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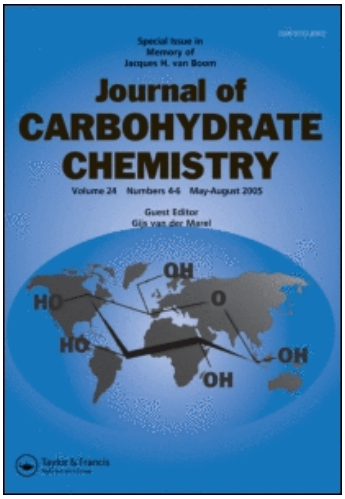

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Synthesis of 5-Aryl-3-Glycosylthio-4-Phenyl-4H-1,2,4-Triazoles and Their Acyclic Analogs Under Conventional and Microwave Conditions

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Synthesis of 5-Aryl-3-Glycosylthio-4-Phenyl-4H-1,2,4-Triazoles and Their Acyclic Analogs Under Conventional and Microwave Conditions

El Sayed H. El-Ashry,[1,2] Nagwa Rashed,[1] Laila F. Awad,[1] El Sayed Ramadan,[1] Somia M. Abdel-Maggeed,[1] and Nagat Rezki[1†]

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Under microwave irradiation (MWI), 4-phenyl-5-substituted-4H-1,2,4-triazole-3-thiol derivatives **7** and **8** were synthesized in a good yield by intramolecular cyclization of the aroyl phenyl thiosemicarbazides **5** and **6**. The respective triazolylglycosides (Str-glycosides) **12**–**17** were obtained by reaction of triazoles **7** and **8** with glycosyl halides **9**–**11** in dry acetone in the presence of potassium carbonate as base under both conventional and MWI conditions. Alkylation of **7** and **8** with haloalchols **18–20** in boiling ethanolic solution containing sodium ethoxide as a base gave the corresponding alkylated analogs **21**–**26**. MWI conditions led to higher yield in shorter reaction time than the conventional method. Treatment of **26** with tosyl chloride gave the unexpected product **29** and not **27** or **28**. Oxidation of **26** with sodium metaperiodate afforded triazole **8** and not the aldehyde **30**. Attempted glycosylation and alkylation of the

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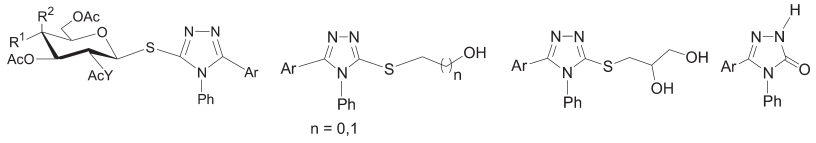
phenolic OH group in triazole **8** were unsuccessful; this was proved by theoretical calculations using the AM1 semi-empirical method.



Keywords 1,2,4-Triazole, Thioglycoside, Alkylation, Microwave irradiation (MWI), AM1 semi-empirical calculation, Hydrogen bonding

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INTRODUCTION

Carbohydrates play significant roles in the molecular recognition process.[1–3] These conclusions have been based on molecular biology studies, which required model glycosides to be available by synthesis to understand their mechanisms. Thus, considerable efforts have been devoted to the synthesis of glycosides,[4–11] of which thioglycosides,[5,8] trichloroacetimidates,[9] glycosyl halides,[10] and modifications thereof[10,11] have been extensively used as glycosyl donors. The glycosylthio-derived heterocycles have been recently reviewed.[5] Although they are widely used as glycosyl donors in glycosidation reactions,[5,12–17] a divergent use of some glycosylthio heterocycles as glycosyl acceptors and, subsequently, as donors have recently attracted much attention for stereoselective synthesis of oligosaccharides.[5] Moreover, they are promising candidates as potential therapeutics and enzyme inhibitors.[5,17,18] Consequently, the modification in the heterocyclic ring would lead to a change of the capability of donor ability of the glycosidic bond and give a better chance for selecting which heterocycles should be used in glycosyl donors or acceptors. Continuing our program for the synthesis of glycosylated heterocycles[5,11,19] and their acyclic analogs,[18,20] the selected heterocycle is a functionalized 1,2,4-triazole ring, a ring of great spectrum of therapeutic importance such as anti-inflammatory, anticonvulsant, and antifungal properties.[21] The methodology for effecting the sequence of reactions utilized microwave irradiation (MWI), which have been used by us[22] and others.[23]

RESULTS AND DISCUSSION

The synthesis of 1,2,4-triazoles started with methyl benzoate (**1**) or methyl salicylate (**2**) that was converted to the acid hydrazides **3** or **4** in 99% and 98% yield, respectively, by MWI for 2 min in a closed Teflon vessel; conventional heating for 4 h was required. When **3** or **4** reacted with phenyl isothiocyanate in ethanol under MWI for 2.5 to 3.0 min, the corresponding aroyl-phenylthiosemicarbazide **5** and **6** were obtained. The dehydrative cyclizations of **5** and **6**

