Bioorganic & Medicinal Chemistry 18 (2010) 1171–1180

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of 1-(D-glucopyranosyl)-1,2,3-triazoles and their evaluation as glycogen phosphorylase inhibitors

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ARTICLE INFO

Article history:
Received 14 September 2009
Revised 9 December 2009
Accepted 15 December 2009
Available online 22 December 2009

Keywords:
1-(D-Glucopyranosyl)-1,2,3-triazole
Glycogen phosphorylase
Inhibitor
Azide–alkyne cycloaddition

ABSTRACT

1-(D-Glucopyranosyl)-1,2,3-triazoles were prepared from per-*O*-acetylated α- and β-D-glucopyranosyl azides as well as per-*O*-benzoylated (β-D-*gluco*-hept-2-ulopyranosylazide)onamide and onic acid methyl-ester by using azide-alkyne cycloaddition catalysed by in situ generated Cu(I) under aqueous conditions. The *O*-acyl protecting groups were removed by the Zemplén protocol. The test compounds were assayed against rabbit muscle glycogen phosphorylase *b* to show that the β-D-glucopyranosyl derivatives were superior inhibitors as compared to the two other series of triazoles.

1. Introduction

Glycogen phosphorylase (GP) is a validated target in the search for new therapies of type 2 diabetes mellitus,[1–5] therefore, the quest for new inhibitors of GP attracts continuous interest in both academia and industry. In the past two decades a very large array of compounds were tested against various forms of GP, and these were amply reviewed.[1,2,6–9] The most populated class of inhibitors of GP is that of the glucose analogues which are structurally characterised by a D-glucopyranose ring having either diverse substituents or spirocyclic moieties attached to the anomeric carbon.[8–11] These compounds primarily bind to the active site of the enzyme although some of them have also been detected by X-ray crystallography at the so-called new allosteric site.[12,13]

N-Acyl-β-D-glucopyranosylamines[14–16] (Chart 1, **A**) were among the first efficient glucose analogue inhibitors of GP. An increase in the size of a properly oriented acyl group (R = 2-naphthyl) made the inhibition stronger, and placing this group farther from the sugar with a rigid spacer (R = 2-(2-naphthyl)vinyl) resulted in the best inhibitor of this series (for a detailed discussion of structure–activity relationship of these compounds see Refs. 9,16). As it was shown by crystallographic studies[9] the larger/longer R substituents had more extensive interactions in the β-channel of the enzyme (an empty space in the direction of the β-anomeric substituent of bound D-glucose surrounded by amino acid side chains of mixed character), and these contacts made the binding tighter. Other representatives of glucopyranosylamines (Chart 1, **B**) had an additional carboxamide group at the anomeric position (actually these are (*N*-acyl-β-D-*gluco*-hept-2-ulopyranosylamine)onamides), and these compounds proved also micromolar inhibitors.[17–20]

With the advent of the copper(I)-catalysed azide–alkyne cycloaddition reaction[21–25] for the selective creation of 1,4-disubstituted 1,2,3-triazole derivatives, several examples show similarity[21] in respect of size, dipolar character, and H-bond acceptor capacity of the amide moiety and the 1,2,3-triazole ring.[26–28] This resemblance underlines the more and more extensive use of the 1,2,3-triazole moiety as a bioisosteric replacement[29–31] for the amide. The high chemical stability of the 1,2,3-triazole ring under various chemical conditions[32] is an additional supportive factor to find new examples of this isosterism. Very recently, we have demonstrated in a short communication[33] that some *N*-acyl-β-D-glucopyranosylamines **A** and 1-(β-D-glucopyranosyl)-4-substituted-1,2,3-triazoles **C** having the same R appendages in the aglycon exhibit reasonable coincidence of inhibition constants against rabbit muscle glycogen phosphorylase *b* (RMGP*b*). Moreover, binding peculiarities as revealed by X-ray crystallographic studies on the corresponding enzyme–inhibitor complexes indicated high similarities in the binding mode for several of the studied pairs.

