Synthesis of novel glycosyl 1,3,4-thiadiazole derivatives

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A convenient and mild protocol for the synthesis of glycosyl 1,3,4-thiadiazole derivatives was developed, which involved the reaction of glycosyl isothiocyanate, hydrazine hydrate, and various aldehydes followed by oxidative cyclisation with ferric ammonium sulfate in methanol. 13 examples of different glycosyl 1,3,4-thiadiazole derivatives were prepared. Good yields (70–87%) have been achieved. The glycosyl 1,3,4-thiadiazole derivatives may find applications in medicinal chemistry and pharmaceutical industry.

Keywords: D-glucosamine, 1,3,4-thiadiazole, glycosyl isothiocyanate

The research of monosaccharides has been highly valued in areas of chemistry and biology due to the unique structures and various biological activities of carbohydrates.[1,2] D-Glucosamine is a naturally occurring compound, present within animal bones, the shells of shellfish and bone marrow. It is the biochemical precursor of all nitrogen-containing sugars, synthesised *in vivo* as glucosamine-6-phosphate.[3] Recent studies have demonstrated that D-glucosamine showed a broad range of biological activities.[4–6] In particular, D-glucosamine can be used as a single pharmacological agent to relieve arthritic complaints and arthritis symptoms in clinics because of its beneficial effects in joint tissues.[7] Advantages of drugs containing glucosamine are the treatment of arthritis without causing side effects. Furthermore, D-glucosamine possesses other biological activities such as antioxidant, anti-inflammatory, antibacterial and antitumour.[8–10] In recent years, the use of hybrid molecules for new drug discovery has increased.[11] Recent efforts have been focused on the chemical synthesis of hybrid molecules where other active groups are connected to the glucosamine unit *via* linkers.[12,13] Carroll *et al*. reported the synthesis of a number of ^{18}F labelled glucosamine derivatives and evaluation of their tumour uptake and normal tissue distribution *in vivo* in a mouse model of cancer by positron emission tomography imaging. Rosso *et al*. have synthesised glucosamine-functionalised poly (ε-caprolactone) (PCL), where the poly (ε-caprolactone) (PCL) linked with the amino group of the glucosamine, thus showing enhanced cell density and spreading over the non-functionalised samples.[14] Ngoje *et al*. prepared a series of tolyl 2-azido-2-deoxy-thio-glucoside donors with different combinations of protecting groups, which can be used in glycosylation reactions to test the correlations between the stereoselectivity and the pattern of the protecting groups.[15] Although the modifications of D-glucosamine have been studied, reports on the synthesis of amino of D-glucosamine linked to a heterocycle are rare, especially the link to 1,3,4-thiadiazoles, which are commonly utilised pharmacophores according to their broad spectrum of biological activities and their lower toxicity and higher stability *in vivo*.[16,17] They have received much attention as useful intermediates and they have a variety of biological activities such as antitumour, antiviral, analgesic, antioxidant and anticancer. In particular, the marketed antiglaucoma drugs acetazolamide and the carbonic anhydrase inhibitor methazolamide contain the thiadiazole nucleus and have showed therapeutic potential. Taking into account the important role of 1,3,4-thiadiazoles in various biological phenomena, we synthesised a series of novel glucosamine derivatives containing 1,3,4-thiadiazole attached to the C(2)-amino group.

A large number of methods have been reported to synthesise 1,3,4-thiadiazoles. Generally, preparation of 1,3,4-thiadiazole involves the use of acidic reagents such as $POCl_3$, H_3PO_4, $HClO_4$, and some strong mineral acid. However, the harsh reaction conditions, limited substrate scope and environmental pollution restricts the use of these methods. What is more, the glycosyl 1,3,4-thiadiazole unit cannot be prepared in such strong acids. Recently, some milder methods have been reported for the synthesis of 1,3,4-thiadiazoles using trimethyl chlorosilane,[18] Lawesson's reagent[19] and tosyl chloride.[20] But these synthetic methods need high temperature, a long time, and require difficult separations. The target compound 1,3,4-thiadiazoles have been synthesised by multi-step procedures in most of the synthetic methods. There is a need to synthesise 1,3,4-thiadiazoles from mild starting materials using mild general and convenient procedures.

Herein, we report a facile, high-yielding synthesis of novel glycosyl 1,3,4-thiadiazole derivatives from a reagent based cyclisation of ferric ammonium sulfate (FAS). The use of the FAS will not suffer from serious environmental and operational issues. This protocol can provide various substituent derivatives of glycosyl 1,3,4-thiadiazole.

