Weiwei Liu*, Quxiang Li*, Fengchang Cheng, Dahua Shi and Zhiling Cao

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

Abstract: A convenient and practical protocol was developed to synthesize glycosyl 1,3,4-oxadiazoles from D-glucosamine with good to excellent yields. The key step involved *p*-TsCl/pyridine-mediated cyclization under mild conditions. Subsequent removal of the acetyl groups in the last step, conducted using the system of NaOMe/MeOH, gave the desired *N*-acetyl-D-glucosamine 1,3,4-oxadiazole derivatives.

Keywords: cyclization; derivatives; D-Glucosamine; 1,3,4-oxadiazole.

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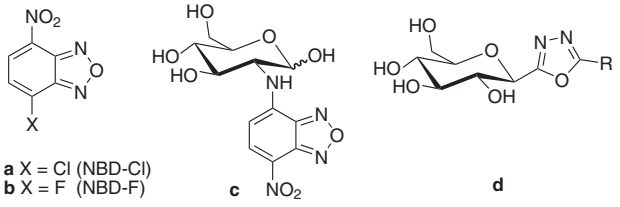
Introduction

The synthesis of novel molecular scaffolds with unique structural and biological properties is an increasingly active area of current chemical research [1]. Glycobiology and carbohydrate chemistry have been paid enormous attention over the past few years owing to the remarkable role played in many biological events [2–4]. D-Glucosamine, a natural amino monosaccharide, widely exists in marine organisms' shell [5] and is an indispensable substance in pharmacology [6]. Moreover, D-glucosamine and its derivatives are found in numerous biologically active molecules such as cell surface *N*-glycoproteins, proteoglycans, glycosphingolipids, lipopolysaccharides, and chitin/chitosan [7–11]. Recent studies have demonstrated that they show a broad range of biological activities like antibacterial, antitumor, antiviral, anticancer, antioxidant, and anti-inflammatory properties [12–15]. Meanwhile, 1,3,4-oxadiazoles are commonly utilized pharmacophores due to their metabolic profile and ability to engage in hydrogen bonding, which has attracted considerable interest in medicinal chemistry, as they are associated with versatile effects, including antifungal, antimicrobial, antihypertensive, antitubercular, immunosuppressive, analgesic, and sedative properties [16–19]. In particular, marketed antihypertensive agents such as tiodazosin and nesapidil as well as antibiotics such as furamizole all contain the oxadiazole system [20–22]. 1,3,4-Oxadiazole-containing compounds are also used as HIV integrase inhibitors and angiogenesis inhibitors [23, 24].

Synthesis of the 7-nitrobenz-2,1,3-oxadiazole derivatives *via* the base-catalyzed reaction of the corresponding halide (either chloride **a** or fluoride **b,** Figure 1) with D-glucosamine to produce the highly fluorescent product **c** [25] has been reported. Another report describes the synthesis of 1,3,4-oxadiazole-linked derivatives of D-glucose **d** by acylation with propiolic acid-DCC or chloroacetyl chloride to give novel inhibitors of glycogen phosphorylase [26].

Chemical modifications of D-glucosamine at the glycoside hydroxy group mainly rely on glycosylation [27, 28], alkylation [29, 30], arylation [31, 32], and phospholipid formation [33, 34]. Synthesis of compounds containing both 1,3,4-oxadiazole and D-glucosamine have not been investigated *via* the links of the nitrogen glycoside. Herein we report a mild and efficient protocol for synthesis of glycosyl 1,3,4-oxadiazole derivatives *via* *p*-TsCl/pyridine mediated cyclization. The *p*-TsCl reagent replaces some



a X = Cl (NBD-Cl)
b X = F (NBD-F)
c
d

Figure 1 1,3,4-Oxadiazole derivatives **a–d**.

