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Note

Synthesis of glycosyl-triazole linked 1,2,4-oxadiazoles

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Abstract—The synthesis of four different types of oxadiazoles containing a terminal acetylenic group is described. Reaction of these oxadiazoles with various azidoglycosides via a copper-catalyzed [3+2] cycloaddition ('click chemistry') afforded the corresponding glycosyl-triazole linked 1,2,4-oxadiazoles in good yields.
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Keywords: Glycosyl azide; 1,2,4-Oxadiazole; [3+2] Cycloaddition; Copper catalyst

1,2,4-Oxadiazoles are a class of important heterocycles. Many compounds incorporating the 1,2,4-oxadiazole ring system showed a large variety of biological properties.[1,2] Moreover, substituted 1,2,4-oxadiazoles have also been receiving considerable attention as heterocyclic amide and ester bioisosteres, and have been implicated in peptide chemistry and in the development of peptidomimetics.[3]

Due to these important biological properties, it would be interesting to incorporate these oxadiazole units in carbohydrate framework. The reason for this is that tying up of sugars to other simpler molecules is often employed to deal with targeting mechanism of action and/or pharmacology.[4] Surprisingly, only a few attempts have been made in order to synthesize carbohydrate oxadiazole. Oxadiazoles linked to a glycofuranose,[5] glycopyranose,[3c,6] and also an unsaturated glycopyranose[7] skeleton have been described in the literature. In a program concerning the incorporation of heterocyclic moieties in carbohydrates, we report in this paper a detailed account of the preparation of a complex triheterocyclic system containing a sugar, a triazole, and an oxadiazole rings in one molecule.

We hypothesized that the oxadiazole framework could be linked to the glycoside using the copper-catalyzed procedure for the [3+2] cycloaddition (or 'click chemistry')[8] between a glycoside containing an anomeric azide functionality and an oxadiazole bearing a terminal acetylenic group. Moreover, it has been shown that the triazole linkage at the anomeric position of carbohydrates is stable under a large variety of acidic or basic conditions.[9]

In order to achieve this goal, we prepared 1,2,4-oxadiazoles bearing a terminal acetylenic group. It was expected that this functionality could be introduced at position 5 (compounds **1a**,**b** and **2a**,**b**) or at position 3 (compounds **3a**,**b** and **4**) of the oxadiazole framework (Scheme 1). The chosen substructures are present in some compounds showing, for example, anti-inflammatory and anti-microbial properties (structures **1**–**3**),[10] or acting as S1P receptor agonist (structures **1**, **3**, and **4**),[2c–f] or IL-8 receptor antagonist (structure **1**).[11]

The synthesis of these four different types of oxadiazoles **1**–**4** carrying a terminal acetylene function is

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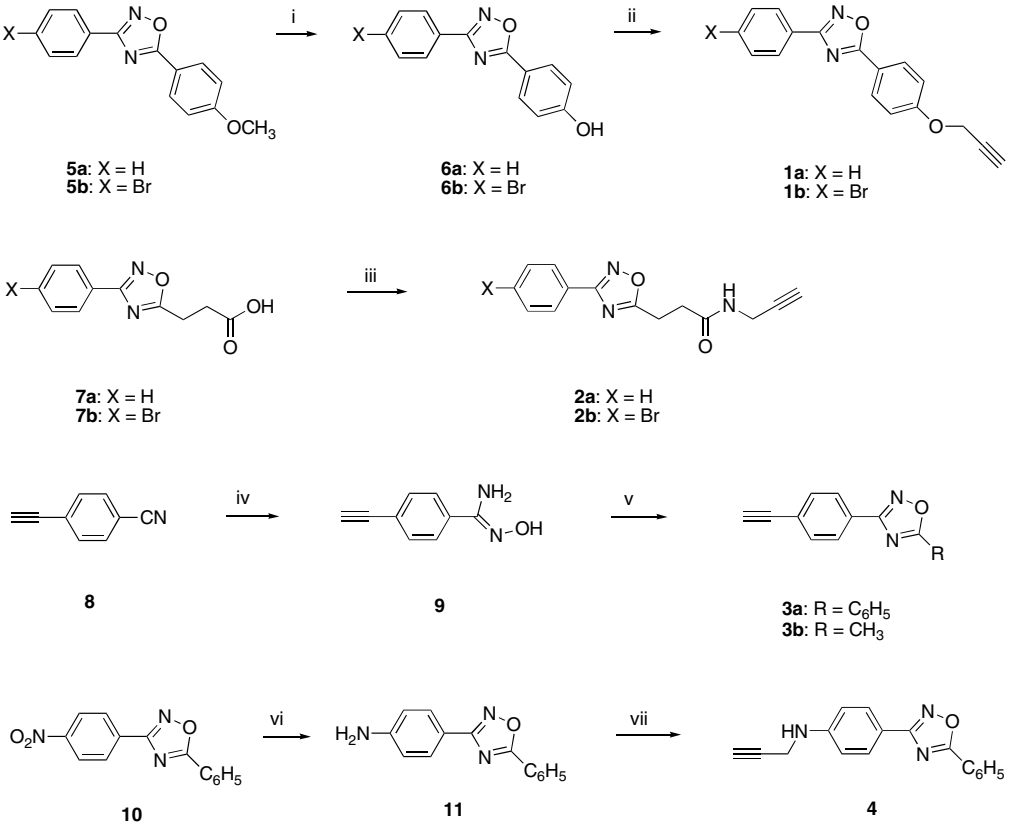


Scheme 1. Synthesis of acetylenic 1,2,4-oxadiazoles **2**, **3**, and **4**. Reagents and conditions: (i) BBr_3, CH_2Cl_2, reflux, 20 h; (ii) $HC{\equiv}CCH_2Br$, K_2CO_3, DMF, rt, 30 h; (iii) $HC{\equiv}CCH_2NH_2$, *N*-CH_3-morpholine, $ClCO_2$–*i*-Bu, 24 h, rt; (iv) NH_2OH, HCl, $NaHCO_3$, then 4-NC–$C_6H_4C{\equiv}CH$, C_2H_5OH, 3 days, rt; (v) $C_6H_5CO_2H$, DCC, CH_2Cl_2, 3 h, rt, then 110–120 °C; (vi) $SnCl_2$, C_2H_5OH, reflux; (vii) $HC{\equiv}CCH_2Br$, K_2CO_3, DMF, rt, 36 h.

depicted in Scheme 1. 5-Anisyl-1,2,4-oxadiazoles **5a**,**b** were obtained by condensation of the corresponding benzamidoximes with *p*-anisoyl chloride.[12] Deprotection of the aryl methyl ether of compounds **5a**,**b** with boron tribromide in dichloromethane afforded 5-(4-hydroxyphenyl) oxadiazoles **6a** and **6b** in 53% and 64% yields, respectively. Condensation of oxadiazoles **6a** and **6b** with propargylic bromide gave the corresponding acetylenic oxadiazoles **1a** and **1b** in 57% and 76% chemical yields, respectively.