Results and discussion

In this procedure, glycosyl isothiocyanate is an important intermediate. Our strategy began with the synthesis of glycosyl isothiocyanate without protection of hydroxyl groups of D-glucosamine hydrochloride **1** in different ways. But to our disappointment, the glycosyl isothiocyanate was not obtained. We speculated that the hydroxyl groups of the D-glucosamine required protection. The benzyl group was selected to protect the hydroxy groups. Gratifyingly, 2-isothiocyanate-1,3,4,6-tetra-*O*-benzyl-2-deoxy-β-D-glucopyranose **6**[21], an important intermediate, can be synthesised from 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine hydrochloride **4** in high yields[22,23] (Scheme 1). To obtain the 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine hydrochloride **4**, the amino group of D-glucosamine hydrochloride **1** was protected by using *p*-methoxybenzaldehyde to provide Schiff's base **2** initially. Then benzylation of the four hydroxyl groups with NaH and BnBr in DMF at a temperature ranging from 0 °C to room temperature for 12 h afforded **3** and was followed by the preparation of 2-amino-1,3,4,6-tetra-*O*-benzyl-2-deoxy-β-D-glucopyranose hydrochloride **4** by

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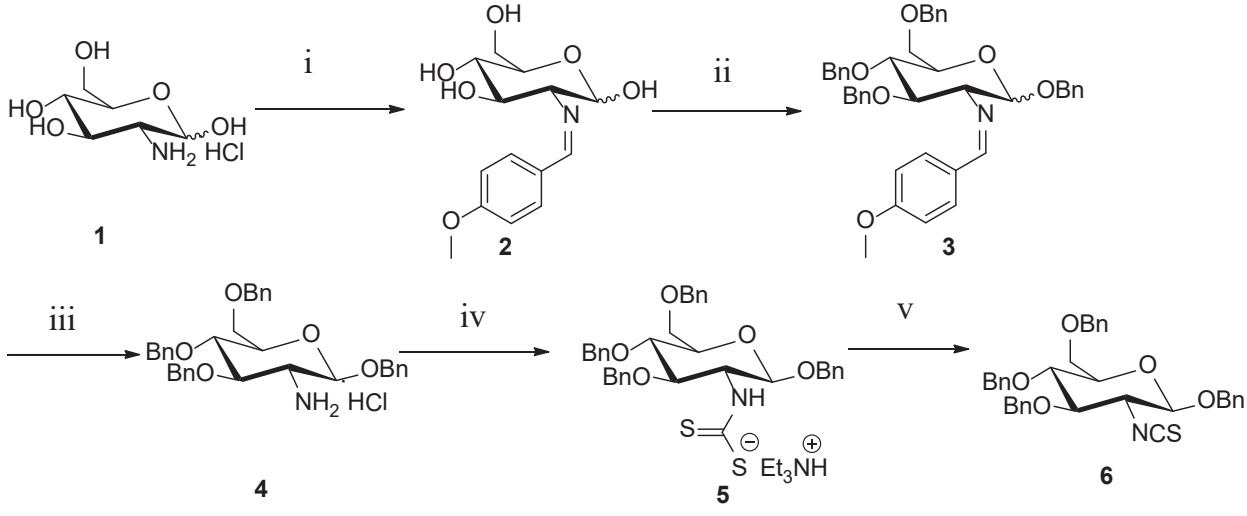
the hydrolysis of **3** with hydrochloric acid. By protection of the hydroxyl groups, the amino group of D-glucosamine can be converted to the isothiocyanate **6** efficiently. To a solution of **4** in acetonitrile was added triethylamine at 0 °C, followed by the addition of carbon disulfide dropwise into the reaction mixture using a syringe pump. The mixture was stirred for 2 h to give the dithiocarbamic acid salts **5**.[24] Tosyl chloride (TsCl) was then added to the reaction mixture. After a further 0.5 h, glycosyl isothiocyanate **6** was obtained by solvent removal and recrystallisation from ethanol in high yield.

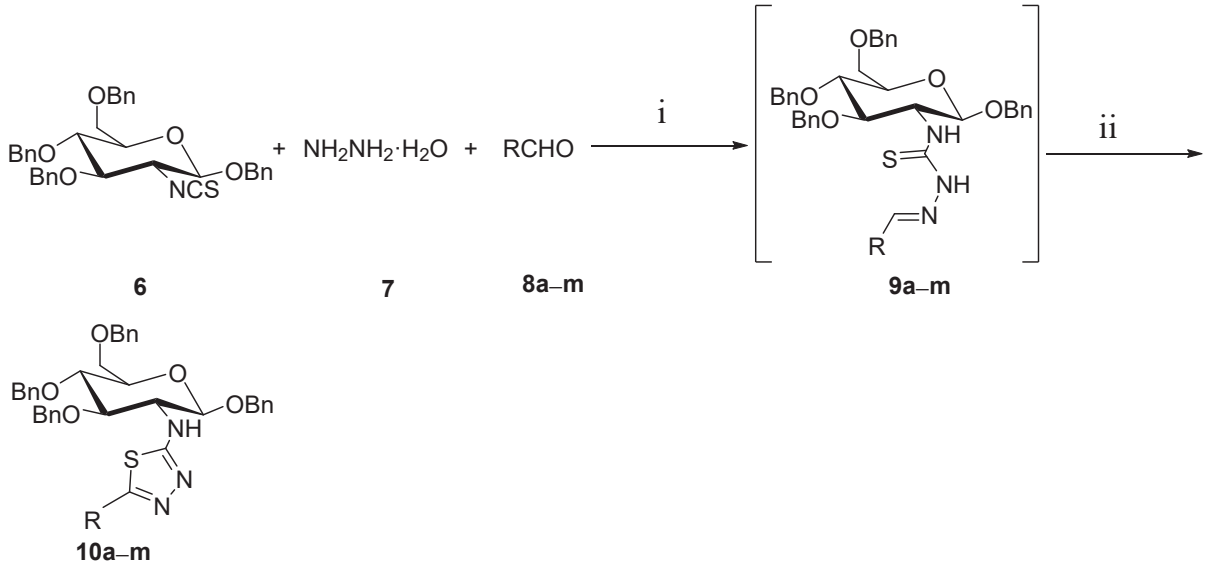
As 2-isothiocyanate-1,3,4,6-tetra-*O*-benzyl-2-deoxy-β-D-glucopyranose can now be obtained in an efficient manner, we have designed a three-component one-pot synthesis of glycosyl 1,3,4-thiadiazole derivatives which involves the reaction of aldehydes **8**, hydrazine hydrate **7** and glycosyl isothiocyanate **6** (Scheme 2). The procedure was divided into two stages. In the first phase, treatment of the glycosyl isothiocyanate **6**, hydrazine hydrate **7** and various aldehydes **8a**–**m** in methanol at 65 °C for 2 h afforded the important intermediate thiosemicarbazones **9a**–**m**. Upon completion of the reaction, as indicated by TLC, the next phase was initiated.