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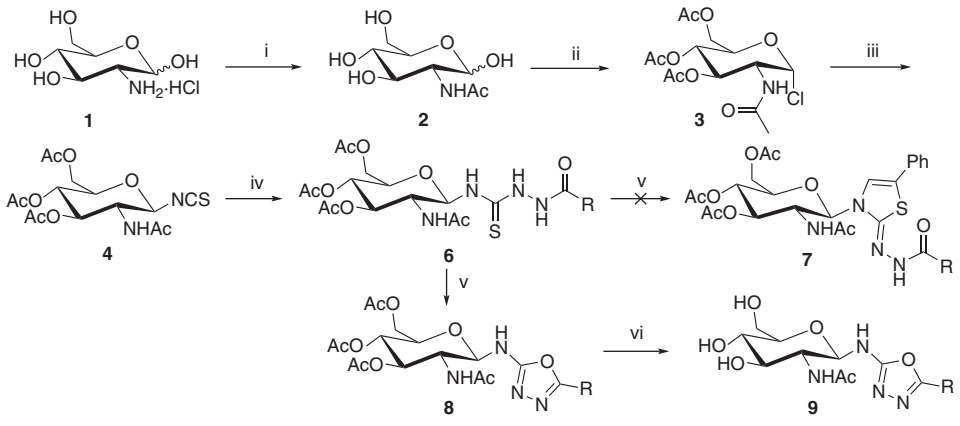
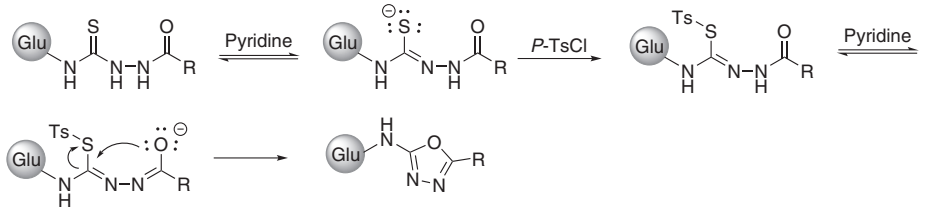


6a, 7a, 8a, 9a: R = CH_3
6b, 7b, 8b, 9b: R = C_6H_5
6c, 7c, 8c, 9c: R = 4-$CH_3C_6H_4$
6d,7d, 8d, 9d: R = 3-$CH_3OC_6H_4$
6e, 7e, 8e, 9e: R = 4-FC_6H_4
6f, 7f, 8f, 9f: R = 4-ClC_6H_4
6g, 7g, 8g, 9g: R = 4-IC_6H_4
6h, 7h, 8h, 9h: R = 4-$NO_2C_6H_4$
6i, 7i, 8i, 9i: R = 4-OHC_6H_4
6j, 7j, 8j, 9j: R = 4-$[(CH_3)_2N]C_6H_4$
6k, 7k, 8k, 9k: R = 2-pyridyl
6l, 7l, 8l, 9l: R = 2-thienyl

Scheme 1 (i) Ac_2O, TEA, MeOH, 0°C; (ii) CH_3COCl, rt; (iii) KSCN, $(n\text{-}C_4H_9)_4NHSO_4$, CH_3CN, 4-Å molecular sieves; (iv) $RCONHNH_2$ (**5**), EtOH, reflux; (v) *p*-TsCl, pyridine, THF, 65°C, or 2-bromoacetophenone, TEA (see text); (vi) NaOMe, MeOH, 23°C.



Scheme 2 Proposed mechanism of cyclization of **6** by the system *p*-TsCl/pyridine in tetrahydrofuran.

sensitive reagents such as $POCl_3$, DCC, concentrated H_2SO_4, among others. Importantly, different substituted derivatives of glycosyl-1,3,4-oxadiazole can also be obtained using the present method.

