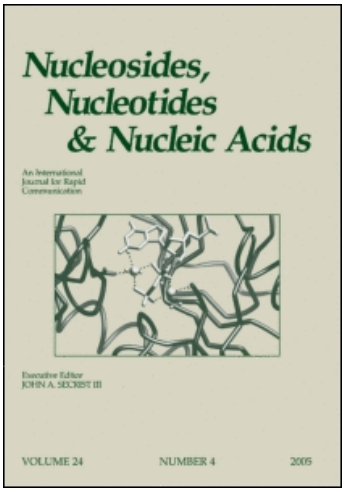

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Novel Simple Efficient Synthetic Approach Toward 6-Substituted-2*H*-[1,2,4]Triazolo[3,4-*b*][1,3,4]Thiadiazole-3-Thiones and First Synthesis and Biological Evaluation of *N*-and *S*-β-D-Glucosides of the[1,2,4]Triazolo [3,4-*b*][1,3,4]Thiadiazole Ring System

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NOVEL SIMPLE EFFICIENT SYNTHETIC APPROACH TOWARD 6-SUBSTITUTED-2*H*-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE-3-THIONES AND FIRST SYNTHESIS AND BIOLOGICAL EVALUATION OF *N*- AND *S*-β-D-GLUCOSIDES OF THE[1,2,4]TRIAZOLO [3,4-*b*][1,3,4]THIADIAZOLE RING SYSTEM

Nasser S. A. M. Khalil □ *Regional Center for Food and Feed, Agricultural Research Center, Giza, Egypt*

□ *Novel simple and efficient synthetic approach for the synthesis of 6-substituted-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thiones is described. Glucosidation of these novel bases with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide followed by chromatographic separation gave the corresponding N- and S-β-D-glucosides. The structure of these two regiosiomers was established chemically and spectroscopically. Antimicrobial screening of two selected regioisomeric compounds against Aspergillus fumigatus, Penicillium italicum, Syncephalastrum racemosum, Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, and Escherichia coli are compared.*

Keywords Synthesis; glucosidation; 1,2,4-triazoles; 2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones; antimicrobial activity

INTRODUCTION

Various 1,2,4-triazoles have been reported to possess antibacterial, antifungal, antiviral, antiinflammatory, antitubercular, anticonvulsant, antidepressant, antihypertensive, analgesic, hypoglycemic, herbicidal, and sedative properties.[1–22] The 1,3,4-thiadiazoles exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric N-C-S moiety.[23] They find applications as antibacterials, antitumor, and antiinflammatory agents, pesticides, herbicides, dyes, lubricants, and analytical reagents.[24] The 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazole derivatives obtained by fusing the bio-labile 1,2,4-triazole and 1,3,4-thiadiazole rings together, are reported

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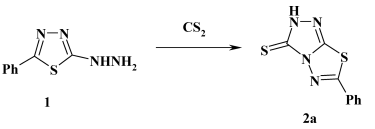
to possess antibacterial, antifungal, antiinflammatory, CNS depressant, hypocholesteremic, antiviral, analgesic, anthelmintic, herbicidal and plant growth regulatory effects.[25]

Prompted by these observations and in continuation of our long-standing interest in the preparation of bio-active molecules,[21,22,26–33] we designed new simple efficient route for the synthesis of 6-substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones. Also, we report here the first synthetic approach of a series of novel 2-*N*- and 3-*S*-*β*-D-glucosyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles as well as a comparable antimicrobial activity of two selected regioisomers against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis,* and *Escherichia coli*.

RESULTS AND DISCUSSION

The only example found in the literature describing the synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole ring system having an active NH group in the 2-position or a possible tautomeric thiol group in the 3-position was described by Potts and Huseby[34] through the reaction of (5-phenyl-1,3,4-thiadiazol-2-yl)hydrazine with carbon disulfide (Equation (1)).

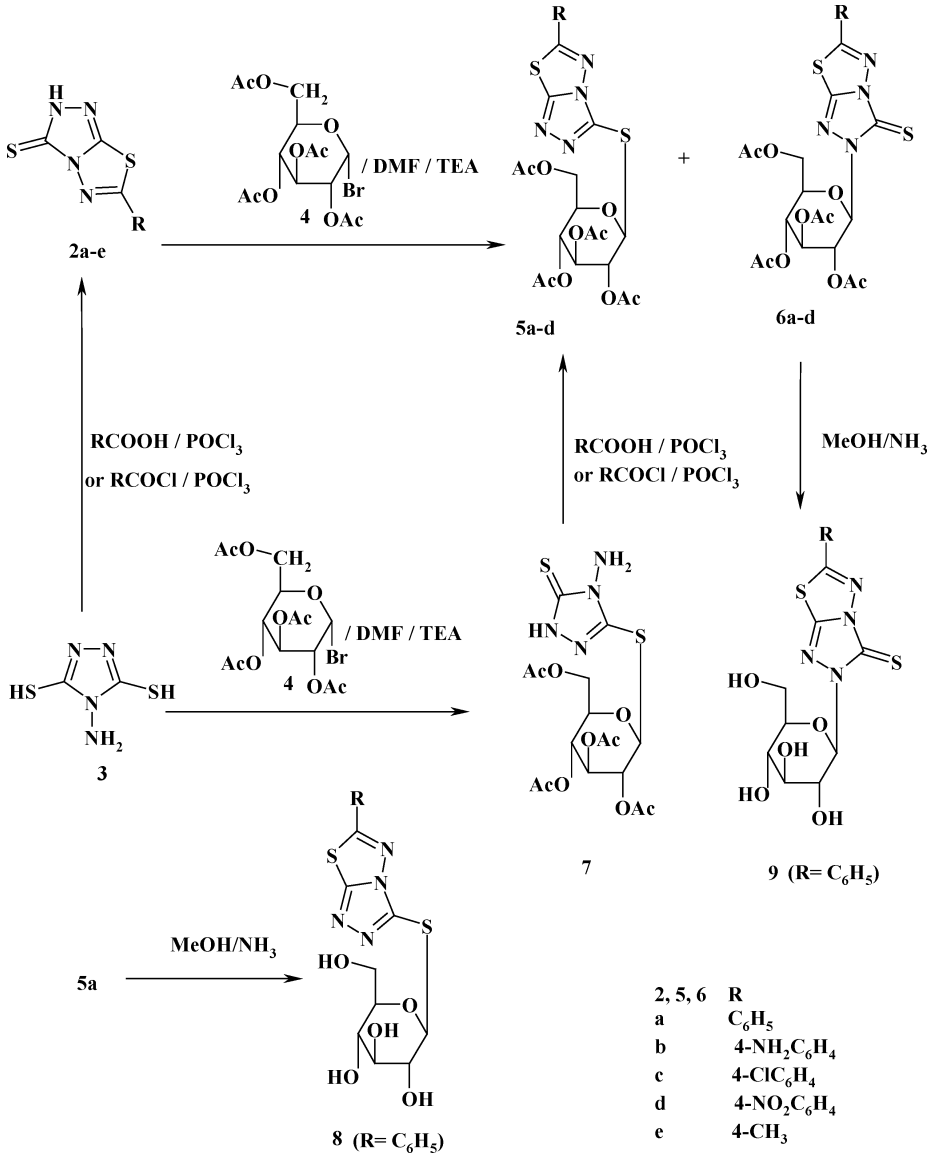


1 2a (1)