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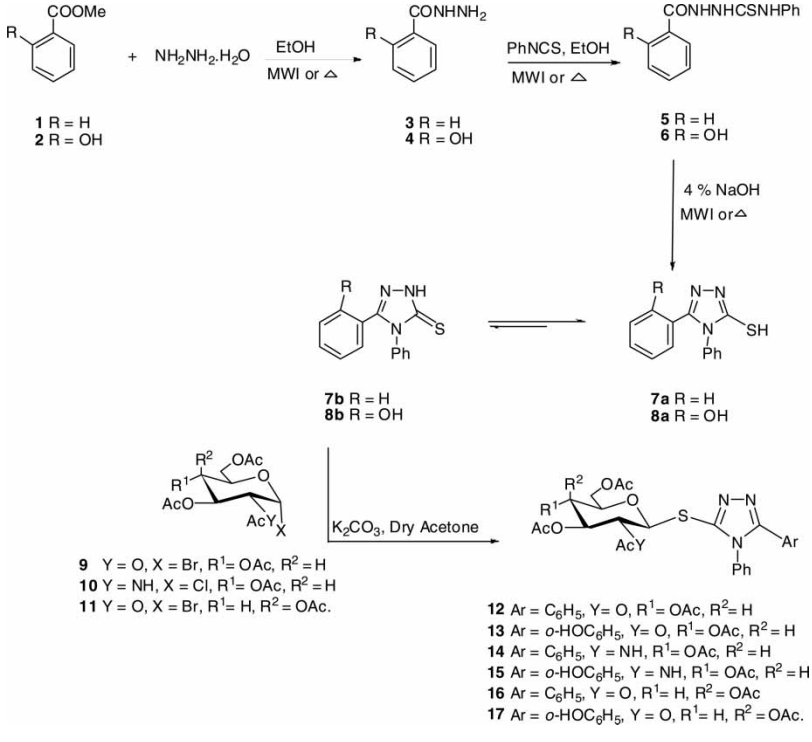
were achieved by 4% aqueous sodium hydroxide to give the corresponding 1,2,4-triazoles **7** and **8**, respectively. Improvements of the yields and shorter reaction times have been achieved under the MWI condition.

The conversion of triazoles **7** and **8** into the respective triazolylglycosides, STr-glycosides **12**–**17** were carried out by the reaction with the glycosyl halides **9**–**11** in the presence of potassium carbonate (Sch. 1). Under conventional conditions, the coupling required stirring for overnight and then heating for 2 to 4 h, whereas these reactions were achieved by MWI for 2.5 to 3.5 min to give better yields (Table 1).

The ^{1}H NMR spectra of compounds **12**–**17** showed characteristic signals corresponding to the aromatic protons at δ_H 6.45 to 7.63 ppm, whereas the singlet corresponding to the phenolic OH for compound **12** was assigned at δ_H 11.61 ppm. Their anomeric protons were assigned as doublet in the range of δ_H 4.82 to 5.64 ppm with $J_{1',2'}$ 9.9 to 10.7 Hz confirming the β-configuration. The 2D NMR spectra (^{1}H-^{1}H DQFCOSY and ^{1}H-^{13}C HMQC) facilitated the spectral assignment of the sugar protons of compounds **12**, **13**, and **15**. Thus, the anomeric proton H-1′ of compound **13** was resonated as doublet at δ_H 5.54 ppm and its carbon at δ_c 83.8 ppm. In the ^{1}H NMR spectrum of



Scheme 1

Table 1: Comparative data of conventional and MW methods for the synthesis of compounds 3–26.

	Conventional method		Microwave method	
Compound No.	**Time (h)**	**Yield (%)**	**Time (min)**	**Yield (%)**
3	4	89	1.0	99
4	4	86	1.0	98
5	6	86	2.5	95
6	6	89	3.0	98
7	4	76	4.5	90
8	4	74	4.0	92
12	18	78	2.5	92
13	18	76	3.0	90
14	20	81	3.0	89
15	18	80	3.0	94
16	19	80	3.5	92
17	20	79	3.0	92
21	2	86	2.0	90
22	3	82	2.5	98
23	4	78	3.0	96
24	3	84	3.0	92
25	4	79	4.0	95
26	4	78	4.0	92

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compound **15** there are four signals in the upper region corresponding to the acetamido and three acetoxy groups. The anomeric proton appeared at δ_H 5.62 ppm as a doublet with $J_{1',2'}$ 10.7 Hz correlated with δ_c 85.4 for C-1′, which are characteristic of a β anomer (Experimental).

The S-acyclic analogs have been also synthesized from the 1,2,4-triazoles **7** and **8** by alkylation with the haloalcohols **18**–**20** in boiling ethanol as solvent and sodium ethoxide as basic catalyst for 2 to 4 h to give the corresponding alkylated analogs **21**–**26**. Improvements of the yields (92%–98%) in shorter reaction time (2–4 min) were achieved when reactions were carried out under MWI.

The structure of **21**–**26** was established on the basis of their elemental analyses and spectral data, which confirmed the success of the alkylation by the appearance of one exchangeable proton at δ_H 4.57 to 5.19 ppm, which was assigned to the OH proton of the acyclic side chain for the compounds **21**–**24** instead of the thiol proton of their precursors. Moreover, their ^{1}H NMR spectra also showed the characteristic triplet corresponding to the SCH_2 protons at δ_H 3.15 to 3.25 ppm with J 6.9 Hz, whereas the CH_2O protons were assigned to the quartet at δ_H 3.67 and 3.44 ppm for compounds **22** and **23**; that of **24** was overlapped with solvent signal. At lower frequency a pentet corresponding to C-2 protons was assigned to the δ_H 1.75 to 1.82 ppm for compounds **23** and **24**.

The ^{1}H NMR spectra of compound **25** showed two characteristic D_2O exchangeable signals at δ_H 4.75 and 5.11 ppm due to two OH protons, which confirmed the success of the thiol alkylation. The SCH_2 protons were assigned to two doublet of doublets at δ_H 3.15 and 3.31 ppm, whereas the terminal methylene protons appeared as multiplet at δ_H 3.32 to 3.41.

