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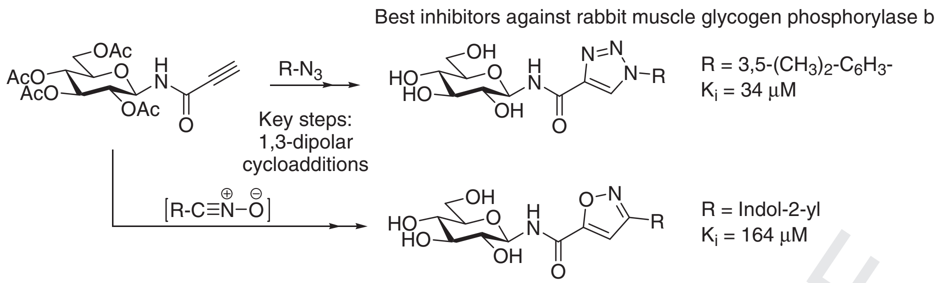
Graphical abstract

Synthesis of heterocyclic *N*-(β-D-glucopyranosyl)carboxamides for inhibition of glycogen phosphorylase pp xxx–xxx

Bálint Kónya, Tibor Docsa, Pál Gergely, László Somsák *



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Synthesis of heterocyclic N-(β-D-glucopyranosyl)carboxamides for inhibition of glycogen phosphorylase

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Glycogen phosphorylase

ABSTRACT

In a DCC-mediated coupling 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine and propiolic acid gave *N*-propynoyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine which was transformed by 1,3-dipolar cycloadditions with aromatic azides and nitrile-oxides to the corresponding *O*-peracetylated *N*-(β-D-glucopyranosyl)-1-substituted-1,2,3-triazole-4-carboxamides and *N*-(β-D-glucopyranosyl)-3-substituted-isoxazole-5-carboxamides, respectively. These compounds were *O*-deacetylated by Zemplén's protocol to be tested as inhibitors of rabbit muscle glycogen phosphorylase b. The best inhibitors of the two series were *N*-(β-D-glucopyranosyl)-1-(3,5-dimethyl-phenyl)-1,2,3-triazole-4-carboxamide (K_i = 34 μM) and *N*-(β-D-glucopyranosyl)-3-(indol-2-yl)-isoxazole-5-carboxamide (K_i = 164 μM).

Q2

1. Introduction

Inhibitors of glycogen phosphorylase (GP) enzymes have been considered as possible means for therapeutic intervention in first of all type 2 diabetes but also other diseased states. For the biochemical rationale behind these considerations the reader is kindly referred to recent review articles.[1–6] As part of an ongoing project to synthesize new glucose derivatives[7] for the inhibition of GP *N*-acyl-β-D-glucopyranosylamines[8] (Chart 1, **I**: e.g. for R = 2-naphthyl K_i (against rabbit muscle GPb, RMGPb) 10 μM[8] or 13 μM[9]) as well as *N*-acyl-*N*′-β-D-glucopyranosyl urea derivatives[4] **II** (R = 2-naphthyl: K_i (RMGPb) 0.35 μM) have been taken as lead structures. Non-classical bioisosteric replacement of the NHCO moiety in **I** by the heterocyclic linker **A** revealed high similarity of the amide (see K_i of **I** above) and the 1,2,3-triazole type (for **IA** R = 2-naphthyl: K_i (RMGPb) 16 μM[9]) inhibitors both in binding strength and structural features of the enzyme–inhibitor complexes.[9,10] Applying the isomeric **B**, **C**, and **D** moieties as linkers resulted in inhibitors of varying efficiency,[11,12] whereby the 3-aryl-5-β-D-glucopyranosyl-1,2,4-oxadiazole (**ID** type) derivatives proved to be the most potent compounds (for the best inhibitor where R = 2-naphthyl the K_i (RMGPb) was 2.4 μM[12]). Very recently we have reported on the synthesis and enzymatic evaluation of a

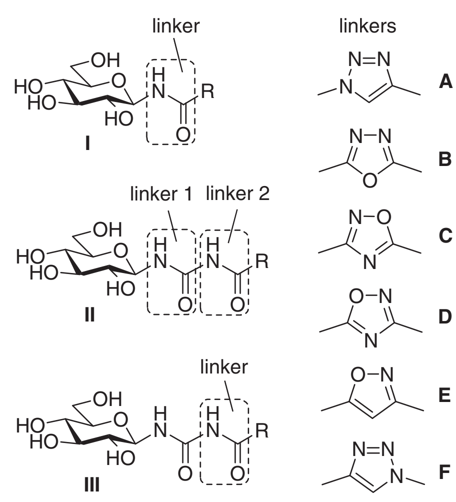

Chart 1.

series of compounds of type **II** with linker 1 and linker 2 being 1,2,3-triazoles **A** and **F** as well as 1,3,4-oxadiazole **B** in various coupling patterns.[13] The best inhibitors against RMGPb were effective in the upper micromolar range (linker 1 = **A**, linker 2 = **B**, R = Ph: K_i 854 μM; linker 1 = **B**, linker 2 = **F**, R = 2-naphthyl: K_i 745 μM).

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Herein we report on the synthesis and enzymatic test of some compounds of type **III** with isoxazole **E** and 1,2,3-triazole **F** as linkers.

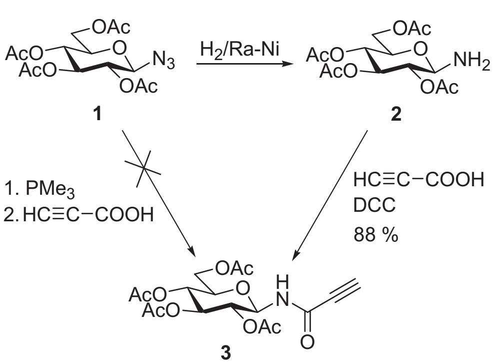
2. Results and discussion

For the preparation of compounds of type **IIIE** and **IIIF** construction of the heterocyclic parts by 1,3-dipolar cycloadditions[14] of an alkyne and nitrile-oxides[15] as well as azides,[16,17] respectively, was envisaged. As the direct transformation of azide **1**[18] by acylation of an in situ generated iminophosphorane[19] with propiolic acid failed, the necessary protected *N*-propynoyl-β-D-glucopyranosylamine **3** was obtained from glucosylamine **2**[20] and propiolic acid by a DCC-mediated coupling in high yield (Scheme 1).

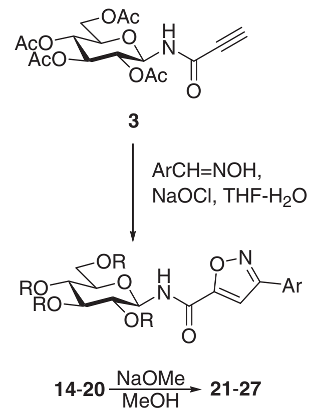
The copper(I) catalyzed cycloaddition reaction (CuAAC) of **3** with aromatic azides was investigated first (Scheme 2). The non-commercial azides were prepared either in situ from the corresponding boronic acids following a recently published procedure[21] or from the related aniline derivatives via diazonium salts.[22] The widely used system $CuSO_4$–L-ascorbic acid was applied to generate the catalyst, and the cycloadducts **4–8** were obtained in high yields. A trial with a recently published catalyst $Cu(PPh_3)_2NO_3$[23] in 2 mol % loading under the same conditions did not significantly improve the yield of **4** (93%).

Alkyne **3** was next transformed with nitrile-oxides which were oxidatively generated in situ from aromatic aldoximes by using domestic bleach.[24] The target compounds **14–20** were obtained in modest to acceptable yields, among which the indole derivatives **19** and **20** having an NH group could be isolated in the lowest yields.

