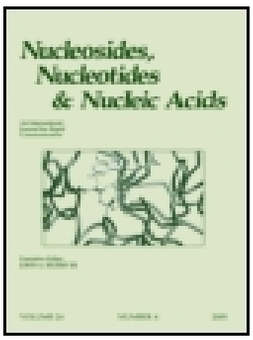

Nucleosides, Nucleotides and Nucleic Acids

ISSN: 1525-7770 (Print) 1532-2335 (Online) Journal homepage: http://www.tandfonline.com/loi/lncn20

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To cite this article: Galal H. Elgemeie, Mamdouh A. Abu-Zaied & Galal A. Nawwar (2018): First novel synthesis of triazole thioglycosides as ribavirin analogues, Nucleosides, Nucleotides and Nucleic Acids, DOI: 10.1080/15257770.2017.1423079

To link to this article: https://doi.org/10.1080/15257770.2017.1423079

NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS
2018, VOL. 0, NO. 0, 1–12
https://doi.org/10.1080/15257770.2017.1423079

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First novel synthesis of triazole thioglycosides as ribavirin analogues

Galal H. Elgemeie[a], Mamdouh A. Abu-Zaied[b], and Galal A. Nawwar[b]

[a]Chemistry Department, Faculty of Science, Helwan University, Helwan, Cairo, Egypt; [b]Green Chemistry Department, National Research Centre, El Bohouth Street, Dokki, Giza, Egypt

ABSTRACT

This study reports a novel and efficient method for the synthesis of the first reported novel class of triazole thioglycosides. These series of compounds were designed through the reaction of potassium cyanocarbonimidodithioate **2** with hydrazine derivatives **3a-d** in EtOH at room temperature to give the corresponding potassium 5-amino-1*H*-1,2,4-triazole-3-thiolates **4a-d**. The latter compounds were treated with tetra-*O*-acetyl-α-D-glucopyranosyl bromide **6a** and tetra-*O*-acetyl-α-D-galactopyranosyl bromide **6b** in DMF at room temperature to give in high yields the corresponding triazole thioglycosides **7a-h**. Treatment of triazole salts **4a–d** with hydrochloric acid afforded the corresponding 3-mercaptotriazoles **5a-d**. Compounds **5a-d** were then reacted with bromoperacetylated sugars **6a,b** in sodium hydride-DMF at ambient temperature to afford the thioglycosyl compounds **7a-h**. Ammonolysis of the triazole thioglycosides **7a-h** afforded the corresponding free thioglycosides **8a-h**. The scope and limitation of the method is demonstrated. The structure of the reaction products was confirmed on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR, MS and ^{13}C NMR).

ARTICLE HISTORY
Received 23 May 2017
Accepted 21 December 2017

KEYWORDS
Triazole thioglycosides; ribavirin analogues; Hepatitis C virus (HCV); potassium cyanocarbonimidodithioate; hetrocyclic thioglycosides

Introduction

Hepatitis C virus (HCV) incurs a major disease burden worldwide. Ribavirin is a triazole nucleoside approved for HCV treatment and is a main member in successful therapeutic protocols.[1] Ribavirin can cause a possible dangerous anemia and can cause substantial teratogenic effects, including possible birth defects and death (Figure 1).[2] Pregnant women should not use ribavirin during pregnancy.[3] Many other negative but less serious effects have been noticed with ribavirin like nausea, itching, dermatitis and fatigue. In view of the facts mentioned, design and synthesis of ribavirin analogues as bioactive lead compounds will continue to be explored.[4] As a part of our current project aimed towards examining synthetic methods for preparation of *S*-glycosylated derivatives of heterocyclic nitrogen bases, we have recently reported the synthesis and antiviral activity of many

CONTACT Galal H. Elgemeie elgemeie@yahoo.com Chemistry Department, Faculty of Science, Helwan University, Helwan, Cairo, Egypt.

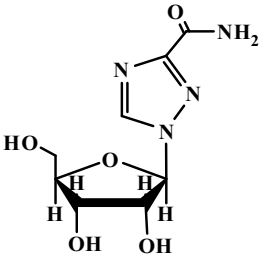
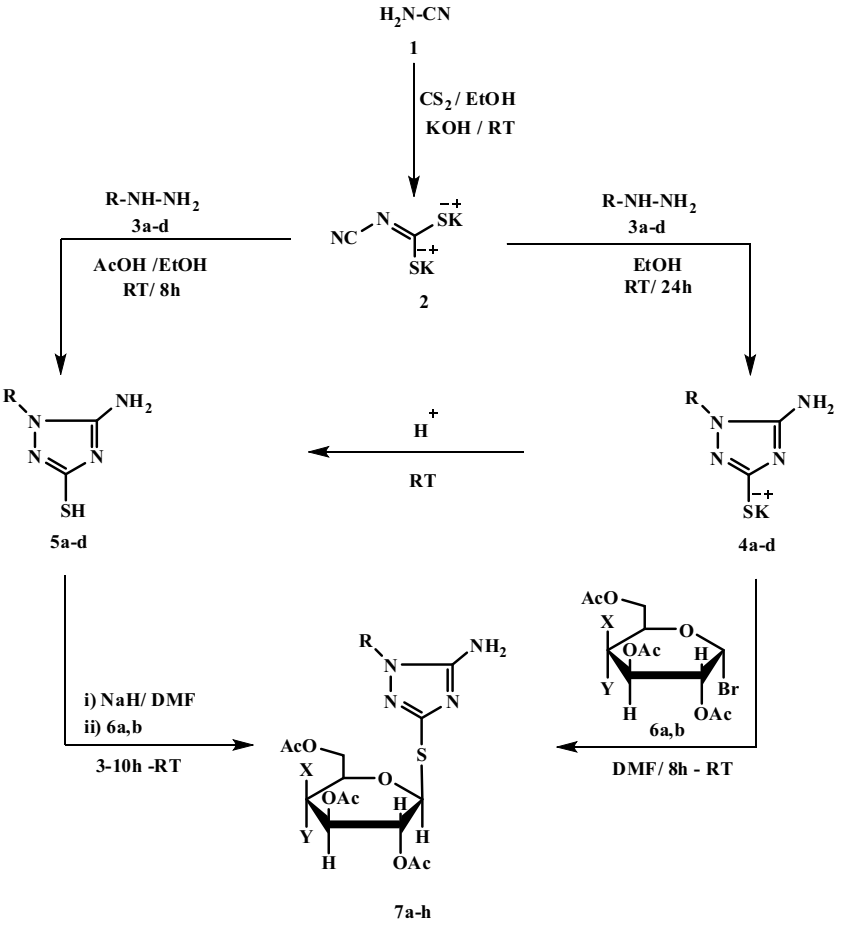


Figure 1. Structure of ribavirin.