Various attempts to glycosylate or alkylate the phenolic OH in **8**, in addition to the S-alkylation, have failed and only S-alkylation or S-glycosylation occurred, these results being later confirmed by theoretical calculations.

Treatment of **26** with tosyl chloride in pyridine at 0°C did not give the expected tosyl derivative **27**. No reaction occurred after 7 d at 0°C or even at rt for 10 d. On heating the reaction mixture at reflux temperature for 6 h, a product was obtained that was characterized by spectral and elemental analysis to be **29** instead of **27** or **28**. The elemental analysis of **29** showed the absence of sulfur element and agreed with the molecular formula $C_{14}H_{11}N_3O_2$. The ^{1}H NMR spectrum of **29** showed only characteristic signals corresponding to the nine aromatic protons as well as two exchangeable signals at δ 9.93 and 11.21 corresponding to NH and phenolic OH protons, respectively.

The unexpected hydrolytic cleavage of the C-S bond in **26** may be rationalized by the occurrence of an intramolecular rearrangement of the presumably formed **27**, which under the influence of base gave the anion **27a** that acts as internal nucleophile, attack C-5 with subsequent C-O bond formation a charge on the nitrogen in the spiro intermediate **27b**, and then cleavage of the *O*-alkyl residue to give **27c** which via the attack of sulfur anion at the β-carbon form **29** (Sch. 2). Moreover, oxidation of **26** with sodium metaperiodate resulted in the formation of the starting material **8** rather than the formation of the aldehydes **30**. Although the product is not the anticipated one under such conditions of reactions of reaction, it is not surprising. Oxidation of the sulfur atom to give the oxide or dioxide derivative can be considered, which let such group readily cleaved to give **8** (Figure 1).

The two tautomeric thiole/thione forms for the 1,2,4-triazoles **7** and **8** may be postulated. The 1,2,4-triazole ring was found to exist in thione or thiol form due to the mobility of the hydrogen atom between the sulfur and nitrogen atoms of the ring. In order to determine which form is predominate, a theoretical study of the tautomerism has been investigated by means of semi-empirical AM1 methods, which were carried out with the MOPAC7 program package.[24] The heat of formation, dipole moment, highest occupied molecular orbital energies (E_{HOMO}), lowest unoccupied molecular orbital energies (E_{LUMO}), and the charge density on triazole heteroatoms as well as the relative stability of the tautomers have been taken into account (Table 2).

The relative stability (RS) calculations from the gas phase AM1 method for the triazole **7** and **8** favored the predominance of the thiol form **7a** and **8a** over thione form **7b** and **8b** with relative stability energy, RS = 7.042,

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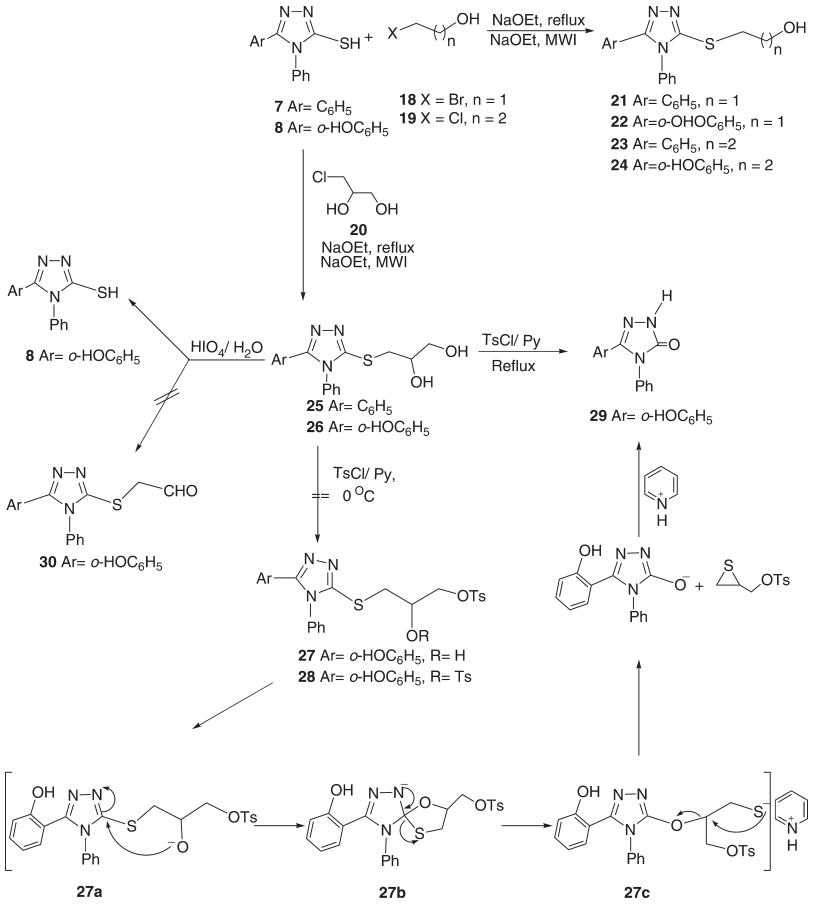

Scheme 2

7.513 kcal · mol^{-1}, respectively. Moreover, the thiol form **8a** ($\Delta H_f = 96.603$ kcal · mol^{-1}) was found to be more stable than the thiol form **7a** ($\Delta H_f = 140.180$ kcal · mol^{-1}) with relative stability energy RS = −33.477 kcal · mol^{-1}. This could be attributed to the hydrogen bonding between the OH phenolic and N-1 triazole atom, which provides higher stability to **8a**. This conclusion has been theoretical confirmed by AM1 optimization of the structure of **8a**, which revealed that the phenolic benzene ring and the triazole ring are planar with dihedral angles of −2.2 and −9.7 degrees corresponding to N(11)-H(21)-O(20)-C(4) and N(11)-C(7)-C(5)-C(4), respectively. Thus, the possibility of hydrogen bonding O-H$^{\cdots}$N(11) became more evident, where the N(11) acts as acceptor, due to the fact that AM1-calculated O-H$^{\cdots}$N(11) hydrogen bonding distances is 2.090 Å, a distance that permit such bonding to take place.