An *N*-(β-D-glucopyranosyl)-4-phenyl-1,2,3-triazol-1-yl-acetamide was also studied as inhibitor of GP.[34] 1-Glycosyl-1,2,3-triazol type compounds were recently investigated as anticancer agents,[35] inhibitors of galectins,[36,37] carbonic anhydrase,[38] and glycosidase

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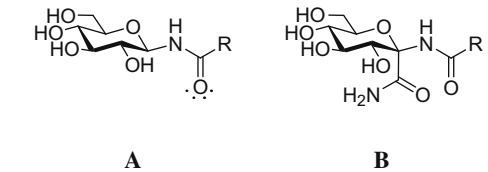
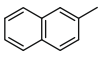
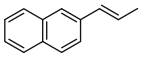
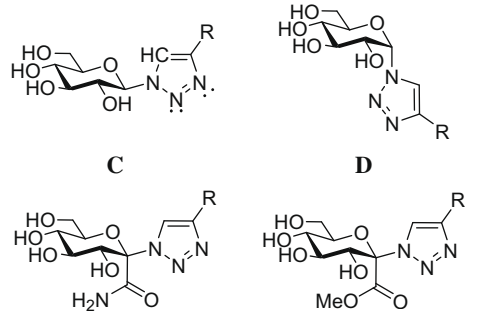
doi:10.1016/j.bmc.2009.12.043



A **B**

R	K_i* [μM]	R	K_i* [μM]
Me	32[14]	Me	310[17,18]
	81[14] 144[15]	OMe	16[19,20]
	10[16] 13[33]		
	3.5[16]		

*Inhibitor constants determined with rabbit muscle GPb



C **D**

E **F**

Chart 1.

enzymes,[39] as well as to their binding affinities to lectins,[40] and cytostatic activity.[41]

In this paper we disclose our investigations on the synthesis of 1-(D-glucopyranosyl)-4-substituted-1,2,3-triazoles of α- (**D**) and β-D-*gluco* (**C**, **E**, **F**) configurations. These compounds were tested as inhibitors of RMGP*b*, and the inhibitions compared to those of the corresponding amide derivatives and other related compounds.

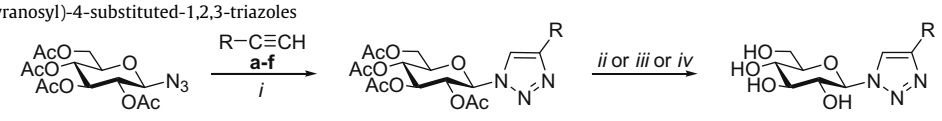
2. Results and discussion

2.1. Syntheses

O-Peracetylated β-D-glucopyranosyl azide[42,43] (**1**) was reacted with terminal alkynes **a**–**f** (Table 1) in water[44] in the presence of $CuSO_4$ and L-ascorbic acid at 70 °C. The cycloadditions proceeded cleanly to complete conversion of the starting material in ~8 h to give the corresponding 1-(β-D-glucopyranosyl)-1,2,3-triazoles **2** in very good yields. Removal of the protecting groups was effected by the Zemplén protocol and compounds **3** were obtained in high yields. Ester **2b** was also treated by NaOH as well as NH_3 in MeOH to get carboxylate **3b*iii*** and carboxamide **3b*iv***, respectively. Other preparations of **2a**,[32] **2b**,[44] **2c**,[44,45,39] **3a**,[32] and **3c**[39] were published.

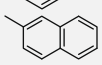
The protected α-D-glucopyranosyl triazoles **5** were obtained in a similar manner from *O*-peracetylated α-D-glucopyranosyl azide[46,43] (**4**). Azide **4** showed no transformation with **a** in the presence of 1.5 mol % Cu catalyst during 8 h. Therefore, higher catalyst load (7.5 mol %) was applied. However, the yields of these reactions in approximately the same reaction times were lower than those for the β-D-derivatives, and probably the higher steric hindrance of the azido group may account for this. This is in accord with the literature experience that the preparation of an *O*-perbenzylated α-D-glucopyranosyl-triazole required an excess of alkyne, 40 mol % catalyst, 48 h reaction time, and elevated temperature.[32] Deprotection by the Zemplén method gave compounds **6**, and carboxylate **6b*iii*** as well as carboxamide **6b*iv*** were obtained as described above.

