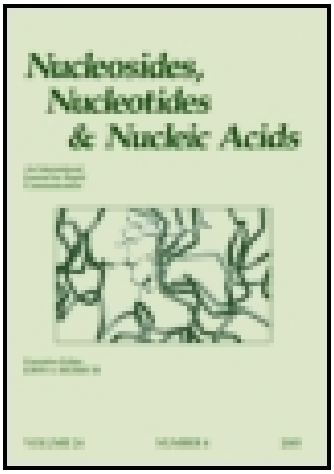

Nucleosides, Nucleotides and Nucleic Acids

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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] PMEA, 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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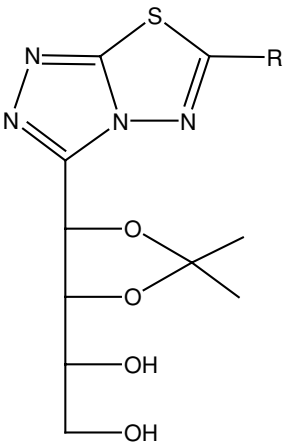


SCHEME 1 6-Alkyl/aryl-3-(1,2-O-isopropylidene-D-*ribo*-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles (**1**).

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

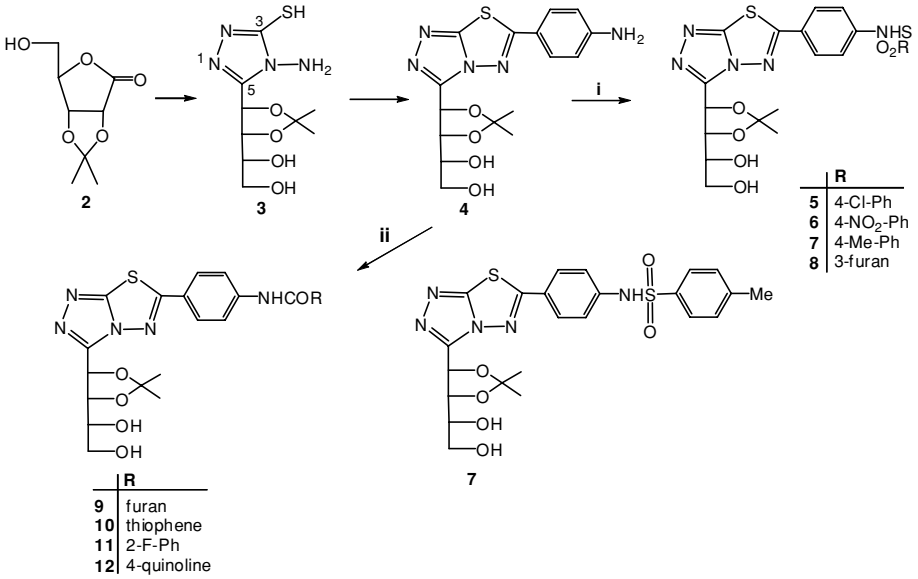
Various substituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and Schiff's bases are associated with diverse pharmacological activities, such as analgesic, antihelminthic, antitubercular, plant growth regulating, antiviral, antifungal, and anticancer properties.[9–16] Recently, we synthesized various 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-isopropylidine-D-*ribono*-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

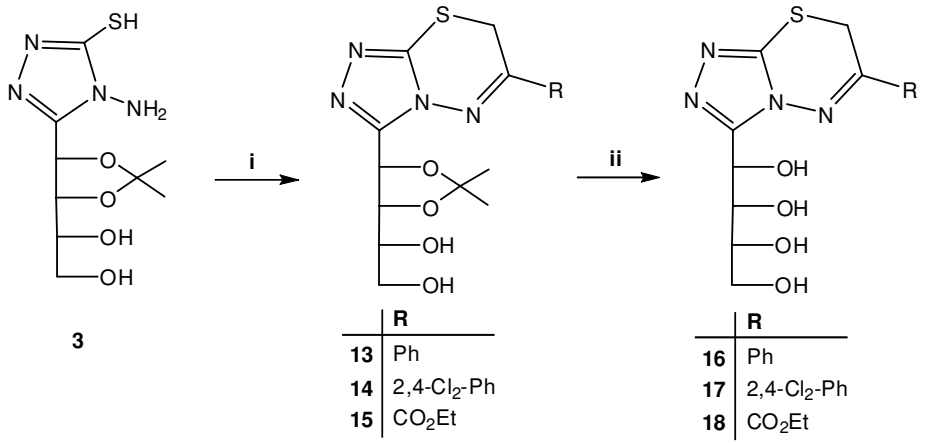
for the preparation of a new series of arylsulphonamides and arylcarboxamides as potential derivatives, and antitumor agents. Thus, treatment of **4** with the appropriate arylsulphonyl chlorides (4-chloro, 4-nitro, 4-methylbenzenesulphonyl- and 3-furylsulphonyl chlorides) as well as the appropriate 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 ^{1}H, ^{13}C NMR, and mass spectra. The ^{1}HNMR 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 ($J_{1',2'}$ ~5.5 Hz, $J_{2',3'}$ ~5.5), respectively. H-3′ appeared as triplet in the δ 4.52–4.63 region ($J_{3',4'b}$ ~ 2.3 Hz, $J_{3',4'a}$ ~ 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 Ragents 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 $^{2}J_{C,H}$ couplings with H-1′ at δ_H 4.84, and $^{3}J_{C,H}$ coupling with H-3′ at δ_H 4.63. Furthermore, a $^{3}J_{C,H}$ coupling between C-6 at δ_C 174.7 and NAr-H-3 and -H-5 at δ_H 6.73.