Results and discussion

First, *N*-acetylglucosamine **2** [35] was prepared from glucosamine hydrochloride **1**. By treatment of **1** with acetic anhydride in the presence of triethylamine (Scheme 1). Compound **4** was synthesized according to the literature protocol [36] using the reaction of glycosyl chloride **3** [37] with potassium thiocyanate in acetonitrile and then treated with various hydrazides **5** in ethanol to yield the key acylthiosemicarbazide intermediates **6**. Initially, compound **6a** (R=CH_3) was selected as substrate to be directly cyclized by treatment with 2-bromoacetophenone in the presence of a catalytic amount of triethylamine but this attempted cyclization did not yield the desired glycosylthiazole **7a**. Fortunately, this treatment produced the glycosyl-1,3,4-oxadiazole **8a**. Encouraged by this result, other substituted acylthiosemicarbazides were investigated to examine the generality of this reaction. To our disappointment, the expected products were obtained in low yield and the procedure was time consuming.

It was thought that acylthiosemicarbazides could be activated toward cyclization of **6** by the reaction with tosyl chloride in the presence of pyridine [38]. Gratifyingly, the desired glycosyl-1,3,4-oxadiazoles **8** were obtained in high yields of up to 90% using this approach. It was found substrates **6** with both electron-withdrawing and electron-donating groups can be smoothly converted to the desired products **8**. Furthermore, it is noteworthy that acylthiosemicarbazides carrying heterocyclic groups such as pyridyl and thienyl also readily participate in the reaction. The proposed mechanism is shown in Scheme 2. The acetyl derivatives **8** were efficiently deprotected to the hydroxyl derivatives **9** as shown in Scheme 1.

Conclusions

The synthesis of a novel class of D-glucosamine-based 1,3,4-oxadiazole derivatives is described. The most noteworthy aspect of this research is the development of a mild and convenient route to the synthesis of glycosyl-1,3,4-oxadiazoles by cyclization of the hydrazides using a system of *p*-TsCl/pyridine. D-Glucosamine and its derivatives play an important role in biomedical research.

Experimental

All chemicals were purchased from commercial sources and used without further purification. Melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance 400 M Hz instrument using DMSO-d_6 or D_2O. 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. Flash column chromatography was performed on silica 200–300 mesh.

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl isothiocyanate (4)

This compound was obtained using the following modification of the previously published procedure [36]. A mixture of glucosamine hydrochloride (**1**, 10 g, 46.37 mmol), acetic anhydride (6.13 mL, 55.64 mmol), and triethylamine (6.46 mL, 46.37 mmol) in methanol (25 mL) was stirred in an ice bath for 4 h. The mixture was filtered, and the solid product **2** was dried and dissolved in acetyl chloride (30 mL). The solution was stirred for 16 h at room temperature and then extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution, dried over $MgSO_4$, and concentrated, and the residue was crystallized from ether to give **3**. A mixture of KSCN (0.58 g, 6 mmol), tetrabutylammonium hydrogen sulfate (0.34 g, 1 mmol), and molecular sieves (4 Å, 3.0 g) in anhydrous acetonitrile (30 mL) was stirred at room temperature for 2.5 h and then treated with compound **3** (1.1 g, 3 mmol)**.** The mixture was heated under reflux until the reaction was completed, as judged by TLC analysis. The resultant suspension was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes) to afford **4** (0.87 g, 75%) as a white solid; mp 158–159°C; ^{1}H NMR (DMSO-d_6): δ 8.25 (d, J = 9 Hz, 1H), 5.36 (d, J = 9 Hz, 1H), 5.11 (t, J = 9 Hz, 1H), 4.9 (t, J = 9 Hz, 1H), 4.12–4.05(m, 4H), 2.03–1.82 (4s, 12H). HRMS (ESI). Calcd for $C_{15}H_{20}N_2O_8SNa$ $(M+Na)^+$: *m/z* 411.0833. Found: *m/z* 411.0844.