This tendency of intramolecular hydrogen bonding decreases the acidity of the phenolic hydrogen atom to be abstracted under the basic catalysts required

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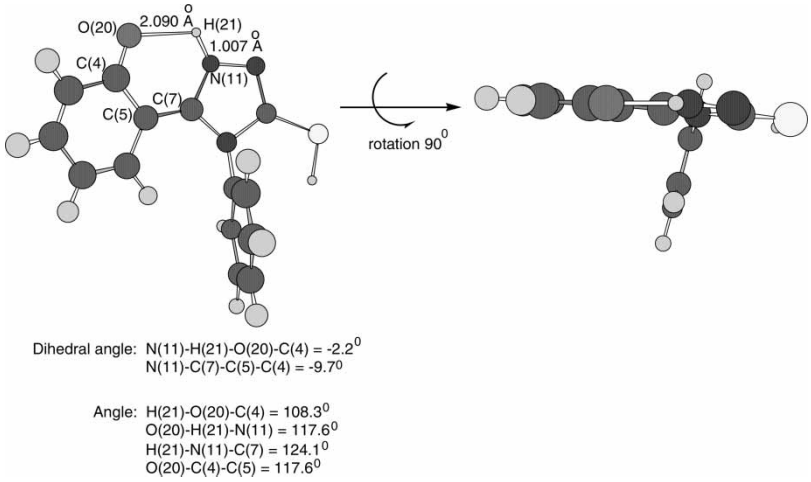

Figure 1

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in the glycosylation and alkylation processes. These theoretical conclusions agreed with the experimental results where several attempts to prepare *O*-substituted phenolic moieties on triazole **8** by reaction with either alkyl halides or sugar halides under different reaction conditions were unsuccessful.

EXPERIMENTAL

Melting points were determined with a Melt-temp apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel 1B-F plates using ethyl acetate-hexane as developing solvent and the spots were detected by UV light absorption. Irradiation was done in a domestic microwave oven EM-230M (1200-watt output power under defrost temperature). The irradiation was done, unless otherwise stated, in a closed Teflon cylindrical vessel, which was placed at the center of a rotating plate inside the oven. The vessel was supported by a frame for safety. The vessel has an outside diameter 6.5 cm and a length of 6.0 cm, whereas the space inside the vessel was 3.0 cm wide and 2.0 cm length. More 2.0 cm in the length inside the vessel was used for the screw of the cover in order to be tight. The oven was adjusted on the defrost mode with the fixed output power. ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol spectrometer (500 MHz). The assignment of ^{1}H NMR spectra was based on chemical shift correlation DQFCOFY spectra, while the assignment of ^{13}C NMR spectra was based on HMQC experiments. Chemical shifts (δ) are given in ppm relative to the signal for TMS as internal standard. Elemental analyses were performed in the unit of Microanalyses at Faculty of Science, Cairo University.

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Table 2: Calculated (AM1) heat of formation (kcal · mol^{-1}), dipole moments (μ, Debye), HOMO orbital energies (E_{HOMO}, eV), LUMO orbital energies (E_{LUMO}, eV), charge density on triazole heteroatoms, and relative stability (kcal · mol^{-1}) for the reactant tautomers.

Tautomer no.	Heat of formation (ΔH_f) kcal · mol^{-1}	Dipole moment Debye	E_{HOMO} (eV)	E_{LUMO} (eV)	Charge density on triazole heteroatoms	Relative stability[a] (RS) kcal · mol^{-1}
7a	140.180	4.806	−8.587	−0.601	(S) 0.218 (N1) −0.063 (N2) − 0.094 (N4) −0.101	(**7b**–**7a**) 7.042
7b	147.222	4.694	−8.539	−0.532	(S) −0.198 (N1) −0.045 (N2) −0.242 (N4) −0.173	
8a	96.603	4.640	−8.857	−0.585	(S) 0.224 (N1) −0.052 (N2) −0.099 (N4) −0.096	(**8b**–**8a**) 7.513 (**8a**–**7a**) −43.577
8b	104.116	3.821	−8.696	−0.506	(S) −0.183 (N1) −0.033 (N2) −0.099 (N4) −0.179	

[a]RS = ΔH_f (thione) − ΔH_f (thiol); minus sign indicates that thione is more stable and vice versa.

Preparation of Acid Hydrazide Derivatives 3, 4; General Procedure

Microwave Method (MW)

A solution of **1** or **2** (1.6 mmol), ethanol (5 mL), and 2.5 equivalent of hydrazine hydrate in a closed Teflon vessel was irradiated for 1 min by MW. The reaction mixture was cooled, and then 5 mL of ice water was added to the solution where a formed precipitate was recrystallized from ethanol to give **3** and **4**, respectively.

Benzoylhydrazine (3). Colorless crystals; mp 115–116°C (Lit[25] mp 113–117°C).

o-Hydroxybenzoyl hydrazine (4). Colorless crystals; mp 149°C (Lit[26] mp 152°C).

