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Novel Simple Efficient Synthetic Approach Toward 6-Substituted-2H-[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-2H-[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 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 regioisomers 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; 2H-[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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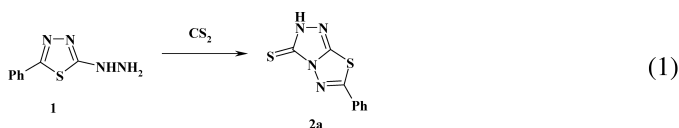
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to possess antibacterial, antifungal, antiinflammatory, CNS depressant, hypocholesteremic, antiviral, analgesic, anthelmintic, herbicidal and plant growth regulatory effects.^[25]

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

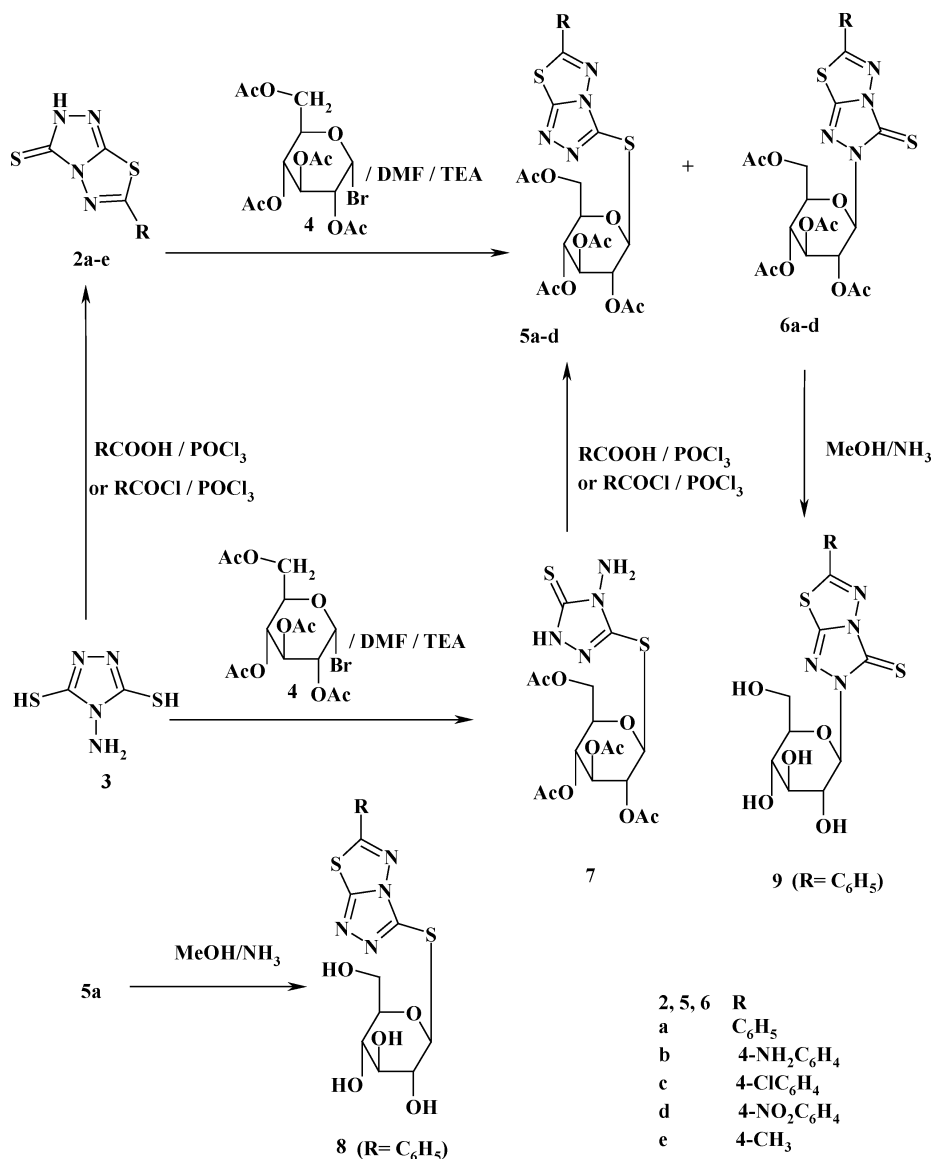
The only example found in the literature describing the synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole ring system having an active NH group in the 2-position or a possible tautomeric thiol group in the 3-position was described by Potts and Huseby^[34] through the reaction of (5-phenyl-1,3,4-thiadiazol-2-yl)hydrazine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



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*-glycosides 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*-glycosyl 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 ($J_{H-1'-H-2'} = 9.0\text{--}9.9$ 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 NO₂ 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 ¹H NMR data of the latter compounds revealed the absence of the acetyl protons at δ 1.91–2.15 and the appearance of the D₂O 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

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

^a100 μ L of each conc. was tested (5, 2.5, 1.0 mg/mL); well diameter = 0.6 cm.