General procedure for the preparation of glycosyl acylthiosemicarbazides 6a–l

Glycosyl isothiocyanate **4** (0.39 g, 1 mmol) was added in one portion to a stirred solution of hydrazide **5** (1 mmol) in 10 mL ethanol. The mixture was heated under reflux for 1.5 h, and then the solvent was removed on a rotary evaporator. The residue was crystallized from aqueous ethanol to obtain the desired product. Characterization of the representative compound **6b** is presented below.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N'*-5-benzoyl thiosemicarbazide (6b):** White solid; yield 87%; mp 202–203°C; IR: *v* 3274, 2931, 2931, 1751, 1668, 1239, 1043, 910 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.29 (br s, 1H), 10.11 (br s, 1H), 8.21 (d, J = 9 Hz, 1H), 8.03 (s, 1H), 7.81 (m, 2H), 7.46 (m, 3H), 5.44(t, J = 9 Hz, 1H), 5.13 (d, J = 10 Hz, 1H), 4.82 (d, J = 9 Hz, 1H), 4.18 (s, 1H), 3.94 (d, J = 11 Hz, 2H), 3.81(s, 1H), 1.95–1.73 (4s, 12H). HRMS (ESI). Calcd for $C_{22}H_{28}N_4O_9SNa$ $(M+Na)^+$: *m/z* 547.1469. Found: *m/z* 547.1478.

General procedure for the preparation of glycosyl 1,3,4-oxadiazoles 8a–l

Tosyl chloride (0.21 g, 1.1 mmol) was added to a stirred solution of acylthiosemicarbazide **6** (1 mmol) and pyridine (0.16 mL, 2.0 mmol) in 5 mL THF. The solution was stirred at 65°C for 6 h and then extracted with dichloromethane (DCM, 20 mL) and distilled water (15 mL). The aqueous layer was re-extracted three times with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated to obtain the crude product, which was purified by column chromatography on silica gel (MeOH/DCM).

