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1,3-Dipolar cycloaddition reactions on carbohydrate-based templates: synthesis of spiro-isoxazolines and 1,2,4-oxadiazoles as glycogen phosphorylase inhibitors

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Abstract—1,3-Dipolar cycloaddition of aryl nitrile oxides to benzyl/acetyl-protected *exo*-glucals and to a benzoylated glucosyl cyanide led in high yield to spiro-isoxazolines and to 3-aryl-5-glucosyl-1,2,4-oxadiazoles, respectively. The choice of the protective groups was important to the outcome of the cycloaddition and for the deprotection of the adducts. Cleavage of the ester protecting groups (acetyl, benzoyl) provided water-soluble spiro-isoxazolines and 3-aryl-5-glucosyl-1,2,4-oxadiazoles, evaluated as glycogen phosphorylase inhibitors. Preliminary tests showed IC_{50} values in the μM range.

Glycogen phosphorylase[1] (GP) is responsible for the conversion of glycogen to glucose (glycogenolysis). It contributes to glucose production, for the glycolysis pathway in muscles, and for delivery of glucose into the bloodstream in the liver. Hepatic glucose production, normally under tight hormonal control, is disregulated in patients suffering from type 2 diabetes. Inhibition[2] of GP is emerging as a viable approach[3] for the treatment of hyperglycaemia.[4,5] The largest family of GP inhibitors consists of glucose derivatives,[2,6–9] such as glucopyranosyl-spiro-oxathiazoles **A**,[10] -spiro-(thio)hydantoins **B**,[7] -benzothiazole[11] or -benzimidazole **C**,[11] -1,2,4-oxadiazoles **D**[12] and -1,3,4-oxadiazoles **E**[11] (Fig. 1). 1,3-Dipolar cycloadditions of nitrile oxides to

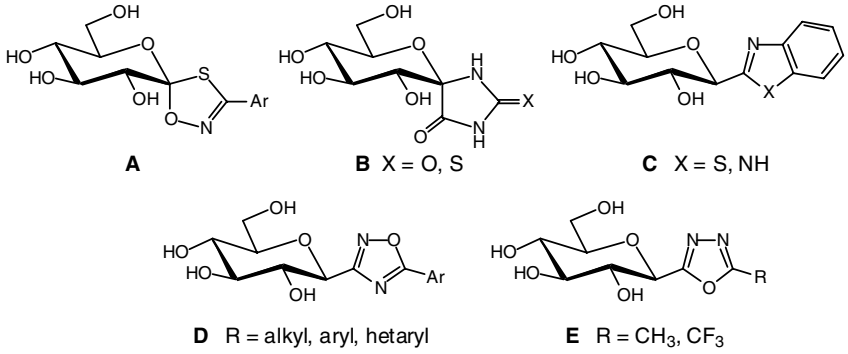

Figure 1. Some known glucose-based inhibitors of GP.

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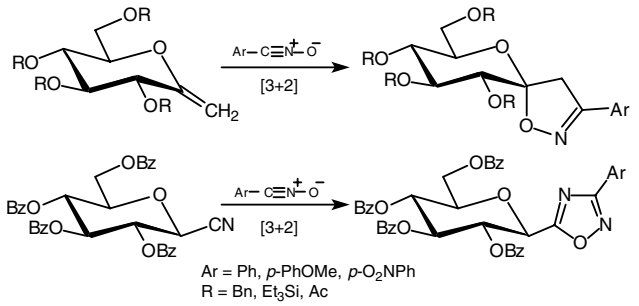


Figure 2. Cycloaddition approaches towards glucose-based heterocycles as potential GP inhibitors.

methylene *exo*-glucals and *C*-glucosyl cyanides (Fig. 2) could lead, respectively, to spiro-isoxazolines and 1,2,4-oxadiazoles, analogous to the aforementioned inhibitors.