Reaction of 3-(1,2,4-oxadiazol-5-yl)propionic acids **7a**,**b**[13] with *iso*butyl chloroformate and propargyl amine afforded acetylenic oxadiazoles **2a** and **2b** in 78% and 71% yields, respectively.

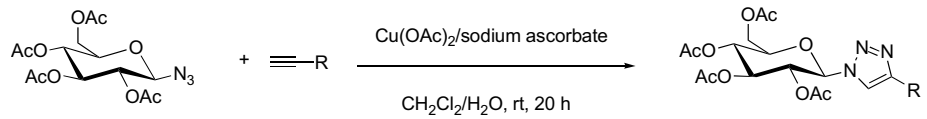
The synthesis of acetylenic oxadiazoles **3a**,**b** was performed in a one-pot reaction starting from 4-ethynylbenzonitrile (**8**). Treatment of nitrile **8** with hydroxylamine hydrochloride in the presence of sodium hydrogencarbonate afforded amidoxime **9**, whose reaction with benzoic acid in the presence of dicyclohexylcarbodiimide, followed by heating at 110 °C, afforded oxadiazole **3a** in an overall yield of 54%. Oxadiazole **3b** was obtained in 61% overall yield by heating of amidoxime **9** with acetic anhydride.

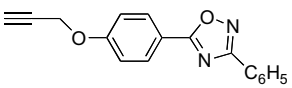
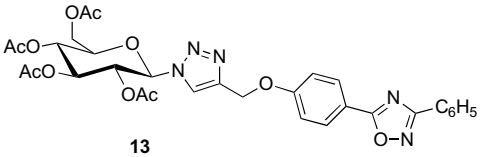
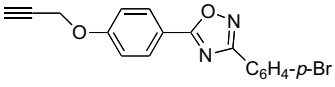
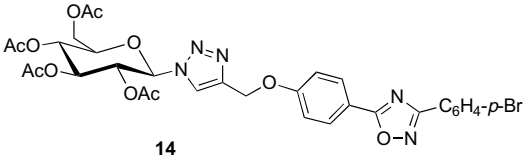
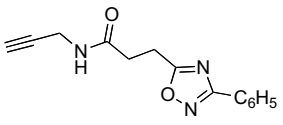
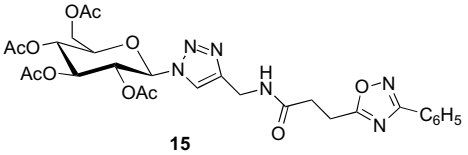
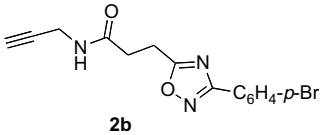
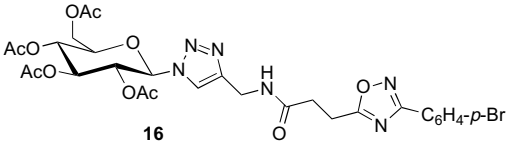
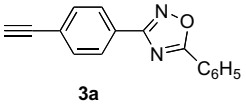
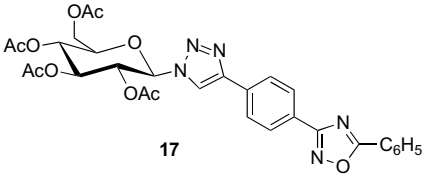
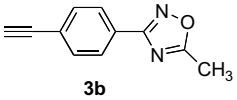
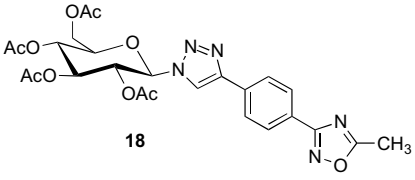
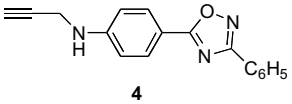
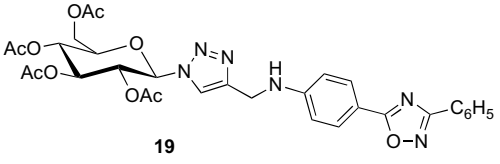
Finally, reduction of 4-nitrophenyl-5-phenyl-1,2,4-oxadiazole **10**[14] with tin chloride gave amino oxadiazole **11**, whose in situ condensation with propargyl bromide afforded acetylenic oxadiazole **4** in 63% overall yield.

The copper(I)-catalyzed 1,3-dipolar cycloaddition of all terminal alkynes **1**–**4** was initially performed with β-glucosyl azide **12** using a 1:1 mixture of dichloromethane and water as the solvent in the presence of $Cu(OAc)_2$ and sodium ascorbate (Table 1).[15] *O*-Propargyloxadiazoles **1a** and **1b** gave the corresponding cycloadducts **13** and **14** in 80% and 60% yields, respectively, after 16 h (Table 1, entries 1 and 2). *N*-Propargylpropaneamido- and 4-propargylaminophenyl-1,2,4-oxadiazoles **2a**, **2b**, and **4** also gave the desired β-glycosyl-triazole linked 1,2,4-oxadiazoles **15**, **16**, and **19**, in 85%, 43%, and 67% yield, respectively (Table 1, entries 3, 4, and 7). Finally, cycloaddition of ethynylphenyl oxadiazoles **3a** and **3b** with azidoglucoside **12** afforded the corresponding cycloadducts **17** and **18** in 61% and 80% chemical yields, respectively.

Among the β-glucosyl 1,2,4-oxadiazoles obtained, bromooxadiazole **16** is an interesting compound for further functionalization. For example, the palladium-catalyzed Suzuki coupling reaction between oxadiazole **14** and phenylboronic acid performed in a water/ethanol/toluene mixture afforded the coupled product **20** in 44% chemical yield (Scheme 2).