In the present work, we report a novel simple and efficient procedure for the synthesis of 6-substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones **2a–e**, which in turn allowed us to an easier entry for the first synthesis of *N*- and *S*-*β*-D-glucosides of the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole ring system. Thus, we found that 6-substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones (**2a–e**) can be obtained directly in excellent yields from the 4-amino-4*H*-[1,2,4]-triazole-3, 5-dithiol (**3**), by its cyclization with the appropriate carboxylic acid or acid chloride in refluxing phosphoryl chloride (Scheme 1).

Glucosidation of compounds **2a–d** with 1.2 molar equivalent of 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide (**4**) gave a chromatographically separable mixture (45–59% overall yield) of two products namely, 3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylthio) -6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**5a–d**) and 2-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-6-aryl-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones (**6a–d**).

The *S*-*β*-D-configuration of compounds **5a–d** and the *N*-*β*-D-configuration of compounds **6a–d** are supported based on spectroscopic



SCHEME 1 Synthesis of *N*- and *S*-glucosides of 6-aryl-[1,2,4]-triazolo[3,4-*b*][1,3,4] thiadiazoles.

evidences. Thus, the appearance of the anomeric protons of compounds **6a–d** more downfield (δ 6.24–6.27) than those of compounds **5a–d** (δ 5.31–5.34) is consistent with similar reported data for *N*-[21,22,26–32,35] and *S*-glycosides,[21,22] and confirms their structures. Such downfield shifts in *N*-glucosyl derivatives is readily explained by the anisotropic deshielding by the C = S (similar downfield shifts of the anomeric proton by an adjacent C = S was reported for pyrimidine[35] and 1,2,4-triazole[21,22] nucleosides). The β-configuration of compounds **5a–d** and **6a–d** is assigned from the

coupling constant values of their anomeric protons ($J_{H\text{-}1'\text{-}H\text{-}2'} = 9.0$–$9.9$ Hz) which are consistent with similar reported data.[21,22,26,27,29–32,35]

Glucosidation of compound **2e** having an electron donating methyl group in the 6- position revealed the same starting materials. Thus, it is interesting to point out that the presence of an aromatic substituent with its known electron withdrawing character in the 6-position of the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole ring system increases the yield of glucosidation with higher yields of the *S*-glucosides (31–45%) than their regioisomeric *N*-glucosides (10–19%). The higher overall glucosidation yield was noticed for compound **2d** having the more electron withdrawing NO_2 group in the 4-postion of the phenyl ring.

Compounds **5a–d** were alternatively synthesized in excellent yields (83–88%) via glucosidation of 4-amino-4*H*-[1,2,4]-triazole-3,5-dithiol (**3**) to give 5-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylthio)-4-amino-2,4-dihydro-[1,2,4]triazole-3-thione (**7**) as the sole product followed by its ring closure using the appropriate aromatic acid or acid chloride in the presence of phosphoryl chloride.

Deacetylation of compounds **5a** and **6a** via methanolic ammonia treatment led to the formation of the free nucleosides **8** and **9**, respectively (Scheme 1). The ^{1}H NMR data of the latter compounds revealed the absence of the acetyl protons at δ 1.91–2.15 and the appearance of the D_2O exchangeable OH protons at δ 4.10–5.59. The IR data of compound **9** as a typical example showed also the absence of the acetyl carbonyl function at 1756 cm^{-1} and the appearance of the characteristic OH band at 3390 (br) cm^{-1}.

Compounds **5c** and **6c** were evaluated for their antifungal and antibacterial activities against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis,* and *Escherichia coli*. The inhibitory effects of the tested compounds against the mentioned organisms are given in Table 1. The inhibitory effect of *S*-*β*-D-glucoside **5c** were studied in comparison with similar effect due to *N*-*β*-D-glucoside **6c**. Thus, compound **5c** showed higher inhibitory effect against *Aspergillus fumigatus*, *Penicillium italicum*, *Staphylococcus aureus*, and *Escherichia coli*. Compound **6c** showed higher inhibitory effect against *Pseudomonas aeruginosa* at concentration 5.0 mg/mL.

CONCLUSION

The present work describes a novel simple efficient synthetic route toward the 6-substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones as well as first access to the *N*- and *S*-*β*-D-glucosides of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole ring system with potential antimicrobial activities. These compounds could serve as possible starting materials for further synthetic transformations. It also expands the synthesis as well as the utility of both base-modified and sugar-modified nucleosides of possible application in the chemotherapy of cancer and viral infections.

TABLE 1 Antimicrobial activity of compounds **5c** and **6c** compared to standard antimicrobial agents

	Compound								
	5c[a]			**6c**[a]			**St.**[b]		
	Concentration (mg/mL)								
Test organisms	1	2.5	5	1	2.5	5	1	2.5	5
Aspergillus fumigatus	0	0	+	0	0	0	++	+++	+++
Penicillium italicum	0	+	+	0	0	+	++	+++	+++
Syncephalastrum racemosum	0	0	0	0	0	0	+++	+++	+++
Candida albicans	0	0	0	0	0	0	++	++	++
Staphylococcus aureus	0	+	+	0	0	+	++	++	++
Pseudomonas aeruginosa	0	0	0	0	0	+	++	+++	+++
Bacillus subtilis	0	0	0	0	0	0	++	+++	+++
Escherichia coli	+	+	+	0	0	0	++	++	++

Note: The test was done using the diffusion agar technique. Inhibition values = 0.1–0.5 cm beyond control = +; Inhibition values = 0.6–1.0 cm beyond control = ++; Inhibition values = 1.0–1.5 cm beyond control = +++; 0 = Not detected.

[a]100 μL of each conc. was tested (5, 2.5, 1.0 mg/mL); well diameter = 0.6 cm.

[b]St. = Reference standard; Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent.