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4-Aroyl-1-phenylthiosemicarbazides 5, 6; General Procedure

A solution of **3** or **4** (1 mmol), ethanol (5 mL), and phenyl isothiocyanate (1.2 mmol) in a closed Teflon vessel was irradiated for 2.5 to 3.0 min by MW. The reaction mixture was cooled to 0°C and the precipitate was recrystallized from ethanol to give **5** and **6**, respectively.

1-Benzoyl-4-phenylthiosemicarbazide (5). Colorless needles; mp 163°C (Lit[25] mp: 165°C).

1-(o-Hydroxybenzoyl)-4-phenylthiosemicarbazide (6). Colorless crystals; mp: 192–194°C (Lit[27] mp 196°C).

5-Aryl-4-phenyl-4H-1,2,4-triazole-3-thiol 7, 8; General Procedure

Conventional Method (CM)

A solution of **5** or **6** (1 mmol) and 4% aqueous sodium hydroxide (5 mL) in a closed Teflon vessel was irradiated for 4.0 to 4.5 min by MW. The mixture was cooled and acidified with diluted HCl and the precipitate was recrystallized from ethanol to give triazoles **7** and **8**, respectively.

4,5-Diphenyl-4H-1,2,4-triazole-3-thiol (7). Colorless crystals; mp: 281–282°C (Lit[25] mp 279–280°C).

5-(o-Hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (8). Colorless crystals; mp 271°C (Lit[28] mp 273°C).

Preparation of Glycosyl-STr 12–17; General Procedure

Conventional Method (CM)

A solution of compounds **7** or **8** (1 mmol) and potassium carbonate (1 mmol) in dry acetone (10 mL) was stirred for 1 h, and then glycosyl halides **9–11** (1.1 mmol) were added. Stirring was continued for overnight, and then the reaction mixture was refluxed for 2 to 4 h, then filtered, washed with acetone, evaporated under reduced pressure, and recrystallized from ethanol or purified by column chromatography (Table 1).

Microwave Method (MW)

A solution of compounds **7** or **8** (1 mmol) and potassium carbonate (0.5 mmol) and glycosyl halides **9–11** (0.55 mmol) in dry acetone (5 mL) in a closed Teflon vessel was irradiated by MW for 2.5 to 3.5 min. The reaction mixture was cooled and processed as described above to give the same products (Table 1).

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4,5-Diphenyl-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-4H-1,2,4-triazole(12). Colorless crystals; mp 123°C; TLC, R_f 0.24 (2:1 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.97$, 1.99, 2.00, 2.01 (4s, 12H, 4 CH_3CO), 3.80 (ddd, 1H, $J_{5',6'} = 2.3$, $J_{5',6''} = 4.6$, $J_{5',4'} = 6.1$ Hz, H-5′), 4.09 (dd, 1H, $J_{6',5'} = 2.3$, $J_{6',6''} = 12.2$ Hz, H-6′), 4.24 (dd, 1H, $J_{6',5'} = 4.6$, $J_{6',6''} = 12.2$ Hz, H-6″), 5.11 (2dd, 2H, $J_{4',3'} = 9.9$, $J_{4',5'} = 6.1$, $J_{2',1'} = 9.9$, $J_{2',3'} = 9.9$ Hz, H-2′, H-4′), 5.27 (t, 1H, $J_{3',2'} = J_{3',4'} = 9.9$ Hz, H-3′), 5.58 (d, 1H, $J_{2',1'} = 9.9$ Hz, H-1′), 7.25–7.44 (m, 10H, Ar-H); ^{13}C NMR (125.7 MHz, $CDCl_3$) $\delta = 20.6$, 20.7 (4 CH_3CO), 61.6 (C-6′), 67.8 (C-4′), 70.0 (C-2′), 73.8 (C-3′), 76.2 (C-5′), 84.3 (C-1′), 110.0, 118.1, 118.7, 127.6, 128.2, 128.6, 129.9, 130.1, 149.6, 155.6 (Ar-C), 169.5, 169.6, 170.6 (CH_3CO); Anal. Calcd for $C_{28}H_{29}N_3O_9S$ (583.61): C, 57.62; H, 5.01; N, 7.20. Found: C, 57.49; H, 5.33; N, 7.29.

5-(o-Hydroxyphenyl)-4-phenyl-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl-thio)-4H-1,2,4-triazole (13). Colorless plates; mp: 146–148°C; TLC, R_f 0.22 (2:1 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.97$, 1.99, 2.00, 2.01 (4s, 12H, 4 OAc), 3.82 (dddd, 1H, $J_{5',6''} = 2.3$, $J_{5',6''} = 4.6$, $J_{5',4'} = 9.2$ Hz, H-5′), 4.11 (dd, 1H, $J_{6',5'} = 2.3$, $J_{6',6''} = 12.2$ Hz, H-6″), 4.25 (dd, 1H, $J_{6'',5'} = 4.6$, $J_{6'',6'} = 12.2$ Hz, H-6″), 5.08 (t, 1H, $J_{4',3'} = 9.9$ Hz, H-4′), 5.12 (dd, 1H, $J_{2',1'} = 10.7$, $J_{2',3'} = 9.2$ Hz, H-2′), 5.25 (t, 1H, $J_{3',2'} = J_{2',3'} = 9.2$ Hz, H-3′), 5.54 (d, 1H, $J_{1',2'} = 10.7$ Hz, H-1′), 6.47–6.54 (m, 2H, Ar-H), 7.05 (d, 1H, $J = 6.9$, Ar-H), 7.17–7.21 (m, 3H, Ar-H), 7.54–7.62 (m, 3H, Ar-H), 11.61 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (125.7 MHz, $CDCl_3$) $\delta = 20.6$, 20.7 (4 CH_3CO), 61.6 (C-6′), 68.1 (C-4′), 69.9 (C-2′), 73.7 (C-3′), 76.3 (C-5′), 83.8 (C-1′), 110.0, 118.1, 118.7, 125.6, 127.8, 130.5, 130.9, 131.7, 134.0 (Ar-C), 169.5, 169.5, 170.0, 170.6 (CH_3CO); Anal. Calcd for $C_{28}H_{29}N_3O_{10}S$ (599.61): C, 56.09; H, 4.87; N, 7.01. Found: C, 56.00; H, 5.06; N, 6.93.