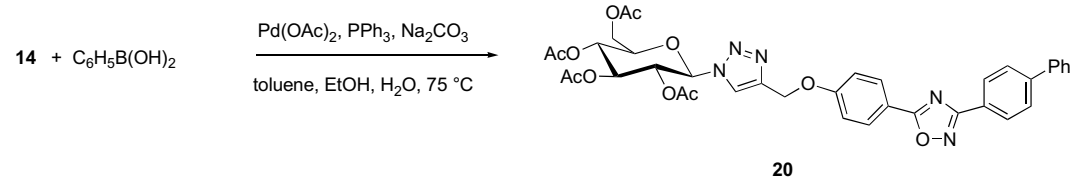
Table 1. Synthesis of glucosyl 1,2,4-oxadiazoles from β-glucosylazide **12** and various acetylenic 1,2,4-oxadiazoles



Entry	Oxadiazole	Products	Yield (%)
1	 **1a**	 **13**	80
2	 **1b**	 **14**	60
3	 **2a**	 **15**	85
4	 **2b**	 **16**	43
5	 **3a**	 **17**	61
6	 **3b**	 **18**	80
7	 **4**	 **19**	67

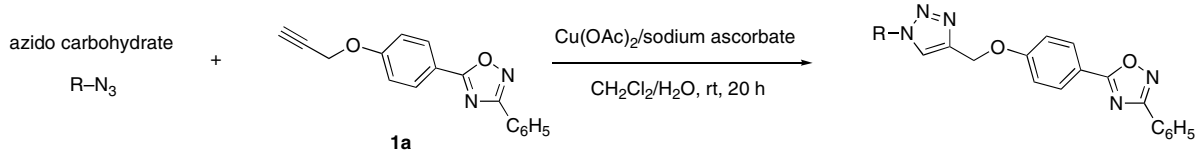
Next, we studied the application of different azidoglycosides in this copper-catalyzed cycloaddition with oxadiazole **1a** (Table 2). From Table 2, β-azidoglucosamine **21**, β-azidogalactoside **22**, and β-azidocellobioside **23** were successfully coupled to the corresponding β-glycosyl-triazole-linked 1,2,4-oxadiazoles **25**, **26**, and **27** in 63%, 70%, and 63% yields, respectively. Finally, reaction of α-azidoglucoside **24** with oxadiazole **1a** provided the corresponding α-D-glucopyranosyl oxadiazole **28** in 67% yield (Tables 3 and 4).

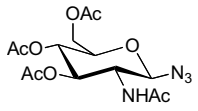
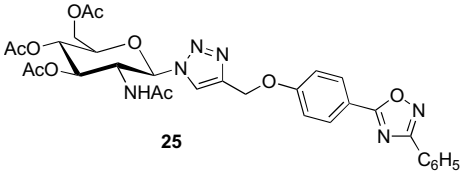
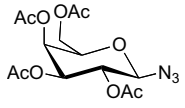
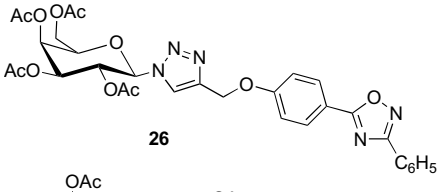
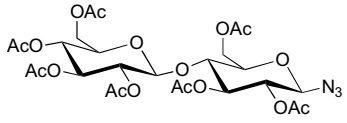
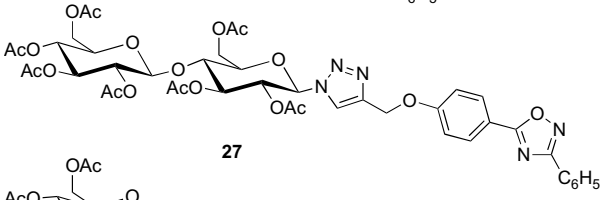
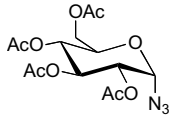
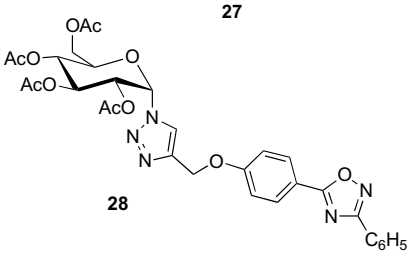
In conclusion, various 1,2,4-oxadiazoles bearing a terminal acetylenic function in their side-chain have been successfully cycloadded to azidoglycosides in good yields via a copper-catalyzed [3+2] reaction. These new compounds with various chain length as spacer between the oxadiazole and the glycoside frameworks represent a



Scheme 2. Synthesis of oxadiazole **20**.

Table 2. Synthesis of glycosyl 1,2,4-oxadiazoles from various azidoglycosides and oxadiazole **1a**



Entry	Azidoglycoside	Product	Yield (%)
1	 **21**	 **25**	63
2	 **22**	 **26**	70
3	 **23**	 **27**	63
4	 **24**	 **28**	67

set of potentially interesting new compounds, whose biological studies are currently in progress.

1. Experimental

1.1. General methods

All commercially available reagents were used as received. All reactions were monitored by TLC analysis (TLC plates GF_{254} E. Merck). Air- and moisture-sensitive reactions were performed under inert atmosphere. Melting points were determined on a Büchi apparatus and are uncorrected. Column chromatography was performed on Silica Gel 60 (230–240 mesh, E. Merck). Optical rotations were recorded using a Perkin–Elmer 241 polarimeter. NMR spectra were recorded with a Bruker AMX 300 spectrometer and referenced as follows: ^{1}H (300 MHz), internal $SiMe_4$ at $\delta = 0.00$ ppm, ^{13}C (75 MHz), internal standard at $\delta = 77.23$ ppm. Exact mass measurements of the molecular ions were obtained on a Finnigan Mat 95 XL spectrometer.

Oxadiazoles **5a**,[12a] **5b**,[12b] **7a**,[13] **7b**,[13] and **10**,[14] 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**12**),[16] 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl azide (**21**),[15] 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide (**22**),[17] 2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-β-D-cellobiosyl azide (**23**),[18] and 2,3,4,6-tetra-*O*-acetyl-α-D-gluco-

Table 3. ^{1}H NMR chemical shifts (δ in ppm, J in Hz) of compounds **13**–**20**, **25**, **26**, and **28**