Table 1
Synthesis of 1-(β-D-glucopyranosyl)-4-substituted-1,2,3-triazoles



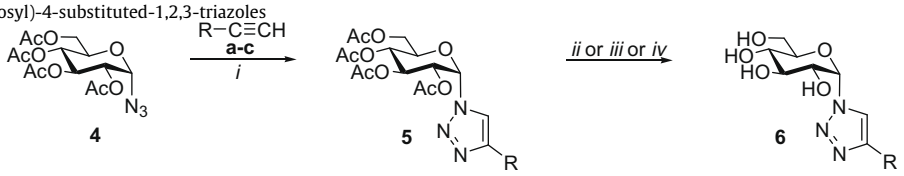
1 **2** **3**

i) 1.5 mol% $CuSO_4$, 20 mol% L-ascorbic acid, H_2O, 70 °C, 8h;
ii) NaOMe/dry MeOH, r. t.; *iii*) NaOH/MeOH, r. t.; *iv*) NH_3/dry MeOH, r. t.

Alkyne	R	Conditions and yields (%)					
		2				**3**	
a	$-CH_2OH$	*i*	65[a]	*ii*		82[b]	
b	$-CO_2Et$	*i*	89[c]	*ii*	**3b*ii***	70	R = CO_2Me
				iii	**3b*iii***	55	R = CO_2Na
				iv	**3b*iv***	86	R = $CONH_2$
c		*i*	58[d]	*ii*		89[e]	
d		*i*	71	*ii*		72	
e		*i*	67	*ii*		95	
f		*i*	96	*ii*		95	

[a] Reported yield by a different method: 92%.[32]
[b] Literature preparation of **3a** by deprotection of per-*O*-acetylated or benzoylated or benzylated 1-β-D-glucopyranosyl-4-acetoxy- or benzoyloxy- or benzyloxymethyl-1,2,3-triazoles.[32]
[c] Reported yield: 92%.[44]
[d] Reported yields by different methods: 85%,[44] 91%,[45] 75%.[39]
[e] Reported yield: 72%.[39]

Table 2
Synthesis of 1-(α-D-glucopyranosyl)-4-substituted-1,2,3-triazoles



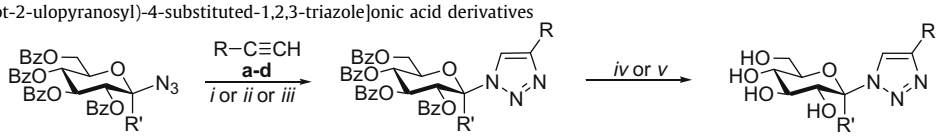
i) 7.5 mol% $CuSO_4$, 20 mol% L-ascorbic acid, H_2O, 70 °C, 8h; *ii*) NaOMe/dry MeOH, r. t.; *iii*) NaOH/MeOH, r. t; *iv*) NH_3/dry MeOH, r. t.

Alkyne	R	Conditions and yields (%)					
		5			**6**		
a	$-CH_2OH$	*i*	36	*ii*		72	
				iii	**6b*ii***	93	R = CO_2Me
b	$-CO_2Et$	*i*	72	*iv*	**6b*iii***	47	R = CO_2Na
				ii	**6b*iv***	81	R = $CONH_2$
c		*i*	39	*ii*		75	

In both series ethyl propiolate (**b**) gave markedly higher yields than the other alkynes that is in accord with previous experiences showing higher reactivity for electron depleted alkynes.[22,25]

Reactions of *O*-perbenzoylated (β-D-*gluco*-hept-2-ulopyranosyl azide)onic acid derivatives **7** and **8** were different in several aspects (Table 3). The aqueous conditions which worked well in the α- and β-D-glucosyl azide (**1** and **4**, respectively) series, facilitated transformations only with the most reactive ethyl propiolate (**b**) while the other alkynes did not react in one day (conditions *i*). However, the conversion of the starting materials **7** and **8** to give **9b** and **10b**, respectively, was not complete in 8 h, a reaction time sufficient for total consumption of **1** and **4** (Tables 1 and 2). This may be accounted for by the sterically more crowded environment of the azido group in **7** and **8** than in **1**. Additionally, the existence of a H-bond between the $CONH_2$ and the azide in amide **7** demonstrated by CD spectroscopy[47] may also disfavour the reaction. Another factor can be the higher solubility of acetylated sugar derivatives in water as compared to that of benzoylated compounds.[48] The possible role of the solubility can be rationalised by the reactions in aqueous CH_3NO_2 (conditions *ii*) and in DMSO (conditions *iii*) with a slightly higher catalyst ratio where both the conversions and the yields raised. Compounds **9** and **10** were deprotected under usual circumstances to give **11** and **12**, respectively.