EXPERIMENTAL

General

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz with a Varian Mercury 300 spectrometer. Elemental analyses were carried out at the Micro Analytical Center, Cairo University, Giza, Egypt. Antimicrobial screening of compounds **5c** and **6c** was carried out at the Medical Mycology Laboratory, Regional Center for Mycology and Biotechnology, Al Azhar University, Cairo, Egypt. The starting 4-amino-4*H*-[1,2,4]-triazole-3,5-dithiol (**3**)[36] and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **(4)**[37] were prepared as reported. TLC was performed on Fluka silica gel 60 F_{254} aluminum sheets, and products were detected using 254 nm light. Fluka silica gel 60 (70–230 mesh) was used for column chromatography.

6-Substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones (2 a–e)

General procedure: A mixture of compound **3** (500 mg, 3.4 mmol) and the appropriate carboxylic acid (3.4 mmol for the synthesis of compounds **2a,b,d,e**) or acid chloride (3.4 mmol for the synthesis of compound **2c**) in phosphoryl chloride (5 mL) was heated at reflux temperature in an oil bath for 8 hours. The excess of phosphoryl chloride was removed under reduced

pressure, the formed residue was diluted with ice-water mixture, and the whole mixture stirred at room temperature for 1 hour. The precipitated solid products were filtered, washed several times with water, dried at room temperature, and recrystallized from *N*,*N*-dimethylformamide.

6-Phenyl-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (2a). Yield 749 mg (94%); pale yellow crystals, m.p. 238–240°C. IR: 3433, 3074, 3020, 1597, 1512, 1450, 1373, 1315, 1246, 1184, 1157, 1076, 1003, 953, 771, 687, 640, 609, 478; ^{1}H NMR (DMSO-d_6) δ 7.52 (tt, 2H, J = 1.8, 7.5 Hz, ArH), 7.65 (tt, 1H, J = 1.8, 7.5 Hz, ArH), 7.87 (td, 2H, J = 1.8, 7.5 Hz, ArH), 8.28 (s, 1H, D_2O exchangeable NH). Anal. Calcd for $C_9H_6N_4S_2$ (234.3): C, 46.14; H, 2.58; N, 23.91; S, 27.37. Found: C, 46.18; H, 2.61; N, 24.20; S, 27.24.

6-(4-Aminophenyl)-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (2b). Yield 831 mg (98%); yellow crystals, m.p. >324°C. IR: 3356, 3220, 3069, 1595, 1508, 1406, 1370, 1317, 1244, 1180, 1095, 1013, 975, 904, 844, 761, 694, 632, 523; ^{1}H NMR; (DMSO-d_6) δ 6.4–6.8 (br s, 2H, D_2O exchangeable NH_2), 7.75 (d, 2H, J = 8.7 Hz, ArH), 7.94 (d, 2H, J = 8.7 Hz, ArH), 10.42 (br s, 1H, D_2O exchangeable NH), Anal. Calcd for $C_9H_7N_5S_2$ (249.3): C, 43.36; H, 2.83; N, 28.09; S, 25.72. Found: C, 43.30; H, 2.77; N, 28.15; S, 25.91.

6-(4-Chlorophenyl)-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (2c). Yield 895 mg (98%); colorless crystals, m.p. 260–262°C. IR: 3425, 3070, 3024, 1593, 1570, 1516, 1455, 1396, 1369, 1311, 1246, 1188, 1092, 1014, 953, 833, 798, 714, 679, 606, 498, 471, 420; ^{1}H NMR (DMSO-d_6) δ 7.62 (td, 2H, J = 1.9, 8.7 Hz, ArH), 7.90 (td, 2H, J = 1.9, 8.7 Hz, ArH). Anal. Calcd for $C_9H_5ClN_4S_2$ (268.7): C, 40.22; H, 1.88; N, 20.85; S, 23.86. Found: C, 40.27; H, 1.84; N, 20.77; S, 23.94.

6-(4-Nitrophenyl)-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (2d). Yield 902 mg (95%); orange yellow crystals, m.p. 244–246°C. IR: 3437, 3036, 1605, 1524, 1454, 1350, 1315, 1250, 1084, 1003, 957, 852, 752, 687, 602, 455, 417; ^{1}H NMR (DMSO-d_6) δ 8.17 (dd, 2H, J = 2.1, 9.0 Hz, ArH), 8.35 (dd, 2H, J = 2.1, 8.7 Hz, ArH). Anal. Calcd for $C_9H_5N_5O_2S_2$ (279.3): C, 38.70; H, 1.80; N, 25.07; S, 22.96. Found: C, 38.88; H, 1.84; N, 25.18; S, 22.93.

6-Methyl-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (2e). Yield 252 mg (43%); pale crystals, m.p. 254–256°C. IR: 3421, 2924, 2859, 1624, 1539, 1458, 1427, 1385, 1200, 1169, 991, 810, 652, 617, 544, 528, 471, 447, 417; ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3 H, CH_3). Anal. Calcd for $C_4H_4N_4S_2$ (172.2): C, 27.90; H, 2.34; N, 32.53; S, 37.23. Found: C, 27.98; H, 2.21; N, 32.44; S, 37.19.

5-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylthio)-4-amino-2,4-dihydro-[1,2,4]triazole-3-thione (7). To a solution of compound **3** (311 mg, 2.1 mmol) in *N*,*N*-dimethylformamide (2.5 mL) and triethylamine (0.36 mL, 2.6 mmol) was added 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **(4)**