Proton (multiplicity)	**13** (Me_2SO-d_6)	**14** (Me_2SO-d_6)	**15** (Me_2SO-d_6)	**16** (Me_2SO-d_6)	**17** ($CDCl_3$)	**18** ($CDCl_3$)	**19** (Me_2SO-d_6)	**20** (Me_2SO-d_6)	**25** (Me_2SO-d_6)	**26** (Me_2SO-d_6)	**28** ($CDCl_3$)
H-1 (d)	6.39 (*J* 9.1)	6.38 (*J* 9.2)	6.31 (*J* 9.0)	6.31 (*J* 9.0)	5.89 (*J* 9.0)	5.94 (*J* 8.8)	6.32 (*J* 9.0)	6.40 (*J* 9.0)	6.14 (*J* 10.0)	6.31 (*J* 9.2)	6.39 (*J* 6.0)
H-2 (dd)	5.69 (*J* 9.4, 9.2)	5.67 (*J* 9.4, 9.2)	5.63 (*J* 9.2, 9.2)	5.63 (*J* 9.4, 9.0)	5.47 (*J* 9.2, 9.0)	5.52 (*J* 9.4, 8.8)	5.65 (*J* 9.6, 9.4)	5.69 (*J* 9.2, 9.2)	5.33 (*J* 10.0, 9.8)	5.62 (*J* 9.6, 9.2)	5.25–5.33[a]
H-3 (dd)	5.57 (*J* 9.4, 9.4)	5.55 (*J* 9.4, 9.4)	5.54 (*J* 9.4, 9.2)	5.54 (*J* 9.4, 9.2)	5.39 (*J* 9.2, 9.2)	5.46 (*J* 9.4, 9.0)	5.53 (*J* 9.6, 9.4)	5.56 (*J* 9.4, 9.4)	5.11 (*J* 9.8, 9.8)	5.48 (*J* 9.6, 3.2)	6.27 (*J* 9.9, 9.4)
H-4 (dd)	5.19 (*J* 9.8, 9.6)	5.19 (*J* 9.8, 9.6)	5.16 (*J* 9.6, 9.6)	5.16 (*J* 9.8, 9.6)	5.22 (*J* 9.8, 9.4)	5.28 (*J* 9.9, 9.1)	5.17 (*J* 9.8, 9.8)	5.19 (*J* 9.8, 9.6)	4.64 (*J* 10.0, 9.8)	5.44 (*J* 3.2, 2.8)	5.25–5.33[a]
H-5 (ddd)	4.37 (*J* 9.8, 5.1, 2.6)	4.36–4.39[a]	4.36[a]	4.36 (*J* 9.8, 5.3, 3.0)	3.98 (*J* 9.8, 5.1, 1.7)	4.05 (*J* 9.9, 5.1, 2.1)	4.37[a]	4.38 (*J* 9.8, 5.3, 1.9)	4.25 (*J* 10.0, 4.9, 2.3)	4.60 (*J* 7.2, 4.9, 2.8)	4.40[b] (*J* 10.0)
H-6 (dd)	4.08 (*J* 12.8, 2.6)	4.08 (*J* 12.8, 3.0)	4.05 (*J* 12.4, 2.2)	4.04 (*J* 12.5, 3.0)	4.10 (*J* 12.6, 1.7)	4.17 (*J* 12.6, 1.9)	4.03[b] (*J* 11.7)	4.09 (*J* 12.8, 2.1)	4.06 (*J* 12.2, 2.3)	4.03 (*J* 11.7, 7.2)	4.04[b] (*J* 12.6)
H-6′ (dd)	4.15 (*J* 12.8, 5.1)	4.15 (*J* 12.8, 5.6)	4.12 (*J* 12.4, 5.5)	4.12 (*J* 12.5, 5.3)	4.28 (*J* 12.6, 5.1)	4.35 (*J* 12.6, 5.1)	4.12 (*J* 11.7, 5.1)	4.16 (J 12.8, 5.5)	4.16 (*J* 12.2, 4.9)	4.14 (*J* 11.7, 4.9)	4.27 (*J* 12.6, 3.6)
Ac	1.77, 1.97, 2.00, 2.03	1.76, 1.96, 2.00, 2.02	1.79, 1.96, 1.99, 2.03	1.79, 1.96, 1.99, 2.03	1.84, 1.98, 2.02, 2.03	1.90, 2.05, 2.09, 2.10	1.74, 1.95, 1.98, 2.02	1.78, 1.97, 2.00, 2.03	1.57, 1.95, 2.00, 2.02	1.79, 1.95, 1.99, 2.20	1.83, 2.04, 2.06, 2.07
=CHN– (s)	8.62	8.61	8.21	8.20	8.04	8.09	8.31	8.62	8.50	8.57	7.76
NH (t)			8.60 (*J* 5.5)	8.59 (*J* 5.5)			6.90 (*J* 4.5)		8.08–8.12[a]		
CH_2O (s)	5.34	5.33						5.34	5.32	5.33	5.36
CH_2N (d)			4.32 (*J* 5.5)	4.31 (*J* 5.5)					4.40 (*J* 4.5)		
Other CH_2 (t)			2.75 (*J* 7.2) 3.21 (*J* 7.2)	2.73 (*J* 7.1) 3.21 (*J* 7.1)		2.68 (s)[c]					
H_{arom}	7.30 (d, 2H, *J* 8.9) 7.60–7.62 (m, 3H) 8.08–8.11 (m, 2H) 8.15 (d, 2H, *J* 8.9)	7.29 (d, 2H, *J* 8.9) 7.81 (d, 2H, *J* 8.5) 8.02 (dd, 2H, *J* 8.5) 8.13 (d, 2H, *J* 8.9)	7.53–7.59 (m, 3H) 7.97–8.00 (m, 2H)	7.77 (br d, 2H, *J* 8.6) 7.92 (br d, 2H, *J* 8.6)	7.48–7.59 (m, 3H) 7.93 (d, 2H, *J* 8.1) 8.16–8.18 (m, 2H) 8.19 (d, 2H, *J* 8.1)	7.96 (d, 2H, *J* 8.3) 8.14 (d, 2H, *J* 8.5)	6.75 (br d, 2H, *J* 8.5) 7.63–7.72 (m, 3H) 7.80 (d, 2H, *J* 8.7) 8.15 (br d, 2H, *J* 8.3)	7.30 (d, 2H, *J* 8.9) 7.41–7.55 (m, 3H) 7.77 (d, 2H, *J* 7.7) 7.91 (d, 2H, *J* 8.3) 8.16 (d, 2H, *J* 8.9) 8.18 (d, 2H, *J* 8.3)	7.31 (d, 2H, *J* 8.9) 7.58–7.62 (m, 3H) 8.08–8.12 (m, 3H) 8.15 (d, 2H, *J* 8.9)	7.32 (d, 2H, *J* 8.9) 7.57–7.62 (m, 3H) 8.09 (br d, 2H, *J* 7.9) 8.15 (br d, 2H, *J* 8.9)	7.15 (d, 2H, *J* 7.9) 7.49–7.52 (m, 3H) 8.15–8.20 (m, 4H)

[a] m.
[b] br d.
[c] CH_3.