4,5-Diphenyl-3-(2′-acetamido-2′-deoxy-3′,4′,6′-tri-O-acetyl-β-D-glucopyranosyl-thio)-4H-1,2,4-triazole (14). Colorless crystals; mp: 152–154°C; TLC, R_f 0.67 (1:1 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.97$, 1.99, 2.02, 2.04 (4s, 12H, 3 OAc, NAc), 3.82–3.90 (m, 1H, H-5′), 4.09 (dd, 1H, $J_{6',5'} = 2.3$, $J_{6',6''} = 13.0$ Hz, H-6′), 4.23 (dd, 1H, $J_{6'',5'} = 5.3$, $J_{6',6''} = 13.0$ Hz, H-6″), 4.27 (ddd, 1H, $J_{2',1'} = 10.7$, $J_{2',3'} = 9.2$, $J_{2',NH} = 8.4$ Hz, H-2′), 5.14 (dd, 1H, $J_{3',2'} = 9.2$, $J_{3',4'} = 9.9$ Hz, H-3′), 5.29 (t, 1H, $J_{4',3'} = J_{4',5'} = 9.2$ Hz, H-4′), 5.58 (d, 1H, $J_{1',2'} = 10.7$ Hz, H-1′), 7.01 (d, 1H, $J_{NH,2'} = 8.4$ Hz, D_2O exchangeable, NHAc), 7.02 (d, 2H, $J = 6.9$, Ar-H), 7.25–7.28 (m, 2H, Ar-H), 7.33–7.39 (m, 3H, Ar), 7.45–7.53 (m, 3H, Ar-H); Anal. Calcd for $C_{28}H_{30}N_4O_8S$ (582.63): C, 57.72; H, 5.19; N, 9.62. Found: C, 57.31; H, 5.02; N, 9.43.

5-(2-Hydroxyphenyl)-4-phenyl-3-(2′-acetamido-2′-deoxy-3′,4′,6′-tri-O-acetyl-β-D-glucopyranosylthio)-4H-1,2,4-triazole (15). Colorless crystals; mp: 162–164°C; TLC, R_f 0.67 (1:1 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.95$, 1.97, 2.01, 2.02 (4s, 12H, 3 OAc, NAc), 3.80 (dddd, 1H, $J_{5',6''} = 2.3$, $J_{5',6'} = 5.3$, $J_{5',4'} = 9.9$ Hz, H-5′), 4.08 (dd, 1H, $J_{6'',5'} = 2.3$, $J_{6'',6'} = 12.2$ Hz, H-6′), 4.27 (dddd, 2H, $J_{6',5'} = 5.3$, $J_{6',6''} = 12.2$, $J_{2',1'} = 10.7$, $J_{2',3'} = 9.9$, $J_{2',NH} = 8.4$ Hz, H-6″, H-2′), 5.07 (t, 1H, $J_{4',3'} = J_{4',5'} = 9.9$ Hz, H-4′), 5.31 (t, 1H, $J_{3',2'} = J_{3',4'} = 9.9$ Hz, H-3′), 5.62 (d, 1H, $J_{1',2'} = 10.7$ Hz, H-1′), 6.45–6.57 (m, 3H, Ar-H), 6.98 (d, 1H, D_2O exchangeable, $J_{NH,2'} = 8.4$ Hz, NHAc), 7.14–7.17 (m, 1H, Ar-H), 7.33 (d, 2H, $J = 7.7$, Ar-H), 7.55–7.63 (m, 3H, Ar-H), 11.43 (s, 1H, D_2O exchangeable OH); ^{13}C NMR (125.7 MHz, $CDCl_3$) $\delta = 20.7$, 20.8, 23.2 (CH_3CO, NAc), 53.2 (C-2′), 61.8 (C-6′), 68.1 (C-4′), 73.6 (C-3′), 76.3 (C-5′), 85.4 (C-1′), 109.9, 117.9, 118.8, 125.8, 127.9, 130.5, 131.8, 133.9 (Ar-C), 169.4, 170.7, 171.1 (CH_3CO); Anal. Calcd for $C_{28}H_{30}N_4O_9S$ (598.63): C, 56.18; H, 5.05; N, 9.36. Found: C, 56.27; H, 5.35; N, 9.12.

4,5-Diphenyl-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosylthio)-4H-1,2,4-triazole (16). Colorless plates; mp 130–131°C; TLC, R_f 0.21 (2:1 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.97$, 1.99, 2.04, 2.12 (4s, 12H, 4 CH_3CO), 3.94–3.96 (m, 1H, H-5′), 4.08 (dd, 1H, $J_{6',5'} = 4.6$, $J_{6',6''} = 12.2$ Hz, H-6′), 4.25 (dd, 1H, $J_{6',5'} = 7.6$, $J_{6',6''} = 12.2$ Hz, H-6″), 5.11 (dd, 1H, $J_{3',2'} = 9.9$, $J_{3',4'} = 3.5$ Hz, H-3′), 5.64 (d, 1H, $J_{1',2'} = 9.9$ Hz, H-1′), 5.28 (t, 1H, $J_{2',1'} = J_{2',3'} = 9.9$ Hz, H-2′), 5.45 (d, 1H, $J_{4',3'} = 3.5$ Hz, H-4′), 7.03 (d, 2H, $J = 6.9$ Hz, Ar-H), 7.24–7.26 (m, 2H, Ar-H), 7.36–7.40 (m, 3H, Ar-H), 7.45–7.52 (m, 3H, Ar-H); Anal. Calcd for $C_{28}H_{29}N_3O_9S$ (583.61): C, 57.62; H, 5.01; N, 7.20. Found: C, 56.92; H, 4.63; N, 6.82.