In the second phase, we commenced our study with benzaldehyde **8a**, **6** and hydrazine hydrate **7** as model substrates to select the optimal reaction conditions. Various catalysts,



Reagents and conditions: (i) NaOH, *p*-methoxybenzaldehyde, H_2O, r.t., yield 81%; (ii) NaH, BnBr, DMF, 0 °C – r.t., yield 75%; (iii) 5 M HCl, acetone, reflux, 85%; (iv) Et_3N, CS_2, 0 °C, 1.5 h; (v) TsCl, 0.5 h, yield 90%.

Scheme 1 Synthesis of 2-isothiocyanate-1,3,4,6-tetra-*O*-benzyl-2-deoxy-β-D-glucopyranose **6**.



a: R = C_6H_5 **e:** R = 3-$NO_2C_6H_4$ **i:** R = 4-FC_6H_4 **m:** R = C_8H_{17}
b: R = 4-$CH_3C_6H_4$ **f:** R = 4-OHC_6H_4 **j:** R = 2,3-di-ClC_6H_3
c: R = 4-$CH_3OC_6H_4$ **g:** R = 4-BrC_6H_4 **k:** R = 2,4-di-ClC_6H_3
d: R = 2-$CH_3OC_6H_4$ **h:** R = 4-ClC_6H_4 **l:** R = $C_{10}H_7$

Reagents and conditions: (i) MeOH, 65 °C. (ii) see table 1

Scheme 2 Synthesis of glycosyl 1,3,4-thiadiazole derivatives **10**.

solvents, temperatures were screened and the results are summarised in Table 1. Two oxidative cyclisation agents were involved to prepare **10a** in our initial efforts: ferric ammonium sulfate and ferric trichloride. When the precursor was treated with ferric chloride as the oxidative cyclisation agent in methanol at 65 °C for 2 h, the product **10a** was not obtained or obtained in very low yield (entries 1–3). Ferric ammonium sulfate (FAS) was then examined as the oxidative cyclisation agent, 1 mmol of the FAS was added to the system and furnished 30% of the desired product **10a** after 2 h of reaction. Raising the amount of FAS to 2 mmol further enhanced the yield to 65%, and when the amount of FAS was raised to 3 mmol, the best result was obtained (entries 4–7). The protic solvents such as ethanol, methanol and the polar solvents like acetonitrile, *N,N*-diethylformamide were tested and the desired product **10a** was obtained with the best yields in the protic solvent methanol (entries 6, 8–10). We also investigated the effect of different temperatures and times on the reaction (entries 6, 11–14). As shown in Table 1, the best reaction conditions for synthesis of **10** were as follows: ferric ammonium sulfate as oxidative cyclisation agent, methanol as solvent at 65 °C for 2 h.

From a mixture of glycosyl isothiocyanate **6** (1 mmol), hydrazine hydrate **7** (1 mmol), benzaldehyde **8a** (1 mmol) and ferric ammonium sulfate (3 mmol), *N*-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-5-phenyl-1,3,4-thiadiazole-2-amine **10a** was isolated in 87% yield. The reaction was carried out in MeOH for 4 h at 65 °C. Subsequently, we examined whether the same system can be applied to various aldehydes. Experimental study indicates that the reaction of glycosyl isothiocyanate **6** with hydrazine hydrate **7** and various aromatic aldehydes and aliphatic aldehydes could be smoothly converted to the desired products as shown in Table 2 in good yields (70–87%). Attempted debenzylation of **10a** was carried out by hydrogenolysis using palladium on activated charcoal.[25] However, the target product was not found, possibly because of the presence of sulfur in the product.

In summary, we have developed a versatile, easy and expeditious one-pot synthesis of 2-glycosylamino-5-aryl-1,3,4-thiadiazole which involves the reaction of glycosyl isothiocyanate **6**, hydrazine hydrate **7**, and various aldehydes **8** followed by oxidative cyclisation with ferric ammonium sulfate (FAS). As D-glucosamine plays an important role in biomedical research, these novel compounds may find applications in a number of fields.