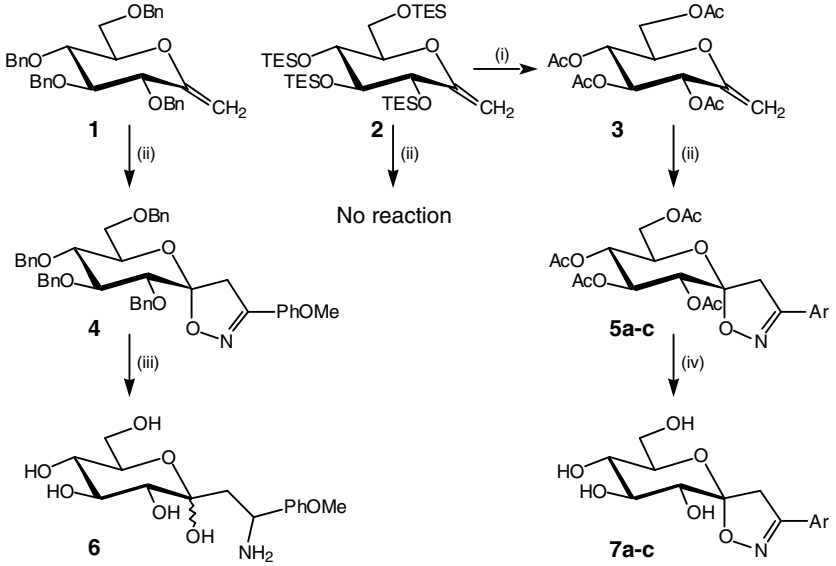
1,3-Dipolar cycloaddition reactions involving carbohydrate derivatives as a dipole or a dipolarophile have been studied extensively.[13] In particular, Gallos et al.[14,15] recently reported the cycloaddition of 3,4- and 5,6-unsaturated sugars with nitrile oxides. Another study by Ikegami and co-workers[16] described the synthesis of an amino-*C*-ketosyl disaccharide by cycloaddition of a nitrone to a methylene *exo*-glycal. Electron-deficient *exo*-glycals were used by Chapleur and co-workers[17,18] for cycloadditions with nitrones and nitrile oxides. Cycloadditions of nitrile oxides to electron-rich *exo*-glycals have been studied only briefly by Rajanbabu and Reddy[19] and more recently by Lieberknecht and co-workers[20] and Ikegami and co-workers[21] using substituted and unsubstituted methylene *exo*-glycals, respectively. These studies focused primarily on the cycloaddition regio- and stereoselectivities without considering the deprotection of the spiro-compounds.

As part of our projects concerning glucose analogs as GP inhibitors,[9,10,12] we have been interested in spirocyclic sugars and *C*-glycosyl heterocyles. We have prepared differently protected methylene *exo*-glucals **1**–**3**[22] using our recently established procedure[23,24] from sugar lactones while the glucosyl cyanide **8** was prepared according to Somsák's method.[25] As reported below, cycloadditions between these dipolarophiles and aryl nitrile oxides and deprotections of the expected cycloadducts were carried out to afford potential GP inhibitors (Scheme 1).

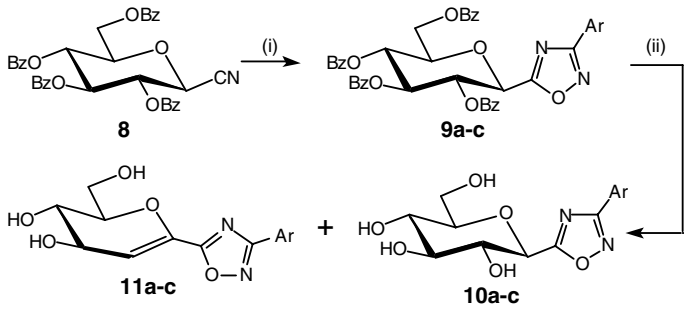
The benzylated *exo*-glucal **1**[23,26] underwent a cycloaddition reaction with *p*-anisonitrile oxide at room temperature to afford the desired spiro-isoxazoline **4**[27] in high yield with complete regio- and stereoselectivity (Table 1). The regiochemistry of the cycloaddition reaction was established from data provided by ^{1}H NMR, ^{13}C NMR and 2D NMR experiments (COSY, HSQC, HMBC). The (*R*) configuration at the spiro-carbon atom of cycloadduct **4** was determined by NOE experiments showing a contact between the methylene protons of the isoxazoline ring and either the H-2 proton of the sugar ring or a benzylic proton (superimposed signals at $\delta = 3.70$–3.82), (H-4 and H-10, following the systematic numbering used in the NMR data), but no enhancement of the H-3 and H-5 signals (H-9 and H-7).

