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Nucleosides, Nucleotides and Nucleic Acids

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New Sulphonamide and Carboxamide Derivatives of Acyclic C-Nucleosides of Triazolo-Thiadiazole and the Thiadiazine Analogues. Synthesis, Anti-HIV, and Antitumor Activities. Part 2

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NEW SULPHONAMIDE AND CARBOXAMIDE DERIVATIVES OF ACYCLIC C-NUCLEOSIDES OF TRIAZOLO-THIADIAZOLE AND THE THIADIAZINE ANALOGUES. SYNTHESIS, ANTI-HIV, AND ANTITUMOR ACTIVITIES. PART 2

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□ A new series of acyclic C-nucleosides 1',2'-O-isopropylidene-D-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles bearing arylsulfonamide (5–8) and arylcarboxamide (9–12) residues have been synthesized under microwave irradiation. Thiadiazines 13–15 have been analogously prepared, and upon acid hydrolysis, afforded the free nucleosides 16–18. The new synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. Compound 7 was also screened against a panel of tumor cell lines consisting of CD4 human T-cells.

Keywords anti-HIV activity; acyclic C-nucleosides; microwave-assisted synthesis; triazolo-thiadiazoles and -thiadiazines; sulphonamides; carboxamides

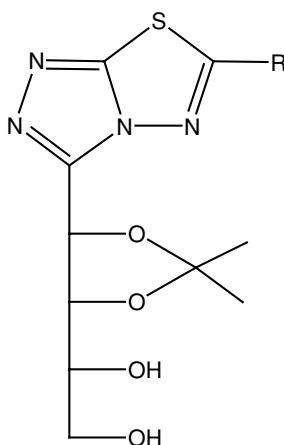
INTRODUCTION

The use of acyclonucleoside analogues as potent antiviral agents (such as the antiherpetic drug ACV (Acyclovir, Zovirax),^[1,2] DHPA,^[3] PMEPA, HPMPA,^[4] HBG, and DHPG^[5,6]) has stimulated extensive research in the synthesis of this class of compounds. Structure-activity relationship studies have shown that the side chains of acyclonucleosides play a crucial

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SCHEME 1 6-Alkyl/aryl-3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl) [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles (1).

role in the interaction of the acyclonucleosides with their antiviral target enzymes^[7] (phosphorylation).

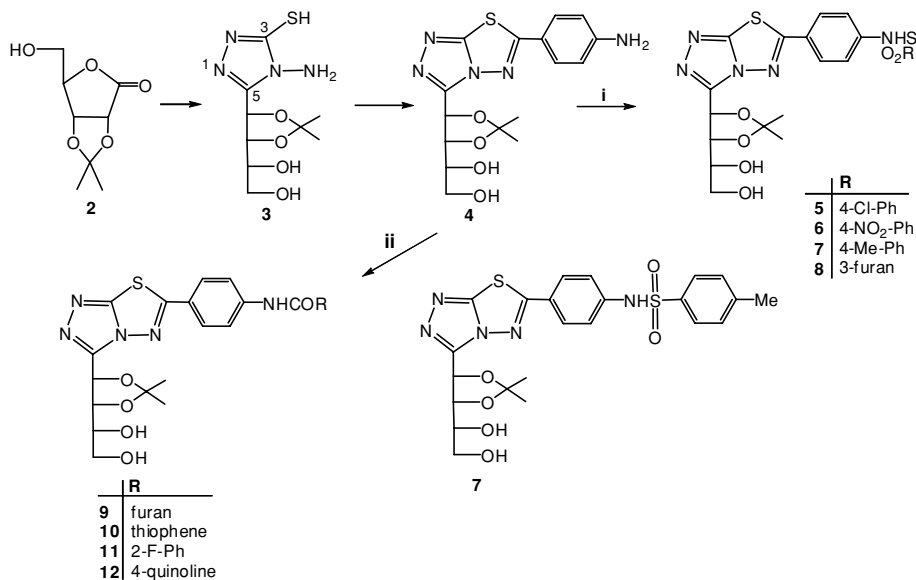
Various substituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and Schiff's bases are associated with diverse pharmacological activities, such as analgesic, antihelminthic, antitubercular, plant growth regulating, antiviral, antifungal, and anticancer properties.^[9–16] Recently, we synthesized various 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 (1), and the corresponding 6-aryl-thiomethyl as their free nucleosides analogues from the treatment of 2,3-*O*-isopropylidene-*D*-ribo-1,4-lactone with thiocarbohydrazide.^[17] As a continuation of our research programs on the development of compounds potentially active against HIV, we synthesized and evaluated new acyclic *C*-nucleosides of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole nucleosides bearing sulfonamide and carboxamide as well as thiadiazine residues. Sulphonamides are used for treatment of certain bacterial infections, *e.g.* the anticonvulsant sultiame^[18] as well as other kinds of infections.^[19] Further, some sulphonamides are considered as competitive folic acid inhibitors in microorganisms, with their activity as bacteriostatic.^[20]