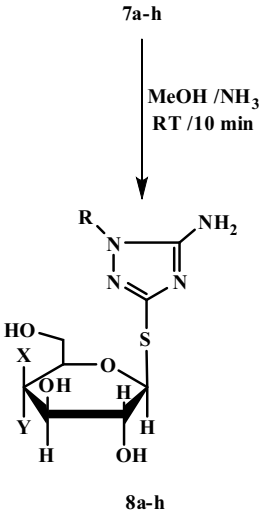
novel heterocyclic *S*-glycosides that have interesting cytotoxic activity, including pyridine *S*-glcosides,[5,6] pyrimidine *S*-glycosides,[7,8] imidazole *S*-glycosides,[9] oxadiazole *S*-glycosides,[10] thiophene *S*-glycosides,[11] quinoline *S*-glycosides,[12] thienopyrazole *S*-glycosides[13] and purine *S*-glycosides.[14,15] We have mentioned in previous research that the dihydropyridine thioglycoside compounds have a strong activity against cancer cells.[16] In the light of these results and other previous researches,[17-19] the aim of this research is to design, synthesize and study the biological activity of triazole thioglycosides carrying carbohydrate residues through *S*-glycosidic bond formation. The prepared triazole thioglycosides are similar to the known drug ribavirin, except that the glycosylation is on the exocyclic sulfur atom and is not on ring nitrogen, and there is a substituted amino on ring triazole while it is carboxamide in the drug ribavirin. To our knowledge, this is the first method that is mentioned for the synthesis of triazole thioglycosides.

Results and discussion

The synthesis was initiated by the condensation of cyanamide **1** and carbon disulfide in ethanolic potassium hydroxide in a simple one-step protocol to give the potassium cyanocarbonimidodithioate **2** (Scheme 1). Compound **2** is readily reacted with one equivalent of hydrazine derivatives **3a-d** in ethanol at room temperature for 24 hours to give the corresponding potassium 5-amino-1*H*-1,2,4-triazole-3-thiolate derivatives **4a–d** in good yields. Acidification of the latter has resulted in the formation of the corresponding 3-mercaptotriazoles **5a-d**. Compounds **4a–d** undergoes reaction with tetra-*O*-acetyl-α-D-glucopyranosyl bromide **6a** and tetra-*O*-acetyl-α-D-galactopyranosyl bromide **6b** in DMF at ambient temperature to give in excellent yields the corresponding triazole *S*-glycosides **7a-h**. It has been confirmed that the *cis*-(α) sugars reacted through an SN^2 reaction mechanism to give the β-glycoside reaction products.[20] The structures of **7a-h** were proved according to their spectral data (IR,^{13}C NMR, ^{1}H NMR). For example, the anomeric proton in the ^{1}H NMR spectrum for **7a** appeared as a doublet at δ 5.62–5.63 ppm with a 10.7 Hz spin-spin coupling constant indicating the β-configuration. The other glucose protons appeared at δ 3.96–5.14 ppm. Compounds **7a–h** can also be prepared by reaction of the triazole-3-thiol derivatives **5a-d** with halo sugars **6a,b** in DMF-sodium hydride at room temperature. The thioglycosides **7a-h** reacted with MeOH-NH_3 at ambient temperature to give the deprotected thioglycoside derivatives **8a-h** in good yields (Schemes 2 and 3). The structures of **8a-h** were proved based on spectral data. Thus,



Scheme 1. Synthetic pathway for triazole thioglycosides 7a-h.



Scheme 2. Synthetic pathway for triazole thioglycosides 8a-h.

3,4,5	R
a	H
b	C_6H_5
c	4-NO_2-C_6H_4
d	2,4-di NO_2-C_6H_3

7	R	X	Y	7	R	X	Y
a	H	H	OAc	e	H	OAc	H
b	C_6H_5	H	OAc	f	C_6H_5	OAc	H
c	4-NO_2-C_6H_4	H	OAc	g	4-NO_2-C_6H_4	OAc	H
d	2,4-di NO_2-C_6H_3	H	OAc	h	2,4-di- NO_2-C_6H_3	OAc	H

8	R	X	Y	8	R	X	Y
a	H	H	OH	e	H	OH	H
b	C_6H_5	H	OH	f	C_6H_5	OH	H
c	4-NO_2-C_6H_4	H	OH	g	4-NO_2-C_6H_4	OH	H
d	2,4-di NO_2-C_6H_3	H	OH	h	2,4-di NO_2-C_6H_3	OH	H

Scheme 3. List of synthesized derivatives 3,4,5a-d; 7a-h; 8a-h.

the anomeric proton in the ^{1}H NMR spectrum for **8a** appeared as a doublet with $J_{1,2} = 9.6$ Hz at δ 4.62–4.63, confirming the presence of only the β-*D*-configuration.

In conclusion, a novel synthesis of an interesting new class of triazole thioglycosides is reported. The results represent a new, simple and economically effective method for the synthesis of ribavirin drug analogues. The simple and ambient temperature reaction conditions, clean reaction products, and availability of starting materials make this approach innovative and useful to the present methods for the formation of triazole glycosides. Further investigations on the use of this method for the preparation of other biologically interesting glycosides will be investigated. The prepared triazole thioglycosides are promising as good starting materials for the preparation of other interesting carbohydrate compounds.