O-Acetyl protecting groups were removed by the Zemplén protocol to give the test compounds **9–13** and **21–27** (Schemes 2 and 3, respectively) in high yields.



Scheme 1.

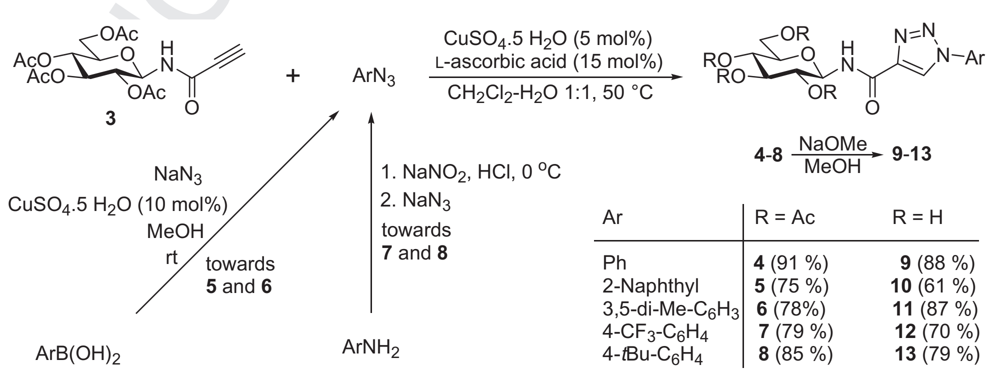


Ar	R = Ac	R = H
Ph	**14** (55 %)	**21** (97 %)
2-Naphthyl	**15** (52 %)	**22** (91 %)
Benzo-[b]-furan-2-yl	**16** (50 %)	**23** (88 %)
Benzo-[b]-thiophen-2-yl	**17** (51 %)	**24** (95 %)
Benzothiazol-2-yl	**18** (30 %)	**25** (90 %)
Indol-2-yl	**19** (24 %)	**26** (76 %)
Indol-3-yl	**20** (20 %)	**27** (70 %)

Scheme 3.

Proton and carbon NMR spectra of triazoles **4–13** and isoxazoles **14–27** contained resonances for the sugar part and the amide moiety of the compounds as expected. In the ^{13}C NMR spectra signals for the triazole C-4 (quaternary) and C-5 (CH) appeared in the 140–143 and 116–121 ppm range, respectively, thereby corroborating the anticipated 1,4-disubstitution pattern of the 1,2,3-triazole in analogy with previously reported compounds.[10] The isoxazole C(4)–H appeared in the 7.2–7.3 ppm range for the protected derivatives **14–20**, and in the 7.5–7.9 ppm range for the unprotected **21–27**. HMBC spectra allowed to identify isoxazole C3 (155–163 ppm) and C5 (162–166 ppm) resonances in the whole series **14–27**. Furthermore, detection of crosspeaks between isoxazole C–H and both the amide CO and a quaternary carbon of the aromatic substituent indicated the formation of 3-aryl-isoxazole-5-carboxamides **14–20** (contrary to the possibility of 3-aryl-isoxazole-4-carboxamide derivatives).

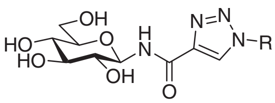
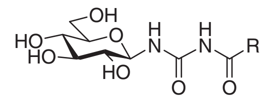
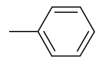
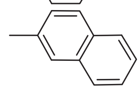
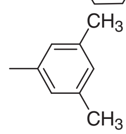
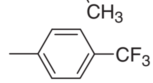
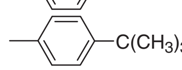
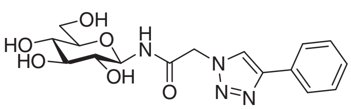
The heterocyclic *N*-(β-D-glucopyranosyl) carboxamides were tested for their inhibitory activity against rabbit muscle glycogen phosphorylase b as described earlier,[8] and the obtained data, together with some relevant literature values, are collected in Table 1. The triazole derivatives **9** and **11–13** had inhibitor constants in the micromolar range. The inactivity of the 2-naphthyl compound

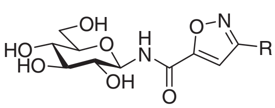
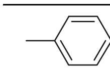
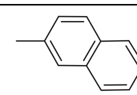
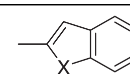
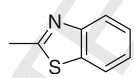
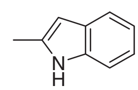
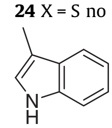


Ar	R = Ac	R = H
Ph	**4** (91 %)	**9** (88 %)
2-Naphthyl	**5** (75 %)	**10** (61 %)
3,5-di-Me-C_6H_3	**6** (78%)	**11** (87 %)
4-CF_3-C_6H_4	**7** (79 %)	**12** (70 %)
4-*t*Bu-C_6H_4	**8** (85 %)	**13** (79 %)

Scheme 2.

Table 1
Inhibition of rabbit muscle glycogen phosphorylase b (RMGPb, K_i [μM])

		R		
9	75		28	4.6[4]
10	No inhibition		29	0.35[4]
11	34		30	0.9[28]
12	51		31	1.8[4]
13	143		32	0.7[4]
 **33**			179[25]	

	R		
	 **21** 172[a]	 **22** no inhibition	 **23** X = O **24** X = S no inhibition
	 **25** no inhibition	 **26** 164[a]	 **27** 207[a]

[a] Calculated from the IC_{50} values by the Cheng–Prusoff equation[29]: $K_i = IC_{50}/(1 + [S]/K_m)$.

10 was surprising especially in the light of very strong inhibition by 2-naphthyl derivatives in other series of glucose based inhibitors,[7] for example, acyl ureas **28**–**32** from which **29** had the highest affinity. While in these latter cases the inhibition became stronger with increasing size of the aromatic part of the molecules, this tendency seemed to be reversed among triazoles **9**–**13**. The relatively weak binding of a more or less similar triazole derivative **33** was attributed to the diminished number of interactions of the inhibitor with the protein as well as to the steric bulk of the aglycone inducing unfavorable changes in the vicinity of the binding site (more specifically the so-called 280s loop next to the catalytic center).[25] The present observations might have a similar origin. In addition, the bioisosteric relationship of the amide and the 1,2,3-triazole moieties, which proved to be valid for *N*-acyl-β-D-glucopyranosylamines and 1-β-D-glucopyranosyl-4-substituted-1,2,3-triazoles[9] outlined in the introduction, cannot be justified for the case of the 'second' NHCO group of the *N*-acyl-*N*′-β-D-glucopyranosyl urea type GP inhibitors.

Inhibition of RMGPb by the isoxazoles **21**–**27** was even weaker. Thus, phenyl-isoxazole **21** had a more than twice less affinity than its triazole counterpart **9**. An increase in the size of the aromatic moiety as in compounds **22**–**25** resulted in a complete loss of activity. Interestingly, the indole derivatives **26** and **27**, in which the steric bulk of the rings must be essentially the same as in **23**–**25**, showed weak binding similar to that of **21**. This might be due to the hydrogen bond donor capacity of this ring system. It can also be envisaged that these compounds bind to the so-called new allosteric (or indole binding) site of the enzyme where some glucose derivatives were also shown to be accommodated.[4,26,27] These points need further investigations.

In summary, 1,3-dipolar cycloadditions of aromatic azides and nitrile-oxides were used as the key steps in the synthesis of *N*-(β-D-glucopyranosyl)-1-substituted-1,2,3-triazole-4-carboxamides and *N*-(β-D-glucopyranosyl)-3-substituted-isoxazole-5-carboxamides, respectively. The new compounds inhibited rabbit muscle glycogen phosphorylase b in the low micromolar range. The amide-1,2,3-triazole bioisosterism could not be verified for the 'second' NHCO part of *N*-acyl-*N*′-β-D-glucopyranosyl ureas.