RESULTS AND DISCUSSION

We recently synthesized a new series of acyclic *C*-nucleosides of 3-(*D*-ribo-tetritol-yl)-5-mercapto-1,2,4-triazoles as well as their [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole analogues^[17] from the opening of a δ -lactone **2** with thiocarbohydrazide in pyridine under microwave irradiation (MWI). In the present work, 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 (**4**), prepared from the corresponding *C*-nucleoside **3**,^[17] was selected as the parent compound

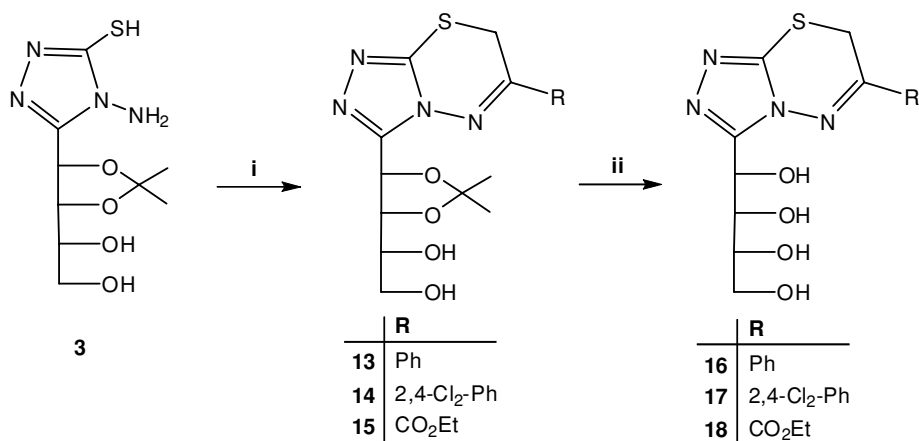
for the preparation of a new series of arylsulphonamides and arylcarboxamides as potential derivatives, and antitumor agents. Thus, treatment of **4** with the appropriate arylsulphonyl chlorides (4-chloro, 4-nitro, 4-methylbenzenesulphonyl- and 3-furysulphonyl chlorides) as well as the appropriate acyl chlorides, (furan-2-carbonyl, thiophene-2-carbonyl, 2-fluorobenzoyl, and quinoline-4-carbonyl chlorides), afforded sulphonamides **5–8** (43–58%) and **9–12** (49–86%), respectively.

The structures of **5–12** were assigned from their ^1H , ^{13}C NMR, and mass spectra. The ^1H NMR spectra (in CDCl_3) of **5–12** showed similar patterns for the sugar protons. H-1' and H-2' appeared as doublets or broad singlets in the δ 4.77–4.89 region and at δ 4.75–4.78 ($J_{1',2'} \sim 5.5$ Hz, $J_{2',3'} \sim 5.5$), respectively. H-3' appeared as triplet in the δ 4.52–4.63 region ($J_{3',4'b} \sim 2.3$ Hz, $J_{3',4'a} \sim 4.2$ Hz). The ^{13}C NMR spectra of **5–12** were fully established (Experimental section), and they contained similar resonance signals for the sugar carbons C-1'–C-4' as well as for the triazolo-thiadiazole ring carbons C-3 (C=N)–C-8 (C=N). In the ^{13}C NMR spectra of **5–12**, the C-6 resonated relatively at higher field (δ 174.3–174.8), while C-3 and C-8 resonated at the δ 161.6–167.1 and δ 146.4–151.1 regions, respectively. The phenyl, furan, thiophene, coumarin, and the isopropylidene carbon atoms were fully assigned (see Experimental section).



SCHEME 2 Reagents and conditions: (i) RSO_2Cl , Et_3N , CH_2Cl_2 , 23°C , 3–4 h; (ii) RCOCl , Et_3N , 23°C , CH_2Cl_2 .