Table 1. 1,3-Dipolar cycloaddition of aromatic nitrile oxides with methylene *exo*-glucals **1** and **3**

exo-Glucals	Ar	Products (%)
1	*p*-MeOPh	**4** (83)
3	*p*-MeOPh	**5a** (83)
3	Ph	**5b** (99)
3	*p*-O_2NPh	**5c** (94)



Scheme 1. Reagents and conditions: (i) TBAF, THF, rt, 4 h then Ac_2O, pyridine, rt, 24 h, 97%; (ii) ArC(Cl)=NOH, Et_3N, CH_2Cl_2, rt, 16 h; (iii) H_2, $Pd(OH)_2$–C 20%, EtOH, rt, 16 h; (iv) NaOMe, MeOH, rt, 2 h.



Scheme 2. Reagents and conditions: (i) ArC(Cl)=NOH, Et_3N, toluene, 110 °C, 16 h; (ii) NaOMe, MeOH/$CHCl_3$ (2/3), rt, 2 h.

However, subsequent hydrogenolysis of the benzyl ethers of **4** occurred with concomitant reductive cleavage of the N–O bond and reduction of the C=N double bond,[16] as evidenced by mass spectroscopy showing a molecular ion $m/z = 329.9$ $[M+H]^+$, supporting structure **6**.[28]

The triethylsilyl (TES) groups appeared to be a suitable alternative to benzyl groups, since their cleavage occurs under mild conditions with fluoride ion. However, attempted cycloadditions of aromatic nitrile oxides to the silylated *exo*-glucal **2** failed to furnish the expected spiro-derivatives. Complete recovery of unreacted **2** was observed even in refluxing toluene. The lack of reactivity could be attributed to the bulkiness of silyl groups in **2** hindering the approach of the nitrile oxide.

The acetyl protective group, characterized by limited steric hindrance and cleavage under mild conditions, appeared as a viable alternative to benzyl and silyl groups. The acetylated methylene *exo*-glucal **3**[29] was obtained from **2** in nearly quantitative yield via a one-pot procedure combining cleavage of silyl ethers and subsequent acetylation. Finally, cycloaddition at room temperature afforded the desired spiro-isoxazolines **5a**–**c** in high yields (Table 1). The regio- and stereochemistries at the anomeric spiro-centre were determined as before by ^{13}C NMR and NOE experiments, which showed unambiguously a contact between the methylene protons of the isoxazoline ring and the H-2 proton of the sugar ring. As expected, methanolysis of the acetates delivered the deprotected spiro-isoxazolines **7a**–**c** in quantitative yields.[30]

Next, we considered the corresponding [3+2] cycloadditions to nitriles[31,32] as an access to 3-aryl-5-*C*-glucosyl-1,2,4-oxadiazoles from the benzoylated β-D-glucosyl cyanide **8**[25] (Scheme 2). Nitrile **8** reacted in refluxing toluene with various aryl nitrile oxides to afford the expected heterocyclic compounds **9a**–**c** in high yields (Table 2).[33] Deprotection of the benzoyl esters under Zemplén conditions provided the deprotected 5-*C*-β-D-glucosyl-1,2,4-oxadiazoles **10a**–**c**[34] (75–92% isolated yield) together with a small amount of the *endo*-glucals **11a**–**c** (4–7% isolated yield).