Experimental

All melting points were measured on a Gallenkamp melting point apparatus. The ^{1}H NMR and ^{13}C NMR spectra were measured on a Jeol-500 MHz spectrometer in DMSO-d_6 or $CDCl_3$ using $Si(CH_3)_4$ as an internal standard at the National Research Centre, Cairo, Egypt. Elemental analyses were carried out at the Microanalytical unit, Faculty of Science, Cairo University. Progress of the reactions was monitored by TLC using aluminum sheets coated with silica gel F254 (Merck). Viewing under a short-wavelength UV lamp effected detection. Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **6a** and tetra-*O*-acetyl-α-D-galactopyranosyl bromide **6b** were prepared according to literature procedures.[21] Compound **4a** was previously reported.[22]

General procedure for the synthesis of (4a-d)

To potassium cyanocarbonimidodithioate **2** (10 mmol) in absolute ethanol (20 mL) was added hydrazine derivatives **3a-d** (10 mmol). The reaction mixture was stirred at room temperature until completion (TLC, 24 h). A precipitate was formed was filtered off and recrystallized from appropriate solvent to give compounds **4a-d**.

Potassium 5-amino-1-phenyl-1H-1,2,4-triazole-3-thiolate (4b)

Yellow solid; (EtOH); yield (84%); mp >300°C; IR (KBr, cm^{-1}) υ 3410,3382 (NH_2), 3039 (CH aromatic). $C_8H_7KN_4S$ (230.33).

Potassium 5-amino-1-(4-nitrophenyl)-1H-1,2,4-triazole-3-thiolate (4c)

Yellow solid; (EtOH); yield (82%); mp >300°C; IR (KBr, cm^{-1}) υ 3368,3345 (NH_2), 3036 (CH aromatic). $C_8H_6KN_5O_2S$ (275.33).

Potassium 5-amino-1-(2,4-dinitrophenyl)-1H-1,2,4-triazole-3-thiolate (4d)

White solid; (EtOH); yield (82%); mp >300°C; IR (KBr, cm^{-1}) υ 3379,3346 (NH_2), 3046 (CH aromatic). $C_8H_5KN_6O_4S$ (320.33).

General procedure for the synthesis of (5a-d)

To a solution of compound **4a-d** (10 mmol) in 20 ml water, drops of hydrochloric acid (36%) was dropped at room temperature (25°C) till just neutral. After an additional stirring, a precipitate thus formed was filtered off and crystallized from methanol to give **5a-d** as yellow solid.

5-Amino-1H-1,2,4-triazole-3-thiol (5a)

Yellow solid; (EtOH); yield (95%); mp 254–255°C; IR (KBr, cm^{-1}) υ 3388 (NH_2), 3364 (NH), 1609 (C=N); ^{1}H NMR (500 MHz, DMSO): δ 6.83 (s, D_2O exch., 2H, NH_2), 10.44 (s, D_2O exch., 1H, NH), 12.89 (s, D_2O exch., 1H, SH). Anal. Calcd. For. $C_2H_4N_4S$ (116.14): C, 20.68; H, 3.47; N, 48.24; S, 27.61. Found: C, 20.54; H, 3.35; N, 48.16; S, 27.54%.

5-Amino-1-phenyl-1H-1,2,4-triazole-3-thiol (5b)

Yellow solid; (EtOH); yield (77%); mp 240–242°C; IR (KBr, cm^{-1}) υ 3384, 3363 (NH_2), 3034 (CH aromatic); ^{1}H NMR (500 MHz, DMSO): δ 6.74 (s, D_2O exch., 2H, NH_2), 7.35-7.76 (m, 5H, C_6H_5), 13.45 (s, D_2O exch., 1H, SH); ^{13}C NMR: δ 123.66 (2C, Ar-C), 135.54 (3C, Ar-C), 143.67 (Ar-C), 158.35 (C-3), 158.63 (C-5). Anal. Calcd. For. $C_8H_8N_4S$ (192.24): C, 49.98; H, 4.19; N, 29.14; S, 16.68. Found: C, 49.86; H, 4.11; N, 29.10; S, 16.56%.

5-Amino-1-(4-nitrophenyl)-1H-1,2,4-triazole-3-thiol (5c)

Yellow solid; (EtOH); yield (77%); mp 248–249°C; IR (KBr, cm^{-1}) υ 3389, 3355 (NH_2), 3076 (CH aromatic), 1604 (C=N); ^{1}H NMR (500 MHz, DMSO): 6.68 (s,

D_2O exch., 2H, NH_2), 8.51-8.64 (m, 4H, C_6H_4), 13.22 (s, D_2O exch., 1H, SH). Anal. Calcd. For. $C_8H_7N_5O_2S$ (237.24): C, 40.50; H, 2.97; N, 29.52; S, 13.52. Found: C, 40.46; H, 2.88; N, 29.43; S, 13.46%.

5-Amino-1-(2,4-dinitrophenyl)-1H-1,2,4-triazole-3-thiol (5d)

Yellow solid; (EtOH); yield (84%); mp 226–228°C; IR (KBr, cm^{-1}) υ 3369, 3346 (NH_2), 3084 (CH aromatic), 1602 (C=N); ^{1}H NMR (500 MHz, DMSO): δ 6.68 (s, D_2O exch., 2H, NH_2), 8.26-8.97 (m, 3H, C_6H_3), 13.24 (s, 1H, SH); ^{13}C NMR: δ 123.11 (Ar-C), 126.82 (Ar-C), 129.44 (Ar-C), 137.25 (Ar-C), 151.36 (Ar-C), 152.41 (Ar-C), 156.95 (C-3), 169.13 (C-5). Anal. Calcd. For. $C_8H_6N_6O_4S$ (282.24): C, 34.04; H, 2.14; N, 29.78; S, 11.36. Found: C, 34.01; H, 2.10; N, 29.66; S, 11.24%.