3. Experimental

3.1. General methods

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined on a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker WP 360 SY (360/90 MHz for $^1H/^{13}C$) and Varian UNITYINOVA 400 WB (400/100 MHz for $^1H/^{13}C$) spectrometers. Chemical shifts are referenced to Me_4Si as the internal reference (^1H) or the residual solvent signal (^{13}C). Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with Silica Gel 60 F_{254} (Merck). TLC plates were inspected by UV light (λ = 254 nm) and after gentle heating for the carbohydrate derivatives. Silica gel column chromatography was performed with Silica Gel Si 60 (40–63 μm) purchased from Merck (Darmstadt, Germany). Organic solutions were dried over anhydrous $MgSO_4$, and concentrated at diminished pressure at 40–50 °C (water bath). Aromatic aldoximes were prepared in the usual way[30] from the corresponding aldehydes purchased from Sigma-Aldrich.

3.2. *N*-Propynoyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl amine (3)

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamine[20] (**2**, 1 g, 2.882 mmol) was dissolved in dry CH_2Cl_2 (20 mL), propiolic acid (355 μL, 2 equiv) and DCC (0.565 g, 1.05 equiv) were added. The mixture was stirred at rt and monitored by TLC (1:1 EtOAc–hexane). After consumption of the amine the solvent was evaporated and the residue was purified by column chromatography (eluent: 1:1 EtOAc–hexane) to give 1.01 g (88%) yellow syrup. R_f = 0.5 (1:1 EtOAc–hexane); $[\alpha]_D$ −31 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 7.27 (d, 1H, *J* = 9.0 Hz, N*H*), 5.20 (t, 1H, *J* = 9.4, 9.4 Hz, H-1), 5.03–4.80 (m, 2H, H-3, H-4), 4.19 (dd, 1H, *J* = 12.0, 3.3 Hz, H-6a), 4.00 (m, 2H, H-2, H-6b), 3.76 (ddd, 1H, *J* = 9.2, 5.0, 3.3 Hz, H-5), 2.97 (s, 1H, C*H*), 1.97, 1.95, 1.92, 1.91 (m, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 171.4, 171.3, 170.6, 170.3 (4xOCOCH$_3$), 153.0 (NHCO), 78.3 (C-1), 77.2 (CCH), 74.3, 73.6, 71.0, 68.7 (C-2–C-5), 61.1 (C-6), 49.7 (CCH), 21.7, 21.4 21.2, 21.2 (4 × OCOCH$_3$). Anal. Calcd for $C_{17}H_{21}NO_{10}$ (399.35): C, 51.13; H, 5.30; N, 3.51. Found: C, 51.33; H, 5.12; N, 3.41.

3.3. General procedure for the Zemplén deacylation

An *O*-peracylated compound (100 mg) was dissolved in dry MeOH (1 mL) and a solution of NaOMe (1 M in MeOH) was added to the solution in a catalytic amount. The reaction mixture was kept at rt. When the reaction was complete (TLC, 7:3 $CHCl_3$–MeOH) the solution was neutralized with a cation exchange resin Amberlyst 15 (H^+ form). Filtration and removal of the solvent resulted in the corresponding deacetylated sugar derivative which, if necessary, was purified by column chromatography.

3.4. General procedures for the Cu(I) catalyzed azide–alkyne cycloaddition

3.4.1. In CH_2Cl_2–water mixtures with organic azides

Equimolar amounts of *N*-propynoyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**3**) and an azide were dissolved in CH_2Cl_2 (7 mL/mmol alkyne). Water (the same volume as that of CH_2Cl_2), $CuSO_4$·5H_2O (5 mol %), L-ascorbic-acid (15 mol %) were added and the mixture was stirred at 50 °C and monitored by TLC (1:1 EtOAc–hexane). After disappearance of the starting materials the reaction mixture was diluted with water and CH_2Cl_2, the phases were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL/mmol). The combined organic layer was dried, the solvent evaporated, and the residue purified by column chromatography (eluent: 1:1 EtOAc–hexane).

3.4.2. In CH_2Cl_2–water mixtures with organic azides prepared in situ from boronic acids

Boronic acid (1 equiv) and NaN_3 (1.2 equiv) were dissolved in MeOH (5 mL/mmol of boronic acid). $CuSO_4$·5H_2O (0.10 equiv) was added and the mixture was stirred overnight at rt. CH_2Cl_2 and water (10 mL of each/mmol of boronic acid), *N*-propynoyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**3**, 0.75 equiv) and L-ascorbic acid (0.5 equiv) were added and the reaction mixture was heated to 50 °C. After consumption of the alkyne (TLC, 1:1 EtOAc–hexane) the reaction mixture was diluted with water and CH_2Cl_2, the phases were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL/mmol). The combined organic layer was dried, the solvent evaporated, and the residue purified by column chromatography (eluent: 1:1 EtOAc–hexane).

3.4.3. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-phenyl-1,2,3-triazole-4-carboxamide (4)

Prepared by general procedure given in Section 3.4.1 from **3** (335 mg, 0.841 mmol) and PhN_3 for 1 day. Yield: 396 mg (91%) white crystals. R_f = 0.43 (1:1 EtOAc–hexane); Mp: 232–234 °C $[\alpha]_D$ −6.9 (*c* 0.54, DMSO) ^{1}H NMR (DMSO-*d*$_6$, 360 MHz) δ (ppm) 9.39 (s, 1H, triazole C*H*), 9.37 (br s, 1H, N*H*), 7.97 (d, 2H, *J* = 7.6 Hz, Ar*H*), 7.64–7.54 (m, 3H, Ar*H*), 5.66 (t, 1H, *J* = 9.1, 9.1 Hz, H-1), 5.41, 5.24, 4.92 (3 pseudo t, *J* = 9.1, 10.6 Hz in each, H-2, H-3, H-4), 4.19–4.44 (m, 2H, H-6a, H-5), 4.01 (dd, 1H, *J* = 11.9, 3.0 Hz, H-6b), 2.01, 2.01, 1.95, 1.91 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR (DMSO-*d*$_6$, 90 MHz) δ (ppm) 171.0, 170.8, 169.9, 169.0 (*C*O), 157.3 (NH*C*O), 140.8 (triazole C-4), 129.2, 128.8, 128.8, 128.5, 125.5, 125.5 (Ar), 116.7 (triazole C-5), 78.1 (C-1), 73.9, 73.1, 70.6, 68.5 (C-2–C-5), 62.0 (C-6), 20.3, 20.2, 20.0 (*C*H$_3$). Anal. Calcd for $C_{23}H_{26}N_4O_{10}$ (518.47): C, 53.28; H, 5.05; N, 10.81. Found: C, 52.88; H, 4.86; N, 10.94.

3.4.4. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-(2-naphthyl)-1,2,3-triazole-4-carboxamide (5)

Prepared by general procedure given in Section 3.4.2 from **3** (696 mg, 1.744 mmol) and 2-naphthylazide (prepared in situ from naphthalene-2-boronic acid (300 mg, 1.744 mmol)). Yield: 743 mg (75%) white crystals. R_f = 0.33 (1:1 EtOAc–hexane); Mp: 223–225 °C $[\alpha]_D$ −1.1 (*c* 0.27, DMSO) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 8.61 (s, 1H, triazole C*H*), 8.14 (br s, 1H, N*H*), 7.89 (m, 5H, Ar*H*), 7.55–7.52 (m, 2H, Ar*H*), 5.45 (t, 1H, *J* = 9.3, 9.3 Hz, H-1), 5.31, 5.11, 5.10 (3 pseudo t, 1H each, *J* = 9.5, 10.5 Hz in each, H-2, H-3, H-4), 4.25 (dd, 1H, *J* = 12.2, 3.8 Hz, H-6a), 4.08 (dd, 1H, *J* = 12.2, 1.9 Hz, H-6b), 3.85 (m, 1H, H-5), 2.03, 1.99, 1.98, 1.96 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 170.8, 170.5, 170.2, 169.7 (*C*O), 160.3 (NH*C*O), 142.8 (triazole C-4), 133.9, 133.3, 130.5 128.5, 128.1, 127.9, 127.6, 119.2 (Ar), 118.8 (triazole C-5), 78.1 (C-1), 73.8, 73.2, 70.6, 68.3 (C-2–C-5), 61.8 (C-6), 20.9, 20.7 (*C*H$_3$). Anal. Calcd for $C_{27}H_{28}N_4O_{10}$ (568.53): C, 57.04; H, 4.96; N, 9.85. Found: C, 56.64; H, 4.77; N, 9.98.