Table 1 Optimising the conditions for the synthesis of **10a** in the second stage

Entry	Reagent	Solvent	Time/h	Temp./°C	**10a** yield /%[b]
1	$FeCl_3$ (10%)	MeOH	2	65	10
2	$FeCl_3$ (3 mmol)	MeOH	2	65	0
3	$ZnCl_2$ (3 mmol)	MeOH	2	65	0
4	FAS (1 mmol)	MeOH	2	65	30
5	FAS (2 mmol)	MeOH	2	65	56
6	FAS (3 mmol)	MeOH	2	65	87
7	FAS (4 mmol)	MeOH	2	65	87
8	FAS (3 mmol)	EtOH	2	65	75
9	FAS (3 mmol)	ACN	2	65	55
10	FAS (3 mmol)	DMF	2	65	64
11	FAS (3 mmol)	MeOH	1	65	75
12	FAS (3 mmol)	MeOH	3	65	85
13	FAS (3 mmol)	MeOH	2	r.t.	0
14	FAS (3 mmol)	MeOH	2	40	30

[a]Reaction condition: **10a** was synthesised from 1 mmol glycosyl isothiocyanate **6**, 1 mmol hydrazine hydrate **7**, and 1 mmol benzaldehyde **8a**, solvent, 15 mL.
[b]Isolated yield.

Experimental

All chemicals were purchased from commercial sources and used without further purification unless otherwise stated. Melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer with KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz at ambient temperature using DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts were reported in ppm. HRMS (ESI) analysis was performed on an Agilent 6230 mass spectrometer. The purity of the compounds was checked by TLC on plates precoated with silica gel GF254.

Synthesis of 2-amino-1,3,4,6-tetra-O-*benzyl-2-deoxy*-β-*D-glucopyranose hydrochloride* (**4**): To a solution of **1** (30 g, 139.1 mmol) in water (150 mL) at room temperature with stirring NaOH (5.6 g, 0.14 mmol) was added, and 15 min later, *p*-methoxybezaldehyde (17.1 mL, 0.14 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for an additional 24 h, after which the resulting white solid was filtered and washed with water (500 mL) to afford 2-(4-methoxy benzylidene)-2-deoxy-β-D-glucopyranose (33.3 g, 81%). To a mixture of 2-(4-methoxy benzylidene)-2-deoxy-β-D-glucopyranose (6.6 g, 22.2 mmol) and benzyl bromide (14 mL, 117.9 mmol) in DMF (50 mL) at 0 °C, NaH (60%, 5 g, 125 mmol) was added portionwise. The reaction mixture was allowed to attain room temperature and stirred for 12 h. After the completion of reaction, the solution was diluted by a large amount of water and extracted with CH_2Cl_2 (3 × 50 mL). The solvent was removed under reduced pressure to give a yellow viscous liquid. The solution of the yellow liquid in acetone (100 mL) was treated with hydrochloric acid (7 mL, 5 N) to afford a white solid after heating at reflux for 1 h. The mixture was filtered and washed with acetone to give **4**: Yield 7.5 g, 59%, (overall yield 50%); m.p. 138—140 °C; IR (ν_{max}/cm^{-1}) KBr: 3438, 3027, 2925, 1502, 1455, 1066, 738, 696; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (s, 3H, NH_2HCl), 7.50–7.23 (m, 18H, ArH), 7.15 (dd, *J* = 6.6, 2.9 Hz, 2H, ArH), 4.81 (dd, *J* = 16.7, 9.8 Hz, 4H, $PhCH_2$, HGlu), 4.73–4.62 (m, 2H, $PhCH_2$), 4.61–4.48 (m, 3H, $PhCH_2$), 3.85 (dd, *J* = 10.0, 8.6 Hz, 1H, HGlu), 3.76–3.56 (m, 4H, HGlu), 3.06 (dd, *J* = 9.8, 8.8 Hz, 1H, HGlu).