General procedure for the synthesis of (7a-h)

Methode A

To a solution of **4a-d** (10 mmol) in dry DMF (20 ml) a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco or (galacto) pyronosyl bromide **6a**,**b** (10 mmol) was dropped within 30 min. Stirring was continued for 8h. After completion, the reaction mixture was poured into ice water and the resulting precipitate was collected by filtration, dried and recrystallized by using an appropriate solvent to give compounds **7a-h.**

Methode B

To a solution of **5a-d** (10 mmol) in dry DMF (20 ml), NaH (15 mmol) was added portionwise through 15 min and the solution stirred at room temperature for another 30 min. Then a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyronosyl bromide **6a**,**b** in DMF (10 mmol) was dropped within 30 min and the reaction mixture was stirred at room temperature until completion (TLC, 3–10 h). After completion, the reaction mixture was poured on ice water and the resulting precipitate was collected by filtration, dried and recrystaiized by using an appropriate solvent to give compounds **7a-h.**

3-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylthio)-1H-1,2,4-triazol-5-amine (7a)

White solid; (EtOH); yield (method A: 76%, method B: 65%); mp 244–246°C; IR (KBr, cm^{-1}) υ 3381 (NH_2), 3365 (NH), 2942 (CH), 1752 (C=O), 1607 (C=N); ^{1}H NMR (500 MHz, DMSO): δ 1.99, 2.01, 2.02, 2.13 (4s, 12H, 4xOAc), 3.96-3.98 (m, 2H, 2H-6′), 4.46-4.49 (m, 1H, H-5′), 4.58 (t, 1H, $J_{4'\text{-}3'} = 9.1$ Hz, $J_{4'\text{-}5'} = 6.9$ Hz, H-4′), 4.66 (t, 1H, $J_{3'\text{-}2'} = 9.7$ Hz, $J_{3'\text{-}4'} = 9.1$ Hz, H-3′), 5.14 (t, 1H, $J_{2'\text{-}1'} = 10.7$ Hz, $J_{2'\text{-}3'} = 9.7$ Hz, H-2′), 5.63 (d, 1H, $J_{1'\text{-}2'} = 10.7$ Hz, H-1′), 6.24 (s, D_2O exch., 2H, NH_2), 10.53 (s, D_2O exch., 1H, NH); ^{13}C NMR: δ 22.44 (4xOAc), 62.54 (C-6′), 68.78 (C-5′), 69.46 (C-4′), 72.82 (C-3′), 75.33 (C-2′), 82.21 (C-1′), 160.24 (C-5), 163.11 (C-3), 174.45 (4C=O). Anal. Calcd. For $C_{16}H_{22}N_4O_9S$ (446.43): C, 43.05; H, 4.97; N, 12.55; S, 7.18. Found: C, 43.01; H, 4.86; N, 12.48; S, 7.12%.

3-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylthio)-1-phenyl)-1H-1,2,4-triazol-5-amine (7b)

White solid; (EtOH); yield (method A: 77%, method B: 63%); mp 235–237°C; IR (KBr, cm^{-1}) υ 3386, 3364 (NH_2), 3053 (CH aromatic), 2965 (CH), 1749 (C=O); ^{1}H NMR (500 MHz, DMSO): δ 1.99, 2.05, 2.12, 2.14 (4s, 12H, 4xOAc), 3.97-4.12 (m, 2H, 2H-6′), 4.22-4.36 (m, 1H, H-5′), 4.35 (t, 1H, 1H, $J_{4'\text{-}3'}$ = 8.9 Hz, $J_{4'\text{-}5'}$ = 6.4 Hz, H-4′), 4.48 (t, 1H, $J_{3'\text{-}2'}$ = 9.4 Hz, $J_{3'\text{-}4'}$ = 8.9 Hz, H-3′), 4.64 (t, 1H, $J_{2'\text{-}1'}$ = 10.8 Hz, $J_{2'\text{-}3'}$ = 9.4 Hz, H-2′), 5.49 (d, 1H, $J_{1'\text{-}2'}$ = 10.8 Hz, H-1′), 6.67 (s, D_2O exch., 2H, NH_2), 7.34–7.62 (m, 5H, C_6 H_5); ^{13}C NMR: δ 22.46 (4xOAc), 62.54 (C-6′), 69.25 (C-5′), 70.32 (C-4′), 72.36 (C-3′), 74.53 (C-2′), 82.68 (C-1′), 125.24 (2C, Ar-C), 134.46 (3C, Ar-C), 141.31 (Ar-C), 159.11 (C-5), 165.28 (C-3), 174.41 (4C=O). Anal. Calcd. For $C_{22}H_{26}N_4O_9S$ (522.53): C, 50.57; H, 5.02; N, 10.72; S, 6.14. Found: C, 50.51; H, 5.00; N, 10.54; S, 6.10%.

3-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylthio)-1-(4-nitrophenyl)-1H-1,2,4-triazol-5-amine (7c)

White solid; (EtOH); yield (method A: 82%, method B: 75%); mp 216–218°C; IR (KBr, cm^{-1}) υ 3390, 3377 (NH_2), 3033(CH aromatic), 2956 (CH), 1751 (C=O), 1608 (C=N); ^{1}H NMR (500 MHz, DMSO): δ 1.99, 2.04, 2.08, 2.10 (4s, 12H, 4xOAc), 4.02-4.18 (m, 2H, 2H-6′), 4.31-4.42 (m, 1H, H-5′), 4.43 (t, 1H, 1H, $J_{4'\text{-}3'}$ = 8.9 Hz, $J_{4'\text{-}5'}$ = 6.9 Hz, H-4′), 4.62 (t, 1H, $J_{3'\text{-}2'}$ = 9.4 Hz, $J_{3'\text{-}4'}$ = 8.9 Hz, H-3′), 4.72 (t, 1H, $J_{2'\text{-}1'}$ = 10.7 Hz, $J_{2'\text{-}3'}$ = 9.4 Hz, H-2′), 5.45 (d,1H, $J_{1'\text{-}2'}$ = 10.7 Hz, H-1′), 6.56 (s, D_2O exch., 2H, NH_2), 8.27–8.65 (m, 4H, C_6 H_4); ^{13}C NMR: δ 21.46 (4xOAc), 62.38 (C-6′), 69.54 (C-5′), 69.85 (C-4′), 73.61 (C-3′), 74.55 (C-2′), 83.34 (C-1′), 122.84 (2C, Ar-C), 132.53 (2C, Ar-C), 152.63 (Ar-C), 158.61 (Ar-C), 158.12 (C-5), 164.26 (C-3), 172.51 (4C=O). Anal. Calcd. For $C_{22}H_{25}N_5O_{11}S$ (567.53): C, 46.56; H, 4.44; N, 12.34; S, 5.65. Found: C, 46.49; H, 4.36; N, 12.25; S, 5.60%.