SCHEME 3 Ragents and conditions: (i) $BrCH_2COAr$, EtOH, 20 min, MWl, 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 acylic *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 ^{1}H-, ^{13}C NMR and mass spectra.

The sugar protons and carbons showed similar patterns to those of compounds **5–12**. CH_2S 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 CH_2S 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 ^{1}H,^{13}C-HSQC[22] spectrum in $CDCl_3$ showed coupling between CH_2S 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, $_{2',3'} = 5.4$ 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 μg/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 ($CC_{50} > 100$ μg/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 (^{1}H) 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 ^{1}H-^{13}C HMBC experiments. 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.

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 (3×15 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-chlorobenzenensulphonamide (5)**. From 4-chlorobenzenesulphonyl chloride (42 mg). Yield: 52 mg (47%); m.p.

134–138°C. ^{1}H 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 (C_8=N); 138.8 (Ar-C-SO_2 + Ar-C-Cl); 130.1, 128.8, 128.1, 127.1, 116.6 (Ar-C); 112.2 (*C*Me_2); 82.3 (C-2′); 69.4 (C-1′); 75.9 (C-3′); 62.1 (C-4′); 26.5, 25.5 (C*Me*$_2$). Anal. calc. for $C_{22}H_{22}ClN_5O_6S_2$ (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 $(M+H)^+$.

***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-nitrobenzenensulphonamide (6)**. From 4-nitrobenzenesulphonyl chloride (44 mg). Yield: 48 mg (43%); semi-solid. ^{1}H NMR ($CDCl_3$): δ 8.11 (dd, 2H, J = 5.8 Hz, 3.1 Hz, *p*-NO_2-Ar-H); 7.92 (d, 2H, J = 5.8 Hz, 3.1 Hz, *p*-NO_2-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-NO_2); 149.8 (C_8=N); 143.9 (Ar-C-SO_2); 128.3, 128.0, 116.7 (Ar-C); 112.5 (*C*Me_2); 82.6 (C-2′); 69.6 (C-1′); 76.2 (C-3′); 62.3 (C-4′); 26.4, 25.3 (C*Me*$_2$). Anal. calc. for $C_{22}H_{22}N_6O_8S_2$ (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 $(M+H)^+$.

***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-methylbenzenensulphonamide (7)**. From 4-methylbenzenesulphonyl chloride (38 mg). Yield: 58 mg (54%); m.p. 128–131°C. ^{1}H 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 (C_8=N); 141.1 (Ar-*C*H_3); 135.9 (Ar-C-SO_2 + Ar-C-NH); 130.9, 128.8, 127.1, 116.5 (Ar-C); 113.1 (*C*Me_2); 82.5 (C-2′); 69.4 (C-1′); 75.6 (C-3′); 62.0 (C-4′); 26.7, 25.4 (C*Me*$_2$). Anal. calc. for $C_{23}H_{25}N_5O_6S_2$ (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 $(M+H)^+$.

***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)furansulphonamide (8)**. From furan-3-sulphonyl chloride (33 mg). Yield: 59 mg (58%); m.p. 128–131°C. ^{1}H NMR (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 (DMSO-d_6): δ 174.3 (C-6); 162.9 (C-3); 146.4 (C_8 = N); 142.7, 130.2, 125.5, 112.5, 112.2 (furan-C + Ar-C); 111.6 (*C*Me_2); 82.2 (C-2′); 78.1 (C-1′); 74.9 (C-3′); 66.9 (C-4′); 26.5,