Compound **7** was selected for further NMR study. From the gradient selected HMBC^[21] spectrum of **7**, C-3 at δ_{C} 162.1 showed a $^2J_{\text{C,H}}$ couplings with H-1' at δ_{H} 4.84, and $^3J_{\text{C,H}}$ coupling with H-3' at δ_{H} 4.63. Furthermore, a $^3J_{\text{C,H}}$ coupling between C-6 at δ_{C} 174.7 and NAr-H-3 and -H-5 at δ_{H} 6.73.



SCHEME 3 Reagents and conditions: (i) BrCH₂COAr, EtOH, 20 min, MWI, 80°C; (ii) 80% HOAc, 80°C, 12 h.

Next, our work was modified by selecting 4-amino-3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)-5-mercapto-1,2,4-triazole (**3**)^[17] as a precursor for the synthesis of new triazolothiadiazine derivatives to examine their antiviral activity in comparison to the triazolo-thiadiazole analogues **5–12**. Thus, heating **3** with phenacyl bromide, 2-bromo-1-(3,4-dichlorophenyl)ethanone, or ethyl 3-bromo-2-oxopropanoate under MWI gave, after purification, the desired acyclic *C*-nucleosides **13–15** in 73, 56, and 87% yield, respectively. Acid hydrolysis of **13–15** with 80% HOAc furnished free nucleosides **16–18** in 88, 81 and 78% yield, respectively.

The structural assignment of **13–18** were made from their ¹H-, ¹³C NMR and mass spectra.

The sugar protons and carbons showed similar patterns to those of compounds **5–12**. CH₂S protons resonated as singlets in the δ_H 3.31–4.39 region, while the carbons resonated in the δ_C 29.0–35.5 region. The formation of the thiadiazine derivative was determined from the HMBC spectrum of **13**, which showed a ²J_{C,H} coupling between CH₂S protons at δ_H 4.39 and C-6 at δ_C 163.2 as well as a ³J_{C,H} coupling with C-9a (C=N) at δ_C 146.2. Further, the gradient-selected ¹H, ¹³C-HSQC^[22] spectrum in CDCl₃ showed coupling between CH₂S protons at δ_H 4.39 and carbon at δ_C 35.4, as well as coupling between H-1'–4'a,b at δ_H 4.97 (d, *J*_{1',2'} = 5.2 Hz), 4.23 (d, *J*_{2',3'} = 5.4 Hz), 4.17 (t, *J*_{3',4'} = 2.2 Hz), 3.58 (m, H-4'a, H-4'b) and C-1'–C-4' at δ_C 72.8, 79.2, 64.3, respectively.

In Vitro Anti-HIV-Assay

All new synthesized compounds were evaluated for their in vitro anti-HIV activity by using the III_B strain for HIV-1 and the ROD strain for HIV-2 in human T-lymphocyte (MT-4) cells. All the tested compounds are inactive,

except **16**, which found to be the only compound from the series inhibiting HIV-2 replication in cell culture (EC_{50} of $17.4 \mu\text{g/mL}$), in comparison to the standard antiviral drugs efavirenz^[23] and capravirine.^[24]

In Vitro Antitumor Assay

Compound **7** was tested in vitro against a panel of tumor cell lines consisting of CD4 human T-cells containing an integrated leukaemia (CCRF-CEM); human acute T-lymphoblastic leukaemia (WIL-2NS); human splenic B-lymphoblastoid cells (CCRF-SB); human acute B-lymphoblastic leukaemia (SK-MEL-28); human skin melanoma (SK-MEL-28); human breast adenocarcinoma (MCF-7); human lung squamous carcinoma (SK-MES-1); human hepatocellular carcinoma (HepG2); human prostate carcinoma (DU-145); human foreskin fibroblast (CRL7065); and human lung fibroblast (MRC-5), using the Microculture Tetrazolium Assay (MTT) method^[25] for estimation of the in vitro tumor-inhibiting activity. Compound **7** was inactive against all tumor cell lines ($CC_{50} > 100 \mu\text{g/mL}$).

EXPERIMENTAL

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 (^1H) and at 62.9 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as the internal standard and on δ scale in ppm. Heteronuclear assignments were verified by ^1H - ^{13}C HMBC experiments. Mass spectra were recorded at 70 eV on EI and FAB mass spectra were measured on a MAT 8200 spectrometer (Finnigan MAT, USA) using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrices. Some molecular ions were detected by doping the sample with Na^+ ion.