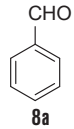
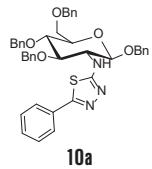
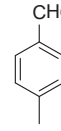
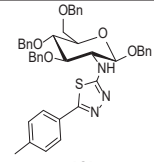
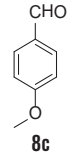
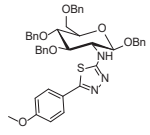
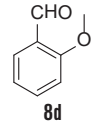
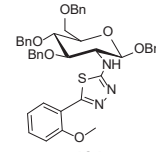
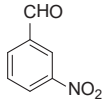
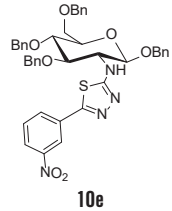
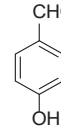
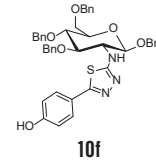
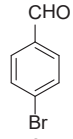
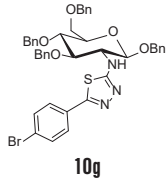
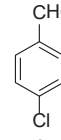
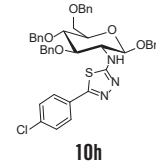
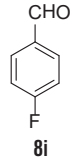
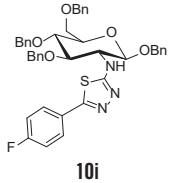
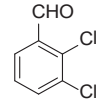
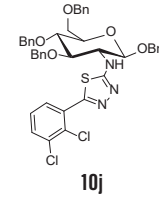
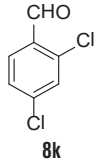
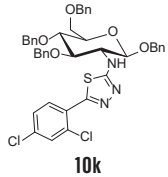
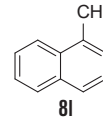
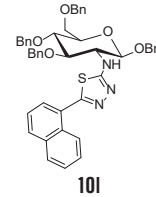
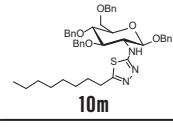
Synthesis of 2-isothiocyanate-1,3,4,6-tetra-O-*benzyl-2-deoxy*-β-*D-glucopyranose* (**6**): To a solution of 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine hydrochloride **4** (1 mmol, 1 equiv.) in acetonitrile (15 mL) was added triethylamine (3 mmol) and then cooled in an ice bath. Carbon disulfide (1 mmol) was then added dropwise into the reaction mixture *via* syringe pump. The mixture was stirred for 2 h followed by the addition of tosyl chloride (TsCl) (1 mmol) and the mixture stirred for another 0.5 h. The crude product was recrystallised from ethanol to give **6**: White amorphous powder; yield 90%; m.p. 55–56 °C; IR (ν_{max}/cm^{-1}) KBr: 3433, 3030, 2873, 2078, 1454, 1359, 1313, 1068; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45–7.25 (m, 18H), 7.24–7.17 (dd, *J* = 7.3, 1.9 Hz, 2H), 4.81 (dd, *J* = 16.7, 9.8 Hz, 4H), 4.73–4.62 (m, 2H), 4.61–4.48 (m, 3H), 3.95–3.87 (m, 2H), 3.67 (ddd, *J* = 14.3, 11.7, 6.9 Hz, 3H), 3.54 (dd, *J* = 11.7, 6.9 Hz, 1H); HRMS (ESI) calcd for $C_{35}H_{35}NO_5SNa$ [M + Na]$^+$: *m/z* 604.2128; found: *m/z* 604.2130.

*Synthesis of N-(1,3,4,6-tetra-O-benzyl-2-deoxy-*β*-D-glucopyranosyl)-5-substituted-1,3,4-thiadiazole-2-amine* (**10a**–**m**)*; general procedure*

To a 50 mL round-bottom flask fitted with a magnetic mixer and containing glycosyl isothiocyanate **6** (1.0 mmol, 1 equiv.), hydrazine hydrate **7** (1.0 mmol, 1 equiv.), and aldehydes **8** (1.0 mmol, 1 equiv.), methanol (15 mL) was injected and the reaction mixture was stirred for 2–3 h at 65 °C. The progress of the reaction was monitored by TLC. Upon completion of the reaction, 3 equiv. of FAS was added to the reaction, which was heated at 65 °C for a further 2–3 h. After the reaction, the resulting mixture was filtered to obtain the filtrate. The filtrate was concentrated, and the crude product was purified by column chromatography on silica gel using a gradient mixture of ethyl acetate and petroleum ether as an eluent to give products **10a**–**m**.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-phenyl-1,3,4-thiadiazole-2-amine* (**10a**): Following the general procedure,

Table 2 Synthesis of the desired product **10**

Entry	Compound **8**	Compound **10**	Yield/%	Entry	Compound **8**	Compound **10**	Yield/%
1	 **8a**	 **10a**	85	2	 **8b**	 **10b**	87
3	 **8c**	 **10c**	80	4	 **8d**	 **10d**	76
5	 **8e**	 **10e**	74	6	 **8f**	 **10f**	81
7	 **8g**	 **10g**	80	8	 **8h**	 **10h**	78
9	 **8i**	 **10i**	76	10	 **8j**	 **10j**	70
11	 **8k**	 **10k**	73	12	 **8l**	 **10l**	86
13	$C_8H_{16}CHO$ **8m**	 **10m**	85				