3.4.5. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-(3,5-dimethyl-phenyl)-1,2,3-triazole-4-carboxamide (6)

Prepared by general procedure given in Section 3.4.2 from **3** (798 mg, 2.00 mmol) and 3,5-dimethyl-phenyl-azide (prepared in situ from 3,5-dimethyl-phenylboronic acid (300 mg, 2.00 mmol)). Yield: 852 mg (78%) yellow syrup. R_f = 0.48 (1:1 EtOAc–hexane) $[\alpha]_D$ −29 (*c* 0.34, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 8.49 (s, 1H, triazole C*H*), 7.94 (d, 1H, *J* = 9.5 Hz, N*H*), 7.32 (s, 2H, Ar*H*), 7.09 (s, 1H, Ar*H*), 5.49 (t, 1H, *J* = 9.5, 9.5 Hz, H-1), 5.37, 5.16, 5.13 (3 pseudo t, 1H each, *J* = 9.5, 10.1 Hz in each, H-2, H-3, H-4), 4.30 (dd, 1H, *J* = 11.9, 4.0 Hz, H-6a), 4.13 (dd, 1H, *J* = 11.9, 1.9 Hz, H-6b), 3.90 (m, 1H, H-5), 2.39 (s, 6H, 2 × C*H*$_3$), 2.07, 2.03, 2.02, 1.99 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 170.8, 170.4, 170.2, 169.6 (*C*O), 160.4 (NH*C*O), 142.4 (triazole C-4), 140.1, 136.4, 136.4, 131.2, 131.2, 124.3 (Ar), 118.8 (triazole C-5), 78.0 (C-1), 73.7, 73.1, 70.5, 68.2 (C-2–C-5), 61.8 (C-6), 21.4, 21.4 (*C*H$_3$), 20.8, 20.7 (*C*H$_3$). Anal. Calcd for $C_{25}H_{30}N_4O_{10}$ (546.53): C, 54.94; H, 5.53; N, 10.25. Found: C, 54.54; H, 5.34; N, 10.38.

3.4.6. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-(4-trifluoromethyl-phenyl)-1,2,3-triazole-4-carboxamide (7)

Prepared by general procedure given in Section 3.4.1 from **3** (426 mg, 1.069 mmol) and 4-CF_3–C_6H_4–N_3 for 1 day. Yield: 495 mg (79%) colorless oil. R_f = 0.48 (1:1 EtOAc–hexane) $[\alpha]_D$

−1.2 (*c* 0.30, DMSO) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 8.77 (s, 1H, triazole C*H*), 8.12 (d, 1H, *J* = 9.5 Hz, N*H*), 7.97 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.83 (d, 2H, *J* = 8.4 Hz, Ar*H*), 5.56 (t, 1H, *J* = 9.4, 9.4 Hz, H-1), 5.40 (t, 1H, *J* = 9.7, 9.7 Hz, one of H-2, H-3, H-4), 5.18–5.05 (m, 2H, two of H-2, H-3, H-4), 4.30 (dd, 1H, *J* = 11.2, 4.0 Hz, H-6a), 4.10 (dd, 1H, *J* = 11.2, 4.0 Hz, H-6b), 3.96 (m, 1H, H-5), 2.05, 2.02, 2.00, 1.98 (4s, 12H, 4 × CH_3); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 170.7, 170.5, 170.0, 169.9 (*C*O), 160.0 (NH*C*O), 143.0 (triazole C-4), 138.8, 131.2 (q, *C*–CF_3, *J* = 34.9 Hz), 127.3, 126.0, 124.9, 124.4 (Ar), 121.9 (q, *C*F_3, *J* = 277 Hz), 120.8 (triazole C-5), 77.9 (C-1), 73.7, 73.0, 70.5, 68.2 (C-2–C-5), 61.7 (C-6), 20.7, 20.6 (*C*H_3). Anal. Calcd for $C_{24}H_{25}F_3N_4O_{10}$ (586.47): C, 49.15; H, 4.30; N, 9.55. Found: C, 48.75; H, 4.11; N, 9.69.

3.4.7. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-(4-*t*butyl-phenyl)-1,2,3-triazole-4-carboxamide (8)

Prepared by general procedure given in Section 3.4.1 from **3** (456 mg, 1.143 mmol) and 4-*t*Bu–C_6H_4–N_3 for 1 day. Yield: 558 mg (85%) white crystals. R_f = 0.49 (1:1 EtOAc–hexane); Mp: 194–196 °C $[\alpha]_D$ −5.4 (*c* 0.33, DMSO) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 8.55 (s, 1H, triazole C*H*), 8.00 (d, 1H, *J* = 9.5 Hz, N*H*), 7.64 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.51 (d, 2H, *J* = 8.6 Hz, Ar*H*), 5.52 (t, 1H, *J* = 9.5, 9.5 Hz, H-1), 5.36, 5.16, 5.10 (3 pseudo t, 1H each, *J* = 9.5, 9.5 Hz in each, H-2, H-3, H-4), 4.26 (dd, 1H, *J* = 11.2, 4.0 Hz, H-6a), 4.08 (dd, 1H, *J* = 11.2, 2.1 Hz, H-6b), 3.90 (m, 1H, H-5), 2.02, 1.99, 1.99, 1.96 (4s, 12H, 4 × CH_3), 1.31 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 170.7, 170.3, 170.1, 169.5 (*C*O), 160.4 (NH*C*O), 152.9 (Ar), 142.5 (triazole C-4), 134.0, 126.8, 126.8, 124.2, 124.2 (Ar), 120.4 (triazole C-5), 77.8 (C-1), 73.6, 73.1, 70.5, 68.2 (C-2–C-5), 61.8 (C-6), 34.9 (*C*(CH$_3$)$_3$), 31.2 (C(*C*H$_3$)$_3$), 20.7, 20.6 (*C*H$_3$). Anal. Calcd for $C_{27}H_{34}N_4O_{10}$ (574.58): C, 56.44; H, 5.96; N, 9.75. Found: C, 56.20; H, 5.76; N, 9.94.

3.4.8. *N*-(β-D-Glucopyranosyl)-1-phenyl-1,2,3-triazole-4-carboxamide (9)

Prepared by general procedure given in Section 3.3 from **4** (200 mg, 0.386 mmol) for 1 h. Yield: 119 mg (88%) white crystals. R_f = 0.53 (7:3 $CHCl_3$–MeOH); Mp: 199–201 °C $[\alpha]_D$ +3.4 (*c* 0.15, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 9.38 (s, 1H, triazole C*H*), 7.98 (d, 2H, *J* = 7.6 Hz, Ar*H*), 7.58 (m, 3H, Ar*H*), 4.89 (d, 1H, *J* = 8.9 Hz, H-1), 3.67 (dd, 1H, *J* = 12.3, 2.9 Hz, H-6a), 3.25–3.09 (m, 5H, H-2, H-3, H-4, H-5, H-6b); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 160.7 (NH*C*O), 143.4 (triazole C-4), 133.3, 131.7, 128.7, 127.9 (Ar), 118.4 (triazole C-5), 80.0 (C-1), 72.9, 71.2 70.1, 68.9 (C-2–C-5), 62.2 (C-6). Anal. Calcd for $C_{15}H_{18}N_4O_6$ (350.33): C, 51.43; H, 5.18; N, 15.99. Found: C, 51.01; H, 4.98; N, 16.05.