(1.07 g, 2.6 mmol) and the reaction mixture was stirred overnight. The next day, the reaction mixture was diluted with ice-water mixture and the formed precipitate was collected by filtration, washed several times with water, and dried at room temperature. The precipitate was extracted with dichloromethane, the solution was concentrated and the residue subjected to silica gel (70–230 mesh) column chromatography. Compound **7** was eluted with 70% ethyl acetate/petroleum ether (b.p. 40–60°C) → 80% ethyl acetate/petroleum ether (b.p. 40–60°C) and recrystallized from ethanol to give 663 mg (66%) of colorless crystals, m.p. 176–178°C (R_f = 0.62, determined on TLC aluminum sheets using ethyl acetate/petroleum ether (b.p. 40–60°C) [60:40, v/v] as a developing system). IR: 3309, 3178, 2946, 1752, 1618, 1511, 1457, 1436, 1373, 1237, 1057, 1040, 950, 912, 818, 725, 671, 627, 601, 560, 488, 461, 428; ^{1}H NMR (DMSO-d_6) δ 1.94, 1.98, 1.99, 2.07 (4 s, 12H, CH_3CO), 3.99 (dd, 1H, $J_{H\text{-}6'\text{-}H\text{-}5'}$ = 2.1Hz, $J_{H\text{-}6'\text{-}H\text{-}6''}$ = 12.6 Hz, H-6′), 4.05 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'}$ = 2.1Hz, $J_{H\text{-}5'\text{-}H\text{-}6''}$ = 4.8 Hz, $J_{H\text{-}5'\text{-}H\text{-}4'}$ = 9.6 Hz, H-5′), 4.11 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'}$ = 4.8 Hz, $J_{H\text{-}6''\text{-}H\text{-}6'}$ = 12.6 Hz, H-6″), 4.95 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'}$ = 9.6 Hz, $J_{H\text{-}4'\text{-}H\text{-}5'}$ = 9.6 Hz, H-4′), 5.07 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 9.3 Hz, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 9.6 Hz, H-3′), 5.38 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'}$ = 9.9 Hz, $J_{H\text{-}2'\text{-}H\text{-}3'}$ = 9.3 Hz, H-2′), 5.57 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.9 Hz, H-1′), 5.58 (s, 2H, D_2O exchangeable NH_2), 13.88 (s, 1H, D_2O exchangeable NH). Anal. Calcd for $C_{16}H_{22}N_4O_9S_2$ (478.5): C, 40.16; H, 4.63; N, 11.71; S, 13.40. Found: C, 40.08; H, 4.52; N, 11.74; S, 13.56.

General Procedures for the Synthesis of Compounds 5a–d and 6a–d

A) To a solution of each of compounds **2a–d** (2.1 mmol) in *N*,*N*-dimethylformamide (2.5 mL) and triethylamine (0.36 mL, 2.6 mmol) was added 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **(4)** (1.07 g, 2.6 mmol) and the reaction mixture was stirred overnight. The next day, the reaction mixture was diluted with ice-water mixture and the formed precipitate was collected by filtration, washed several times with water, and dried at room temperature. The precipitate was extracted with dichloromethane, the solution was concentrated, and the residue subjected to silica gel (70–230 mesh) column chromatography. Compounds **6a–d** were eluted first with 50% ethyl acetate/petroleum ether (b.p. 40–60°C) → 70% ethyl acetate/petroleum ether (b.p. 40–60°C), followed by compounds **5a–d** with 80% ethyl acetate/petroleum ether (b.p. 40–60°C) → 10% methanol/ethyl acetate. The chromatographically separated crude products were recrystallized from dichloromethane/petroleum ether (b.p. 40–60°C). R_f values of the latter compounds were determined on TLC aluminum sheets using ethyl acetate/petroleum ether (b.p. 40–60°C) [60:40, v/v] as a developing system.

B) A mixture of compound **7** (478 mg, 1.0 mmol) and the appropriate carboxylic acid (1 mmol; for the synthesis of compounds **5a**, **b**, **d**) or acid chloride (1 mmol for the synthesis of compound **5c**) in phosphoryl chloride (2 mL) was heated at reflux temperature in an oil bath for 8 hours. The excess of phosphoryl chloride was removed under reduced pressure and the formed residue was extracted with dichloromethane, washed with KOH solution (0.1 M, 2 × 100 mL) then water (4 × 100 mL), and dried (Na_2SO_4). The solvent was then removed under reduced pressure and the formed residue was recrystallized from dichloromethane/petroleum ether (b.p. 40–60°C). R_f values of the latter compounds were determined on TLC aluminum sheets using ethyl acetate/petroleum ether (b.p. 40–60°C) [60:40, v/v] as a developing system.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylthio)-6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (5a). Yield 439 mg (37%, A), 497 mg (88%, B); yellow crystals, m.p. 154–156°C (R_f = 0.65). IR; 3054, 2925, 2713, 1747, 1603, 1444, 1413, 1376, 1352, 1311, 1267, 1189, 1158, 1096, 1028, 970, 817, 758, 703, 637, 593, 530; ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3 H, CH_3CO), 1.97 (s, 6 H, CH_3CO), 2.05 (s, 3 H, CH_3CO), 3.74 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'}$ = 2.1Hz, $J_{H\text{-}5'\text{-}H\text{-}6''}$ = 4.8 Hz, $J_{H\text{-}5'\text{-}H\text{-}4'}$ = 10.2Hz, H-5′), 4.02 (dd, 1H, $J_{H\text{-}6'\text{-}H\text{-}5'}$ = 2.1Hz, $J_{H\text{-}6'\text{-}H\text{-}6''}$ = 12.3 Hz, H-6′), 4.16 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'}$ = 4.8 Hz, $J_{H\text{-}6''\text{-}H\text{-}6'}$ = 12.3 Hz, H-6″), 5.07 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'}$ = 9.6 Hz, $J_{H\text{-}4'\text{-}H\text{-}5'}$ = 10.2Hz, H-4′), 5.15 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 9.3 Hz, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 9.6 Hz, H-3′), 5.24 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'}$ = 9.9 Hz, $J_{H\text{-}2'\text{-}H\text{-}3'}$ = 9.3 Hz, H-2′), 5.33 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.9 Hz, H-1′), 7.49 (t, 2H, J = 8.7 Hz, ArH), 7.54 (t, 1H, J = 8.7 Hz, ArH), 7.84 (dd, 2H, J = 1.8, 8.7 Hz, ArH). Anal. Calcd for $C_{23}H_{24}N_4O_9S_2$ (564.6): C, 48.93; H, 4.28; N, 9.92; S, 11.36. Found: C, 49.11; H, 4.21; N, 10.10; S, 11.22.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylthio)-6-(4-aminophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (5b). Yield 426 mg (35%, A), 498 mg (86%, B); yellow crystals, m.p. 130–132°C (R_f = 0.11). IR: 3375, 3229, 3033, 2943, 1751, 1628, 1605, 1497, 1458, 1373, 1311, 1227, 1180, 1038, 949, 914, 833, 756, 690, 667, 602, 513, 482, 447, 417; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3 H, CH_3CO), 1.97 (s, 6 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 3.51 (br, 2H, D_2O exchangeable NH_2), 3.73 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'}$ = 2.1Hz, $J_{H\text{-}5'\text{-}H\text{-}6''}$ = 4.8 Hz, $J_{H\text{-}5'\text{-}H\text{-}4'}$ = 9.9 Hz, H-5′), 4.02 (d, 1H, $J_{H\text{-}6'\text{-}H\text{-}6''}$ = 12.3 Hz, H-6′), 4.16 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'}$ = 4.8 Hz, $J_{H\text{-}6''\text{-}H\text{-}6'}$ = 12.3 Hz, H-6″), 5.07 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'}$ = 9.6 Hz, $J_{H\text{-}4'\text{-}H\text{-}5'}$ = 9.9 Hz, H-4′), 5.17 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 9.3 Hz, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 9.6 Hz, H-3′), 5.24 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'}$ = 9.9 Hz, $J_{H\text{-}2'\text{-}H\text{-}3'}$ = 9.3 Hz, H-2′), 5.31 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.9 Hz, H-1′), 6.68 (d, 2H, J = 8.7 Hz, ArH), 7.60 (d, 2H, J = 8.7 Hz, ArH). Anal. Calcd for $C_{23}H_{25}N_5O_9S_2$ (579.6): C, 47.66; H, 4.35; N, 12.08; S, 11.06. Found: C, 47.74; H, 4.48; N, 12.14; S, 11.01.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylthio)-6-(4-chlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (5c). Yield 390 mg (31%, A), 497 mg (83%, B); yellow crystals, m.p. 108–110°C (R_f = 0.72). IR: 3033, 2942, 1749,