Table 4. ^{13}C NMR chemical shifts (δ in ppm, $CDCl_3$) of compounds **13**–**20**, **25**, **26**, and **28**

Compound	13	14	15	16	17	18	19	20	25	26	28
C-1	86.2	86.2	86.0	86.0	86.3	86.3	86.1	86.3	85.1	86.6	81.9
C-2	70.7	70.7	70.8	70.8	70.7	70.7	70.6	70.7	52.4	68.3	70.2
C-3	72.9	72.9	73.0	72.9	73.1	73.0	73.0	72.9	72.8	71.0	70.7
C-4	68.0	68.1	68.0	68.0	68.4	68.1	68.1	68.1	68.3	67.3	68.3
C-5	75.6	75.5	75.4	75.4	75.6	75.6	75.5	75.6	73.8	74.4	71.7
C-6	62.3	62.3	61.9	61.8	62.0	61.9	61.9	62.3	62.1	62.3	62.3
$=CHN_{triaz}$	115.7	115.7	121.6	121.5	118.9	118.8	116.6	115.7	116.1	115.7	115.6
$=CN_{triaz}$	144.6	144.5	145.7	145.6	148.1	148.0	146.7	144.2	142.6	144.4	143.5
$C_{oxadiaz}$	169.2	168.4	168.5	169.1	168.4	167.1	169.2	169.3	168.4	169.1	169.2
	175.8	175.9	179.3	179.5	177.5	177.5	175.5	175.8	175.5	175.7	175.8
C_{arom}	117.9	117.6	126.1	125.8	124.7	126.6	120.6	117.9	116.4	117.8	118.0
	121.8	121.8	126.4	126.1	126.7	127.2	124.9	126.3	124.2	121.9	125.6
	127.4	125.9	127.1	126.3	127.4	128.3	128.5	127.5	126.6	127.4	127.4
	127.9	126.4	127.7	129.2	128.5	132.9	129.4	127.9	127.4	127.8	127.9
	129.2	129.3	129.2	132.5	128.6	168.4	132.9	128.3	129.6	129.2	129.2
	130.5	130.5	131.5	169.1	129.5		150.1	129.3	130.3	130.4	130.5
	131.5	132.4	168.6		133.0			130.5	131.9	131.5	131.5
	161.9	162.0			133.2			140.6	162.1	161.9	161.9
					169.0			162.0			
CH_3CO	20.5	20.5	20.5	20.5	20.6	20.6[a]	20.5	20.5	20.6	20.6	20.6
	20.8	20.8	20.9[a]	20.8	21.0	20.9	20.8	20.8	20.7	20.9	20.9
	20.9	20.9	21.0	20.9	21.1	21.1	20.9	20.9	20.8	21.0[a]	21.0[a]
	21.1	21.0		21.0	26.0		21.1	21.1	22.6		
CH_3CO	169.3	169.3	169.2	169.7	169.4	169.4	169.3	169.4	168.7	169.4	169.2
	169.7	169.7	169.7	170.3	169.7	169.7	169.8	169.7	169.8	170.1	170.0
	170.3	170.2	170.3	170.8	170.3	169.3	170.3	170.3	169.9	170.3	170.5
	170.8	170.8	170.9	170.9	170.8	170.8	170.9	170.8	170.0	170.7	170.8
Other CH_2	61.9	61.9	22.7	22.6		12.8[b]	39.7	61.9	61.6	61.6	61.6
			32.3	32.3							
			35.3	35.2							

[a] Two carbon signals.
[b] Methyl group.

pyranosyl azide (**24**),[19] were prepared according to known literature procedures.

1.2. Synthesis of 3-aryl-5-(4-hydroxyphenyl)-1,2,4-oxadiazoles 6a,b

A 1 M soln of BBr_3 in CH_2Cl_2 (20 mL, 20 mmol) was added slowly at −78 °C to a soln of oxadiazole **5** (6.6 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was allowed to warm at rt, and then refluxed for 20 h. The reaction mixture was treated with water (20 mL) to hydrolyze the excess of BBr_3. After separation of the organic phase, the aq phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with satd aq $NaHCO_3$, then brine, and finally dried over Na_2SO_4. Removal of the solvent under diminished pressure gave a residue that was purified by column chromatography over silica gel to give the corresponding 5-hydroxyphenyl oxadiazole **6**.

1.2.1. 3-Phenyl-5-(4-hydroxyphenyl)-1,2,4-oxadiazole (6a). Prepared from **5a** (1.67 g); 0.832 g (53%); colorless solid; mp 161 °C, lit.[20] 169–171 °C; R_f 0.59 (4:1 CH_2Cl_2–EtOAc); ^1H NMR ($CDCl_3$): δ 6.07 (br s, 1H, OH), 6.98 (br d, 2H, J 8.9 Hz, H_{arom}), 7.50–7.53 (m, 3H, H_{arom}), 8.11–8.17 (m, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 116.5, 127.3, 127.9, 129.3, 130.6, 155.1, 169.2, 176.0; HREIMS: m/z 238.0741. Calcd for $C_{14}H_{10}N_2O_2$ $[M]^+$: 238.0742.

1.2.2. 3-(4-Bromophenyl)-5-(4-hydroxyphenyl)-1,2,4-oxadiazole (6b). Prepared from **5b** (2.18 g); 1.34 g (64%); colorless solid; mp 216 °C; R_f 0.63 (4:1 CH_2Cl_2–EtOAc); ^1H NMR ($CDCl_3$): δ 5.39 (br s, 1H, OH), 6.99 (d, 2H, J 8.3 Hz, H_{arom}), 7.65 (d, 2H, J 8.3 Hz, H_{arom}), 8.03 (d, 2H, J 8.3 Hz, H_{arom}), 8.12 (d, 2H, J 8.5 Hz, H_{arom}); ^{13}C NMR (DMSO-d_6): δ 114.3, 116.5, 125.3, 125.9, 129.2, 130.4, 132.4, 162.4, 167.5, 175.9; HREIMS: m/z 315.9857. Calcd for $C_{14}H_9B_rN_2O_2$ $[M]^+$: 315.9847.

1.3. Synthesis of oxadiazoles 1a,b

8-(4-Hydroxyphenyl)oxadiazole **6** (1.26 mmol) and K_2CO_3 (260 mg, 1.9 mmol) were suspended in anhyd DMF (8 mL). Propargyl bromide (220 mg, 1.9 mmol, 80% sol in toluene) was slowly added under a N_2 atmosphere, and the reaction mixture was stirred for 30 h at rt. Cold water (20 mL) was added to the contents, and the mixture thus obtained was extracted with ethyl ace-

tate (3 × 20 mL). The combined organic layers were washed with satd aq $NaHCO_3$, brine, and finally dried (Na_2SO_4). The solvent was removed under diminished pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding acetylenic oxadiazoles **1**.