1-(2,4-Dinitrophenyl)-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-1H-1,2,4-triazol-5-amine (7d)

White solid; (EtOH); yield (method A 80%, method B: 75%); mp 208–210°C; ^{1}H NMR (500 MHz, DMSO): δ 1.99, 2.02, 2.08, 2.11 (4s, 12H, 4xOAc), 4.02-4.13 (m, 2H, 2H-6′), 4.28-4.36 (m, 1H, H-5′), 4.56 (t, 1H, 1H, $J_{4'\text{-}3'}$ = 9.1 Hz, $J_{4'\text{-}5'}$ = 6.6 Hz, H-4′), 4.64 (t, 1H, $J_{3'\text{-}2'}$ = 9.3 Hz, $J_{3'\text{-}4'}$ = 9.1 Hz, H-3′), 4.82 (t, 1H, $J_{2'\text{-}1'}$ = 10.2 Hz, $J_{2'\text{-}3'}$ = 9.3 Hz, H-2′), 5.62 (d, 1H, $J_{1'\text{-}2'}$ = 10.2 Hz, H-1′), 6.48 (s, D_2O exch., 2H, NH_2), 8.33–8.89 (m, 3H, C_6 H_3); ^{13}C NMR: δ 21.44 (4xOAc), 62.11 (C-6′), 68.26 (C-5′), 69.76 (C-4′), 70.12 (C-3′), 71.86 (C-2′), 83.47 (C-1′), 122.25 (Ar-C), 130.47 (Ar-C), 132.74 (Ar-C), 139.62 (Ar-C), 151.48 (Ar-C), 152.61 (Ar-C), 158.63 (C-5), 165.26 (C-3), 174.16 (4C=O). Anal. Calcd. For $C_{22}H_{24}N_6O_{13}S$ (612.52): C, 43.14; H, 3.95; N, 13.72; S, 5.23. Found: C, 43.10; H, 3.80; N, 13.64; S, 5.13%.

3-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylthio)-1H-1,2,4-triazol-5-amine (7e)

White solid; (EtOH); yield (method A: 79%, method B: 70%); mp 252–254°C; ^{1}H NMR (500 MHz, DMSO): δ 2.02, 2.04, 2.09, 2.11 (4s, 12H, 4xOAc), 3.99-4.03

(m, 2H, 2H-6′), 4.12-4.27 (m, 1H, H-5′), 4.34 (t, 1H, 1H, $J_{4'\text{-}3'}$ = 2.4 Hz, $J_{4'\text{-}5'}$ = 3.1 Hz, H-4′), 4.48 (t, 1H, $J_{3'\text{-}2'}$ = 9.2 Hz, $J_{3'\text{-}4'}$ = 2.4 Hz, H-3′), 5.08 (t, 1H, $J_{2'\text{-}1'}$ = 10.3 Hz, $J_{2'\text{-}3'}$ = 9.2 Hz, H-2′), 5.43 (d, 1H, $J_{1'\text{-}2'}$ = 10.3 Hz, H-1′), 6.63 (s, D_2O exch., 2H, NH_2), 10.43 (s, D_2O exch., 1H, NH); ^{13}C NMR: δ 21.64 (4xOAc), 62.66 (C-6′), 67.62 (C-5′), 69.11 (C-4′), 70.54 (C-3′), 72.42 (C-2′), 84.13 (C-1′), 161.18 (C-5), 164.34 (C-3), 173.62 (4C=O). Anal. Calcd. For $C_{16}H_{22}N_4O_9S$ (446.43): C, 43.05; H, 4.97; N, 12.55; S, 7.18. Found: C, 43.01; H, 4.86; N, 12.48; S, 7.12%.

3-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosylthio)-1-phenyl)-1H-1,2,4-triazol-5-amine (7f)

White solid; (EtOH); yield (method A: 75%, method B: 67%); mp 248–250°C; IR (KBr, cm^{-1}) υ 3392, 3365 (NH_2), 3048 (CH aromatic), 2955 (CH), 1744 (C=O); ^1H NMR (500 MHz, DMSO): δ 1.99, 2.05, 2.08, 2.17 (4s, 12H, 4xOAc), 3.98-4.01 (m, 2H, 2H-6′), 4.09-4.25 (m, 1H, H-5′), 4.28 (t, 1H, $J_{4'\text{-}3'}$ = 2.6 Hz, $J_{4'\text{-}5'}$ = 3.2 Hz, H-4′), 4.42 (t, 1H, $J_{3'\text{-}2'}$ = 9.0 Hz, $J_{3'\text{-}4'}$ = 2.6 Hz, H-3′), 4.55 (t, 1H, $J_{2'\text{-}1'}$ = 10.4 Hz, $J_{2'\text{-}3'}$ = 9.0 Hz, H-2′), 5.37 (d, 1H, $J_{1'\text{-}2'}$ = 10.4 Hz, H-1′), 6.59 (s, D_2O exch., 2H, NH_2), 7.32–7.74 (m, 5H, C_6H_5); ^{13}C NMR: δ 22.26 (4xOAc), 62.64 (C-6′), 69.18 (C-5′), 71.81 (C-4′), 73.42 (C-3′), 74.69 (C-2′), 83.86 (C-1′), 123.33 (2C, Ar-C), 134.64 (3C, Ar-C), 143.41(Ar-C), 158.26 (C-5), 164.56 (C3), 172.68 (4C=O). Anal. Calcd. For $C_{22}H_{26}N_4O_9S$ (522.53): C, 50.57; H, 5.02; N, 10.72; S, 6.14. Found: C, 50.51; H, 5.00; N, 10.54; S, 6.10%.