General Procedure of Arylsulphonamide Derivatives of 1',2'-O-isopropylidene-D-ribo-tetritol-1-yl)[1,2,4] triazolo[3,4-b][1,3,4] thiadiazols (5–8)

To a solution of **4** (75 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) containing Et_3N (20 mg, 0.20 mmol) was added arylsulphonyl chloride (0.20 mmol) with stirring at 23°C for 3–4 hours. The solution was evaporated to dryness and the residue was partitioned between CH_2Cl_2 ($3 \times 15 \text{ mL}$) and water (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to 2 mL, then applied to a SiO_2 column. Gradient elution with MeOH (0–10%) and CH_2Cl_2 afforded the desired sulphonamide products.

N-(4-(3-(1,2-*O*-Isopropylidene-D-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)phenyl)-4-chlorobenzenesulphonamide (**5**). From 4-chlorobenzenesulphonyl chloride (42 mg). Yield: 52 mg (47%); m.p.

134–138°C. ^1H NMR (CDCl_3): δ 10.08 (s, 1H, NH); 7.68–7.38 (m, 6H, Ar-H); 6.51 (dd, 2H, $J = 5.7$ Hz, 3.0 Hz, Ar-H); 4.86 (d, 1H, $J_{1',2'} = 5.5$ Hz, H-1'); 4.70 (d, 1H, $J_{2',3'} = 5.6$ Hz, H-2'); 4.59 (t, 1H, $J_{3',4'b} = 2.1$ Hz, H-3'); 4.04 (dd, 1H, $J_{3',4'a} = 4.2$ Hz, H-4'a); 3.95 (dd, 1H, $J_{4a',4'b} = 12.0$ Hz H-4'b); 1.45, 1.34 (2xs, 6H, CMe_2). ^{13}C NMR (CDCl_3): δ 174.6 (C-6); 167.1 (C-3); 151.1 ($\text{C}_8=\text{N}$); 138.8 (Ar-C-SO₂ + Ar-C-Cl); 130.1, 128.8, 128.1, 127.1, 116.6 (Ar-C); 112.2 (CMe_2); 82.3 (C-2'); 69.4 (C-1'); 75.9 (C-3'); 62.1 (C-4'); 26.5, 25.5 (CMe_2). Anal. calc. for $\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}_6\text{S}_2$ (552.02): C, 47.87; H, 4.02; N, 12.69. Found; C, 47.62; H, 3.92; N, 12.45. MS: m/z (FAB) 552/554 ($\text{M}+\text{H}$)⁺.

***N*-(4-(3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)phenyl)-4-nitrobenzenesulphonamide (6).** From 4-nitrobenzenesulphonyl chloride (44 mg). Yield: 48 mg (43%); semi-solid. ^1H NMR (CDCl_3): δ 8.11 (dd, 2H, $J = 5.8$ Hz, 3.1 Hz, *p*-NO₂-Ar-H); 7.92 (d, 2H, $J = 5.8$ Hz, 3.1 Hz, *p*-NO₂-Ar-H); 7.57 (dd, 2H, $J = 5.6$ Hz, 3.0 Hz, Ar-H); 6.51 (dd, 2H, $J = 5.6$ Hz, 3.0 Hz, Ar-H); 4.89 (d, 1H, $J_{1',2'} = 5.3$ Hz, H-1'); 4.75 (d, 1H, $J_{2',3'} = 5.5$ Hz, H-2'); 4.57 (t, 1H, $J_{3',4'b} = 2.2$ Hz, H-3'); 4.11 (dd, 1H, $J_{3',4'a} = 4.3$ Hz, H-4'a); 3.97 (dd, 1H, $J_{4a',4'b} = 12.1$ Hz H-4'b); 1.43, 1.33 (2xs, 6H, CMe_2). ^{13}C NMR (CDCl_3): δ 174.8 (C-6); 167.0 (C-3); 150.3 (Ar-C-NO₂); 149.8 ($\text{C}_8=\text{N}$); 143.9 (Ar-C-SO₂); 128.3, 128.0, 116.7 (Ar-C); 112.5 (CMe_2); 82.6 (C-2'); 69.6 (C-1'); 76.2 (C-3'); 62.3 (C-4'); 26.4, 25.3 (CMe_2). Anal. calc. for $\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_8\text{S}_2$ (562.58): C, 46.97; H, 3.94; N, 14.94. Found; C, 46.77; H, 3.86; N, 14.72. MS: m/z (FAB) 563 ($\text{M}+\text{H}$)⁺.