1.3.1. 3-Phenyl-5-[4-(prop-2-yn-1-yloxy)phenyl]-1,2,4-oxadiazole (1a). Prepared from **6a** (300 mg); 198 mg (57%); colorless solid; mp 107 °C; R_f 0.82 (3:2 petroleum ether–EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.58 (t, 1H, *J* 2.4 Hz, C≡CH), 4.79 (d, 2H, *J* 2.4 Hz, CH_2), 7.13 (d, 2H, *J* 8.9 Hz, H_{arom}), 7.49–7.52 (m, 3H, H_{arom}), 8.15–8.20 (m, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 56.3, 76.7, 78.1, 115.8, 118.1, 127.9, 129.2, 130.4, 131.5, 161.4, 169.2, 175.9; HREIMS: *m*/*z* calcd for $C_{17}H_{12}N_2O_2$ $[M]^+$: 276.0899; found: 276.0901.

1.3.2. 3-(4-Bromophenyl)-5-[4-(prop-2-yn-1-yloxy)phenyl]-1,2,4-oxadiazole (1b). Prepared from **6b** (399 mg); 340 mg (76%); colorless solid; mp 153 °C; R_f 0.85 (3:2 petroleum ether–EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.50 (t, 1H, *J* 2.4 Hz, C≡CH), 4.79 (d, 2H, *J* 2.4 Hz, CH_2), 7.04 (d, 2H, *J* 8.9 Hz, H_{arom}), 7.56 (br d, 2H, *J* 8.7 Hz, H_{arom}), 7.95 (br d, 2H, *J* 8.7 Hz, H_{arom}), 8.07 (br d, 2H, *J* 8.9 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 56.3, 76.7, 78.0, 115.8, 117.9, 126.0, 126.4, 129.4, 130.4, 132.5, 161.5, 168.5, 176.0; HREIMS: *m*/*z* 353.9991. Calcd for $C_{17}H_{11}BrN_2O_2$ $[M]^+$: 354.0004.

1.4. Synthesis of oxadiazoles 2

To a soln of oxadiazole **7** (0.92 mmol) in anhyd THF (10 mL) maintained at −25 °C and under a nitrogen atmosphere were successfully added *N*-methyl-morpholine (93 mg, 0.92 mmol), *iso*butyl chloroformate (130 mg, 0.92 mmol), and propargylamine (60 mg, 1.0 mmol). After being stirred at rt for 24 h, the solvent was removed under diminished pressure, water (10 mL) was added, and the pH of the mixture was adjusted between 1 and 2 with aq 1 N HCl. The aq soln was extracted with EtOAc (3 × 20 mL), the combined organic phases were washed with satd aq $NaHCO_3$ (3 × 10 mL), and brine. Removal of the solvent under diminished pressure afforded oxadiazole **2**, which was recrystallized from a CH_2Cl_2–hexane mixture.

1.4.1. 3-(3-Phenyl-1,2,4-oxadiazol-5-yl)-*N*-(prop-2-yn-1-yl)propanamide (2a). Prepared from **7a** (200 mg); 183 mg (78%); colorless solid; mp 98 °C; R_f 0.48 (4:1 CH_2Cl_2–EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.23 (t, 1H, *J* 2.5 Hz, C≡CH), 2.82 (t, 2H, *J* 7.2 Hz, CH_2), 3.32 (t, 2H, *J* 7.2 Hz, CH_2), 4.09 (dd, 2H, *J* 5.2, 2.5 Hz, NCH_2), 5.95 (br s, 1H, NH), 7.44–7.51 (m, 3H, H_{arom}), 8.05 (dd, 2H, *J* 7.7, 2.0 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 22.7, 29.8, 32.4, 72.2, 79.7, 127.1, 127.8, 129.2, 131.6, 168.6, 170.4, 179.1; HREIMS: *m*/*z* 255.1023. Calcd for $C_{14}H_{13}N_3O_2$ $[M]^+$: 255.1009.

1.4.2. 3-[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl]-*N*-(prop-2-yn-1-yl)propanamide (2b). Prepared from **7b** (273 mg); 218 mg (71%); colorless solid; mp 170 °C; R_f 0.52 (4:1 CH_2Cl_2–EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.24 (t, 1H, *J* 2.5 Hz, C≡CH), 2.81 (t, 2H, *J* 7.2 Hz, CH_2), 3.31 (t, 2H, *J* 7.2 Hz, CH_2), 4.08 (dd, 2H, *J* 5.2, 2.5 Hz, NCH_2), 5.94 (br s, 1H, NH), 7.62 (br d, 2H, *J* 8.5 Hz, H_{arom}), 7.93 (br d, 2H, *J* 8.5 Hz, H_{arom}); ^{13}C NMR (DMSO-d_6) 21.1, 27.2, 30.0, 72.3, 80.3, 124.3, 124.8, 128.2, 131.6, 166.0, 169.0, 179.5; HREIMS: *m*/*z* 333.0122. Calcd for $C_{14}H_{12}BrN_3O_2$ $[M]^+$: 333.0113.

1.5. 4-Ethynylbenzamidoxime (9)

To a soln of hydroxylamine hydrochloride (540 mg, 7.8 mmol) and sodium hydrogencarbonate (655 mg, 7.8 mmol) in water (20 mL) was added a soln of 4-ethynylbenzonitrile (**8**) (500 mg, 3.9 mmol) in ethanol (20 mL). After being stirred for 3 days at rt, the solvent was removed under diminished pressure and the residue was extracted with ethyl acetate (3 × 20 mL). Removal of the solvent under diminished pressure gave a solid that was crystallized in CH_2Cl_2 to give 4-ethynylbenzamidoxime **9** (540 mg, 93%) as a colorless solid: mp 132–133 °C (CH_2Cl_2); R_f 0.35 (2:1 petroleum ether–EtOAc); ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 1H, OH), 3.16 (s, 1H, C≡CH), 4.86 (br s, 2H, NH_2), 7.52 (br d, 2H, *J* 7.8 Hz, H_{arom}), 7.60 (br d, 2H, *J* 7.8 Hz, H_{arom}). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.15; H, 4.86; N, 17.67.