Table 3
Synthesis of [1-(β-D-*gluco*-hept-2-ulopyranosyl)-4-substituted-1,2,3-triazole]onic acid derivatives



i) 7.5 mol% $CuSO_4$, 20 mol% L-ascorbic acid, H_2O, 70 °C; *ii*) 11 mol% $CuSO_4$, 30 mol% L-ascorbic acid, H_2O:CH_3NO_2 2:1, 70 °C; *iii*) 11 mol% $CuSO_4$, 30 mol% L-ascorbic acid, DMSO, 70 °C; *iv*) NaOMe/dry MeOH, r. t.; *v*) NaOH/MeOH, r. t.

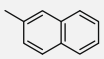
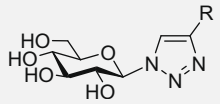
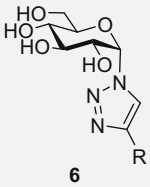
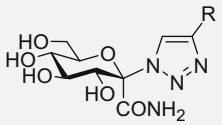
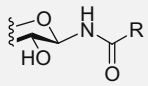
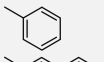
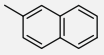
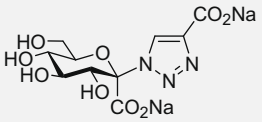
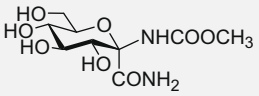
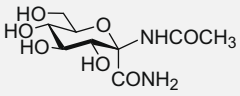
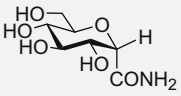
Alkyne	R	Conditions and yields (%)							
				R. time	Conversion	Yield			
a	$-CH_2OH$	*i*	**9a**	1 d	No reaction				
		ii		2 d	43	67	*iv*	**11a**	68
		iii		1 d	51	75			
b	$-CO_2Et$	*i*	**9b**	8 h	63	56	*v*	**11b**	R = CO_2Na 67
		i	**10b**	8 h	74	70	*v*	**12b**	R = CO_2Na 35
c		*i*	**9c**	1 d	No reaction				
							iv	**11c**	92
		ii		2 d	44	98			
		iii		1 d	73	83			
d		*i*	**9d**	1 d	No reaction				
							iv	**11d**	81
		ii		2 d	37	86			
		iii		1 d	63	87			

Table 4
Inhibition (K_i or $^*IC_{50}$ [μM]) of rabbit muscle glycogen phosphorylase *b* by the new compounds and the corresponding *N*-acyl-β-D-glucopyranosylamines (**13**)

R		 **3**		 **6**		 **11**	 **13**
$-CH_2OH$	**a**	26 14[33]		670*		No inh. at 625 μM	20 18[33]
$-CO_2Me$	**3bii**	500*	**6bii**	30% at 625 μM		–	210[55]
$-CO_2Na$	**3biii**	20% at 625 μM	**6biii**	400*	**11b**	No inh. at 625 μM	–
$-CONH_2$	**3biv**	350*	**6biv**	No inh. at 625 μM		–	–
	**c**	162 151[33]		No inh. at 625 μM		No inh. at 625 μM	81[14] 144[15]
	**d**	36 16[33]		–		780*	10[16] 13[33]
	**e**	625* 136[33]		–		–	444[16]
	**f**	600*		–		–	1100*[16]
$-CH_3$							**14** 32[14]
 **12b** No inh. at 625 μM			 **15** 16[19,20]		 **16** 310[17,18]		 **17** 370[51]

2.2. Inhibition studies

The new 1-(D-glucopyranosyl)-1,2,3-triazole derivatives were evaluated as inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGP*b*) as described earlier,[15,49] and the results are collected in Table 4. For comparison, inhibitory efficiencies of *N*-acyl-β-D-glucopyranosylamines (**13**) with the same R group are also shown. Among the three series of triazoles **3**, **6** and **11** the β-D-glucopyranosyl derivatives **3** exhibit the strongest inhibition with some compounds (**3a**, **3d**) in the low micromolar range. The α-D-glucopyranosyl derivatives **6** are generally significantly less efficient, except carboxylate **6b*iii*** showing slightly stronger inhibition than the corresponding β-D-configured **3b*iii***. Compounds **11** are non-inhibitory with the exception of the 2-naphthyl derivative **11d** which is a very weak inhibitor.