the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and benzaldehyde **8a** (0.106 mL) afforded **10a**: White amorphous powder; yield 0.59 g, 85%; m.p. 141–142 °C; IR (ν_{max}/cm^{-1}) KBr: 3421, 3176, 3030, 2922, 2868, 1573, 1519, 1497, 1359, 1120, 1068; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, J = 8.0 Hz, 1H, NH), 7.75 (t, J = 7.7 Hz, 2H, ArH), 7.52–7.43 (m, 3H, ArH), 7.41–7.27 (m, 8H, ArH), 7.26–7.11 (m, 12H, ArH), 4.82 (d, J = 12.0 Hz, 1H, H-1), 4.71 (m, 4H, CH_2Ph), 4.58 (m, 4H, CH_2Ph), 3.87 (t, J = 8 Hz, 1H, H-4), 3.78–3.68 (m, 2H, H-6$_a$, H-6$_b$), 3.62–3.52 (m, 3H, H-3, H-5, H-2); HRMS (ESI) calcd for $C_{42}H_{41}N_3O_5SNa$ [M + Na]$^+$: *m/z* 722.2659; found: *m/z* 722.2666.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(4-methylphenyl)-1,3,4-thiadiazole-2-amine* (**10b**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and 4-methyl benzaldehyde **8b** (0.1 mL) afforded **10b**: White amorphous powder; yield 0.62 g, 87%; m.p. 52 °C; IR (ν_{max}/cm^{-1}) KBr: 3440, 3029, 2866, 1623, 1453, 1360, 1210, 1062; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, J = 8.0 Hz, 1H, NH), 7.66 (d, J = 8.0 Hz, 2H, ArH), 7.43–7.12 (m, 22H, ArH), 4.83 (d, J = 12.0 Hz, 1H, H-1), 4.77–4.65 (m, 4H, CH_2Ph), 4.64–4.51 (m, 4H, CH_2Ph), 3.86 (t, J = 8 Hz, 1H, H-4), 3.80–3.36 (m, 5H, H-6$_a$, H-6$_b$, H-3, H-5, H-2), 2.36 (s, 3H); HRMS (ESI) calcd for $C_{43}H_{43}N_3O_5SNa$ [M + Na]$^+$: *m/z* 736.2816; found: *m/z* 736.2823.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(4-methoxyphenyl)-1,3,4-thiadiazole-2-amine* (**10c**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and *p*-methoxybenzaldehyde **8c** (0.12 mL) afforded **10c**: Yellow amorphous powder; yield 0.58 g, 80%; m.p. 105–106 °C; IR (ν_{max}/cm^{-1}) KBr: 3421, 3029, 2928, 1607, 1577, 1521, 1453, 1253, 1069; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 9.0 Hz, 1H, NH), 7.71–7.67 (m, 2H, ArH), 7.39–7.27 (m, 8H, ArH), 7.25–7.13 (m, 12H, ArH), 7.06–7.01 (m, 2H, ArH), 4.82 (d, J = 12.5 Hz, 1H, NH), 4.75–4.67 (m, 4H, CH_2Ph), 4.63–4.52 (m, 4H, CH_2Ph), 3.85 (t, J = 9.5 Hz, 1H, H-4), 3.81 (s, 3H, OCH_3), 3.77–3.67 (m, 2H, H-6$_a$, H-6$_b$), 3.60–3.55 (m, 3H, H-3, H-5, H-2); HRMS (ESI) calcd for $C_{43}H_{43}N_3O_6SNa$ [M + Na]$^+$: *m/z* 752.2765; found: *m/z* 752.2767.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(2-methoxyphenyl)-1,3,4-thiadiazole-2-amine* (**10d**): Following