5-(o-Hydroxyphenyl)-4-phenyl-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl-thio)-4H-1,2,4-triazole (17). Colorless crystals; mp 118–119°C, TLC, R_f 0.21 (2:1 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.76$, 1.95, 1.96, 2.12 (4s, 12H, 4 OAc), 3.94–3.96 (m, 1H, H-5′), 4.08 (dd, 1H, $J_{6',5'} = 4.6$,

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$J_{6',6''} = 12.2$ Hz, H-6′), 4.25 (dd, 1H, $J_{6'',5'} = 7.7$, $J_{6'',6'} = 12.2$ Hz, H-6″), 4.82 (d, 1H, $J_{1',2'} = 9.9$ Hz, H-1′), 5.05 (dd, 1H, $J_{3',4'} = 3.1$, $J_{3',2'} = 9.9$ Hz, H-3′), 5.26 (t, 1H, $J_{2',1'} = J_{2',3'} = 9.9$ Hz, H-2′), 5.41 (d, 1H, $J_{4',3'} = 3.1$ Hz, H-4′), 7.23–7.37 (m, 5 H, Ar-H), 7.46 (d, 2H, $J = 7.7$ Hz, Ar-H), 7.58 (d, 2H, $J = 7.7$ Hz, Ar-H), 10.12 (s, 1H, D_2O exchangeable, OH); Anal. Calcd for $C_{28}H_{29}N_3O_{10}S$ (599.61): C, 56.09; H, 4.87; N, 7.01. Found: C, 56.46; H, 5.09; N, 7.08.

Preparation of Alkylated Analogs 21–26; General Procedure

Conventional Method (CM)

To a solution of compounds **7** or **8** (1 mmol) in an ethanolic solution of sodium ethoxide prepared from sodium metal (0.0023 g) in ethanol (15 mL) was added hydroxyl alkylating agents **18**–**20**. The reaction mixture was heated for 2 to 4 h, concentrated, cooled, diluted with water, and left overnight. The precipitate was washed with water and recrystallized from ethanol.

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Microwave Method (MW)

To a solution of compounds **7** or**8** (0.33 mmol) in an ethanolic solution of sodium ethoxide prepared from sodium metal (0.76 mg) in ethanol (5 mL) in a closed Teflon vessel was irradiated by MW for 2 to 4 min. The reaction mixture was cooled and processed as described above to give the same products (Table 1).

4,5-Diphenyl-3-[(2-hydroxyeth-1-yl)thio]-4H-1,2,4-triazole (21). Colorless crystals; mp 152–153°C; ^{1}H NMR (DMSO-d_6) $\delta = 3.15$ (t, 2H, $J = 6.9$ Hz, SCH_2), 3.66 (m, 2H, CH_2O), 5.19 (bt, 1H, D_2O exchangeable, OH), 7.16–7.18 (m, 1H, Ar-H), 7.23–7.28 (m, 3H, Ar-H), 7.30–7.34 (m, 4 H, Ar-H), 7.40–7.42 (m, 2H, Ar-H); Anal. Calcd for $C_{16}H_{15}N_3OS$ (297.38): C, 64.62; H, 5.08; N, 14.13. Found: C, 64.90; H, 5.23; N, 14.39.

3-[(2-Hydroxyeth-1-yl)thio]-5-(o-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole (22). Colorless crystals; mp 160–161°C; ^{1}H NMR (DMSO-d_6) $\delta = 3.25$ (t, 2H, $J = 6.9$ Hz, SCH_2), 3.67 (q, 2H, $J = 4.5$, $J = 6.9$ Hz, CH_2O), 5.06 (t, 1H, $J = 6.1$, D_2O exchangeable, OH), 6.71–6.76 (m, 2H, Ar-H), 7.12 (d, 1H, $J = 9.2$, Ar-H), 7.17–7.21 (m, 1H, Ar-H), 7.26–7.28 (m, 2H, Ar-H), 7.42–7.43 (m, 3H, Ar-H), 10.19 (s, 1H, D_2O exchangeable, OH); Anal. Calcd for $C_{16}H_{15}N_3O_2S$ (313.38): C, 61.32; H, 4.82; N, 13.41. Found: C, 61.28; H, 4.63; N, 13.18.

3-[(3-Hydroxyprop-1-yl)thio]-4,5-diphenyl-4H-1,2,4-triazole (23). Colorless crystals; mp 148°C; ^{1}H NMR (DMSO-d_6) $\delta = 1.75$–1.79 (pentet, 2H, $J = 6.9$ Hz, $CH_2CH_2CH_2$), 3.16 (t, 2H, $J = 6.9$ Hz, SCH_2), 3.44 (q, 2H, $J = 5.4$, $J = 10.7$ Hz,

CH_2O), 4.57 (t, 1H, $J = 5.4$ Hz, D_2O exchangeable, OH), 7.28–7.31 (m, 3H, Ar-H), 7.35–7.37 (m, 3H, Ar-H), 7.50–7.51 (m, 4 H, Ar-H); Anal. Calcd for $C_{17}H_{17}N_3OS$ (311.40): C, 65.57; H, 5.50; N, 13.49. Found: C, 65.18; H, 5.23; N, 13.16.