***N*-(4-(3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)phenyl)-4-methylbenzenesulphonamide (7).** From 4-methylbenzenesulphonyl chloride (38 mg). Yield: 58 mg (54%); m.p. 128–131°C. ^1H NMR (CDCl_3): δ 7.70 (dd., 1H, $J = 5.4$ Hz, 3.3 Hz, Ar-H); 7.53 (dd, 2H, $J = 5.4$ Hz, 3.3 Hz, Ar-H); 6.73 (dd, 2H, $J = 5.5$ Hz, 3.2 Hz, Ar-H); 4.84 (d, 1H, $J_{1',2'} = 5.6$ Hz, H-1'); 4.78 (d, 1H, $J_{2',3'} = 5.6$ Hz, H-2'); 4.63 (t, 1H, $J_{3',4'b} = 2.0$ Hz, H-3'); 4.10 (dd, 1H, $J_{3',4'a} = 4.3$ Hz, H-4'a); 3.99 (dd, 1H, $J_{4a',4'b} = 12.0$ Hz H-4'b); 2.00 (s, 3H, Ar-Me); 1.47, 1.38 (2xs, 6H, CMe_2). ^{13}C NMR (CDCl_3): δ 174.7 (C-6); 162.1 (C-3); 148.1 ($\text{C}_8=\text{N}$); 141.1 (Ar-CH₃); 135.9 (Ar-C-SO₂ + Ar-C-NH); 130.9, 128.8, 127.1, 116.5 (Ar-C); 113.1 (CMe_2); 82.5 (C-2'); 69.4 (C-1'); 75.6 (C-3'); 62.0 (C-4'); 26.7, 25.4 (CMe_2). Anal. calc. for $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_6\text{S}_2$ (531.60): C, 51.96; H, 4.74; N, 13.17. Found; C, 51.73; H, 4.59; N, 12.93. MS: m/z (FAB) 532 ($\text{M}+\text{H}$)⁺.

***N*-(4-(3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)phenyl)furan-3-sulphonamide (8).** From furan-3-sulphonyl chloride (33 mg). Yield: 59 mg (58%); m.p. 128–131°C. ^1H NMR ($\text{DMSO}-d_6$): δ 10.48 (s, 1H, NH); 7.97–7.16 (m., 3H, furan-H + Ar-H); 4.77 (s, 2H, H-1', H-2'); 4.61 (t, 1H, $J_{3',4'b} = 2.2$ Hz, H-3'); 3.62 (m, 2H, H-4'a; H-4'b); 1.35, 1.30 (2xs, 6H, CMe_2). ^{13}C NMR ($\text{DMSO}-d_6$): δ 174.3 (C-6); 162.9 (C-3); 146.4 ($\text{C}_8 = \text{N}$); 142.7, 130.2, 125.5, 112.5, 112.2 (furan-C + Ar-C); 111.6 (CMe_2); 82.2 (C-2'); 78.1 (C-1'); 74.9 (C-3'); 66.9 (C-4'); 26.5,

25.1 (CMe₂). Anal. calc. for C₂₀H₂₁N₅O₇S₂ (507.54): C, 47.33; H, 4.17; N, 13.80. Found; C, 47.11; H, 4.08; N, 13.58. MS: *m/z* (FAB) 508 (M+H)⁺.

Arylcarboxamide derivatives of 1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazols (9–12). These compounds were prepared following the same method for the preparation of 5–8, from 4 (94 mg, 0.25 mmol) and acyl chloride (0.25 mmol).

3-(1,2-*O*-Isopropylidene-*D*-ribo-tetritol-1-yl)-6-(4-*N*-phenylfuran-2-carboxamido)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (9). From furan-2-carbonyl chloride (32 mg). Yield: 100 mg (86%); m.p. 165–166°C. ¹H NMR (CDCl₃): δ 10.12 (s, 1H, NH); 7.95–6.70 (m, 7H, Ar-H + furan-H); 4.89 (d, 1H, *J*_{1',2'} = 5.3 Hz, H-1'); 4.77 (br s, 1H, H-2'); 4.55 (t, 1H, *J*_{3',4'b} = 2.0 Hz, H-3'); 3.60 (m, 2H, H-4'a, H-4'b); 1.32, 1.27 (2xs, 6H, CMe₂). ¹³C NMR (CDCl₃): δ 173.8 (C-6); 161.8 (C-3 + C=O); 146.8 (C₈=N + furan-C-CO); 135.7; 130.2, 128.1, 122.1, 111.2 (Ar-C + furan-C); 111.0 (CMe₂); 82.3 (C-2'); 74.3 (C-1'); 69.2 (C-3'); 65.3 (C-4'); 26.3, 25.2 (CMe₂). Anal. calc. for C₂₁H₂₁N₅O₆S (471.49): C, 53.50; H, 4.49; N, 14.85. Found; C, 53.32; H, 4.41; N, 14.61. MS: *m/z* (FAB) 472 (M+H)⁺.