the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and 2-methoxybenzaldehyde **8d** (0.12 mL) afforded **10d**: Yellow amorphous powder; yield 0.55 g, 76%; m.p. 73–74 °C; IR (ν_{max}/cm^{-1}) KBr: 3442, 3029, 3922, 1599, 1497, 1453, 1360, 1257, 1065; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, *J* = 7.2 Hz, 1H, NH), 8.12 (dd, *J* = 7.8, 1.6 Hz, 1H, ArH), 7.50–7.43 (m, 1H, ArH), 7.41–7.28 (m, 8H, ArH), 7.25–7.07 (m, 14H, ArH), 4.83 (d, *J* = 12.0 Hz, 1H, H-1), 4.76–4.67 (m, 4H, CH_2Ph), 4.62–4.52 (m, 4H, CH_2Ph), 3.94 (s, 3H), 3.87 (t, *J* = 8 Hz, 1H, H-4), 3.79–3.68 (m, 2H, H-6$_a$, H-6$_b$), 3.58 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{43}H_{43}N_3O_6SNa$ [M + Na]$^+$: *m/z* 752.2765; found: *m/z* 752.2776.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(4-nitrophenyl)-1,3,4-thiadiazole-2-amine* (**10e**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and 3-nitrobenzaldehyde **8e** (0.15 g) afforded **10e**: Yellow amorphous powder; yield 0.55 g, 74%; m.p. 140–141 °C; IR (ν_{max}/cm^{-1}) KBr: 3441, 3030, 2917, 1585, 1531, 1453, 1350, 1216, 1064; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (d, *J* = 9.1 Hz, 1H, NH), 8.50 (s, 1H), 8.31–8.25 (d, *J* = 8.0 Hz, 1H, ArH), 8.16 (d, *J* = 8.0 Hz, 1H, ArH), 7.78 (t, *J* = 8.0 Hz, 1H, ArH), 7.41–7.28 (m, 8H, ArH), 7.26–7.13 (m, 12H, ArH), 4.83 (d, *J* = 12.4 Hz, 1H, H-1), 4.71 (m, 4H, CH_2Ph), 4.64–4.52 (m, 4H, CH_2Ph), 3.87 (t, *J* = 8.0 Hz, 1H, H-1), 3.79–3.67 (m, 2H, H-6$_a$, H-6$_b$), 3.65–3.55 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{42}H_{40}N_4O_7SNa$ [M + Na]$^+$: *m/z* 767.2510; found: *m/z* 757.2502.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(4-hydroxylphenyl)-1,3,4-thiadiazole-2-amine* (**10f**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and p-hydroxybenzaldehyde **8f** (0.12 g) afforded **10f**: White amorphous powder; yield 0.58 g, 81%; m.p. 82–84 °C; IR (ν_{max}/cm^{-1}) KBr: 3421, 2922, 1607, 1453, 1361, 1283, 1052; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, OH), 8.23 (d, *J* = 8.4 Hz, 1H, NH), 7.58 (d, *J* = 8.7 Hz, 2H, ArH), 7.41–7.28 (m, 9H, ArH), 7.26–7.14 (m, 11H, ArH), 6.85 (d, *J* = 8.7 Hz, 2H, ArH), 4.82 (d, *J* = 12.4 Hz, 1H, H-1), 4.77–4.66 (m, 4H, CH_2Ph), 4.62–4.52 (m, 4H, CH_2Ph), 3.87 (t, *J* = 8.0 Hz, 1H, H-4), 3.77–3.67 (m, 2H, H-6$_a$, H-6$_b$), 3.58 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{42}H_{41}N_3O_6SNa$ [M + Na]$^+$: *m/z* 738.2608; found: *m/z* 738.2607.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(4-bromophenyl)-1,3,4-thiadiazole-2-amine* (**10g**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and 4-bromobenzaldehyde **8g** (0.185 g) afforded **10g**: White amorphous powder; yield 0.62 g, 80%; m.p. 142–143 °C; IR (ν_{max}/cm^{-1}) KBr: 3439, 3030, 2924, 1564, 1497, 1453, 1362, 1066; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, *J* = 9.0 Hz, 1H, NH), 7.73–7.65 (m, 4H, ArH), 7.40–7.28 (m, 8H, ArH), 7.25–7.12 (m, 12H, ArH), 4.82 (d, *J* = 12.5 Hz, 1H, H-1), 4.71 (m, 4H, CH_2Ph), 4.57 (m, 4H, CH_2Ph), 3.86 (t, *J* = 8.0 Hz, 1H, H-4), 3.78–3.67 (m, 2H, H-6$_a$, H-6$_b$), 3.63–3.53 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{42}H_{40}BrN_3O_5SNa$ [M + Na]$^+$: *m/z* 800.1764; found: *m/z* 800.1767.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(4-chlorophenyl)-1,3,4-thiadiazole-2-amine* (**10h**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and *p*-chlorobenzaldehyde **8h** (0.14 g) afforded **10h**: White amorphous powder; yield 0.57 g, 78%; m.p. 128–129 °C; IR (ν_{max}/cm^{-1}) KBr: 3441, 3030, 2924, 1585, 1497, 1398, 1065; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, *J* = 9.0 Hz, 1H, NH), 7.78 (d, *J* = 8.6 Hz, 2H, ArH), 7.55 (d, *J* = 8.6 Hz, 2H, ArH), 7.41–7.28 (m, 8H, ArH), 7.25–7.12 (m, 12H, ArH), 4.82 (d, *J* = 12.5 Hz, 1H, H-1), 4.76–4.66 (m, 4H, CH_2Ph), 4.63–4.52 (m, 4H, CH_2Ph), 3.86 (t, *J* = 8.0 Hz, 1H, H-4), 3.79–3.67 (m, 2H, H-6$_a$, H-6$_b$), 3.63–3.52 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{42}H_{40}ClN_3O_5SNa$ [M + Na]$^+$: *m/z* 756.2269; found: *m/z* 756.2278.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(4-fluorophenyl)-1,3,4-thiadiazole-2-amine* (**10i**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and *p*-fluorobenzaldehyde **8i** (0.107 mL) afforded **10i**: Pink amorphous powder; yield 0.54 g, 76%; m.p. 142–143 °C; IR (ν_{max}/cm^{-1}) KBr: 3431, 3030, 2919, 1601, 1586, 1517, 1363, 1228, 1068; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, *J* = 9.0 Hz, 1H, NH), 7.81 (dd, *J* = 8.8, 5.4 Hz, 2H, ArH), 7.41–7.27 (m, 10H, ArH), 7.26–7.12 (m, 12H, ArH), 4.82 (d, *J* = 12.5 Hz, 1H, H-1), 4.77–4.67 (m, 4H, CH_2Ph), 4.57 (m, 4H, CH_2Ph), 3.87 (t, *J* = 8.0 Hz, 1H, H-4), 3.78–3.67 (m, 2H, H-6$_a$, H-6$_b$), 3.64–3.53 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{42}H_{40}ClN_3O_5SNa$ [M + Na]$^+$: *m/z* 740.2565; found: *m/z* 740.2570.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(2,3-dichlorophenyl)-1,3,4-thiadiazole-2-amine* (**10j**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and 2,3-dichlorobenzaldehyde **8j** (0.175 g) afforded **10j**: White amorphous powder; yield 0.53 g, 70%; m.p. 137–138 °C; IR (ν_{max}/cm^{-1}) KBr: 3441, 3028, 2916, 1572, 1496, 1453, 1396, 1357, 1216, 1068. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (d, *J* = 9.1 Hz, 1H, NH), 7.93 (dd, *J* = 7.9, 1.3 Hz, 1H, ArH), 7.78 (dd, *J* = 8.0, 1.4 Hz, 1H, ArH), 7.51 (t, *J* = 8.0 Hz, 1H, ArH), 7.40–7.28 (m, 8H, ArH), 7.26–7.12 (m, 12H, ArH), 4.84 (d, *J* = 12.4 Hz, 1H, H-1), 4.77–4.67 (m, 4H, CH_2Ph), 4.64–4.51 (m, 4H, CH_2Ph), 3.84 (t, *J* = 8.0 Hz, 1H, H-4), 3.79–3.67 (m, 2H, H-6$_a$, H-6$_b$), 3.64–3.56 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{42}H_{39}Cl_2N_3O_5SNa$ [M + Na]$^+$: *m/z* 790.1880; found: *m/z* 790.1882.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-(2,4-dichlorophenyl)-1,3,4-thiadiazole-2-amine* (**10k**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and 2,4-dichlorobenzaldehyde **8k** (0.175 g) afforded **10k**: White amorphous powder; yield 0.56 g, 73%; m.p. 115–117 °C; IR (ν_{max}/cm^{-1}) KBr: 3433, 3204, 3025, 1549, 1482, 1355, 1309, 1059; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (d, *J* = 9.1 Hz, 1H, NH), 8.04 (d, *J* = 8.6 Hz, 1H, ArH), 7.81 (d, *J* = 2.1 Hz, 1H, ArH), 7.58 (dd, *J* = 8.6, 2.1 Hz, 1H, ArH), 7.40–7.27 (m, 8H, ArH), 7.25–7.12 (m, 12H, ArH), 4.83 (d, *J* = 12.4 Hz, 1H, H-1), 4.72 (m, 4H, CH_2Ph), 4.64–4.51 (m, 4H, CH_2Ph), 3.84 (t, *J* = 8.1 Hz, 1H, H-4), 3.79–3.68 (m, 2H, H-6$_a$, H-6$_b$), 3.64–3.54 (m, 3H, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{42}H_{39}Cl_2N_3O_5SNa$ [M + Na]$^+$: *m/z* 790.1880; found: *m/z* 790.1857.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-naphthyl-1,3,4-thiadiazole-2-amine* (**10l**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and 1-naphthaldehyde **8l** (0.156 g) afforded **10l**: Yellow amorphous powder; yield 0.64 g, 86%); m.p. 161–163 °C; IR (ν_{max}/cm^{-1}) KBr: 3432, 3172, 3028, 2917, 1562, 1512, 1357, 1215, 1070; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.74–8.65 (m, 1H, ArH), 8.39 (d, *J* = 9.1 Hz, 1H, NH), 8.05 (t, *J* = 7.7 Hz, 2H, ArH), 7.71 (d, *J* = 7.0 Hz, 1H, ArH), 7.67–7.56 (m, 3H, ArH), 7.41–7.15 (m, 20H, ArH), 4.86 (d, *J* = 12.4 Hz, 1H, H-1), 4.80–4.70 (m, 4H, CH_2Ph), 4.67–4.50 (m, 4H, CH_2Ph), 3.90 (t, *J* = 8.0 Hz, 1H, H-4), 3.80–3.68 (m, 2H, H-6$_a$, H-6$_b$), 3.69–3.57 (m, 3H, H-5, H-3, H-2); HRMS (ESI) calcd for $C_{46}H_{43}N_3O_5SNa$ [M + Na]$^+$: *m/z* 772.2816; found: *m/z* 772.2818.