3.4.9. *N*-(β-D-Glucopyranosyl)-1-(2-naphthyl)-1,2,3-triazole-4-carboxamide (10)

Prepared by general procedure given in Section 3.3 from **5** (180 mg, 0.317 mmol) for 2 h. Yield: 77 mg (61%) white crystals. R_f = 0.51 (7:3 $CHCl_3$–MeOH); Mp: 275–277 °C (decomp.) $[\alpha]_D$ +4.4 (*c* 0.34, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 9.35 (s, 1H, triazole CH), 8.50 (s, 1H, Ar*H*), 8.17 (d, 1H, *J* = 8.9 Hz, Ar*H*), 8.12–7.98 (m, 3H, Ar*H*), 7.69–7.59 (m, 2H, Ar*H*), 4.95 (d, 1H, *J* = 9.0 Hz, H-1), 3.66 (dd, 1H, *J* = 10.9, 2.0 Hz, H-6a), 3.50–3.33 (m, 2H, H-3, H-6b), 3.29–3.10 (m, 3H, H-2, H-4, H-5); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 160.3 (NHCO), 142.0 (triazole C-4), 134.6, 131.9, 129.6, 129.4, 128.0, 127.7, 127.1, 124.4 (Ar), 119.1 (triazole C-5), 80.2 (C-1), 72.1, 71.3 70.1, 68.7 (C-2–C-5), 62.1 (C-6). Anal. Calcd for $C_{19}H_{20}N_4O_6$ (400.39): C, 57.00; H, 5.03; N, 13.99. Found: C, 56.60; H, 4.86; N, 14.04.

3.4.10. *N*-(β-D-Glucopyranosyl)-1-(3,5-dimethyl-phenyl)-1,2,3-triazole-4-carboxamide (11)

Prepared by general procedure given in Section 3.3 from **6** (180 mg, 0.317 mmol) for 1 h. Yield: 104 mg (87%) white crystals. R_f = 0.74 (7:3 $CHCl_3$–MeOH); Mp: 145–147 °C $[\alpha]_D$ +1.7 (*c* 0.33, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 9.15 (s, 1H, triazole C*H*), 7.52 (s, 2H, Ar*H*), 7.15 (s, 1H, Ar*H*), 4.93 (d, 1H, *J* = 9.0 Hz, H-1), 3.65 (dd, 1H, *J* = 11.0, 2.1 Hz, H-6a), 3.51–3.32 (m, 2H, H-3, H-6b), 3.31–3.12 (m, 3H, H-2, H-4, H-5), 2.34 (s, 6H, 2xCH_3); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 160.7 (NH*C*O), 143.3 (triazole C-4), 140.2, 136.5, 133.2, 127.1, 126.4, 126.0 (Ar), 118.3 (triazole C-5), 80.0 (C-1), 72.7, 71.2, 70.3, 68.8 (C-2–C-5), 61.9 (C-6). Anal. Calcd for $C_{17}H_{22}N_4O_6$ (378.38): C, 53.96; H, 5.86; N, 14.81. Found: C, 53.56; H, 5.73; N, 14.94.

3.4.11. *N*-(β-D-Glucopyranosyl)-1-(4-trifluoromethyl-phenyl)-1,2,3-triazole-4-carboxamide (12)

Prepared by general procedure given in Section 3.3 from **7** (200 mg, 0.341 mmol) for 2 h. Yield: 100 mg (70%) white crystals. R_f = 0.57 (7:3 $CHCl_3$–MeOH); Mp: 241–243 °C $[\alpha]_D$ +4.5 (*c* 0.60, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 9.35 (s, 1H, triazole C*H*), 8.16 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.98 (d, 2H, *J* = 8.6 Hz, Ar*H*), 4.94 (d, 1H, *J* = 9.0 Hz, H-1), 3.64 (dd, 1H, *J* = 12.9, 2.4 Hz, H-6a), 3.41–3.35 (m, 2H, H-3, H-6b), 3.29–3.06 (m, 3H, H-2, H-4, H-5); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 160.5 (NH*C*O), 143.8 (triazole C-4), 139.4, 130.0, 129.7 (q, *C*–CF_3, *J* = 30.4 Hz), 128.0, 127.7, (Ar), 122.7 (q, *C*F_3, *J* = 273.2 Hz), 116.7 (triazole C-5), 80.0 (C-1), 72.4, 71.3, 70.4, 69.0 (C-2, C-3, C-4, C-5), 62.0 (C-6). Anal. Calcd for $C_{16}H_{17}F_3N_4O_6$ (418.32): C, 45.94; H, 4.10; N, 13.39. Found: C, 45.54; H, 3.91; N, 13.53.

3.4.12. *N*-(β-D-Glucopyranosyl)-1-(4-*t*butyl-phenyl)-1,2,3-triazole-4-carboxamide (13)

Prepared by general procedure given in Section 3.3 from **8** (200 mg, 0.348 mmol) for 2 hour. Yield: 111 mg (79%) white crystals. R_f = 0.62 (7:3 $CHCl_3$–MeOH); Mp: 207–209 °C $[\alpha]_D$ +1.9 (*c* 0.34, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 9.06 (s, 1H, triazol C*H*), 7.75 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.58 (d, 2H, *J* = 8.5 Hz, Ar*H*), 4.94 (d, 1H, *J* = 8.9 Hz, H-1), 3.65 (dd, 1H, *J* = 11.4, 2.3 Hz, H-6a), 3.51–3.34 (m, 2H, H-3, H-6b), 3.23 (m, 3H, H-2, H-4, H-5), 1.25 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 161.5 (NH*C*O), 153.4 (Ar), 143.5 (triazole C-4), 134.5, 127.9, 127.6, 121.4, 121.1 (Ar), 120.2 (triazole C-5), 80.3 (C-1), 72.1, 71.2, 70.3, 69.1 (C-2–C-5), 61.9 (C-6), 35.4 (*C*(CH$_3$)$_3$), 31.8 (C(*C*H$_3$)$_3$). Anal. Calcd for $C_{19}H_{26}N_4O_6$ (406.43): C, 56.15; H, 6.45; N, 13.79. Found: C, 55.78; H, 6.25; N, 13.95.

3.5. General procedure for the nitrile-oxide cycloaddition

A solution of *N*-propynoyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-amine (0.5 mmol) and an arenecarbaldoxime (0.55 mmol, 1.1 equiv) in THF (4 mL) was stirred at rt under Argon. 0.2 M NaOCl solution (20 mL) was slowly added dropwise in 5 h with a syringe pump. The reaction was stirred at rt for an additional 12 h, then the reaction mixture was diluted with water and EtOAc, the phases were separated and the aqueous layer was washed with EtOAc (2 × 30 mL/mmol). The combined organic layer was dried, the solvent evaporated, and the residue purified by column chromatography (eluent: 2:3 EtOAc–hexane).

3.5.1. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-phenyl-isoxazole-5-carboxamide (14)

Prepared by general procedure given in Section 3.5 from **3** (248 mg, 0.621 mmol) and benzaldoxime (83 mg, 0.683 mmol).