Table 2. 1,3-Dipolar cycloaddition of aromatic nitrile oxides with β-D-glucosyl cyanide **8**

Cycloadducts	Ar	Yields (%)
9a	*p*-MeOPh	90
9b	Ph	94
9c	*p*-O_2NPh	99

In summary, we developed short and convenient routes to glucose-derived spiro-isoxazolines and 3-aryl-5-*C*-glucosyl-1,2,4-oxadiazoles, based on [3+2] cycloaddition reactions to acetyl- and benzyl-protected *exo*-glucals or a benzoylated β-D-glucopyranosyl cyanide. Use of ester protective groups gave access to the corresponding deprotected water-soluble motifs, analogous to known inhibitors of glycogen phosphorylase. Indeed, preliminary tests showed that 5-β-D-glucopyranosyl-3-phenyl-1,2,4-oxadiazole **10b** inhibited significantly ($IC_{50} = 64$ μM) rabbit muscle GP*b* (unphosphorylated isoform). In contrast, 3-β-D-glucopyranosyl-5-phenyl-1,2,4-oxadiazole, an isomer of **10b**, had a low inhibitory activity towards GP ($IC_{50} = 1.49$ mM).[12] Therefore, the 3-aryl-5-β-D-glucopyranosyl-1,2,4-oxadiazole series appears to be more promising for GP inhibition. Such glucose-based analogues are currently investigated and their syntheses, inhibitory activities as well as data obtained from crystallographic studies will be reported in due course.

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References and notes

1. Johnson, L. N. *FASEB J.* **1992**, *6*, 2274–2282.
2. Oikonomakos, N. G. *Curr. Protein Pept. Sci.* **2002**, *3*, 561–586.
3. Moller, D. E. *Nature* **2001**, *414*, 821–827.