^bSt. = 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. ¹H 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 F₂₅₄ 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; ¹H 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, D₂O exchangeable NH). Anal. Calcd for C₉H₆N₄S₂ (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; ¹H NMR (DMSO-*d*₆) δ 6.4–6.8 (br s, 2H, D₂O exchangeable NH₂), 7.75 (d, 2H, *J* = 8.7 Hz, ArH), 7.94 (d, 2H, *J* = 8.7 Hz, ArH), 10.42 (br s, 1H, D₂O exchangeable NH). Anal. Calcd for C₉H₇N₅S₂ (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; ¹H 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 C₉H₅ClN₄S₂ (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; ¹H 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 C₉H₅N₅O₂S₂ (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; ¹H NMR (DMSO-*d*₆) δ 2.71 (s, 3 H, CH₃). Anal. Calcd for C₄H₄N₄S₂ (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; ^1H NMR (DMSO- d_6) δ 1.94, 1.98, 1.99, 2.07 (4 s, 12H, CH_3CO), 3.99 (dd, 1H, $J_{\text{H-6}'\text{-H-5}'} = 2.1\text{ Hz}$, $J_{\text{H-6}'\text{-H-6}''} = 12.6\text{ Hz}$, H-6'), 4.05 (ddd, 1H, $J_{\text{H-5}'\text{-H-6}'} = 2.1\text{ Hz}$, $J_{\text{H-5}'\text{-H-6}''} = 4.8\text{ Hz}$, $J_{\text{H-5}'\text{-H-4}'} = 9.6\text{ Hz}$, H-5'), 4.11 (dd, 1H, $J_{\text{H-6}''\text{-H-5}'} = 4.8\text{ Hz}$, $J_{\text{H-6}''\text{-H-6}'} = 12.6\text{ Hz}$, H-6''), 4.95 (t, 1H, $J_{\text{H-4}'\text{-H-3}'} = 9.6\text{ Hz}$, $J_{\text{H-4}'\text{-H-5}'} = 9.6\text{ Hz}$, H-4'), 5.07 (t, 1H, $J_{\text{H-3}'\text{-H-2}'} = 9.3\text{ Hz}$, $J_{\text{H-3}'\text{-H-4}'} = 9.6\text{ Hz}$, H-3'), 5.38 (t, 1H, $J_{\text{H-2}'\text{-H-1}'} = 9.9\text{ Hz}$, $J_{\text{H-2}'\text{-H-3}'} = 9.3\text{ Hz}$, H-2'), 5.57 (d, 1H, $J_{\text{H-1}'\text{-H-2}'} = 9.9\text{ Hz}$, H-1'), 5.58 (s, 2H, D_2O exchangeable NH_2), 13.88 (s, 1H, D_2O exchangeable NH). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_9\text{S}_2$ (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; ^1H 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, $J_{\text{H-5'-H-6'}} = 2.1\text{Hz}$, $J_{\text{H-5'-H-6''}} = 4.8\text{Hz}$, $J_{\text{H-5'-H-4'}} = 10.2\text{Hz}$, H-5'), 4.02 (dd, 1H, $J_{\text{H-6'-H-5'}} = 2.1\text{Hz}$, $J_{\text{H-6'-H-6''}} = 12.3\text{Hz}$, H-6'), 4.16 (dd, 1H, $J_{\text{H-6''-H-5'}} = 4.8\text{Hz}$, $J_{\text{H-6''-H-6'}} = 12.3\text{Hz}$, H-6''), 5.07 (t, 1H, $J_{\text{H-4'-H-3'}} = 9.6\text{Hz}$, $J_{\text{H-4'-H-5'}} = 10.2\text{Hz}$, H-4'), 5.15 (t, 1H, $J_{\text{H-3'-H-2'}} = 9.3\text{Hz}$, $J_{\text{H-3'-H-4'}} = 9.6\text{Hz}$, H-3'), 5.24 (t, 1H, $J_{\text{H-2'-H-1'}} = 9.9\text{Hz}$, $J_{\text{H-2'-H-3'}} = 9.3\text{Hz}$, H-2'), 5.33 (d, 1H, $J_{\text{H-1'-H-2'}} = 9.9\text{Hz}$, H-1'), 7.49 (t, 2H, $J = 8.7\text{Hz}$, ArH), 7.54 (t, 1H, $J = 8.7\text{Hz}$, ArH), 7.84 (dd, 2H, $J = 1.8$, 8.7 Hz, ArH). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_9\text{S}_2$ (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; ^1H 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, $J_{\text{H-5'-H-6'}} = 2.1\text{Hz}$, $J_{\text{H-5'-H-6''}} = 4.8\text{Hz}$, $J_{\text{H-5'-H-4'}} = 9.9\text{Hz}$, H-5'), 4.02 (d, 1H, $J_{\text{H-6'-H-6''}} = 12.3\text{Hz}$, H-6'), 4.16 (dd, 1H, $J_{\text{H-6''-H-5'}} = 4.8\text{Hz}$, $J_{\text{H-6''-H-6'}} = 12.3\text{Hz}$, H-6''), 5.07 (t, 1H, $J_{\text{H-4'-H-3'}} = 9.6\text{Hz}$, $J_{\text{H-4'-H-5'}} = 9.9\text{Hz}$, H-4'), 5.17 (t, 1H, $J_{\text{H-3'-H-2'}} = 9.3\text{Hz}$, $J_{\text{H-3'-H-4'}} = 9.6\text{Hz}$, H-3'), 5.24 (t, 1H, $J_{\text{H-2'-H-1'}} = 9.9\text{Hz}$, $J_{\text{H-2'-H-3'}} = 9.3\text{Hz}$, H-2'), 5.31 (d, 1H, $J_{\text{H-1'-H-2'}} = 9.9\text{Hz}$, H-1'), 6.68 (d, 2H, $J = 8.7\text{Hz}$, ArH), 7.60 (d, 2H, $J = 8.7\text{Hz}$, ArH). Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_9\text{S}_2$ (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; ^1H NMR (CDCl_3) δ 1.93, 1.97, 1.98, 2.05 (4s, 12H, CH_3CO), 3.75 (ddd, 1H, $J_{\text{H-5'-H-6'}} = 2.1\text{ Hz}$, $J_{\text{H-5'-H-6''}} = 4.8\text{ Hz}$, $J_{\text{H-5'-H-4'}} = 9.9\text{ Hz}$, H-5'), 4.03 (dd, 1H, $J_{\text{H-6'-H-5'}} = 2.1\text{ Hz}$, $J_{\text{H-6'-H-6''}} = 12.6\text{ Hz}$, H-6'), 4.16 (dd, 1H, $J_{\text{H-6'-H-5'}} = 4.8\text{ Hz}$, $J_{\text{H-6'-H-6''}} = 12.6\text{ Hz}$, H-6''), 5.07 (t, 1H, $J_{\text{H-4'-H-3'}} = 9.6\text{ Hz}$, $J_{\text{H-4'-H-5'}} = 9.9\text{ Hz}$, H-4'), 5.15 (t, 1H, $J_{\text{H-3'-H-2'}} = 9.3\text{ Hz}$, $J_{\text{H-3'-H-4'}} = 9.6\text{ Hz}$, H-3'), 5.24 (t, 1H, $J_{\text{H-2'-H-1'}} = 9.9\text{ Hz}$, $J_{\text{H-2'-H-3'}} = 9.3\text{ Hz}$, H-2'), 5.34 (d, 1H, $J_{\text{H-1'-H-2'}} = 9.9\text{ Hz}$, H-1'), 7.49 (td, 2H, $J = 2.1, 8.7\text{ Hz}$, ArH), 7.81 (td, 2H, $J = 2.1, 8.7\text{ Hz}$, ArH). Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{ClN}_4\text{O}_9\text{S}_2$ (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; ^1H 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, $J_{\text{H-5'-H-6'}} = 2.1\text{ Hz}$, $J_{\text{H-5'-H-6''}} = 4.8\text{ Hz}$, $J_{\text{H-5'-H-4'}} = 10.2\text{ Hz}$, H-5'), 4.02 (dd, 1H, $J_{\text{H-6'-H-5'}} = 2.1\text{ Hz}$, $J_{\text{H-6'-H-6''}} = 12.6\text{ Hz}$, H-6'), 4.13 (dd, 1H, $J_{\text{H-6'-H-5'}} = 4.8\text{ Hz}$, $J_{\text{H-6'-H-6''}} = 12.6\text{ Hz}$, H-6''), 5.06 (t, 1H, $J_{\text{H-4'-H-3'}} = 9.9\text{ Hz}$, $J_{\text{H-4'-H-5'}} = 10.2\text{ Hz}$, H-4'), 5.14 (t, 1H, $J_{\text{H-3'-H-2'}} = 9.0\text{ Hz}$, $J_{\text{H-3'-H-4'}} = 9.9\text{ Hz}$, H-3'), 5.24 (t, 1H, $J_{\text{H-2'-H-1'}} = 9.9\text{ Hz}$, $J_{\text{H-2'-H-3'}} = 9.0\text{ Hz}$, H-2'), 5.33 (d, 1H, $J_{\text{H-1'-H-2'}} = 9.9\text{ Hz}$, H-1'), 8.09 (td, 2H, $J = 2.1, 9.0\text{ Hz}$, ArH), 8.36 (td, 2H, $J = 2.1, 9.0\text{ Hz}$, ArH). Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_{11}\text{S}_2$ (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-2H-[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; ^1H NMR (CDCl_3) δ 1.92, 2.02, 2.07, 2.15 (4 s, 12H, CH_3CO), 4.02 (ddd, 1H, $J_{\text{H-5'-H-6'}} = 2.1\text{ Hz}$, $J_{\text{H-5'-H-6''}} = 4.8\text{ Hz}$, $J_{\text{H-5'-H-4'}} = 9.9\text{ Hz}$, H-5'), 4.15 (dd, 1H, $J_{\text{H-6'-H-5'}} = 2.1\text{ Hz}$, $J_{\text{H-6'-H-6''}} = 12.6\text{ Hz}$, H-6'), 4.31 (dd, 1H, $J_{\text{H-6'-H-5'}} = 4.8\text{ Hz}$, $J_{\text{H-6'-H-6''}} = 12.6\text{ Hz}$, H-6''), 5.23 (t, 1H, $J_{\text{H-4'-H-3'}} = 9.3\text{ Hz}$, $J_{\text{H-4'-H-5'}} = 9.9\text{ Hz}$, H-4'), 5.43 (t, 1H, $J_{\text{H-3'-H-2'}} = 9.6\text{ Hz}$, $J_{\text{H-3'-H-4'}} = 9.3\text{ Hz}$, H-3'), 5.72 (t, 1H, $J_{\text{H-2'-H-1'}} = 9.3\text{ Hz}$, $J_{\text{H-2'-H-3'}} = 9.6\text{ Hz}$, H-2'), 6.27 (d, 1H, $J_{\text{H-1'-H-2'}} = 9.3\text{ Hz}$, H-1'), 7.55 (m, 3 H, ArH), 7.90 (td, 2H, $J = 1.6, 7.5\text{ Hz}$, ArH). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_9\text{S}_2$ (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)-2H-[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; ^1H NMR (CDCl_3) δ 1.90, 2.04, 2.05, 2.14 (4 s, 12H, CH_3CO), 4.01 (ddd, 1H, $J_{\text{H-5'-H-6'}} = 2.1\text{ Hz}$, $J_{\text{H-5'-H-6''}} = 4.8\text{ Hz}$, $J_{\text{H-5'-H-4'}} = 9.9\text{ Hz}$, H-5'), 4.14 (dd,

1H, $J_{\text{H-6}'\text{-H-5}'} = 2.1\text{ Hz}$, $J_{\text{H-6}'\text{-H-6}''} = 12.6\text{ Hz}$, H-6'), 4.29 (dd, 1H, $J_{\text{H-6}''\text{-H-5}'} = 4.8\text{ Hz}$, $J_{\text{H-6}''\text{-H-6}'} = 12.6\text{ Hz}$, H-6''), 5.22 (t, 1H, $J_{\text{H-4}'\text{-H-3}'} = 9.3\text{ Hz}$, $J_{\text{H-4}'\text{-H-5}'} = 9.9\text{ Hz}$, H-4'), 5.42 (t, 1H, $J_{\text{H-3}'\text{-H-2}'} = 9.6\text{ Hz}$, $J_{\text{H-3}'\text{-H-4}'} = 9.3\text{ Hz}$, H-3'), 5.43 (s, 2H, D₂O exchangeable NH₂), 5.51 (t, 1H, $J_{\text{H-2}'\text{-H-1}'} = 9.3\text{ Hz}$, $J_{\text{H-2}'\text{-H-3}'} = 9.6\text{ Hz}$, H-2'), 6.25 (d, 1H, $J_{\text{H-1}'\text{-H-2}'} = 9.3\text{ Hz}$, H-1'), 6.67 (d, 2H, $J = 8.7\text{ Hz}$, ArH), 7.64 (d, 2H, $J = 8.7\text{ Hz}$, ArH). Anal. Calcd for C₂₃H₂₅N₅O₉S₂ (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; ¹H NMR (CDCl₃) δ 1.93, 2.06, 2.07, 2.15 (4 s, 12H, CH₃CO), 4.02 (ddd, 1H, $J_{\text{H-5}'\text{-H-6}'} = 2.1\text{ Hz}$, $J_{\text{H-5}'\text{-H-6}''} = 4.8\text{ Hz}$, $J_{\text{H-5}'\text{-H-4}'} = 9.9\text{ Hz}$, H-5'), 4.15 (dd, 1H, $J_{\text{H-6}'\text{-H-5}'} = 2.1\text{ Hz}$, $J_{\text{H-6}'\text{-H-6}''} = 12.6\text{ Hz}$, H-6'), 4.31 (dd, 1H, $J_{\text{H-6}''\text{-H-5}'} = 4.8\text{ Hz}$, $J_{\text{H-6}''\text{-H-6}'} = 12.6\text{ Hz}$, H-6''), 5.23 (t, 1H, $J_{\text{H-4}'\text{-H-3}'} = 9.6\text{ Hz}$, $J_{\text{H-4}'\text{-H-5}'} = 9.9\text{ Hz}$, H-4'), 5.43 (t, 1H, $J_{\text{H-3}'\text{-H-2}'} = 9.3\text{ Hz}$, $J_{\text{H-3}'\text{-H-4}'} = 9.6\text{ Hz}$, H-3'), 5.72 (t, 1H, $J_{\text{H-2}'\text{-H-1}'} = J_{\text{H-2}'\text{-H-3}'} = 9.3\text{ Hz}$, H-2'), 6.27 (d, 1H, $J_{\text{H-1}'\text{-H-2}'} = 9.3\text{ Hz}$, H-1'), 7.51 (td, 2H, $J = 2.1, 