Yield: 177 mg (55%) white crystals. R_f = 0.31 (2:3 EtOAc–hexane); Mp: 212–214 °C $[\alpha]_D$ −4 (c 0.21, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 7.82–7.79 (m, 2H, Ar*H*), 7.41 (d, 1H, *J* = 9.2 Hz, N*H*), 7.40–7.35 (m, 3H, Ar*H*), 7.20 (s, 1H, isoxazole C*H*), 5.37, 5.32, 5.07 (3 pseudo t, 4H, *J* = 9.5, 9.5 Hz in each, H-1, H-2, H-3, H-4), 4.30 (dd, 1H, *J* = 11.9, 2.8 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.6, 2.2 Hz, H-6b) 3.82 (ddd, 1H, *J* = 9.2, 4.0, 2.6 Hz, H-5), 2.01, 1.98 (2s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 170.9, 170.7, 170.0, 169.6 (*C*O), 165.5 (isoxazole C-5), 162.6 (isoxazole C-3), 156.1 (NH*C*O), 130.8, 129.2, 129.2, 127.9, 127.0, 127.0 (Ar), 106.4 (isoxazole *C*H), 78.2 (C-1), 74.0, 72.8, 70.6, 68.2 (C-2–C-5), 61.7 (C-6), 20.8, 20.7 (OCO*C*H$_3$). Anal. Calcd for $C_{24}H_{26}N_2O_{11}$ (518.47): C, 55.60; H, 5.05; N, 5.40. Found: C, 55.20; H, 4.87; N, 5.57.

3.5.2. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(2-naphthyl)-isoxazole-5-carboxamide (15)

Prepared by general procedure given in Section 3.5 from **3** (388 mg, 0.972 mmol) and naphthalene-2-carbaldoxime (200 mg, 1.069 mmol). Yield: 288 mg (52%) white crystals. R_f = 0.40 (2:3 EtOAc–hexane); Mp: 202–204 °C $[\alpha]_D$ −7.8 (c 0.24, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 8.12 (s, 1H, Ar*H*), 7.83–7.76 (m, 4H, Ar*H*), 7.62 (d, 1H, *J* = 9.2 Hz, N*H*), 7.46–7.43 (m, 2H, Ar*H*), 7.31 (s, 1H, isoxazole C*H*), 5.42, 5.34, 5.12, 5.08 (4 pseudo t, 4H, *J* = 9.2, 9.5 Hz in each, H-1, H-2, H-3, H-4), 4.32 (dd, 1H, *J* = 11.9, 5.1 Hz, H-6a), 4.14 (dd, 1H, *J* = 11.9, 2.8 Hz, H-6b) 3.89 (ddd, 1H, *J* = 9.2, 5.1, 2.8 Hz, H-5), 2.00, 1.99, 1.98, 1.96 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 171.2, 171.0, 170.4, 170.0 (*C*O), 163.7 (isoxazole C-5), 163.0 (isoxazole C-3), 156.5 (NH*C*O), 134.6, 133.5, 129.4, 128.9, 128.2, 127.8, 127.4, 127.3, 125.5, 124.0 (Ar), 106.8 (isoxazole *C*H), 78.5 (C-1), 74.2, 73.2, 70.9, 68.5 (C-2–C-5), 62.1 (C-6), 21.1, 21.0 (*C*H$_3$). Anal. Calcd for $C_{28}H_{28}N_2O_{11}$ (568.53): C, 59.15; H, 4.96; N, 4.93. Found: C, 58.85; H, 4.77; N, 5.07.

3.5.3. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(benzo-[*b*]-furan-2-yl)-isoxazole-5-carboxamide (16)

Prepared by general procedure given in Section 3.5 from **3** (200 mg, 0.501 mmol) and benzo-[*b*]-furan-2-carbaldoxime (89 mg, 1.551 mmol). Yield: 141 mg (50%) yellow oil. R_f = 0.39 (2:3 EtOAc–hexane) $[\alpha]_D$ −6.7 (c 0.45, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 7.62–7.55 (m, 2H, Ar*H*), 7.47 (d, 1H, *J* = 9.2 Hz, N*H*), 7.32–7.19 (m, 3H, Ar*H*, isoxazole C*H*), 5.40, 5.33, 5.10, 5.08 (4 pseudo t, 4H, *J* = 9.2, 9.5 Hz in each, H-1, H-2, H-3, H-4), 4.27 (dd, 1H, *J* = 12.1, 5.2 Hz, H-6a), 4.06 (dd, 1H, *J* = 12.1, 2.8 Hz, H-6b), 3.84 (ddd, 1H, *J* = 9.2, 5.2, 2.8 Hz, H-5), 2.01, 1.99, 1.98, 1.96 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 170.9, 170.7, 170.0, 169.6 (*C*O), 162.6 (isoxazole C-5), 156.0 (isoxazole C-3), 155.7 (NH*C*O), 155.4, 144.5, 127.8, 126.4, 123.8, 122.0 (Ar), 106.3 (isoxazole *C*H), 78.2 (C-1), 74.0, 72.9, 70.6, 68.2 (C-2–C-5), 61.7 (C-6), 20.8, 20.7 (*C*H$_3$). Anal. Calcd for $C_{26}H_{26}N_2O_{12}$ (558.49): C, 55.91; H, 4.69; N, 5.02. Found: C, 55.50; H, 4.50; N, 5.18.

3.5.4. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(benzo-[*b*]-thiophen-2-yl)-isoxazole-5-carboxamide (17)

Prepared by general procedure given in Section 3.5 from **3** (204 mg, 0.513 mmol) and benzo-[*b*]-thiophen-2-carbaldoxime (100 mg, 0.564 mmol). Yield: 151 mg (51%) yellow crystals. R_f = 0.29 (2:3 EtOAc–hexane); Mp: 192–194 °C (decomp.) $[\alpha]_D$ −7 (c 0.21, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 7.77 (d, 1H, *J* = 9.3 Hz, N*H*), 7.70–7.68 (m, 2H, Ar*H*), 7.59 (s, 1H, Ar*H*), 7.32–7.29 (m, 2H, Ar*H*), 7.21 (s, 1H, isoxazole C*H*), 5.40, 5.33, 5.11, 5.07 (4 pseudo t, 4H, *J* = 9.2, 9.5 Hz in each, H-1, H-2, H-3, H-4), 4.32 (dd, 1H, *J* = 12.0, 2.9 Hz, H-6a), 4.13 (dd, 1H, *J* = 12.0, 5.3 Hz, H-6b), 3.90 (ddd, 1H, *J* = 9.2, 5.3, 2.9 Hz, H-5), 2.00, 1.99, 1.98, 1.96 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 171.0, 170.8, 170.0, 169.6 (*C*O), 162.7 (isoxazole C-5), 159.0 (isoxazole C-3), 155.9 (NH*C*O), 129.3, 126.2, 125.6, 125.0, 124.5, 122.6 (Ar), 106.4 (isoxazole *C*H), 78.2 (C-1), 73.9, 72.9, 70.6, 68.2 (C-2–C-5), 61.8 (C-6), 20.8, 20.7, 20.6 (*C*H$_3$). Anal. Calcd for $C_{26}H_{26}N_2O_{11}S$ (574.56): C, 54.35; H, 4.56; N, 4.88. Found: C, 53.93; H, 4.36; N, 5.03.