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-methyl-1,3,4-oxadiazole-2-amine (8a):** White solid; yield 84%; mp 148–149°C; IR: *v* 3326, 2928, 1749, 1663, 1243, 1041, 913 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.33 (d, J = 9 Hz, 1H), 8.06 (d, J = 9 Hz, 1H), 5.18 (m, 2H), 4.85 (t, J = 10 Hz, 1H), 4.20 (dd, J = 12 and 4 Hz, 1H), 3.93 (dd, J = 20 and 10 Hz, 3H), 1.98–1.74 (4s, 12H), 1.24 (s, 3H). HRMS (ESI). Calcd for $C_{17}H_{24}N_4O_9Na$ $(M+Na)^+$: *m/z* 451.1435. Found: *m/z* 451.1477.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-phenyl-1,3,4-oxadiazole-2-amine (8b):** White solid; yield 90%; mp 231–232°C; IR: *v* 3220, 2966, 1749, 1663, 1616, 1228, 1049, 917 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.86 (d, J = 10 Hz, 1H), 8.08 (d, J = 9 Hz, 1H), 7.85 (dd, J = 7 and 4 Hz, 2H), 7.55 (m, 3H), 5.21(m, 2H), 4.87 (t, J = 10 Hz, 1H), 4.20 (dd, J = 12 and 4 Hz, 1H), 3.99 (q, J = 9 Hz, 3H), 1.98–1.74 (4s, 12H). HRMS (ESI). Calcd for $C_{22}H_{26}N_4O_9Na$ (M+Na)+: *m/z* 513.1592. Found: *m/z* 513.1594.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-methylphenyl)-1,3,4-oxadiazole-2-amine (8c):** White solid; yield 92%; mp 194–195°C; IR: *v* 3315, 2926, 1749, 1667, 1621, 1227, 1043, 916 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.79 (d, J = 9 Hz, 1H), 8.06 (d, J = 9 Hz, 1H), 7.73 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H), 5.20 (td, J = 10 and 5 Hz, 2H), 4.87 (t, J = 10 Hz, 1H), 4.19 (m, 1H), 3.97 (t, J = 10 Hz, 3H), 2.37 (s, 3H), 1.96–1.74 (4s, 12H). HRMS (ESI). Calcd for $C_{23}H_{28}N_4O_9Na$ $(M+Na)^+$: m/z 527.1748. Found: m/z 527.1750.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole-2-amine (8d):** White solid; yield 88%; mp193–194°C; IR: *v* 3316, 2946, 1746, 1666, 1622, 1242, 1044, 917 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.84 (d, J = 10 Hz, 1H), 8.05 (d, J = 9 Hz, 1H), 7.43 (m, 2H), 7.31 (s, 1H), 7.10 (d, J = 8 Hz, 1H), 5.18 (td, J = 10 and 4 Hz, 2H), 4.86 (t, J = 10 Hz, 1H), 4.18 (dd, J = 12 and 4 Hz, 1H), 3.97 (m, 3H), 3.81 (s, 3 H), 1.94–1.72 (4s, 12H). HRMS (ESI). Calcd for $C_{23}H_{28}N_4O_{10}Na$ $(M+Na)^+$: m/z 543.1698. Found: m/z 543.1703.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole-2-amine (8e):** White solid; yield 82%; mp 210–211°C; IR: *v* 3383, 2957, 1749, 1668, 1624, 1227, 1045, 917 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.83 (d, *J* = 10 Hz, 1H), 8.06 (d, *J* = 9 Hz, 1H), 7.90 (dd, *J* = 9 and 5 Hz, 2H), 7.41 (t, *J* = 9 Hz, 2H), 5.20 (td, *J* = 10 and 6 Hz, 2H), 4.87 (t, *J* = 10 Hz, 1H), 4.19 (dd, *J* = 12 and 5 Hz, 1H), 3.98 (m, 3H), 1.96–1.74 (4s, 12H). HRMS (ESI). Calcd for $C_{22}H_{26}FN_4O_9$ $(M+H)^+$: *m/z* 509.1678. Found: *m/z* 509.1692.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole-2-amine (8f):** White solid; yield 64%; mp 189–190°C; IR: *v* 3321, 2952, 1743, 1666, 1617, 1245, 1041, 916 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.97 (d, *J* = 10 Hz, 1H), 8.08 (d, *J* = 9 Hz, 1H), 7.86 (dd, *J* = 8 and 2 Hz, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.54 (td, *J* = 8 and 6 Hz, 2H), 5.20 (td, *J* = 10 and 6 Hz, 2H), 4.87 (t, *J* = 10 Hz, 1H), 4.20 (dd, *J* = 12 and 4 Hz, 1H), 3.97 (m, 3H), 1.96–1.75 (4s, 12H). HRMS (ESI). Calcd for $C_{22}H_{25}ClN_4O_9Na$ $(M+Na)^+$: *m/z* 547.1202. Found: *m/z* 547.1212.