H, CH_2S); 3.85 (dd, 1H, $J_{3',4'a} = 2.3$ Hz, H-4′a); 3.78 (dd, 1H, $J_{4a',4'b} = 12.0$ Hz H-4′b); 3.77 (s, 3H, OMe); 1.43, 1.31 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 175.1 (C-6); 160.1 (C-3); 157.9 (C-8); 133.7, 128.6, 127.4, 125.0 (Ar-C); 114.4 (*C*Me_2); 82.7 (C-2′); 78.3 (C-1′); 75.6 (C-3′); 61.4 (C-4′); 55.2 (OMe); 45.7 (CH_2S); 26.6, 25.3 (CMe_2). Anal. calc. for $C_{18}H_{22}N_4O_5S_2$ (438.52): C, 49.30; H, 5.06; N, 12.78. Found; C, 49.02; H, 4.89; N, 12.52. MS: *m/z* (FAB) 439 $(M+H)^+$.

6-(Alkyl/aryl-thiomethyl)-3-(D-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (28–30)

These compounds were prepared from **25–276** (0.30 mmol), as oily or solid product, by following the procedure used for the preparation of **4**.

***3-(D-Ribo-tetritol-1-yl)-6-(phenylthio)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole* (28).** From **25** (122 mg). Yield: 94 mg (85%); oil. ^1H NMR (DMSO-d_6): δ 7.41–7.23 (m, 5H, ArH); 4.41 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.22 (dd, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.19 (t, 1H, $J_{3',4'b} = 2.3$ Hz, H-3′); 4.12 (br s., 6H, CH_2S, 4xOH); 3.56 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.4 (C-6); 166.2 (C-3); 148.0 (C-8); 134.6, 129.1, 128.9, 1267.4 (Ar-C); 85.3 (C-2′); 69.3 (C-3′); 68.6 (C-1′); 60.4 (C-4′); 37.0 (CH_2S). MS: *m/z* (FAB) 391 $(M+Na)^+$.

***6-(Benzylthiomethyl)-3-(D-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole* (29).** From **26** (127 mg). Yield: 95 mg (83%); oil. ^1H NMR (DMSO-d_6): δ 7.42–7.28 (m, 5H, ArH); 4.46 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1′); 4.18 (d, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.01 (t, 1H, $J_{3',4'b} = 2.5$ Hz, H-3′); 4.82–4.20 (br s, 4H, 4xOH); 4.07 (s, 2H, SCH_2); 3.55 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.4 (C-6); 166.2 (C-3); 148.0 (C-8); 134.6, 129.1, 128.9, 1267.4 (Ar-C); 85.3 (C-2′); 69.3 (C-3′); 68.6 (C-1′); 60.4 (C-4′); 37.9 (CH_2S). MS: *m/z* (FAB) 405 $(M+Na)^+$.

***3-(D-Ribo-tetritol-1-yl)-6-((4-methoxyphenylthio)methyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole* (30).** From **27** (132 mg). Yield: 108 mg (90%); oil.^1H NMR (DMSO-d_6): δ 7.35 (d, 2H, $J = 8.9$ Hz, Ar-H); 6.91 (d, 2H, $J = 8.9$ Hz, Ar-H) 4.41 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 4.22 (d, 1H, $J_{2',3'} = 5.4$ Hz, H-2′); 4.12 (t, 1H, $J_{3',4'b} = 2.0$ Hz, H-3′); 4.06 (br s, 6H, CH_2S, 4xOH); 3.59 (s, 3H, OMe); 3.56 (m, 2H, H-4′a, H-4′b). ^{13}C NMR (DMSO-d_6): δ 176.6 (C-6); 166.1 (C-3); 148.7 (C-8); 133.3, 124.6, 121.6, 114.7 (Ar-C); 85.4 (C-2′); 69.4 (C-3′); 68.7 (C-1′); 60.5 (C-4′); 55.2 (OMe); 41.2. (CH_2S). MS: *m/z* (FAB) 421 $(M+Na)^+$.

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