1642, 1597, 1571, 1467, 1381, 1225, 1036, 957, 917, 828, 682, 603, 495, 473; ^{1}H NMR ($CDCl_3$) δ 1.93, 1.97, 1.98, 2.05 (4s, 12H, CH_3CO), 3.75 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'} = 2.1$Hz, $J_{H\text{-}5'\text{-}H\text{-}6''} = 4.8$ Hz, $J_{H\text{-}5'\text{-}H\text{-}4'} = 9.9$ Hz, H-5′), 4.03 (dd, 1H, $J_{H\text{-}6'\text{-}H\text{-}5'} = 2.1$Hz, $J_{H\text{-}6'\text{-}H\text{-}6''} = 12.6$ Hz, H-6′), 4.16 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'} = 4.8$ Hz, $J_{H\text{-}6''\text{-}H\text{-}6'} = 12.6$ Hz, H-6″), 5.07 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'} = 9.6$ Hz, $J_{H\text{-}4'\text{-}H\text{-}5'} = 9.9$ Hz, H-4′), 5.15 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'} = 9.3$ Hz, $J_{H\text{-}3'\text{-}H\text{-}4'} = 9.6$ Hz, H-3′), 5.24 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'} = 9.9$ Hz, $J_{H\text{-}2'\text{-}H\text{-}3'} = 9.3$ Hz, H-2′), 5.34 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'} = 9.9$ Hz, H-1′), 7.49 (td, 2H, $J = 2.1$, 8.7 Hz, ArH), 7.81 (td, 2H, $J = 2.1$, 8.7 Hz, ArH). Anal. Calcd for $C_{23}H_{23}ClN_4O_9S_2$ (599.0): C, 46.12; H, 3.87; N, 9.35; S, 10.71. Found: C, 46.08; H, 3.90; N, 9.21; S, 10.70.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylthio)-6-(4-nitrophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (5d). Yield 576 mg (45%, A), 536 mg (88%, B); yellow crystals, m.p. 178–180°C ($R_f = 0.14$). IR: 3040, 2943, 2889, 2854, 1743, 1605, 1527, 1454, 1373, 1346, 1300, 1223, 1092, 1034, 984, 953, 914, 856, 795, 752, 717, 687, 644, 617, 598, 536, 459, 432; ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3 H, CH_3CO), 1.960 (s, 3 H, CH_3CO), 1.963 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 3.75 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'} = 2.1$Hz, $J_{H\text{-}5'\text{-}H\text{-}6''} = 4.8$ Hz, $J_{H\text{-}5'\text{-}H\text{-}4'} = 10.2$Hz, H-5′), 4.02 (dd, 1H, $J_{H\text{-}6'\text{-}H\text{-}5'} = 2.1$Hz, $J_{H\text{-}6'\text{-}H\text{-}6''} = 12.6$ Hz, H-6′), 4.13 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'} = 4.8$ Hz, $J_{H\text{-}6''\text{-}H\text{-}6'} = 12.6$ Hz, H-6″), 5.06 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'} = 9.9$ Hz, $J_{H\text{-}4'\text{-}H\text{-}5'} = 10.2$Hz, H-4′), 5.14 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'} = 9.0$ Hz, $J_{H\text{-}3'\text{-}H\text{-}4'} = 9.9$ Hz, H-3′), 5.24 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'} = 9.9$ Hz, $J_{H\text{-}2'\text{-}H\text{-}3'} = 9.0$ Hz, H-2′), 5.33 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'} = 9.9$ Hz, H-1′), 8.09 (td, 2H, $J = 2.1$, 9.0 Hz, ArH), 8.36 (td, 2H, $J = 2.1$, 9.0 Hz, ArH). Anal. Calcd for $C_{23}H_{23}N_5O_{11}S_2$ (609.6): C, 45.32; H, 3.80; N, 11.49; S, 10.52. Found: C, 45.19; H, 3.96; N, 11.39; S, 10.47.

2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-phenyl-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (6a). Yield 119 mg (10%, A); yellow crystals, m.p. 188–190°C. IR: 2921, 2853, 1756, 1552, 1525, 1446, 1395, 1323, 1232, 1036, 1004, 923, 761, 688, 601; ^{1}H NMR ($CDCl_3$) δ 1.92, 2.02, 2.07, 2.15 (4 s, 12H, CH_3CO), 4.02 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'} = 2.1$Hz, $J_{H\text{-}5'\text{-}H\text{-}6''} = 4.8$ Hz, $J_{H\text{-}5'\text{-}H\text{-}4'} = 9.9$ Hz, H-5′), 4.15 (dd, 1H, $J_{H\text{-}6'\text{-}H\text{-}5'} = 2.1$Hz, $J_{H\text{-}6'\text{-}H\text{-}6''} = 12.6$ Hz, H-6′), 4.31 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'} = 4.8$ Hz, $J_{H\text{-}6''\text{-}H\text{-}6'} = 12.6$ Hz, H-6″), 5.23 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'} = 9.3$ Hz, $J_{H\text{-}4'\text{-}H\text{-}5'} = 9.9$ Hz, H-4′), 5.43 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'} = 9.6$ Hz, $J_{H\text{-}3'\text{-}H\text{-}4'} = 9.3$ Hz, H-3′), 5.72 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'} = 9.3$ Hz, $J_{H\text{-}2'\text{-}H\text{-}3'} = 9.6$ Hz, H-2′), 6.27 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'} = 9.3$ Hz, H-1′), 7.55 (m, 3 H, ArH), 7.90 (td, 2H, $J = 1.6$, 7.5 Hz, ArH). Anal. Calcd for $C_{23}H_{24}N_4O_9S_2$ (564.6): C, 48.93; H, 4.28; N, 9.92; S, 11.36. Found: C, 49.09; H, 4.19; N, 9.89; S, 11.39.