3-(1,2-*O*-Isopropylidene-*D*-ribo-tetritol-1-yl)-6-(4-*N*-phenylthiophene-2-carboxamido)[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazole (10). From thiophene-2-carbonyl chloride (37 mg). Yield: mg (86%); oil. ¹H NMR (CDCl₃): δ 7.95–7.621 (m, 6H, Ar-H + thiophene-H); 7.31 (t, 1H, *J* = 5.3 Hz, thiophene-H); 4.90 (d, 1H, *J*_{1',2'} = 5.2 Hz, H-1'); 4.72 (d, 1H, *J*_{2',3'} = 5.3 Hz, H-2'); 4.52 (t, 1H, *J*_{3',4'b} = 2.3 Hz, H-3'); 3.63 (m, 2H, H-4'a, H-4'b); 1.34, 1.29 (2xs, 6H, CMe₂). ¹³C NMR (CDCl₃): δ 174.5 (C-6); 161.6 (C-3 + C=O); 146.7 (C₈=N); 136.9; 135.3, 128.1, 122.1 (Ar-C + thiophene-C); 111.2 (CMe₂); 82.4 (C-2'); 74.6 (C-1'); 69.1 (C-3'); 65.5 (C-4'); 26.6, 25.3 (CMe₂). MS: *m/z* (FAB) 510 (M+Na)⁺.

6-(2-Fluoro-4-*N*-Phenylbenzamido)-3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazole (11). From 2-fluorobenzoyl chloride (40 mg). Yield: (49%); oil. ¹H NMR (CDCl₃): δ 10.21 (s, 1H, NH); 7.97–7.20 (m., 8H, Ar-H); 4.79 (d, 1H, *J*_{1',2'} = 5.3 Hz, H-1'); 4.78 (br s, 1H, H-2'); 4.55 (t, 1H, *J*_{3',4'b} = 2.5 Hz, H-3'); 3.63 (m, 2H, H-4'a, H-4'b); 1.37, 1.32 (2xs, 6H, CMe₂). ¹³C NMR (CDCl₃): δ 174.7 (C-6); 163.2 (C=O); 162.9 (C-3); 158.1 (d, *J*_{C,F} = 218 Hz, Ar-C-F); 146.7 (C₈=N); 132.7, 130.0, 127.1, 125.5, 122.2, 112.5, (Ar-C); 111.9 (CMe₂); 82.7 (C-2'); 78.3 (C-1'); 75.2 (C-3'); 66.6 (C-4'); 26.2, 25.0 (CMe₂). MS: *m/z* (FAB) 499/501 (M+H)⁺.

3-(1,2-*O*-Isopropylidene-*D*-ribo-tetritol-1-yl)-6-(4-*N*-phenylquinolon-4-carboxamido)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (12). From quinoline-4-carbonyl chloride (48 mg). Yield: (53%); semi-solid. ¹H NMR (600 MHz, CDCl₃): δ 7.93–7.60 (m, 5H, Ar-H); 7.35–7.18 (m., 3H, Ar-H); 4.82 (d, 1H, *J*_{1',2'} = 5.2 Hz, H-1'); 4.65 (d, 1H, *J*_{1',2'} = 5.4 Hz, H-2'); 4.57 (t, 1H, *J*_{3',4'b} = 2.6 Hz, H-3'); 3.69 (m, 2H, H-4'a, H-4'b); 1.35, 1.33 (2xs, 6H, CMe₂).

^{13}C NMR (CDCl_3): δ 174.3 (C-6); 172.0 (N-C=O), 162.2 (C-3); 160.1 (C=O, coumarin); 151.7 (C-4, coumarin), 149.8 (C-8a, coumarin); 146.9 ($\text{C}_8=\text{N}$); 134.8, 129.1, 128.1, 127.7, 127.1, 122.0, 115.9 (Ar-C); 112.0 (CMe_2); 82.1 (C-2'); 78.0 (C-1'); 75.4 (C-3'); 66.5 (C-4'); 26.0, 25.2 (CMe_2). Anal. calc. for $\text{C}_{26}\text{H}_{23}\text{N}_5\text{O}_7\text{S}$ (549.56): C, 56.82; H, 4.22; N, 12.74. Found; C, 56.50; H, 4.05; N, 12.64. MS: m/z (FAB) 572 ($\text{M}+\text{Na}$) $^+$.

General Preparation of 6-Aryl or Alkyl-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines (13–15).