1.6. 3-(4-Ethynylphenyl)-5-phenyl-1,2,4-oxadiazole (3a)

To a soln of 4-ethynylbenzamidoxime **9** (0.5 g, 3.47 mmol) in anhyd CH_2Cl_2 (30 mL) was added benzoic acid (0.85 g, 6.94 mmol), followed by DCC (1.43 g, 6.94 mmol), at rt and under a nitrogen atmosphere. After being stirred for 3 h, the solid was filtered off, the solvent was removed under diminished pressure, and the residue was submitted to the cyclodehydration reaction at 110–120 °C for 4 h. The resulting mixture was submitted to column chromatography on silica gel (7:3 hexane–EtOAc) to give oxadiazole **3a** (461 mg, 54%) as a colorless solid: mp 99–100 °C; R_f 0.6 (7:3 hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 1H, C≡CH), 7.51–7.63 (m, 5H, H_{arom}), 8.13 (br d, 2H, *J* 6.7 Hz, H_{arom}), 8.21 (br d, 2H, *J* 6.7 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 79.7, 83.5, 124.5, 125.3, 127.5, 127.8, 128.6, 129.5, 133.0, 133.2, 168.7, 176.3; HREIMS: *m*/*z* 246.0805. Calcd for $C_{16}H_{10}N_2O$ $[M]^+$: 246.7930.

1.7. 3-(4-Ethynylphenyl)-5-methyl-1,2,4-oxadiazole (3b)

A mixture of 4-ethynylbenzamidoxime (**9**) (0.5 g, 3.13 mmol) and Ac_2O (10 mL) was heated at reflux temperature for 4 h. The mixture was cooled to rt, and neutralized with satd aq NaOH until pH 7.0. The organic product was extracted with EtOAc (3 × 5 mL). Removal of the solvent under diminished pressure gave a residue that was purified by column chromatography on silica gel (3:2 petroleum ether–EtOAc) to give oxadiazole **3b** (350 mg, 61%) as a colorless solid: mp 71 °C; R_f 0.65 (3:2 petroleum ether–EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 3H, CH_3), 3.21 (s, 1H, C≡CH), 7.58 (br d, 2H, J 8.5 Hz, H_{arom}), 8.02 (br d, 2H, J 8.7 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 12.7, 79.7, 83.4, 125.3, 127.4, 127.6, 132.9, 168.2, 177.1; HREIMS: m/z 184.0636. Calcd for $C_{11}H_8N_2O$ $[M]^+$: 184.0636.

1.8. [4-(5-Phenyl-1,2,4-oxadiazol-3-yl)phenyl](prop-2-yn-1-yl)amine (4)

A soln of nitrooxadiazole **10** (1.1 g, 4.1 mmol) in EtOH (50 mL) was refluxed in the presence of $SnCl_2$ (3.1 g, 16.4 mmol). After total consumption of the starting material as shown by TLC, the mixture was basified with satd aq $NaHCO_3$ until pH 8.0, and extracted with ethyl acetate (3 × 100 mL). Removal of the solvent under diminished pressure furnished crude 4-aminophenyl-5-phenyl-1,2,4-oxadiazole **11**, which was used in the next step without further purification. To a suspension of aminooxadiazole **11** (400 mg, 1.7 mmol) and potassium carbonate (470 mg, 3.4 mmol) in anhyd DMF (10 mL) was added slowly propargyl bromide (400 mg, 3.4 mmol) in toluene (80% soln). After being stirred for 36 h at rt, water (10 mL) was added, and the organic product was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4). Solvent removal under diminished pressure gave a residue that was purified by chromatography on silica gel using petroleum ether–EtOAc (3:2) as the eluent to afford oxadiazole **4** (320 mg, 68%) as a yellow solid: mp 117 °C; R_f 0.71 (3:2 petroleum ether–EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.26 (t, 1H, J 2.4 Hz, C≡CH), 3.99 (d, 2H, J 2.4 Hz, CH_2), 4.27 (br s, 1H, NH), 6.76 (br d, 2H, J 8.9 Hz, H_{arom}), 7.26–7.61 (m, 3H, H_{arom}), 8.02 (br d, 2H, J 8.9 Hz, H_{arom}), 8.20 (br d, 2H, J 7.9 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 33.7, 72.1, 80.7, 113.5, 117.1, 124.9, 128.5, 129.3, 129.4, 132.9, 149.6, 169.3, 175.5; HREIMS: m/z 275.1062. Calcd for $C_{17}H_{13}N_3O$ $[M]^+$: 275.1059.

1.9. General procedure for the preparation of carbohydrate–triazole linked oxadiazole derivatives

The azidosugar (1 mmol) and acetylenic oxadiazole (1.1 mmol) were suspended in 1:1 mixture of CH_2Cl_2 and water (4 mL). To this soln was added a mixture of $Cu(OAc)_2$ (36 mg, 0.2 mmol) and sodium ascorbate (79 mg, 0.4 mmol). The resulting mixture was stirred under nitrogen at rt until TLC analysis indicated complete consumption of the product. The mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was separated, and the aq phase was extracted again with CH_2Cl_2 (5 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent under diminished pressure gave a residue that was purified by column chromatography on silica using the indicated eluent to give the corresponding carbohydrate–triazole linked 1,2,4-oxadiazole.

1.9.1. 5-(4-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-3-phenyl-1,2,4-oxadiazole (13).

Prepared from **12** (373 mg) and **1a** (303.6 mg); 519.7 mg (80%); colorless solid; mp 173 °C; R_f 0.25 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{20}$ −31.5 (c 1.0, CH_2Cl_2); HRESIMS: m/z 672.1922. Calcd for $C_{31}H_{31}N_5O_{11}Na$ $[M+Na]^+$: 672.1918. Anal. Calcd for $C_{31}H_{31}N_5O_{11}$: C, 57.32; H, 4.81. Found: C, 57.22; H, 4.78.

1.9.2. 5-(4-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-3-(4-bromophenyl)-1,2,4-oxadiazole (14).

Prepared from **12** (373 mg) and **1b** (390 mg); 343.5 mg (60%); colorless solid; mp 227 °C; R_f 0.34 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{20}$ −29 (c 1.0, CH_2Cl_2); HRESIMS m/z 729.1118. Calcd for $C_{31}H_{31}BrN_5O_{11}$ $[M+H]^+$: 729.1132. Anal. Calcd for $C_{31}H_{30}BrN_5O_{11}$: C, 51.11; H, 4.15. Found: C, 50.90; H, 4.21.

1.9.3. *N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanamide (15).

Prepared from **12** (373 mg) and **2a** (280.5 mg); 534 mg (85%); colorless solid; mp 153 °C; R_f 0.46 (EtOAc); $[\alpha]_D^{20}$ −19.2 (c 1.0, CH_2Cl_2); HRESIMS m/z 651.2029. Calcd for $C_{28}H_{32}N_6O_{11}Na$ $[M+Na]^+$: 651.2027.

1.9.4. *N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3-[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]propanamide (16).