2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-(4-aminophenyl)-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (6b). Yield 231 mg (19%, A); yellow crystals, m.p. 116–118°C, with shrinkage at 90°C ($R_f = 0.5$). IR: 3483, 3381, 3029, 2957, 1751, 1607, 1496, 1371, 1229, 1037, 913, 834, 601, 421; ^{1}HN MR ($CDCl_3$) δ 1.90, 2.04, 2.05, 2.14 (4 s, 12H, CH_3CO), 4.01 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'} = 2.1$Hz, $J_{H\text{-}5'\text{-}H\text{-}6''} = 4.8$ Hz, $J_{H\text{-}5'\text{-}H\text{-}4'} = 9.9$ Hz, H-5′), 4.14 (dd,

1H, $J_{H\text{-}6'\text{-}H\text{-}5'}$ = 2.1Hz, $J_{H\text{-}6'\text{-}H\text{-}6''}$ = 12.6 Hz, H-6′), 4.29 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'}$ = 4.8 Hz, $J_{H\text{-}6''\text{-}H\text{-}6'}$ = 12.6 Hz, H-6″), 5.22 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'}$ = 9.3 Hz, $J_{H\text{-}4'\text{-}H\text{-}5'}$ = 9.9 Hz, H-4′), 5.42 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 9.6 Hz, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 9.3 Hz, H-3′), 5.43 (s, 2H, D_2O exchangeable NH_2), 5.51 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'}$ = 9.3 Hz, $J_{H\text{-}2'\text{-}H\text{-}3'}$ = 9.6 Hz, H-2′), 6.25 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.3 Hz, H-1′), 6.67 (d, 2H, J = 8.7 Hz, ArH), 7.64 (d, 2H, J = 8.7 Hz, ArH). Anal. Calcd for $C_{23}H_{25}N_5O_9S_2$ (579.6): C, 47.66; H, 4.35; N, 12.08; S, 11.06. Found: C, 47.57; H, 4.28; N, 12.12; S, 11.01.

2-(2, 3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-(4-chlorophenyl)-2*H*-[1, 2,4] triazolo[3,4-*b*] [1,3,4]thiadiazole-3-thione (6c). Yield 176 mg (14%, A); yellow crystals, m.p. 84–86°C (R_f = 0.83). IR: 3091, 2962, 2930, 2848, 2420, 2108, 1750, 1595, 1551, 1524, 1485, 1370, 1225, 1158, 1090, 1036, 1002, 953, 925, 833, 795, 758, 726, 683, 648, 599, 523, 496, 460; ^{1}H NMR ($CDCl_3$) δ 1.93, 2.06, 2.07, 2.15 (4 s, 12H, CH_3CO), 4.02 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'}$ = 2.1Hz, $J_{H\text{-}5'\text{-}H\text{-}6''}$ = 4.8 Hz, $J_{H\text{-}5'\text{-}H\text{-}4'}$ = 9.9 Hz, H-5′), 4.15 (dd, 1H, $J_{H\text{-}6'\text{-}H\text{-}5'}$ = 2.1Hz, $J_{H\text{-}6'\text{-}H\text{-}6''}$ = 12.6 Hz, H-6′), 4.31 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'}$ = 4.8 Hz, $J_{H\text{-}6''\text{-}H\text{-}6'}$ = 12.6 Hz, H-6″), 5.23 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'}$ = 9.6 Hz, $J_{H\text{-}4'\text{-}H\text{-}5'}$ = 9.9 Hz, H-4′), 5.43 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 9.3 Hz, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 9.6 Hz, H-3′), 5.72 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'}$ = $J_{H\text{-}2'\text{-}H\text{-}3'}$ = 9.3 Hz, H-2′), 6.27 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.3 Hz, H-1′), 7.51 (td, 2H, J = 2.1, 8.7 Hz, ArH), 7.85 (td, 2H, J = 2.1, 8.7 Hz, ArH). Anal. Calcd for $C_{23}H_{23}ClN_4O_9S_2$ (599.0): C, 46.12; H, 3.87; N, 9.35; S, 10.71. Found: C, 45.98; H, 3.88; N, 9.26; S, 10.85.

2-(2, 3, 4, 6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6-(4-nitrophenyl)-2*H*-[1, 2,4]triazolo[3, 4-*b*] [1,3,4]thiadiazole-3-thione (6d). Yield 179 mg (14%, A); yellow crystals, m.p. 178–180°C(R_f = 0.64). IR; 3104, 3074, 2928, 2846, 1751, 1605, 1532, 1486, 1454, 1373, 1348, 1228, 1038, 1004, 955, 924, 854, 794, 752, 724, 687, 637, 599; ^{1}H NMR ($CDCl_3$) δ 1.90, 2.00, 2.04, 2.13 (4s, 12H, CH_3CO), 4.02 (ddd, 1H, $J_{H\text{-}5'\text{-}H\text{-}6'}$ = 2.1Hz, $J_{H\text{-}5'\text{-}H\text{-}6''}$ = 4.8 Hz, $J_{H\text{-}5'\text{-}H\text{-}4'}$ = 10.2Hz, H-5′), 4.14 (dd, 1H, $J_{H\text{-}6'\text{-}H\text{-}5'}$ = 2.1Hz, $J_{H\text{-}6'\text{-}H\text{-}6''}$ = 12.6 Hz, H-6′), 4.29 (dd, 1H, $J_{H\text{-}6''\text{-}H\text{-}5'}$ = 4.8 Hz, $J_{H\text{-}6''\text{-}H\text{-}6'}$ = 12.6 Hz, H-6″), 5.21 (t, 1H, $J_{H\text{-}4'\text{-}H\text{-}3'}$ = 9.6 Hz, $J_{H\text{-}4'\text{-}H\text{-}5'}$ = 10.2Hz, H-4′), 5.42 (t, 1H, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 9.3 Hz, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 9.6 Hz, H-3′), 5.68 (t, 1H, $J_{H\text{-}2'\text{-}H\text{-}1'}$ = 9.0 Hz, $J_{H\text{-}2'\text{-}H\text{-}3'}$ = 9.3 Hz, H-2′), 6.24 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.0 Hz, H-1′), 8.10 (dd, 2H, J = 1.8, 8.7 Hz, ArH), 8.37 (dd, 2H, J = 1.8, 8.7 Hz, ArH). Anal. Calcd for $C_{23}H_{23}N_5O_{11}S_2$ (609.6): C, 45.32; H, 3.80; N, 11.49; S, 10.52. Found: C, 45.28; H, 3.79; N, 11.63; S, 10.49.