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-iodophenyl)-1,3,4-oxadiazole-2-amine (8g):** White solid; yield 78%; mp 224–225°C; IR: *v* 3421, 2924, 1747, 1662, 1624, 1224, 1045, 915 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.89 (d, *J* = 10 Hz, 1H), 8.06 (d, *J* = 9 Hz, 1H), 7.93 (d, *J* = 9 Hz, 2H), 7.61 (d, *J* = 9 Hz, 2H), 5.20 (td, *J* = 10 and 4 Hz, 2H), 4.87 (t, *J* = 10 Hz, 1H), 4.19 (dd, *J* = 12 and 4 Hz, 1H), 3.98 (m, 3H), 1.98–1.74 (4s, 12 H). HRMS (ESI). Calcd for $C_{22}H_{25}IN_4O_9Na$ $(M+Na)^+$: *m/z* 639.0558. Found: *m/z* 639.0547.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole-2-amine (8h):** Yellow solid; yield 75%; mp 205–206°C; IR: *v* 3334, 2956, 1746, 1665, 1617, 1225, 1046, 917 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.13 (d, *J* = 10 Hz, 1H), 8.39 (d, *J* = 9 Hz, 2H), 8.09 (d, *J* = 9 Hz, 3H), 5.23 (m, 2H), 4.87 (t, *J* = 10 Hz, 1H), 4.20 (m, 1H), 4.00 (m, 3H), 1.97–1.74 (4s, 12H). HRMS (ESI). Calcd for $C_{22}H_{26}N_5O_{11}$ $(M+H)^+$: *m/z* 536.1623. Found: *m/z* 536.1621.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazole-2-amine (8i):** White solid; yield 80%; mp 182–184°C; IR: *v* 3392, 3054, 1752, 1630, 1611, 1238, 1045, 916 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.12 (s, 1H), 8.65 (d, *J* = 10 Hz, 1H), 8.04 (d, *J* = 9 Hz, 1H), 7.67 (d, *J* = 9 Hz, 2H), 6.90 (d, *J* = 9 Hz, 2H), 5.18 (dt, *J* = 14 and 10 Hz, 2H), 4.86 (t, *J* = 10 Hz, 1H), 4.19 (dd, *J* = 12 and 4 Hz, 1H), 3.96 (m, 3H), 1.98–1.74 (4s, 12H). HRMS (ESI). Calcd for $C_{22}H_{26}N_4O_{10}Na$ $(M+Na)^+$: *m/z* 529.1541. Found: *m/z* 529.1537.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-*N*,*N*-dimethylphenyl-1,3,4-oxadiazole-2-amine (8j):** White solid; yield 87%; mp 222–223°C; IR: *v* 3421, 2924, 1747, 1662, 1624, 1224, 1045, 915 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.58 (d, *J* = 10 Hz, 1H), 8.05 (d, *J* = 9 Hz, 1H), 7.63 (d, *J* = 9 Hz, 2H), 6.80 (d, *J* = 9 Hz, 2H), 5.18 (dt, *J* = 17 and 10 Hz, 2H), 4.86 (t, *J* = 10 Hz, 1H), 4.20 (dd, *J* = 12 and 4 Hz, 1H), 3.96 (m, 3H), 2.99 (s, 6H), 1.99–1.75 (4s, 12H). HRMS (ESI). Calcd for $C_{24}H_{31}N_5O_9Na$ $(M+Na)^+$: *m/z* 556.2014. Found: *m/z* 556.2015.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(2-pyridyl)-1,3,4-oxadiazole-2-amine (8k):** Yellow solid; yield 79%; mp182–184°C; IR: *v* 3393, 2926, 1750, 1665, 1618, 1227, 1049, 916 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.03 (d, *J* = 2 Hz, 1H), 8.95 (d, *J* = 10 Hz, 1H), 8.72 (d, *J* = 4 Hz, 1H), 8.21 (dt, *J* = 8.0 and 2 Hz, 1H), 8.05 (d, *J* = 9 Hz, 1H), 7.59 (dd, *J* = 8 and 5 Hz, 1H), 5.21 (dt, *J* = 10 and 2 Hz, 2H), 4.89 (dd, *J* = 12 and 7 Hz, 1H), 4.01 (dd, *J* = 12 and 4 Hz, 1H), 3.98 (m, 3H), 1.99–1.74 (4s, 12H). HRMS (ESI). Calcd for $C_{21}H_{25}N_5O_9Na$ $(M+Na)^+$: *m/z* 514.1544. Found: *m/z* 514.1548.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(2-thienyl)-1,3,4-oxadiazole-2-amine (8l):** White solid; yield 81%; mp 204–206°C; IR: *v* 3406, 2964, 1749, 1662, 1623, 1240, 1038, 905 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.85 (d, *J* = 10 Hz, 1H), 8.04 (d, *J* = 9 Hz, 1H), 8.04 (d, *J* = 9 Hz, 1H), 7.81 (d, *J* = 5 Hz, 1H), 7.59 (d, *J* = 3 Hz, 1H), 7.23 (dd, *J* = 5 and 3 Hz, 1H), 5.18 (dt, *J* = 14 and 10 Hz, 2H), 4.86 (t, *J* = 10 Hz, 1H), 4.20 (dd, *J* = 12 and 5 Hz, 1H), 4.00 (m, 3H), 1.98–1.74 (4s, 12H). HRMS (ESI). Calcd for $C_{20}H_{24}N_4O_9SNa$ $(M+Na)^+$: *m/z* 519.1156. Found: *m/z* 519.1163.