3-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosylthio)-1-(4-nitrophenyl)-1H-1,2,4-triazol-5-amine (7g)

White solid; (EtOH); yield (method A: 80%, method B: 75%); mp 238–240°C; IR (KBr, cm^{-1}) υ 3387, 3365 (NH_2), 2936 (CH aromatic), 1756 (C=O), 1596 (C=N); ^1H NMR (500 MHz, DMSO): δ 1.98, 1.99, 2.06, 2.12 (4s, 12H, 4xOAc), 4.24-4.31 (m, 2H, 2H-6′), 4.36-4.52 (m, 1H, H-5′), 4.54 (t, 1H, $J_{4'\text{-}3'}$ = 2.8 Hz, $J_{4'\text{-}5'}$ = 2.6 Hz, H-4′), 4.58 (t, 1H, $J_{3'\text{-}2'}$ = 9.3 Hz, $J_{3'\text{-}4'}$ = 2.8 Hz, H-3′), 4.63 (t, 1H, $J_{2'\text{-}1'}$ = 10.6 Hz, $J_{2'\text{-}3'}$ = 9.3 Hz, H-2′), 5.39 (d, 1H, $J_{1'\text{-}2'}$ = 10.6 Hz, H-1′), 6.46 (s, D_2O exch., 2H, NH_2), 8.35–8.78 (m, 4H, C_6H_4); ^{13}C NMR: δ 22.24 (4xOAc), 62.56 (C-6′), 68.84 (C-5′), 70.35 (C-4′), 72.84 (C-3′), 74.61 (C-2′), 84.52 (C-1′), 123.64 (2C, Ar-C), 130.36 (2C, Ar-C), 148.52 (Ar-C), 155.74 (Ar-C), 159.26 (C-5), 165.42 (C-3), 172.66(4C=O). Anal. Calcd. For $C_{22}H_{25}N_5O_{11}S$ (567.53): C, 46.56; H, 4.44; N, 12.34; S, 5.65. Found: C, 46.49; H, 4.36; N, 12.25; S, 5.60%.

1-(2,4-Dinitrophenyl)-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosylthio)-1H-1,2,4-triazol-5-amine (7h)

White solid; (EtOH); yield (method A: 84%, method B: 75%); mp 242–244°C; ^1H NMR (500 MHz, DMSO): δ 1.98, 1.99, 2.00, 2.02 (4s, 12H, 4xOAc), 4.24-4.31 (m, 2H, 2H-6′), 4.36-4.47 (m, 1H, H-5′), 4.57 (t, 1H, $J_{4'\text{-}3'}$ = 2.6 Hz, $J_{4'\text{-}5'}$ = 2.4 Hz, H-4′), 4.59 (t, 1H, $J_{3'\text{-}2'}$ = 9.1 Hz, $J_{3'\text{-}4'}$ = 2.6 Hz, H-3′), 4.73 (t, 1H, $J_{2'\text{-}1'}$ = 10.6 Hz, $J_{2'\text{-}3'}$ = 9.1 Hz, H-2′), 5.55 (d, 1H, $J_{1'\text{-}2'}$ = 10.6 Hz, H-1′), 6.55 (s, D_2O exch., 2H,

NH_2), 8.36–8.87 (m, 3H, C_6 H_3); ^{13}C NMR: δ 22.65 (4xOAc), 62.53 (C-6′), 69.46 (C-5′), 70.43 (C-4′), 72.54 (C-3′), 74.46 (C-2′), 84.56 (C-1′), 123.44 (Ar-C), 134.26 (2Ar-C), 135.96 (Ar-C), 152.66 (Ar-C), 156.61 (Ar-C), 157.82 (C-5), 164.63 (C-3), 174.54 (4C=O). Anal. Calcd. For $C_{22}H_{24}N_6O_{13}S$ (612.52): C, 43.14; H, 3.95; N, 13.72; S, 5.23. Found: C, 43.10; H, 3.80; N, 13.64; S, 5.13%.

General procedure for the synthesis of (8a-h)

Dry gaseous of ammonia was passed through a solution of protected nucleoside **7a**-**h** (10 mmol) in dry methanol (20 mL) for 10 min with cooling and stirring, then the reaction mixture was stirred at room temperature until the reaction was judged complete by TLC (9-10h) using ($CHCl_3$/MeOH 9:1) (Rf, 0.54-0.56). The resulting mixture was concentrated under reduced pressure to afford a solid residue which washed several times by boiling chloroform. The residue was dried, purified by column chromatography using chloroform/methanol (9:1) and crystallized from appropriate solvent to give corresponding compounds **8a**-**h**.

3-(β-D-Glucopyranosylthio)-1H-1,2,4-triazol-5-amine (8a)

White solid; (EtOH); yield (69%); mp 172–173°C; IR (KBr, cm^{-1}) υ 3558 (OH), 3376,3339 (NH_2), 3251 (NH), 2949 (CH), 1614 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32-3.41 (m, 2H, 2H-6′), 3.64-3.72 (m, 1H, H-5′), 4.02 (t, 1H, $J_{4'\text{-}3'}$ = 8.9 Hz, $J_{4'\text{-}5'}$ = 6.6 Hz, H-4′), 4.22 (t, 1H, $J_{3'\text{-}2'}$ = 9.6 Hz, $J_{3'\text{-}4'}$ = 8.9 Hz, H-3′), 4.36 (t, 1H, $J_{2'\text{-}1'}$ = 9.6 Hz, $J_{2'\text{-}3'}$ = 9.6 Hz, H-2′), 4.63 (d, 1H, $J_{1'\text{-}2'}$ = 9.6 Hz, H-1′), 4.86 (s, D_2O exch., 1H, 6′–OH), 4.98 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.42 (s, D_2O exch., 2H, NH_2), 10.78 (s, D_2O exch., 1H, NH); ^{13}C NMR: δ 62.16 (C-6′), 68.24 (C-5′), 69.56 (C-4′), 72.48 (C-3′), 74.52 (C-2′), 86.32 (C-1′), 161.28 (C-5), 163.12 (C-3). Anal. Calcd. For $C_8H_{14}N_4O_5S$ (278.29): C, 34.53; H, 5.07; N, 20.13; S, 11.52. Found: C, 34.40; H, 5.01; N, 20.09; S, 11.43%.