A solution of **3** (69 mg, 0.25 mmol) and phenacyl bromide, 2-bromo-1-(3,4-dichlorophenyl)ethanone, or ethyl 3-bromo-2-oxopropanoate (0.25 mmol) in EtOH (5 mL) was heated at 80°C under MWI for 20 minutes. After cooling, the solution was evaporated to dryness and the residue was partitioned between CHCl_3 (3×30 mL) and water (30 mL). The combined organic extracts was dried, filtered and evaporated to dryness to give the desired products.

3-(1,2-O-Isopropylidene-D-ribo-tetritol-1-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (13). From phenacyl bromide (50 mg). Yield: 69 mg (73%) as yellow powder; m.p. 132–136°C. ^1H NMR ($\text{DMSO}-d_6$): δ 7.86 (m, 2H, Ar-H); 7.55–7.42 (m., 3H, Ar-H); 4.97 (d, 1H, $J_{1',2'} = 5.2$ Hz, H-1'); 4.23 (d, 1H, $J_{2',3'} = 5.4$ Hz, H-2'); 4.17 (t, 1H, $J_{3',4'} = 2.2$ Hz, H-3'); 3.58 (m, 2H, H-4'a, H-4'b); 4.39 (s, 2H, SCH_2); 1.37, 1.33 (2xs, 6H, CMe_2). ^{13}C NMR ($\text{DMSO}-d_6$): δ 163.2 (C-6); 154.2 (C-3); 146.2 ($\text{C}_9=\text{N}$); 134.0, 131.2, 129.2, 127.8 (Ar-C); 110.6 (CMe_2); 79.2 (C-2'); 72.8 (C-1'); 70.0 (C-3'); 64.3 (C-4'); 35.5 (SCH_2); 25.3, 22.6 (CMe_2). Anal. calc. for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$ (376.43): C, 54.24; H, 5.36; N, 14.88. Found; C, 54.02; H, 5.27; N, 14.68. MS: m/z (FAB) 377 ($\text{M}+\text{H}$) $^+$.

6-(2,4-Chlorophenyl)-3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (14). From 2-bromo-1-(3,4-dichlorophenyl)ethanone (67 mg). Yield: 62 mg (56%) as a white solid; m.p. 106–108°C. ^1H NMR ($\text{DMSO}-d_6$): δ 7.50–7.26 (m, 3H, Ar-H); 4.98 (d, 1H, $J_{1',2'} = 5.1$ Hz, H-1'); 4.25 (d, 1H, $J_{2',3'} = 2.1$ Hz, H-2'); 4.17 (t, 1H, $J_{3',4'} = 2.3$ Hz, H-3'); 3.58 (m, 2H, H-4'a, H-4'b); 4.38 (s, 2H, SCH_2); 1.40, 1.37 (2xs, 6H, CMe_2). ^{13}C NMR ($\text{DMSO}-d_6$): δ 164.2 (C-6); 153.7 (C-3); 146.9 ($\text{C}_9=\text{N}$); 137.7 (Ar-Cl-Cl); 135.3 (Ar-C-Cl + ArC); 131.0, 128.4, 127.7 (Ar-C); 11.2 (CMe_2); 84.8 (C-2'); 69.1 (C-1'); 68.4 (C-3'); 60.3 (C-4'); 35.3 (SCH_2); 25.7, 22.5 (CMe_2). Anal. calc. for $\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_4\text{S}$ (445.32): C, 45.85; H, 4.07; N, 12.58. Found; C, 45.66; H, 4.01; N, 12.37. MS: m/z (FAB) 445/447 ($\text{M}+\text{H}$) $^+$.

Ethyl 3-(1,2-O-isopropylidene-D-ribo-tetritol-1-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-carboxylate (15). From ethyl 3-bromo-2-oxopropanoate (45 mg). Yield: 81 mg (87%); oil. ^1H NMR (CDCl_3): δ 4.91 (d, 1H, $J_{1',2'} = 5.2$ Hz, H-1'); 4.41 (d, 1H, $J_{2',3'} = 5.3$ Hz, H-2'); 4.18 (q, 2H, $J = 7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); 3.70 (d, 1H, $J_{2',3'} = 5.1$ Hz, H-3'); 3.62 (m, 2H, H-4'a, H-4'b);

3.31 (s, 2H, SCH₂); 1.46, 1.36 (2xs, 6H, CMe₂); 1.28 (t, 3H, CO₂CH₂CH₃). ¹³C NMR (DMSO-*d*₆): δ 163.7 (C-6); 163.1 (C=O); 154.5 (C-3); 146.6 (C₉=N); 113.2 (CMe₂); 83.6 (C-2'); 68.8 (C-1'); 68.2 (C-3'); 64.0 (C-4'); 29.0 (SCH₂). 26.5, 25.4 (CMe₂). MS: *m/z* (FAB) 373 (M+H)⁺.