3.5.5. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(benzo-[*b*]-thiazol-2-yl)-isoxazole-5-carboxamide (18)

Prepared by general procedure given in Section 3.5 from **3** (200 mg, 0.501 mmol) and benzo-[*b*]-thiazol-2-carbaldoxime (98 mg, 0.551 mmol). Yield: 86 mg (30%) white crystals. R_f = 0.39 (2:3 EtOAc–hexane); Mp: 179–181 °C $[\alpha]_D$ −7.6 (c 0.19, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 8.10 (d, 1H, *J* = 9.2 Hz, N*H*) 8.01 (m, 2H, Ar*H*), 7.59–7.52 (m, 2H, Ar*H*), 7.27 (s, 1H, isoxazole C*H*), 5.47, 5.39, 5.18, 5.14 (4 pseudo t, 4H, *J* = 9.2, 9.6 Hz each, H-1, H-2, H-3, H-4), 4.38 (dd, 1H, *J* = 11.9, 5.3 Hz, H-6a), 4.17 (dd, 1H, *J* = 11.9, 2.8 Hz, H-6b), 3.94 (ddd, 1H, *J* = 9.2, 5.3, 2.8 Hz, H-5), 2.06, 2.06, 2.04, 2.03 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 171.0, 170.8, 170.0, 169.6 (*C*O), 162.4 (isoxazole C-5), 161.1 (benzothiazole C-2), 158.3 (isoxazole C-3), 156.3 (NH*C*O), 152.5, 136.3, 126.9, 125.5, 123.7, 122.7 (Ar), 102.8 (isoxazole *C*H), 78.0 (C-1), 73.8, 72.6, 71.0, 68.8 (C-2–C-5), 61.8 (C-6), 20.8, 20.7, 20.6 (*C*H$_3$). Anal. Calcd for $C_{25}H_{25}N_3O_{11}S$ (575.54): C, 52.17; H, 4.38; N, 7.30. Found: C, 51.87; H, 4.20; N, 7.45.

3.5.6. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(indol-2-yl)-isoxazole-5-carboxamide (19)

Prepared by general procedure given in Section 3.5 from **3** (300 mg, 0.752 mmol) and indol-2-carbaldoxime (132 mg, 0.827 mmol). Yield: 100 mg (24%) yellow oil. R_f = 0.44 (2:3 EtOAc–hexane) $[\alpha]_D$ −8.1 (c 0.23, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 8.24 (s, 1H, indol N*H*), 7.70–7.41 (m, 5H, Ar*H*, indol C*H*), 7.29 (s, 1H, isoxazole C*H*), 5.50, 5.42, 5.15, 5.11 (4 pseudo t, 4H, *J* = 9.2, 9.6 Hz each, H-1, H-2, H-3, H-4), 4.35 (dd, 1H, *J* = 11.9, 5.3 Hz, H-6a), 4.22 (dd, 1H, *J* = 11.9, 2.9 Hz, H-6b), 4.00 (ddd, 1H, *J* = 9.2, 5.3, 2.9 Hz, H-5), 2.02, 2.00, 1.99, 1.98 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 171.2, 170.8, 170.1, 169.5 (*C*O), 162.6 (isoxazole C-5), 158.8 (isoxazole C-3), 156.9 (NH*C*O), 137.1, 135.2, 128.4, 122.6, 121.9, 121.3 118.4 (Ar, indol C-2), 101.0, 100.2 (isoxazole *C*H, indol *C*H), 78.1 (C-1), 74.0, 72.7, 71.0, 68.4 (C-2–C-5), 61.9 (C-6), 20.5, 20.5, 20.4, 20.4 (*C*H$_3$). Anal. Calcd for $C_{26}H_{27}N_3O_{11}$ (557.51): C, 56.01; H, 4.88; N, 7.54. Found: C, 55.61; H, 4.69; N, 7.68.

3.5.7. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(indol-3-yl)-isoxazole-5-carboxamide (20)

Prepared by general procedure given in Section 3.5 from **3** (400 mg, 1.00 mmol) and indol-3-carbaldoxime (177 mg, 1.10 mmol). Yield: 110 mg (20%) yellow oil. R_f = 0.49 (2:3 EtOAc–hexane) $[\alpha]_D$ −5.6 (c 0.15, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 7.75 (s, 1H, indol N*H*), 7.64–7.36 (m, 5H, Ar*H*, indol C*H*), 7.28 (s, 1H, isoxazole C*H*), 5.49, 5.40, 5.17, 5.10 (4 pseudo t, 4H, *J* = 9.2, 9.6 Hz each, H-1, H-2, H-3, H-4), 4.24 (dd, 1H, *J* = 11.9, 5.3 Hz, H-6a), 4.19 (dd, 1H, *J* = 11.9, 3.0 Hz, H-6b), 4.01 (ddd, 1H, *J* = 9.2, 5.3, 3.0 Hz, H-5), 2.02, 2.00, 1.99, 1.98 (4s, 12H, 4 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 171.4, 171.2, 170.4, 170.0 (*C*O), 164.9 (isoxazole C-5), 160.0 (isoxazole C-3), 156.1 (NHCO), 139.1, 133.0, 125.5, 121.5, 120.0, 119.6 112.8 (Ar, indol C-2), 101.9, 101.0 (isoxazole *C*H, indol *C*H), 78.5 (C-1), 73.7, 73.0, 71.1, 68.2 (C-2–C-5), 61.5 (C-6), 20.7, 20.6 (*C*H$_3$). Anal. Calcd for $C_{26}H_{27}N_3O_{11}$ (557.51): C, 56.01; H, 4.88; N, 7.54. Found: C, 55.32; H, 4.59; N, 7.64.

3.5.8. *N*-(β-D-Glucopyranosyl)-3-phenyl-isoxazole-5-carboxamide (21)

Prepared by general procedure given in Section 3.3 from **14** (80 mg, 0.154 mmol) for 1 hour. Yield: 52 mg (97%) white solid. R_f = 0.47 (7:3 $CHCl_3$–MeOH); Mp: 215–217 °C (decomp.) $[\alpha]_D$ +7.8 (*c* 0.23, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 7.92–7.90 (m, 2H, Ar*H*), 7.80 (s, 1H, isoxazole C*H*), 7.55–7.53 (m, 3H, Ar*H*), 4.88 (t, 1H, *J* = 9.3, 9.3 Hz, H-1), 3.68–3.35 (m, 3H, H-6a, H-2, H-3), 3.27–3.08 (m, 3H, H-6b, H-5, H-4); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 164.0 (isoxazole C-5), 162.5 (isoxazole C-3), 156.2 (NHCO), 130.8, 130.7, 129.4, 129.3, 127.9, 126.7, (Ar), 105.0 (isoxazole *C*H), 80.1 (C-1), 79.0, 77.3, 71.6, 69.9 (C-2–C-5), 61.0 (C-6). Anal. Calcd for $C_{16}H_{18}N_2O_7$ (350.32): C, 54.86; H, 5.18; N, 8.00. Found: C, 54.47; H, 5.00; N, 8.14.

3.5.9. *N*-(β-D-Glucopyranosyl)-3-(2-naphthyl)-isoxazole-5-carboxamide (22)

Prepared by general procedure given in Section 3.3 from **15** (160 mg, 0.281 mmol) for 1.5 h. Yield: 102 mg (91%) white solid. R_f = 0.51 (7:3 $CHCl_3$–MeOH); Mp: 218–220 °C (decomp.) $[\alpha]_D$ +6.0 (*c* 0.25, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 8.54 (s, 1H, Ar*H*), 8.10–7.99 (m, 4H, Ar*H*), 7.88 (s, 1H, isoxazole C*H*), 7.65–7.62 (m, 2H, Ar*H*), 5.12–4.93 (m, 4H, H-1, H-2, H-3, H-4), 3.70 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 3.22 (ddd, 1H, *J* = 9.0, 5.0, 3.0 Hz, H-5), 3.12 (dd, 1H, *J* = 12.0, 3.0 Hz, H-6b); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 164.0 (isoxazole C-5), 162.2 (isoxazole C-3), 156.0 (NHCO), 133.8, 132.9, 129.0, 128.6, 128.6, 127.9, 127.6, 127.1, 127.0, 126.9, 125.2, 123.5 (Ar), 105.4 (isoxazole *C*H), 79.8 (C-1), 79.0, 77.5, 71.9, 70.0 (C-2–C-5), 61.0 (C-6). Anal. Calcd for $C_{20}H_{20}N_2O_7$ (400.38): C, 60.00; H, 5.03; N, 7.00. Found: C, 59.64; H, 4.89; N, 7.20.