25.1 (C*Me*$_2$). Anal. calc. for $C_{20}H_{21}N_5O_7S_2$ (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. ^{1}H NMR ($CDCl_3$): 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, CMe_2). ^{13}C NMR ($CDCl_3$): δ 173.8 (C-6); 161.8 (C-3 + C=O); 146.8 (C_8=N + furan-*C*-CO); 135.7; 130.2, 128.1, 122.1, 111.2 (Ar-C + furan-C); 111.0 (*C*Me_2); 82.3 (C-2′); 74.3 (C-1′); 69.2 (C-3′); 65.3 (C-4′); 26.3, 25.2 (C*Me*$_2$). Anal. calc. for $C_{21}H_{21}N_5O_6S$ (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. ^{1}H NMR ($CDCl_3$): 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, CMe_2). ^{13}C NMR ($CDCl_3$): δ 174.5 (C-6); 161.6 (C-3 + C=O); 146.7 (C_8=N); 136.9; 135.3, 128.1, 122.1 (Ar-C + thiophene-C); 111.2 (*C*Me_2); 82.4 (C-2′); 74.6 (C-1′); 69.1 (C-3′); 65.5 (C-4′); 26.6, 25.3 (C*Me*$_2$). 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. ^{1}H NMR ($CDCl_3$): 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, CMe_2). ^{13}C NMR ($CDCl_3$): 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 (C_8=N); 132.7, 130.0, 127.1, 125.5, 122.2, 112.5, (Ar-C); 111.9 (*C*Me_2); 82.7 (C-2′); 78.3 (C-1′); 75.2 (C-3′); 66.6 (C-4′); 26.2, 25.0 (C*Me*$_2$). 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. ^{1}H NMR (600 MHz, $CDCl_3$): 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, CMe_2).

^{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 (C_8=N); 134.8, 129.1, 128.1, 127.7, 127.1, 122.0, 115.9 (Ar-C); 112.0 (*C*Me_2); 82.1 (C-2′); 78.0 (C-1′); 75.4 (C-3′); 66.5 (C-4′); 26.0, 25.2 (C*Me*$_2$). Anal. calc. for $C_{26}H_{23}N_5O_7S$ (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 $(M+Na)^+$.

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. ^{1}H NMR (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 (DMSO-d_6): δ 163.2 (C-6); 154.2 (C-3); 146.2 (C_9=N); 134.0, 131.2, 129.2, 127.8 (Ar-C); 110.6 (*C*Me_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 (C*Me*$_2$). Anal. calc. for $C_{17}H_{20}N_4O_4S$ (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 $(M+H)^+$.

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. ^{1}H NMR (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, $J_{3',4'}$ = 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-4b′); 4.38 (s, 2H, SCH_2); 1.40, 1.37 (2xs, 6H, CMe_2). ^{13}C NMR (DMSO-d_6): δ 164.2 (C-6); 153.7 (C-3); 146.9 (C_9=N); 137.7 (Ar-Cl-Cl); 135.3 (Ar-C-Cl + ArC); 131.0, 128.4, 127.7 (Ar-C); 11.2 (*C*Me_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 (C*Me*$_2$). Anal. calc. for $C_{17}H_{18}Cl_2N_4O_4S$ (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 $(M+H)^+$.

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. ^{1}H 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, $CO_2CH_2CH_3$); 3.70 (d, 1H, $J_{2',3'}$ = 5.1 Hz, H-3′); 3.62 (m, 2H, H-4′a, H-4b′);

3.31 (s, 2H, SCH_2); 1.46, 1.36 (2xs, 6H, CMe_2); 1.28 (t, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (DMSO-d_6): δ 163.7 (C-6); 163.1 (C = O); 154.5 (C-3); 146.6 (C_9=N); 113.2 (CMe_2); 83.6 (C-2′); 68.8 (C-1′); 68.2 (C-3′); 64.0 (C-4′); 29.0 (SCH_2). 26.5, 25.4 (CMe_2). 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, SCH_2). ^{13}C NMR (DMSO-d_6): δ 162.9 (C-6); 154.8 (C-3); 147.1 (C_9 = 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 (SCH_2). Anal. calc. for $C_{14}H_{16}N_4O_4S$ (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, SCH_2). ^{13}C NMR (DMSO-d_6): δ 163.6 (C-6); 154.5 (C-3); 146.5 (C_9=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 (SCH_2). Anal. calc. for $C_{14}H_{14}Cl_2N_4O_4S$ (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, $CO_2CH_2CH_3$); 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, SCH_2); 1.27 (t, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (DMSO-d_6): δ 163.2 (C-6); 162.9 (C=O); 154.3 (C-3); 146.8 (C_9=N); 83.9 (C-2′); 69.0 (C-1′); 68.9 (C-3′); 64.2 (C-4′); 29.2 (SCH_2). Anal. calc. for $C_{11}H_{16}N_4O_6S$ (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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