4. Zimmet, P.; Alberti, K. G. M. M.; Shaw, J. *Nature* **2001**, *414*, 782–861.
5. Treadway, J. L.; Mendys, P.; Hoover, D. J. *Exp. Opin. Invest. Drugs* **2001**, *10*, 439–454.
6. Somsák, L.; Nagy, V.; Hadady, Z.; Docsa, T.; Gergely, P. *Curr. Pharm. Des.* **2003**, *9*, 1177–1189.
7. Somsák, L.; Nagy, V.; Hadady, Z.; Felföldi, N.; Docsa, T.; Gergely, P. In *Frontiers in Medicinal Chemistry*; Reitz, A. B., Kordik, C. P., Choudhary, M. I., Atta ur Rahman, Eds.; Bentham Science, 2005; Vol. 2, pp 253–272.
8. Chrysina, E. D.; Kosmopoulou, M. N.; Tiraidis, C.; Kardakaris, R.; Bischler, N.; Leonidas, D. D.; Hadady, Z.; Somsák, L.; Docsa, T.; Gergely, P.; Oikonomakos, N. G. *Protein Sci.* **2005**, *14*, 873–888.
9. Oikonomakos, N. G.; Kosmopoulou, M.; Zographos, S. E.; Leonidas, D. D.; Chrysina, E. D.; Somsák, L.; Nagy, V.; Praly, J.-P.; Docsa, T.; Tóth, B.; Gergely, P. *Eur. J. Biochem.* **2002**, *269*, 1684–1696.
10. Praly, J.-P.; Boyé, S.; Joseph, B.; Rollin, P. *Tetrahedron Lett.* **1993**, *34*, 3419–3420.
11. Hadady, Z.; Tóth, M.; Somsák, L. *Arkivoc* **2004**, *vii*, 140–149.
12. Benltifa, M.; Vidal, S.; Fenet, B.; Msaddek, M.; Goekjian, P. G.; Praly, J.-P.; Brunyánszki, A.; Docsa, T.; Gergely, P. *Eur. J. Org. Chem.*, in press.
13. Osborn, H. M. I.; Gemmel, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419–2438.
14. Gallos, J. K.; Koftis, T. V.; Koumbis, A. E.; Moutsos, V. I. *Synlett* **1999**, *8*, 1289–1291.
15. Gallos, J. K.; Koftis, T. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 415–423.
16. Li, X.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Tetrahedron Lett.* **2004**, *45*, 4123–4126.
17. Taillefumier, C.; Enderlin, G.; Chapleur, Y. *Lett. Org. Chem.* **2005**, *2*, 226–230.
18. Enderlin, G.; Taillefumier, C.; Didierjean, C.; Chapleur, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2459–2474.
19. Rajanbabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458–5461.
20. Colinas, P. A.; Jäger, V.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 1071–1074.
21. Li, X.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Heterocycles* **2003**, *59*, 547–571.
22. (a) Lancelin, J.-M.; Pougny, J.-R.; Sinaÿ, P. *Carbohydr. Res.* **1985**, *136*, 369–374; for a recent review on *exo*-glycals, see: (b) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292.
23. Gueyrard, D.; Haddoub, R.; Said Bacar, N.; Salem, A.; Goekjian, P. G. *Synlett* **2005**, 520–523.
24. Gueyrard, D.; Fontaine, P.; Goekjian, P. G. *Synthesis* **2006**, 1499–1503.
25. Somsák, L.; Nagy, V. *Tetrahedron: Asymmetry* **2000**, *11*, 1719–1727.
26. Benzylated *exo*-glucal **1** has been previously reported: see Ref. 22a and Yang, W.-B.; Yang, Y.-Y.; Gu, Y.-F.; Wang, S.-H.; Chang, C.-C.; Lin, C.-H. *J. Org. Chem.* **2002**, *67*, 3773–3782.
27. Typical procedure for 1,3-dipolar cycloaddition on methylene *exo*-glucals: To a solution of the methylene *exo*-glucal (0.3 mmol) and hydroximoyl chloride (5 equiv) in anhydrous dichloromethane (5 mL), a solution of triethylamine (7.5 equiv) in dry dichloromethane (2 mL) was added dropwise (syringe pump, 8 h). The mixture was stirred overnight at room temperature. After concentration, the crude material was purified by flash chromatography to afford the desired spiro-isoxazolines **4** and **5a**–**c**. Selected data for (5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-3-(4-methoxyphenyl)-1,6-dioxa-2-azaspiro[4,5]dec-2-ene (**4**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.05$ (s, 2H, H-4), 3.59 (dd, 1H, $J = 1.7$, 10.9 Hz, CH_2OBn), 3.70–3.82 (m, 2H, H-10, CH_2OBn), 3.82 (s, 3H, OMe), 3.84 (t, 1H, $J = 9.6$ Hz, H-8), 4.08 (m, 1H, H-7), 4.15 (t, 1H, $J = 9.4$ Hz, H-9), 4.43 (d, 1H, $J = 12.2$ Hz, OCH_2Ph), 4.57 (d, 1H, $J = 10.8$ Hz, OCH_2Ph), 4.59 (d, 1H, $J = 12.2$ Hz, OCH_2Ph), 4.71 (d, 1H, $J = 12.0$ Hz, OCH_2Ph), 4.86 (d, 1H, $J = 10.8$ Hz, OCH_2Ph), 4.94 (s, 2H, OCH_2Ph), 4.99 (d, 1H, $J = 12.0$ Hz, OCH_2Ph), 6.89 (d, 2H, $J = 8.9$ Hz, H-ar), 7.17–7.40 (m, 20H, OCH$_2$*Ph*), 7.49 (d, 2H, $J = 8.9$ Hz, H-ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.2$ (C-4), 55.3 (OCH_3), 68.0 (*C*H$_2$OBn), 72.4 (C-7), 73.4, 74.7, 74.9, 75.7 (*C*H$_2$Ph), 77.7 (C-8), 78.3 (C-10), 84.0 (C-9), 108.6 (C-5), 114.0 (2C, C-ar), 121.6 (C-ar), 127.6, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, (C-ar), 137.8, 138.1, 138.3 (C-ar), 157.2 (C-3), 161.6 (C-ar). MS (ESI) $m/z = 686.1$ [M+H]$^+$, 1371.0 [2M+H]$^+$. HRMS (ESI) $m/z = C_{43}H_{44}NO_7$ [M+H]$^+$ calcd 686.3118, found 686.3116.
Selected data for (5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(acetoxy)-7-[(acetoxy)methyl]-3-(4-methoxyphenyl)-1,6-dioxa-2-azaspiro[4,5]dec-2-ene (**5a**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.00$ (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.29 (d, 1H, $J = 17.7$ Hz, H-4a), 3.38 (d, 1H, $J = 17.7$ Hz, H-4b), 3.83 (s, 3H, OCH_3), 4.03 (dd, 1H, $J = 2.0$, 12.6 Hz, CH_2OAc), 4.27 (dd, 1H, $J = 3.7$, 12.6 Hz, CH_2OAc), 4.34 (ddd, 1H, $J = 2.0$, 3.7, 10.1 Hz, H-7), 5.19 (dd, 1H, $J = 9.5$, 10.1 Hz, H-8), 5.41 (d, 1H, $J = 10.0$ Hz, H-10), 5.53 (dd, 1H, $J = 10.0$, 9.5 Hz, H-9), 6.91 (d, 2H, $J = 8.9$ Hz, H-ar), 7.58 (d, 2H, $J = 8.9$ Hz, H-ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.6$ (CH_3), 20.6 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 43.5 (C-4), 55.4 (OCH_3), 61.4 (*C*H$_2$OAc), 67.8 (C-8), 69.1 (C-10), 69.2 (C-7), 71.6 (C-9), 106.7 (C-5), 114.2 (2C, C-ar), 120.6 (C-ar), 128.5 (2C, C-ar), 157.3 (C-3), 161.6 (C-ar), 169.6, 169.8, 170.3, 170.6 (4*C*OCH$_3$). MS (ESI) $m/z = 493.9$ [M+H]$^+$, 516.0 [M+Na]$^+$, 986.6 [2M+H]$^+$, 1008.7 [2M+Na]$^+$. HRMS (ESI) $m/z = C_{23}H_{27}NO_{11}Na$ [M+Na]$^+$ calcd 516.1481, found 516.1488.
28. The NMR spectra of the hydrogenation product suggested that the reduction of the C=N double bond might be stereoselective. However, neither the selectivity of the reduction nor the stereochemistry of the major product have been established at this time. For stereoselective reduction of isoxazolines with $LiAlH_4$, see De Blas, J.; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett.* **1995**, *6*, 1035–1038.
29. Acetylated *exo*-glucal **3** has been previously reported: Tóth, M.; Köver, K. E.; Bényei, A.; Somsák, L. *Org. Biomol. Chem.* **2003**, *1*, 4039–4046.
30. Selected data for (5*R*,7*R*,8*R*,9*S*,10*R*)-7-(hydroxymethyl)-3-(*p*-methoxyphenyl)-1,6-dioxa-2-azaspiro[4,5]dec-2-ene-8,9,10-triol (**7a**): ^{1}H NMR (500 MHz, CD_3OD, 55 °C): $\delta = 3.31$ (m, 1H, H-4a), 3.44 (dd, 1H, $J = 8.9$, 9.2 Hz, H-8), 3.58 (d, 1H, $J = 9.8$ Hz, H-10), 3.68–3.83 (m, 5H, H-4b, CH_2OH, H-7, H-9), 3.84 (s, 3H, OCH_3), 6.97 (d, 2H, $J = 8.1$ Hz, H-ar), 7.62 (d, 2H, $J = 8.1$ Hz, H-ar). ^{13}C NMR (125 MHz, CD_3OD, 55 °C): $\delta = 44.6$ (C-4), 56.0 (OCH_3), 62.6 (*C*H$_2$OH), 71.7 (C-8), 73.3 (C-10), 75.9 (C-9), 76.4 (C-7), 110.7 (C-5), 115.4 (2C, C-ar), 123.1 (C-ar), 129.5 (2C, C-ar), 159.5 (C-3), 163.2 (C-ar). MS (ESI) $m/z = 326.0$ [M+H]$^+$, 348.0 [M+Na]$^+$, 672.9 [2M+Na]$^+$, 997.6 [3M+Na]$^+$. HRMS (ESI) $m/z = C_{15}H_{20}N_1O_7$ [M+H]$^+$ calcd 326.1240, found 326.1243.
31. Huisgen, R.; Mack, W.; Anneser, E. *Tetrahedron Lett.* **1961**, *2*, 587–589.
32. Hemming, K. *J. Chem. Res. (S)* **2001**, 209–216.
33. Typical procedure for 1,3-dipolar cycloaddition on β-D-glucosyl cyanide **8**: To a solution of compound **8** (0.5 mmol) and hydroximoyl chloride (5 equiv) in distilled