General procedure for deprotection of *O*-acetyl-substituted compounds 8 to hydroxy derivatives 9

A solution of compound **8** (0.5 mmol) in methanol (5 mL) was treated with sodium methoxide (1 M in methanol, 0.2 mL). The mixture was stirred at ambient temperature for 2 h and then neutralized with Amberlite IR 120 H^+ resin and filtered. The filtrate was concentrated to afford the deprotected product **9**. Selected products **9c,d,g,j** are characterized below.

***N*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-(4-methylphenyl)-1,3,4-oxadiazole-2-amine (9c):** White solid; yield 95%; mp 197–198°C; IR: *v* 3419, 1629, 1579, 1413, 1316, 1052, 820 cm^{-1}; ^1H NMR (D_2O): δ 7.72 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 4.79 (t, *J* = 9 Hz, 1H), 3.66–3.15 (m, 6H), 2.34 (s, 3H), 1.81(s, 3H). HRMS (ESI). Calcd for $C_{17}H_{22}N_4O_6Na$ $(M+Na)^+$: *m/z* 401.1432. Found: *m/z* 401.1439.

***N*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole-2-amine (9d):** White solid; yield 92%; mp 172–173°C; IR: *v* 3416, 1629, 1581, 1424, 1287, 1042, 853 cm^{-1}; ^1H NMR (D_2O): δ 7.46 (d, *J* = 8 Hz, 1H), 7.32 (dd, *J* = 3 and 2 Hz, 1H), 7.11 (m, 1H), 4.78 (t, *J* = 9 Hz, 1H), 3.83 (s, 3H), 3.65–3.12 (m, 6H), 1.79 (s, 3H). HRMS (ESI). Calcd for $C_{17}H_{22}N_4O_7K$ $(M+K)^+$: *m/z* 433.1120. Found: *m/z* 433.1120.

***N*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-(4-iodophenyl)-1,3,4-oxadiazole-2-amine (9g):** White solid; yield 84%; m.p168–169°C; IR: *v* 3388, 2923, 1626, 1530, 1386, 1067, 892 cm^{-1}; ^1H NMR (D_2O): δ 7.92 (m, 2H), 7.68 (m, 2H), 4.90 (t, *J* = 10 Hz, 1H), 3.90–3.39 (m, 6H), 1.99 (s, 1H). HRMS (ESI). Calcd for $C_{16}H_{19}IN_4O_6Na$ $(M+Na)^+$: *m/z* 513.0241. Found: *m/z* 513.0246.

***N*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-(4-*N*,*N*-dimehylphenyl-1,3,4-oxadiazole-2-amine (9j):** White solid; yield 89%; mp179–180°C; IR: *v* 3447, 2914, 1626, 1578, 1439, 1082, 814 cm^{-1}; ^1H NMR (D_2O): δ 7.71 (d, *J* = 9 Hz, 2H), 6.85 (d, *J* = 9 Hz, 2H), 4.84 (t, *J* = 10 Hz, 1H), 372 (dd, *J* = 16 and 10 Hz, 2H), 3.54 (dd, *J* = 12 and 5 Hz, 1H), 3.48 (t, *J* = 9 Hz, 1H), 3.34 (m, 1H), 3.24 (t, *J* = 9 Hz, 1H), 3.02 (s, 6H), 1.90 (s, 3H). HRMS (ESI). Calcd for $C_{18}H_{25}N_5O_6Na$ $(M+Na)^+$: *m/z* 430.1697. Found: *m/z* 430.1695.

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