3-(β-D-Glucopyranosylthio)-1-phenyl-1H-1,2,4-triazol-5-amine (8b)

White solid; (EtOH); yield (78%); mp 182–183°C; IR (KBr, cm^{-1}) υ 3514 (OH), 3397, 3356 (NH_2), 3056 (CH aromatic), 1615 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54-3.65 (m, 2H, 2H-6′), 3.74-3.81 (m,1H, H-5′), 4.18 (t, 1H, $J_{4'\text{-}3'}$ = 8.6 Hz, $J_{4'\text{-}5'}$ = 6.4 Hz, H-4′), 4.38 (t, 1H, $J_{3'\text{-}2'}$ = 10.1 Hz, $J_{3'\text{-}4'}$ = 8.6 Hz, H-3′), 4.42 (t, 1H, $J_{2'\text{-}1'}$ = 10.9 Hz, $J_{2'\text{-}3'}$ = 10.1 Hz, H-2′), 4.80 (d, 1H, $J_{1'\text{-}2'}$ = 10.9 Hz, H-1′), 4.84 (s, D_2O exch., 1H, 6′–OH), 5.00 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.69 (s, D_2O exch., 2H, NH_2), 7.36–7.76 (m, 5H, C_6H_5); ^{13}C NMR: δ 62.57 (C-6′), 71.68 (C-5′), 73.41 (C-4′), 75.23 (C-3′), 76.42 (C-2′), 85.84 (C-1′), 126.15 (2C, Ar-C), 130.41 (3C, Ar-C), 142.64 (Ar-C), 158.65 (C-5), 164.32 (C-3). Anal. Calcd. For $C_{14}H_{18}N_4O_5S$ (354.38): C, 47.45; H, 5.12; N, 15.81; S, 9.05. Found: C, 47.34; H, 5.06; N, 15.58; S, 9.01%.

3-(β-D-Glucopyranosylthio)-1-(4-nitrophenyl)-1H-1,2,4-triazol-5-amine (8c)

White solid; (EtOH); yield (68%); mp 180–181°C; IR (KBr, cm^{-1}) υ 3502 (OH), 3365, 3324 (NH_2), 3049 (CH aromatic), 2955 (CH), 1615 (C=N); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 3.65-3.72 (m, 2H, 2H-6′), 3.86-3.89 (m, 1H, H-5′), 3.92 (t, 1H, $J_{4'-3'} = 8.3$ Hz, $J_{4'-5'} = 6.9$ Hz, H-4′), 4.24 (t, 1H, $J_{3'-2'} = 9.9$ Hz, $J_{3'-4'} = 8.3$ Hz, H-3′), 4.37 (t, 1H, $J_{2'-1'} = 10.4$ Hz, $J_{2'-3'} = 9.9$ Hz, H-2′), 4.46 (d, 1H, $J_{1'-2'} = 10.4$ Hz, H-1′), 4.82 (s, D_2O exch., 1H, 6′–OH), 5.04 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.77 (s, D_2O exch., 2H, NH_2), 8.24–8.62 (m, 4H, C_6H_4). Anal. Calcd. For $C_{14}H_{17}N_5O_7S$ (399.38): C, 42.10; H, 4.29; N, 17.54; S, 8.03. Fond: C, 42.25; H, 4.12; N, 17.36; S, 8.01%.

1-(2,4-Dinitrophenyl)-3-(β-D-glucopyranosylthio)-1H-1,2,4-triazol-5-amine (8d)

White solid; (EtOH); yield (72%); mp 186–187°C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.47-3.52 (m, 2H, 2H-6′), 3.63-3.69 (m, 1H, H-5′), 3.71 (t, 1H, $J_{4'-3'} = 9.2$ Hz, $J_{4'-5'} = 8.4$ Hz, H-4′), 3.84 (t, 1H, $J_{3'-2'} = 9.3$ Hz, $J_{3'-4'} = 9.2$ Hz, H-3′), 4.47 (t, 1H, $J_{2'-1'} = 10.7$ Hz, $J_{2'-3'} = 9.3$ Hz, H-2′), 4.52 (d, 1H, $J_{1'-2'} = 10.7$ Hz, H-1′), 4.81 (s, D_2O exch., 1H, 6′–OH), 4.95 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.85 (s, D_2O exch., 2H, NH_2), 8.35–9.23 (m, 3H, C_6H_3); ^{13}C NMR: δ 62.21 (C-6′), 69.78 (C-5′), 72.43 (C-4′), 75.62 (C-3′), 78.66 (C-2′), 84.78 (C-1′), 123.41 (Ar-C), 128.76 (Ar-C), 133.84 (Ar-C), 136.53 (Ar-C), 154.52 (Ar-C), 156.31 (Ar-C), 158.35 (C-5), 165.46 (C-3). Anal. Calcd. For $C_{14}H_{16}N_6O_9S$ (444.38): C, 37.84; H, 3.63; N, 18.91; S, 7.22. Found: C, 37.52; H, 3.29; N, 18.82; S, 7.13%.