General Procedure of Preparation of Free C-Nucleosides (16–18)

A solution of **13–15** (0.50 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 ether (3 × 15 mL). The aq. layer was evaporated to dryness to give the desired product as oil, semi-solid, or crystalline solid.

3-(D-Ribo-tetritol-1-yl)-6-phenyl-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazine (16). From **13** (173 mg). Yield: 148 mg (88%); m.p. 75–78°C. ¹H NMR (DMSO-*d*₆): δ 7.87 (m, 2H, Ar-H); 7.51–7.41 (m., 3H, Ar-H); 4.38 (d, 1H, *J*_{1',2'} = 5.3 Hz, H-1'); 4.21 (d, 1H, *J*_{2',3'} = 5.3 Hz, H-2'); 4.12 (t, 1H, *J*_{3',4'} = 2.3 Hz, H-3'); 3.57 (m, 2H, H-4'a, H-4'b); 4.31 (s, 2H, SCH₂). ¹³C NMR (DMSO-*d*₆): δ 162.9 (C-6); 154.8 (C-3); 147.1 (C₉ = N); 133.8, 128.4, 127.7, 125.9 (Ar-C); 85.1 (C-2'); 69.2 (C-1'); 68.4 (C-3'); 60.3 (C-4'); 35.3 (SCH₂). Anal. calc. for C₁₄H₁₆N₄O₄S (336.37): C, 49.99; H, 4.79; N, 16.66. Found; C, 49.72; H, 4.69; N, 16.46. MS: *m/z* (FAB) 358/360 (M+Na)⁺.

6-(2,4-Dichlorophenyl)-3-(D-ribo-tetritol-1-yl)-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazine (17). From **14** (222 mg). Yield: 180 mg (81%); amorphous. ¹H NMR (DMSO-*d*₆): δ 7.51–7.29 (m., 3H, Ar-H); 4.41 (d, 1H, *J*_{1',2'} = 5.2 Hz, H-1'); 4.23 (d, 1H, *J*_{2',3'} = 5.2 Hz, H-2'); 4.19 (t, 1H, *J*_{3',4'} = 2.3 Hz, H-3'); 3.56 (m, 2H, H-4'a, H-4'b); 4.36 (s, 2H, SCH₂). ¹³C NMR (DMSO-*d*₆): δ 163.6 (C-6); 154.5 (C-3); 146.5 (C₉=N); 137.5 (Ar-Cl-Cl); 135.2 (Ar-C-Cl, ArC); 131.1, 128.7, 127.7 (Ar-C); 85.0 (C-2'); 69.0 (C-1'); 68.5 (C-3'); 60.1 (C-4'); 35.0 (SCH₂). Anal. calc. for C₁₄H₁₄Cl₂N₄O₄S (404.04): C, 41.49; H, 3.48; N, 13.83. Found; C, 41.27; H, 3.40; N, 13.62. MS: *m/z* (FAB) 426/428 (M+Na)⁺.

Ethyl 3-(D-ribo-tetritol-1-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-6-carboxylate (18). From **15** (186 mg). Yield: 145 mg (78%); semi-solid. ¹H NMR (DMSO-*d*₆): δ 4.55 (d, 1H, *J*_{1',2'} = 5.0 Hz, H-1'); 4.16 (q, 2H, *J* = 7.1 Hz, CO₂CH₂CH₃); 3.76 (d, 1H, *J*_{2',3'} = 5.2 Hz, H-2'); 3.39 (t, 1H, *J*_{3',4'} = 2.2 Hz, H-3'); 3.61 (m, 2H, H-4'a, H-4'b); 3.33 (s, 2H, SCH₂); 1.27 (t, 3H, CO₂CH₂CH₃). ¹³C NMR (DMSO-*d*₆): δ 163.2 (C-6); 162.9 (C=O); 154.3 (C-3); 146.8 (C₉=N); 83.9 (C-2'); 69.0 (C-1'); 68.9 (C-3'); 64.2 (C-4'); 29.2 (SCH₂). Anal. calc. for C₁₁H₁₆N₄O₆S (323.33): C, 39.75; H, 4.85; N, 16.86. Found; C, 39.49; H, 4.78; N, 16.62. MS: *m/z* (FAB) 346 (M+Na)⁺.

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