Deacetylation of Compounds 5a and 6a

General procedure: Dry gaseous ammonia was passed through a solution of each of compounds **5a** and **6a** (1 mmol) in dry methanol (10 mL) for about 1 hour with cooling and stirring then the reaction mixture was stirred at room temperature over night. The resulting mixture was then concentrated at reduced pressure to afford a solid residue which was washed several

times via boiling in chloroform (100 mL) and decantation. The residue was dried at room temperature, column chromatographed (chloroform → 20% methanol/chloroform), and recrystallized from methanol to give colorless crystals of compounds **8** and **9**. R_f values of the latter compounds were determined using TLC aluminum sheets using chloroform/methanol (80:20, v/v) as a developing system.

3-(β-D-glucopyranosylthio)-6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (8). Yield 277 mg (75%); colorless crystals, m.p. 144–146°C (R_f = 0.49). ^{1}H NMR (DMSO-d_6) δ 3.14–3.59 (m, 6 H, H-2′, H-3′, H-4′, H-5′, H-6′, H-6″), 4.10 (d, 1H, J = 3.9 Hz, D_2O-exchangeable OH), 5.03 (br s, 1H D_2O-exchangeable OH), 5.14 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.0 Hz, H-1′), 5.18 (br d, 1H, J = 6.9 Hz, D_2O-exchangeable OH), 5.59 (br s, 1H, D_2O-exchangeable OH), 7.57–7.70 (m, 3 H, ArH), 7.97 (d, 2H, J = 7.5 Hz, ArH). Anal. Calcd for $C_{15}H_{16}N_4O_5S_2$ (396.4): C, 45.45; H, 4.07; N, 14.13; S, 16.18. Found: C, 44.51; H, 4.13; N, 14.02; S, 16.22.

2-β-D-Glucopyranosyl)-6-phenyl-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (9). Yield 314 mg (85%); colorless crystals, m.p. 276–278°C (R_f = 0.75). IR: 3390 (br), 3059, 2914, 2863, 1569, 1533, 1475, 1446, 1394, 1317, 1288, 1260, 1078, 1055, 941, 893, 858, 761, 690, 599; ^{1}H NMR (DMSO-d_6) δ 3.28–4.36 (m, 6 H, H-2′, H-3′, H-4′, H-5′, H-6′, 6″), 4.68 (t, 1H, $J_{OH\text{-}H\text{-}6'}$ = 5.4 Hz, $J_{OH\text{-}H\text{-}6''}$ = 5.7 Hz, D_2O-exchangeable 6′-OH), 5.12 (d, 1H, J = 5.4 Hz D_2O-exchangeable OH), 5.24 (d, 1H, J = 5.1Hz D_2O-exchangeable OH), 5.48 (d, 1H, J = 5.4 Hz, D_2O-exchangeable OH), 5.84 (d, 1H, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 9.0 Hz, H-1′), 7.57–7.66 (m, 3 H, ArH), 7.90 (t, 1H, J = 7.5 Hz, ArH), 8.00 (dd, 1H, J = 1.2, 7.5 Hz, ArH). Anal. Calcd for $C_{15}H_{16}N_4O_5S_2$ (396.4): C, 45.45; H, 4.07; N, 14.13; S, 16.18. Found: C, 44.31; H, 4.03; N, 14.17; S, 16.35.

REFERENCES

1. Jones, D.H.; Slack, R.; Squires, S.; Wooldridge, K.R.H. Antiviral chemotherapy. I. The activity of pyridine and quinoline derivatives against neurovaccina in mice. *J. Med. Chem.***1965**, 8, 676–680.
2. Goswami, B.N.; Kataky, J.C.S.; Baruah, J.N. Synthesis and antibacterial activity of 1-(2,4-dichlorobenzoyl)-4-substituted thiosemicarbazides, 1,2,4-triazoles and their methyl derivatives. *J. Heterocycl. Chem.* **1984**, 21, 1225–1229.
3. Holla, B.S.; Kalluraya, B.; Sridhar, K.R. Synthesis of 4-(5-nitro-2-furfurylidene)amino-3-mercapto-5-(substituted)-1,2,4-triazoles as possible antibacterial agents. *Curr. Sci.* **1987**, 56, 236–238.
4. Holla, B.S.; Poojary, K.N.; Kalluraya, B.; Gowda, P.V. Synthesis, characterisation and antifungal activity of some *N*-bridged heterocycles derived from 3-(3-bromo-4-methoxyphenyl)-4-amino-5-mercapto-1,2,4-triazole. *Farmaco* **1996**, 51, 793–799.
5. Abdou, N.A.; Amin, F.M. Synthesis and biological activity of certain 5-mercapto-3-(3-pyridyl)-4*H*-1,2,4-triazole derivatives. *Mansoura J. Pharm. Sci.* **1990**, 6, 25–29.
6. Mishra, R.K.; Tewari, R.K.; Srivastava, S.K.; Bahel, S.C. Synthesis and antifungal activity of some 1,4-disubstitued-thiosemicarbazides, 2,5-disubstituted-1,3,4-thiadiazoles and 3,4-disubstituted-5-mercapto-1,2,4-triazoles. *J. Indian Chem. Soc.* **1991**, 68, 110–112.
7. Unangst, P.C.; Shurum, G.P.; Connor, D.T.; Dyer, R.D.; Schrier, D.J. Novel 1,2,4-oxadiazoles and 1,2,4-thiadiazoles as dual 5-lipoxygenase and cyclooxygenase inhibitors. *J. Med. Chem.* **1992**, 35, 3691–3698.
8. Mullican, M.D.; Wilson, M.W.; Connor, D.T.; Kostlan, C.R.; Schrier, D.J.; Dyer, R.D. Design of 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally active, nonulcerogenic antiinflammatory agents. *J. Med. Chem.* **1993**, 36, 1090–1099.