toluene (10 mL), a solution of triethylamine (7.5 equiv) in dry toluene (2 mL) was added dropwise (syringe pump, 8 h) at 110 °C. The mixture was stirred overnight at 110 °C. After evaporation, the crude material was purified by flash chromatography to afford the desired spiro-isoxazolines **9a**–**c**.

Selected data for 5-*C*-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3-(*p*-methoxyphenyl)-1,2,4-oxadiazole (**9a**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.81$ (s, 3H, OCH_3), 4.38 (m, 1H, H-5′), 4.56 (dd, 1H, $J = 4.8$, 12.3 Hz, H-6′a), 4.70 (dd, 1H, $J = 1.9$, 12.3 Hz, H-6′b), 5.23 (d, 1H, $J = 9.0$ Hz, H-1′), 5.86 (t, 1H, $J = 9.3$ Hz, H-4′), 6.06 (m, 2H, H-2′, H-3′), 6.89 (d, 2H, $J = 8.7$ Hz, H-ar), 7.28–7.55 (m, 12H, H-ar), 7.85–8.05 (m, 10H, H-ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.8$ (OCH_3), 63.4 (C-6′), 69.5 (C-4′), 71.1 (C-2′ or 3′), 72.9 (C-1′), 74.2 (C-2′ or 3′), 77.6 (C-5′), 114.6 (C-ar), 119.0 (C-ar), 128.8, 128.8, 128.9, 129.0 (C-ar), 129.1 (C-ar), 129.1 (C-ar), 129.6, 129.9 (C-ar), 130.2, 130.3, 133.6, 133.8, 133.9, 134.0, 162.5, 165.2 (C-ar), 165.6, 166.2, 166.6 (4C, *C*OPh), 168.6 (C-3), 173.5 (C-5). MS (LSIMS, NBA) $m/z = 755$ $[M+H]^+$. HRMS (LSIMS, NBA) $m/z =$ $C_{43}H_{35}N_2O_{11}$ $[M+H]^+$ calcd 755.2241, found 755.2242.

34. Selected data for 5-*C*-(β-D-glucopyranosyl)-3-(*p*-methoxyphenyl)-1,2,4-oxadiazole (**10a**): ^{1}H NMR (300 MHz, CD_3OD): $\delta = 3.43$–3.50 (m, 3H, H-3′, H-4′, H-5′), 3.72 (dd, 1H, $J = 4.8$, 12.3 Hz, H-6′a), 3.79 (t, 1H, $J = 9.6$ Hz, H-2′), 3.86 (s, 3H, OCH_3), 3.91 (d, 1H, $J = 12.3$ Hz, H-6′b), 4.63 (d, 1H, $J = 9.6$ Hz, H-1′), 7.05 (d, 2H, $J = 8.9$ Hz, H-ar), 8.00 (d, 2H, $J =$ 8.9 Hz, H-ar). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 56.0$ (OCH_3), 62.8 (C-6′), 71.2 (C-4′), 74.0 (C-2′), 75.2 (C-1′), 79.2 (C-3′), 83.0 (C-5′), 115.2 (2C, C-ar), 120.0 (C-ar), 130.1 (2C, C-ar), 163.8 (C-ar), 169.3 (C-3), 177.9 (C-5). MS (LSIMS, glycerol) $m/z = 339$ $[M+H]^+$. HRMS (LSIMS, glycerol) $m/z =$ $C_{15}H_{19}N_2O_7$ $[M+H]^+$ calcd 339.1192, found 339.1191.