Prepared from **12** (373 mg) and **2b** (367 mg); 237 mg (43%); colorless solid; mp 82 °C; R_f 0.41 (EtOAc); $[\alpha]_D^{20}$ −18.0 (c 1.0, CH_2Cl_2); HRESIMS: m/z 729.1118. Calcd for $C_{28}H_{31}BrN_6O_{11}Na$ $[M+Na]^+$: 729.1131.

1.9.5. 3-{4-[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]phenyl}-5-phenyl-1,2,4-oxadiazole (17).

Prepared from **12** (373 mg) and **3a** (270.6 mg); 378 mg (61%); colorless solid; mp 232 °C; R_f 0.41 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{20}$ −60.5 (c 1.0, CH_2Cl_2);

HRESIMS: *m*/*z* 642.1812. Calcd for $C_{30}H_{29}N_5O_{10}Na$ $[M+Na]^+$: 642.1812.

1.9.6. 3-{4-[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]phenyl}-5-methyl-1,2,4-oxadiazole (18). Prepared from **12** (373 mg) and **3b** (202 mg); 446 mg (80%); colorless solid; mp 230 °C; R_f 0.75 (EtOAc); $[\alpha]_D^{20}$ −65 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{25}H_{27}N_5O_{10}$: C, 53.86; H, 4.88. Found: C, 53.09; H, 4.96.

1.9.7. *N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-4-(5-phenyl-1,2,4-oxadiazol-3-yl)aniline (19). Prepared from **12** (373 mg) and **4** (302 mg); 434.5 mg (67%); colorless solid; mp 201 °C; R_f 0.63 (EtOAc); $[\alpha]_D^{20}$ −24 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{31}H_{32}N_6O_{10}$: C, 57.40; H, 4.97; N, 12.96. Found: C, 57.28; H, 4.96; N, 12.67.

1.9.8. 5-(4-{[1-(3,4,6-Tri-*O*-acetyl-2-acetylamino-2-deoxy-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-3-phenyl-1,2,4-oxadiazole (25). Prepared from **1a** (303.6 mg) and **21** (372 mg); 408.6 mg (63%); colorless solid; mp 246 °C; R_f 0.44 (EtOAc); $[\alpha]_D^{20}$ −44 (*c* 0.5, CH_2Cl_2); HRESIMS: *m*/*z* 671.2071. Calcd for $C_{31}H_{32}N_6O_{10}Na$ $[M+Na]^+$: 671.2077.

1.9.9. 5-(4-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-3-phenyl-1,2,4-oxadiazole (26). Prepared from **1a** (303.6 mg) and **22** (373 mg); 389 mg (70%); colorless solid: mp 187 °C; R_f 0.37 (7:3 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −15 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{31}H_{31}N_5O_{11}$: C, 57.32; H, 4.81. Found: C, 57.03; H, 4.78.

1.9.10. 5-(4-{[1-(2,2′,3,3′,4′,6,6′-Hepta-*O*-acetyl-β-D-cellobiosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-1,2,4-oxadiazole (27). Prepared from **1a** (303.6 mg) and **23** (661 mg); 591 mg (63%); colorless solid; mp 233 °C; R_f 0.32 (7:3 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −27 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.85 (s, 3H, OAc), 1.99 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.68 (ddd, 1H, *J* 9.6, 4.2, 2.3 Hz, H-5′), 3.93–3.98 (m, 2H, H-5, H-6), 4.05 (dd, 1H, *J* 12.4, 2.3 Hz, H-6′), 4.16 (dd, 1H, *J* 12.4, 4.2 Hz, H-6′), 4.38 (dd, 1H, *J* 12.4, 4.2 Hz, H-6), 4.54 (dd, 1H, *J* 8.1, 7.9 Hz, H-3), 4.57 (d, 1H, *J* 8.1 Hz, H-1′), 4.96 (dd, 1H, *J* 9.0, 8.1 Hz, H-2′), 5.08 (dd, 1H, *J* 9.6, 9.4 Hz, H-4′), 5.17 (dd, 1H, *J* 9.4, 9.0 Hz, H-3′), 5.31 (s, 2H, CH_2O), 5.36–5.44 (m, 2H, H-4, H-2), 5.83 (d, 1H, *J* 8.8 Hz, H-1), 7.13 (d, 2H, *J* 8.9 Hz, H_{arom}), 7.49–7.52 (m, 3H, H_{arom}), 7.82 (s, 1H, =CHN), 8.15–8.19 (m, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.8, 20.9, 21.1, 21.2, 62.0, 62.4, 68.2, 70.9, 72.0, 72.5, 72.7, 73.2, 76.2, 76.5, 86.0, 101.2, 115.7, 117.9, 121.8, 127.5, 127.9, 129.3, 130.5, 131.5, 144.5, 162.0, 169.2, 169.4, 169.5, 169.7, 169.9, 170.6, 170.8, 175.8. Anal. Calcd for $C_{41}H_{47}N_5O_{19}$: C, 55.07; H, 5.01. Found: C, 54.76; H, 5.06.

1.9.11. 5-(4-{[1-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-3-phenyl-1,2,4-oxadiazole (28). Prepared from **1a** (303.6 mg) and **24** (373 mg); 435 mg (67%); colorless solid; mp 109 °C; R_f 0.2 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{20}$ +79 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{31}H_{31}N_5O_{11}$: C, 57.32; H, 4.81. Found: C, 56.94; H, 4.82.

1.10. 3-Biphenyl-4-yl-5-(4-{[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-1,2,4-oxadiazole (20)

$Pd(OAc)_2$ (0.3 mg, 1.1 μmol) and PPh_3 (0.9 mg, 3.3 μmol) were placed in a flask under argon. Degassed water (0.5 mL) and ethanol (0.5 mL) were added, and the soln was stirred for 30 min at rt. A suspension of bromooxadiazole **14** (80 mg, 0.11 mmol) and phenylboronic acid (15 mg, 0.12 mmol) in a mixture of toluene (3 mL) and ethanol (1.5 mL) was then added to the flask, followed by Na_2CO_3 (35 mg, 0.33 mmol) dissolved in water (1 mL). The resulting mixture was stirred at 70 °C for 16 h. The two phases were separated, the ethanol–water layer was washed twice with toluene. The combined organic phases were dried over Na_2SO_4, and concentrated under diminished pressure. Purification of the crude product by chromatography on silica gel using petroleum ether–EtOAc (3:2) as the eluent gave the coupling product **20** (35 mg, 44%) as a colorless solid: mp 237 °C; R_f 0.36 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{20}$ −29 (*c* 0.5, CH_2Cl_2); HRESIMS: *m*/*z* 748.2236. Calcd for $C_{37}H_{35}N_5O_{11}Na$ $[M+Na]^+$: 748.2231.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.07.011.

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