8.7\text{ Hz}$, ArH), 7.85 (td, 2H, $J = 2.1, 8.7\text{ Hz}$, ArH). Anal. Calcd for C₂₃H₂₃ClN₄O₉S₂ (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; ¹H NMR (CDCl₃) δ 1.90, 2.00, 2.04, 2.13 (4s, 12H, CH₃CO), 4.02 (ddd, 1H, $J_{\text{H-5}'\text{-H-6}'} = 2.1\text{ Hz}$, $J_{\text{H-5}'\text{-H-6}''} = 4.8\text{ Hz}$, $J_{\text{H-5}'\text{-H-4}'} = 10.2\text{ Hz}$, H-5'), 4.14 (dd, 1H, $J_{\text{H-6}'\text{-H-5}'} = 2.1\text{ Hz}$, $J_{\text{H-6}'\text{-H-6}''} = 12.6\text{ Hz}$, H-6'), 4.29 (dd, 1H, $J_{\text{H-6}''\text{-H-5}'} = 4.8\text{ Hz}$, $J_{\text{H-6}''\text{-H-6}'} = 12.6\text{ Hz}$, H-6''), 5.21 (t, 1H, $J_{\text{H-4}'\text{-H-3}'} = 9.6\text{ Hz}$, $J_{\text{H-4}'\text{-H-5}'} = 10.2\text{ Hz}$, H-4'), 5.42 (t, 1H, $J_{\text{H-3}'\text{-H-2}'} = 9.3\text{ Hz}$, $J_{\text{H-3}'\text{-H-4}'} = 9.6\text{ Hz}$, H-3'), 5.68 (t, 1H, $J_{\text{H-2}'\text{-H-1}'} = 9.0\text{ Hz}$, $J_{\text{H-2}'\text{-H-3}'} = 9.3\text{ Hz}$, H-2'), 6.24 (d, 1H, $J_{\text{H-1}'\text{-H-2}'} = 9.0\text{ Hz}$, H-1'), 8.10 (dd, 2H, $J = 1.8, 8.7\text{ Hz}$, ArH), 8.37 (dd, 2H, $J = 1.8, 8.7\text{ Hz}$, ArH). Anal. Calcd for C₂₃H₂₃N₅O₁₁S₂ (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 \rightarrow 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). ^1H 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, D₂O-exchangeable OH), 5.03 (br s, 1H D₂O-exchangeable OH), 5.14 (d, 1H, $J_{\text{H-1'-H-2'}}$ = 9.0 Hz, H-1'), 5.18 (br d, 1H, J = 6.9 Hz, D₂O-exchangeable OH), 5.59 (br s, 1H, D₂O-exchangeable OH), 7.57–7.70 (m, 3 H, ArH), 7.97 (d, 2H, J = 7.5 Hz, ArH). Anal. Calcd for C₁₅H₁₆N₄O₅S₂ (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-2H-[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; ^1H 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, $J_{\text{OH-H-6'}}$ = 5.4 Hz, $J_{\text{OH-H-6''}}$ = 5.7 Hz, D₂O-exchangeable 6'-OH), 5.12 (d, 1H, J = 5.4 Hz D₂O-exchangeable OH), 5.24 (d, 1H, J = 5.1 Hz D₂O-exchangeable OH), 5.48 (d, 1H, J = 5.4 Hz, D₂O-exchangeable OH), 5.84 (d, 1H, $J_{\text{H-1'-H-2'}}$ = 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 C₁₅H₁₆N₄O₅S₂ (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.

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