3-[(3-Hydroxyprop-1-yl)thio]-5-(o-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole (24). Colorless crystals; mp 140–142°C; ^{1}H NMR (DMSO-d_6) $\delta = 1.78$–1.82 (pentet, 2H, $CH_2CH_2CH_2$), 3.16 (t, 2H, $J = 6.9$ Hz, SCH_2), 3.40–3.41 (m, under solvent peak 2H, CH_2O), 4.61 (t, 1H, $J = 4.6$ Hz, D_2O exchangeable, OH), 6.71–6.77 (m, 2H, Ar-H), 7.11 (d, 1H, $J = 7.7$, Ar-H), 7.17–7.20 (m, 1H, Ar-H), 7.26–7.28 (m, 2H, Ar-H), 7.42–7.43 (m, 3H, Ar-H), 10.21 (s, 1H, D_2O exchangeable, OH); Anal. Calcd for $C_{17}H_{17}N_3O_2S$ (327.40): C, 62.36; H, 5.23; N, 12.83. Found: C, 62.51; H, 5.47; N, 13.09.

3-[(2,3-Dihydroxyprop-1-yl)thio]-4,5-diphenyl-4H-1,2,4-triazole (25). Colorless crystals; mp 138–140°C; ^{1}H NMR (DMSO-d_6) $\delta = 3.15$ (dd, 1H, $J = 5.4$, $J = 6.9$, $J = 10.7$ Hz, SCH_2), 3.31 (dd, 1H, $J = 5.4$, $J = 10.7$ Hz, SCH_2), 3.32–3.41 (m, 2H, CH_2O), 3.68–3.73 (m, 1H, CHO), 4.75 (t, 1H, $J = 6.2$ Hz, D_2O exchangeable, OH), 5.11 (d, 1H, $J = 5.4$ Hz, D_2O exchangeable, OH), 7.28–7.38 (m, 7 H, Ar-H), 7.50–7.52 (m, 3H, Ar-H); Anal. Calcd for $C_{17}H_{17}N_3O_2S$ (327.40): C, 62.36; H, 5.23; N, 12.83. Found: C, 62.09; H, 5.49; N, 13.01.

3-[(2,3-Dihydroxyprop-1-yl)thio]-5-(o-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole (26). Colorless crystals; mp 122–123°C; ^{1}H NMR (DMSO-d_6) $\delta = 3.17$ (dd, 1H, $J = 6.9$, $J = 7.7$, $J = 10.7$ Hz, SCH_2), 3.32 (dd, 1H, $J = 5.4$, $J = 10.7$ Hz, SCH_2), 3.35–3.39 (m, 2H, CH_2O), 3.75 (ddd, 1H, $J = 5.4$, $J = 6.1$, $J = 10.7$ Hz, CHO), 4.75 (d, 1H, $J = 5.4$ Hz, D_2O exchangeable, OH), 5.12 (d, 1H, $J = 5.4$ Hz, D_2O exchangeable, OH), 6.71–6.77 (m, 2H, Ar-H), 7.11 (d, 1H, $J = 7.7$, Ar-H), 7.17–7.20 (m, 1H, Ar-H), 7.28–7.30 (m, 2H, Ar-H), 7.43–7.44 (m, 3H, Ar-H), 10.20 (s, 1H, D_2O exchangeable, OH); Anal. Calcd for $C_{17}H_{17}N_3O_3S$ (343.40): C, 59.46; H, 4.99; N, 12.24. Found: C, 59.73H, 5.13; N, 12.13.

Action of tosyl chloride in pyridine on 3-[(2,3-Dihydroxyprop-1-yl)thio]-5-(o-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole (26). A cold solution of **26** (1 mmol) in pyridine (5 mL) was treated with *p*-toluenesulfonyl chloride (1.1 mmol) during 1 h at 0°C. The reaction mixture was then heated under reflux for 6 h. After cooling, the reaction mixture was poured onto ice-cold water (15 mL). The resulting solution was extracted with methylene chloride (3×20 mL), washed with water, and dried over anhydrous Na_2SO_4. It was evaporated under reduced pressure and then the resulting solid was recrystallized with ethanol to give 5-(*o*-hydroxyphenyl)-4-phenyl-1,2,4-triazol-3-one**(29)**; mp 251–252°C. ^{1}H NMR (DMSO-d_6) $\delta = 6.56$–6.64

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(m, 2H, Ar-H), 7.02–7.04 (m, 1H, Ar-H), 7.21–7.26 (m, 2H, Ar-H), 7.34–7.37 (m, 2H, Ar-H), 7.55–7.56 (m, 2H, Ar-H), 9.93 (s, 1H, D_2O exchangeable NH), 11.21 (s, 1H, D_2O exchangeable OH); Anal. Calcd for $C_{14}H_{11}N_3O_2$ (253.26): C, 66.40; H, 4.38; N, 16.59. Found: C, 66.11; H, 4.23; N, 16.45.

Oxidation of 2-[(2,3-dihydroxyprop-1-yl)thio]-5-(o-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole with sodium metaperiodate. To a solution of **26** (1 mmol) in distilled water (5 mL), a solution of sodium metaperiodate (1.5 mmol) in distilled water (5 mL) was added. The reaction mixture was stirred for 3 h, and then left for overnight. The product was recrystallized from ethanol to give **8**; mp: 271°C; (Lit[27] mp 273°C).

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