3.5.10. *N*-(β-D-Glucopyranosyl)-3-(benzo-[*b*]-furan-2-yl)-isoxazole-5-carboxamide (23)

Prepared by general procedure given in Section 3.3 from **16** (120 mg, 0.215 mmol) for 1 h. Yield: 74 mg (88%) yellow solid. R_f = 0.55 (7:3 $CHCl_3$–MeOH); Mp: 196–198 °C $[\alpha]_D$ +9 (*c* 0.18, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 7.79–7.72 (m, 4H, Ar*H*, benzofuran C*H*, isoxazole C*H*), 7.48–7.33 (m, 2H, Ar*H*), 4.87 (d, 1H, *J* = 9.3 Hz, H-1), 3.46–3.10 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 164.0 (isoxazole C-5), 155.0 (isoxazole C-3), 154.9 (NHCO), 154.6 (benzofuran C-2), 145.6, 127.5, 126.6, 123.9, 123.0, 122.4 (Ar), 111.8 (benzofuran C-3), 108.9 (isoxazole *C*H), 79.9 (C-1), 79.0, 77.4, 71.9, 69.9 (C-2–C-5), 60.9 (C-6). Anal. Calcd for $C_{18}H_{18}N_2O_8$ (390.34): C, 55.39; H, 4.65; N, 7.18. Found: C, 54.89; H, 4.46; N, 7.32.

3.5.11. *N*-(β-D-Glucopyranosyl)-3-(benzo-[*b*]-thiophen-2-yl)-isoxazole-5-carboxamide (24)

Prepared by general procedure given in Section 3.3 from **17** (120 mg, 0.209 mmol) for 1 h. Yield: 81 mg (95%) yellow solid. R_f = 0.51 (7:3 $CHCl_3$–MeOH); Mp: 234–236 °C $[\alpha]_D$ +7.8 (*c* 0.25, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 8.16 (s, 1H, benzothiophen C*H*), 8.08–7.95 (m, 2H, Ar*H*), 7.83 (s, 1H, isoxazole C*H*), 7.48–7.46 (m, 2H, Ar*H*), 5.07 (d, 1H, *J* = 9.2 Hz, H-1), 4.97–4.91 (m, 2H, H-2, H-3), 3.70 (ddd, 1H, *J* = 9.0, 3.7, 2.6 Hz, H-5), 3.46–3.17 (m, 3H, H-4, H-6a, H-6b); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 163.9 (isoxazole C-5), 155.7 (isoxazole C-3), 155.0 (NHCO), 154.8 (benzothiophen C-2), 144.6, 127.6, 126.6, 124.0, 122.3, 122.0 (Ar), 112.0 (benzothiophen C-3), 109.0 (isoxazole CH), 80.0 (C-1), 79.2, 77.4, 72.0, 70.0 (C-2–C-5), 61.0 (C-6). Anal. Calcd for $C_{18}H_{18}N_2O_7S$ (406.41): C, 53.20; H, 4.46; N, 6.89. Found: C, 52.81; H, 4.28; N, 7.03.

3.5.12. *N*-(β-D-Glucopyranosyl)-3-(benzo-[*b*]-thiazol-2-yl)-isoxazole-5-carboxamide (25)

Prepared by general procedure given in Section 3.3 from **18** (80 mg, 0.139 mmol) for 1 h. Yield: 51 mg (90%) yellow solid. R_f = 0.55 (7:3 $CHCl_3$–MeOH); Mp: 223–225 °C $[\alpha]_D$ +5.8 (*c* 0.19, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 7.90–7.82 (m, 2H, Ar*H*), 7.78 (s, 1H, isoxazole C*H*), 7.67–7.51 (m, 2H, Ar*H*), 4.78 (t, 1H, *J* = 9.3, 9.3 Hz, H-1), 4.60–4.44 (m, 2H, H-2, H-3), 3.54–3.31 (m, 3H, H-6a, H-6b, H-4), 3.22 (ddd, 1H, *J* = 9.3, 4.0, 2.3 Hz, H-5); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 166.5 (isoxazole C-5), 161.9 (isoxazole C-3), 160.3 (benzothiazole C-2), 158.9 (NH*C*O), 150.4, 136.5, 127.3, 126.3, 125.5, 123.2 (Ar), 108.4 (isoxazole *C*H), 81.8 (C-1), 73.6, 71.5, 70.9, 69.7 (C-2–C-5), 62.5 (C-6). Anal. Calcd for $C_{17}H_{17}N_3O_7S$ (407.40): C, 50.12; H, 4.21; N, 10.31. Found: C, 49.72; H, 4.03; N, 10.50.

3.5.13. *N*-(β-D-Glucopyranosyl)-3-(indol-2-yl)-isoxazole-5-carboxamide (26)

Prepared by general procedure given in Section 3.3 from **19** (100 mg, 0.179 mmol) for 2 h. Yield: 53 mg (76%) yellow oil. R_f = 0.45 (7:3 $CHCl_3$–MeOH) $[\alpha]_D$ +1 (*c* 0.10, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 7.61–7.51 (m, 3H, Ar*H*, isoxazole C*H*), 7.35–7.19 (m, 2H, Ar*H*, indol C*H*), 4.97 (d, 1H, *J* = 10.6 Hz, H-1), 3.50–3.07 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 164.0 (isoxazole C-5), 156.8 (isoxazole C-3), 155.4 (NHCO), 147.9, 136.0, 132.3, 125.9, 123.6, 121.5, 118.9 (Ar, indol C-2), 113.3, 110.2 (isoxazole *C*H, indol *C*H), 80.6 (C-1), 79.9, 77.7, 73.0, 70.3 (C-2–C-5), 61.6 (C-6). Anal. Calcd for $C_{18}H_{19}N_3O_7$ (389.36): C, 55.53; H, 4.92; N, 10.79. Found: C, 55.13; H, 4.73; N, 10.93.

3.5.14. *N*-(β-D-Glucopyranosyl)-3-(indol-3-yl)-isoxazole-5-carboxamide (27)

Prepared by general procedure given in Section 3.3 from **20** (100 mg, 0.179 mmol) for 1.5 h. Yield: 49 mg (70%) yellow oil. R_f = 0.40 (7:3 $CHCl_3$–MeOH) $[\alpha]_D$ +3 (*c* 0.10, DMSO) ^{1}H NMR (DMSO-d_6 + D_2O, 360 MHz) δ (ppm) 7.90 (s, 1H, isoxazole C*H*), 7.60–7.42 (m, 2H, Ar*H*), 7.34–7.02 (m, 3H, Ar*H*, indol C*H*), 4.96 (d, 1H, *J* = 9.2 Hz, H-1), 3.53–3.12 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b); ^{13}C NMR (DMSO-d_6 + D_2O, 90 MHz) δ (ppm) 163.6 (isoxazole C-5), 157.2 (isoxazole C-3), 156.0 (NHCO), 139.1, 133.0, 129.8, 125.6, 124.0, 122.0, 119.1 (Ar, indol C-2), 111.9, 107.3 (isoxazole *C*H, indol *C*H), 80.2 (C-1), 79.7, 78.2, 72.4, 69.9 (C-2–C-5), 61.0 (C-6). Anal. Calcd for $C_{18}H_{19}N_3O_7$ (389.36): C, 55.53; H, 4.92; N, 10.79. Found: C, 55.25; H, 4.69; N, 10.88.

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