3-(β-D-Galactopyranosylthio)-1H-1,2,4-triazol-5-amine (8e)

White solid; (EtOH); yield (69%); mp 228–230°C; IR (KBr, cm^{-1}) υ 3498 (OH), 3382,3346 (NH_2), 3275 (NH), 2964 (CH), 1606 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22-3.28 (m, 2H, 2H-6′), 3.46-3.51 (m, 1H, H-5′), 3.64 (t, 1H, $J_{4'-3'} = 3.1$ Hz, $J_{4'-5'} = 2.3$ Hz, H-4′), 4.02 (t, 1H, $J_{3'-2'} = 9.1$ Hz, $J_{3'-4'} = 3.1$ Hz, H-3′), 4.23 (t, 1H, $J_{2'-1'} = 9.6$ Hz, $J_{2'-3'} = 9.1$ Hz, H-2′), 4.55 (d, 1H, $J_{1'-2'} = 9.6$ Hz, H-1′), 4.89 (s, D_2O exch., 1H, 6′–OH), 4.99 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.98(s, D_2O exch., 2H, NH_2), 10.89 (s, D_2O exch., 1H, NH); ^{13}C NMR: δ 62.42 (C-6′), 67.33 (C-5′), 69.21 (C-4′), 70.26 (C-3′), 76.43(C-2′), 84.57 (C-1′), 162.41 (C-5), 163.52 (C-3). Anal. Calcd. For $C_8H_{14}N_4O_5S$ (278.29): C, 34.53; H, 5.07; N, 20.13; S, 11.52. Found: C, 34.40; H, 5.01; N, 20.09; S, 11.43%.

3-(β-D-Galactopyranosylthio)-1-phenyl-1H-1,2,4-triazol-5-amine (8f)

White solid; (EtOH); yield (72%); mp 210–212°C; IR (KBr, cm^{-1}) υ 3520 (OH), 3383, 3347 (NH_2), 3069 (CH aromatic), 2962 (CH), 1604 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22-3.27 (m, 2H, 2H-6′), 3.45-3.51 (m, 1H, H-5′), 3.62 (t, 1H, $J_{4'-3'} = 3.4$ Hz, $J_{4'-5'} = 3.1$ Hz, H-4′), 3.95 (t, 1H, $J_{3'-2'} = 9.3$ Hz, $J_{3'-4'} = 3.4$ Hz, H-3′), 4.26 (t, 1H, $J_{2'-1'} = 9.7$ Hz, $J_{2'-3'} = 9.3$ Hz, H-2′), 4.64 (d, 1H, $J_{1'-2'} = 9.7$ Hz, H-1′), 4.81 (s, D_2O exch., 1H, 6′–OH), 5.26 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.88 (s, D_2O exch., 2H, NH_2), 7.32–7.75 (m, 5H, C_6H_5); ^{13}C NMR: δ 62.36 (C-6′), 70.54 (C-5′), 72.66 (C-4′), 74.72 (C-3′), 76.41 (C-2′), 84.76 (C-1′), 126.11 (2C, Ar-C), 132.29 (3C, Ar-C), 144.62 (Ar-C), 159.43 (C-5), 163.28 (C-3). Anal. Calcd. For $C_{14}H_{18}N_4O_5S$ (354.38): C, 47.45; H, 5.12; N, 15.81; S, 9.05. Found: C, 47.34; H, 5.06; N, 15.58; S, 9.01%.

3-(β-D-Galactopyranosylthio)-1-(4-nitrophenyl)-1H-1,2,4-triazol-5-amine (8g)

White solid; (EtOH); yield (70%); mp 206–208°C; IR (KBr, cm^{-1}) υ 3514 (OH), 3372, 3329 (NH_2), 3052 (CH aromatic), 2968 (CH), 1610 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44-3.49 (m, 2H, 2H-6′), 3.62-3.69 (m, 1H, H-5′), 3.81 (t, 1H, $J_{4'\text{-}3'} = 2.7$ Hz, $J_{4'\text{-}5'} = 2.5$ Hz, H-4′), 4.19 (t, 1H, $J_{3'\text{-}2'} = 9.2$ Hz, $J_{3'\text{-}4'} = 2.7$ Hz, H-3′), 4.32 (t, 1H, $J_{2'\text{-}1'} = 10.6$ Hz, $J_{2'\text{-}3'} = 9.2$ Hz, H-2′), 4.48 (d, 1H, $J_{1'\text{-}2'} = 10.6$ Hz, H-1′), 4.87 (s, D_2O exch., 1H, 6′–OH), 5.15 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.89 (s, D_2O exch., 2H, NH_2), 8.26–8.54 (m, 4H, C_6H_4). Anal. Calcd. For $C_{14}H_{17}N_5O_7S$ (399.38): C, 42.10; H, 4.29; N, 17.54; S, 8.03. Found: C, 42.25; H, 4.12; N, 17.36; S, 8.01%.

1-(2,4-Dinitrophenyl)-3-(β-D-galactopyranosylthio)-1H-1,2,4-triazol-5-amine (8h)

White solid; (EtOH); yield (76%); mp 194–195°C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.42-3.45 (m, 2H, 2H-6′), 3.59-3.62 (m, 1H, H-5′), 3.64 (t, 1H, $J_{4'\text{-}3'} = 2.9$ Hz, $J_{4'\text{-}5'} = 2.4$ Hz, H-4′), 3.69 (t, 1H, $J_{3'\text{-}2'} = 10.1$ Hz, $J_{3'\text{-}4'} = 2.9$ Hz, H-3′), 4.26 (t, 1H, $J_{2'\text{-}1'} = 10.2$ Hz, $J_{2'\text{-}3'} = 10.1$ Hz, H-2′), 4.43 (d, 1H, $J_{1'\text{-}2'} = 10.2$ Hz, H-1′), 4.86 (s, D_2O exch., 1H, 6′–OH), 4.94 (s, D_2O exch., 3H, 2′–OH, 3′–OH, and 4′–OH), 6.75 (s, D_2O exch., 2H, NH_2), 8.38–9.34 (m, 3H, C_6H_3); ^{13}C NMR: δ 62.44 (C-6′), 67.94 (C-5′), 72.67 (C-4′), 74.73 (C-3′), 79.52 (C-2′), 85.94 (C-1′), 123.74 (Ar-C), 132.26 (Ar-C), 135.73 (Ar-C), 139.51 (Ar-C), 148.66 (Ar-C), 153.61 (Ar-C), 157.74 (C-5), 167.28 (C-3). Anal. Calcd. For $C_{14}H_{16}N_6O_9S$ (444.38): C, 37.84; H, 3.63; N, 18.91; S, 7.22. Found: C, 37.52; H, 3.29; N, 18.82; S, 7.13%.

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