9. Sugden, J.K.; Yoloye, T.O. Medicinal applications of indole derivatives. *Pharm. Acta Helv.* **1978**, 53, 65–92.
10. Shams El-Dine, Sh.A.; Hazzaa, A.A.B. Synthesis of compounds with potential fungicidal activity. *Pharmazie* **1974**, 29, 761–763.
11. Misato, T.; Ko, K.; Honma, Y.; Konno, K.; Taniyama, E. 1,3,4-thiadiazole derivatives as fungicides. Jpn. Kokai Tokkyo Koho 77 25,028, 1977; *Chem. Abstr.* **1977**, 87, 147054 a.
12. Cansiz, A.; Servi, S.; Koparir, M.; Altintas, M.; Digrak, M. Synthesis and biological activities of some Mannich bases of 5-(2-furyl)-1,2,4-triazole-3-thiones. *J. Chem. Soc. Pak.* **2001**, 23, 237–240.
13. Stillings, M.R.; Welbourn, A.P.; Walter, D.S. Substituted 1,3,4-thiadiazoles with anticonvulsant activity. 2. Aminoalkyl derivatives. *J. Med. Chem.* **1986**, 29, 2280–2284.
14. Kane, J.M.; Dudley, M.W.; Sorensen, S.M.; Miller, F.P. 2,4-Dihydro-3*H*-1,2,4-triazole-3-thiones as potential antidepressant agents. *J. Med. Chem.* **1988**, 31, 1253–1258.
15. George, T.; Mehta, D.V.; Tahilramani R.; David, J.; Talwalker, P.K. Synthesis of some s-triazoles with potential analgesic and antiinflammatory activities. *J. Med. Chem.* **1971**, 14, 335–338.
16. Srivastava, U.; Khan, R.H.; Bahel, S.C. Synthesis of fungicidal 1,2,4-triazoles and related compounds. *Bokin Bobai.* **1979**, 7, T414–T417.
17. Rudnicka, W.; Osmailowska, Z. Cyanoalkylation of 4-amino-1,2,4-triazol-3-thione. *Acta Pol. Pharm.* **1979**, 36, 411–419.
18. Shu-Qing, K.; Sun-Yung, T.; Ki, T.; Hung-Shan, C. *Wei Sheng Wu Hsueh Pao* **1980**, 20, 208–212.
19. Singh, H.; Yadav, L.D.S.; Bhattacharya, B.K. Synthesis of some new bis(1,2,4-triazol-3-yl) disulfides, sulfides and sulfones as potential pestcides. *J. Indian Chem. Soc.* **1979**, 56, 1013–1016.
20. Gall, M.; Lahti, R.A.; Rudzik, A.D.; Duchamp, D.J.; Chidester, C.; Scahill, T. Novel anxiolytic agents derived from .alpha.-amino-.alpha.-phenyl-o-tolyl-4*H*-triazoles and –imidazoles. *J. Med. Chem.* **1978**, 21, 542–548.
21. Khalil, N.S.A.M. Efficient synthesis, structure, and antimicrobial activity of some novel *N*- and *S*-β-**D**-glucosides of 5-pyridin-3-yl-1,2,4-triazoles. *Carbohydr. Res.* **2006**, 341, 2187–2199.
22. Abbas, A.A.; Khalil, N.S.A.M. Synthesis of some new 1,3/ or 1,4-bis(glucopyranosyl-1,2,4-triazol-5-ylthio)propanes/ or butanes as potential antimicrobial agents. *Nucleosides Nucleotides Nucleic Acids* **2005**, 24, 1353–1372.
23. Omar, A.M.E.; Aboul Wafa, O.M. Synthesis and in vitro antimicrobial and antifungal properties of some novel 1,3,4-thiadiazole and *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. *J. Heterocycl. Chem.* **1986**, 23, 1339–1341.
24. Kurtzer, F. In *Advances in Heterocyclic Chemistry*, eds. A.R. Katritzky, A.J. Boulton, A.J. Academic Press, New York, 1965, vol. 5, p. 165.
25. Zhang, Z.Y.; Sun, X.W. *s*-Triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives. *Heterocycles* **1998**, 48, 561–584.
26. Khalil, N.S.A.M.; Mansour, A.K.; Eid, M.M. Synthesis of some novel 6-benzyl(or substituted benzyl)-2-β-**D**-glucopyranosyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazines as potential antimicrobial chemotherapeutics. *Nucleosides Nucleotides Nucleic Acids* **2004**, 23, 1889–1910.
27. Khalil, N.S.A.M. Synthesis of some novel *N*-ribosyl-1,2,4-triazin-6(1*H*)-/ones or thiones as potential antibacterial and antifungal chemotherapeutics. *Nucleosides Nucleotides Nucleic Acids* **2005**, 24, 111–120.
28. Khalil, N.S.A.M. Synthesis of novel α-L-arabinopyranosides of β-lactams with potential antimicrobial activity. *Nucleosides Nucleotides Nucleic Acids* **2005**, 24, 1277–1287.
29. Mansour, A.K.; Eid, M.M.; Khalil, N.S.A.M. Selective synthesis and reactions of 6-substituted-2-β-galactosyl-1,2,4-triazines of potential anticancer activity. *Nucleosides Nucleotides Nucleic Acids* **2003**, 22, 21–44.
30. Mansour, A.K.; Eid, M.M.; Khalil, N.S.A.M. Synthesis of some new 2-α-L-arabinopyranosyl-1,2,4-triazines as potential antitumor chemotherapeutics. *Nucleosides Nucleotides Nucleic Acids* **2003**, 22, 1805–1823.
31. Mansour, A.K.; Eid, M.M.; Khalil, N.S.A.M. Synthesis of some *N*-galactosides of 3-aryl-5-benzyl (or substituted benzyl)-1,2,4-triazin-6(1*H*)-/ones or thiones of expected biological activity. *Nucleosides Nucleotides Nucleic Acids* **2003**, 22, 1825–1833.
32. Mansour, A.K.; Ibrahim, Y.A.; Khalil, N.S.A.M. Selective synthesis and structure of 6-arylvinyl-2- and 4- glucosyl-1,2,4-triazines of expected interesting biological activity. *Nucleosides Nucleotides* **1999**, 18, 2265–2283.

33. Mansour, A.K.; Eid, M.M.; and Khalil, N.S.A.M. Synthesis and reactions of some new heterocyclic carbohydrazides and related compounds as potential anticancer agents. *Molecules* **2003**, 8, 744–755.
34. Potts, K.T.; Huseby, R.M. 1,2,4-Triazoles. XVI. Derivatives of the s-triazolo[3,4-*b*][1,3,4]thiadiazole ring system. *J. Org. Chem.* **1966**, 31, 3528–3531.
35. Cleve, G.; Hoyer, G.A.; Schulz, G.; Vorbrüggen, H. Synthesis of nucleosides. VIII. NMR and CD spectra of pyrimidine nucleosides and their 2-thio analogs. *Chem. Ber.* **1973**, 106, 3062–3072.
36. Sandstrom, J. Cyclizations of thiocarbohydrazide and its monohydrazones. III. Reactions with carbon disulfide in pyridine. *Acta Chem. Scand.* **1961**, 15, 1295–1302.
37. Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R.; eds. *Vogel's Textbook of Practical Organic Chemistry*, Longman Group UK, Ltd., England, 1989, 5th ed., p. 647.