N-*(1,3,4,6-tetra*-O-*benzyl-2-deoxy*-β-*D-glucopyranosyl)-5-octyl-1,3,4-thiadiazole-2-amine* (**10m**): Following the general procedure, the reaction of glycosyl isothiocyanate **6** (0.58 g), hydrazine hydrate **7** (0.1 mL), and nonanal **8m** (0.18 mL) afforded **10m**: Yellow amorphous powder; yield 0.62 g, 85%; m.p. 68–69 °C; IR (ν_{max}/cm^{-1}) KBr: 3322, 3029, 2922, 1533, 1497, 1452, 1307, 1060; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, *J* = 8.5 Hz, 1H, NH), 7.40–7.13 (m, 20H, ArH), 4.81 (d, *J* = 12.4 Hz, 1H, H-1), 4.74–4.63 (m, 4H, CH_2Ph), 4.56 (m, 4H, CH_2Ph), 3.81 (t, *J* = 8.0 Hz, 1H, H-4), 3.77–3.66 (m, 2H, H-6$_a$, H-6$_b$), 3.59–3.48 (m, 3H, H-5, H-3, H-2), 1.61 (m, 2H, CH_2), 1.25 (m, 12H, CH_2), 0.85 (t, *J* = 6.8 Hz, 3H, CH_3); HRMS (ESI) calcd for $C_{44}H_{53}N_3O_5SNa$ [M + Na]$^+$: *m/z* 758.3598; found: *m/z* 758.3609.

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Electronic Supplementary Information

The ESI [1H NMR and HRMS (ESI) spectral data Fig. S1–S28] is available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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