The higher activities of the β-anomers compared to those of the α-derivatives are in accord with literature results showing stronger inhibition for several β-anomeric derivatives over their α-counterparts (e.g., CH_2N_3, $CH_2OSO_2CH_3$, $CONHCH_3$, $CONHNH_2$, $CONHCH_2CH_2OH$,[50,51] $NHCOCF_3$[15] as substituents of the anomeric carbon). The observable but weak inhibition by **6a** and **6b*iii*** may reveal favourable polar/ionic contacts with the enzyme, however, does not break the general tendency that α-anomeric substituents of the D-glucopyranosyl ring are not really efficient to make a good inhibitor.

A comparison of series **3** to **11** clearly shows that the introduction of a $CONH_2$ group in the α-position is highly detrimental for the inhibition. Among compounds with an α-$CONH_2$ substituent only methyl carbamate **15** (β-$NHCOOCH_3$) was reported to show considerable inhibition,[19,20] while in case of other β-substituents (β-$NHCOCH_3$ (**16**), or β-N_3 K_i = 1800 μM) the activity proved significantly weaker.[17,18] Introduction of an α-$CONH_2$ makes a weaker inhibitor also from *N*-acetyl-β-D-glucopyranosylamine (compare **14** and **16**). Compounds **11** can also be considered as derivatives of anhydro-heptonamide **17** to show that the inhibition becomes weaker even in this comparison.

Compounds of the series **3** and **13** with the same R group show very similar inhibition in most cases. In both series the hydroxymethyl (**a**) and 2-naphthyl (**d**) derivatives are the most efficient ones, and the similarity is remarkable also for the other pairs. X-ray crystallography revealed a very high degree of similitude in the binding modes of **3a** and **13a** as well as of **3d** and **13d** at the catalytic site of RMGP*b*.[33] Although for other investigated pairs (**3c** and **13c**; **3e** and **13e**) the structural similarity of the enzyme–inhibitor complexes was not so profound, it was suggested that these observations form the basis of a bioisosteric relationship of amide and 1,2,3-triazoles for the glycogen phosphorylase case. Other possibilities for non-classical heterocyclic bioisosteres of amide have been reported.[52]

It is also noticeable that the 2-naphthyl derivatives **3d**, **11d** and **13d** are the strongest inhibitors in each corresponding class of compounds. This observation corroborates several other findings[52–54] and indicate the importance of extensive interactions of the inhibitors in the β-channel of the enzyme.

3. Conclusion

Copper(I)-catalysed azide–alkyne cycloaddition reaction was used to prepare *O*-acetyl or *O*-benzoyl protected 1-D-glycopyranosyl-1,2,3-triazoles of the α- and β-D-glucopyranosyl as well as (β-D-*gluco*-hept-2-ulopyranosyl)onic acid derivatives series. Removal of the protecting groups according to the Zemplén protocol gave test compounds which were assayed as inhibitors of rabbit muscle glycogen phosphorylase *b*. The 1-(β-D-glucopyranosyl)-1,2,3-triazoles proved the best inhibitors among the three series of compounds exhibiting inhibition constants in the low micromolar range. The α-D-configured derivatives were almost inefficient, and the introduction of an α-$CONH_2$ group at the anomeric position of the β-D-configured series also resulted in a practical loss of activity. 1-(β-D-Glucopyranosyl)-1,2,3-triazoles and *N*-acyl-β-D-glucopyranosylamines are remarkably similar in their inhibition properties.

As X-ray crystallography demonstrated similarity of the binding mode at the catalytic site, these observations confirm the bioisosteric relationship of amides and 1,2,3-triazoles for the glycogen phosphorylase case, as well.

4. Experimental

4.1. General methods

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at rt. NMR spectra were recorded with Bruker 200 (200/50 MHz for $^1H/^{13}C$), Bruker 360 (360/90 MHz for $^1H/^{13}C$) or Avance DRX 500 (500/125 MHz for $^1H/^{13}C$) spectrometers. Chemical shifts are referenced to Me_4Si (^1H), or to the residual solvent signals (^{13}C). TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck), and the plates were visualised under UV light and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Dichloromethane was distilled from P_4O_{10} and acetone from $CaSO_4$) and stored over 4 Å molecular sieves. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated under diminished pressure at 40–50 °C (water bath). Propargyl alcohol (**a**), ethyl propiolate (**b**), phenylacetylene (**c**), and 3-phenyl-1-propyne (**f**) and pentamethylcyclopentadienyl-bis(triphenylphosphine)ruthenium(II) chloride were purchased from Aldrich. 1-[56] and 2-Naphthylacetylene[57] were synthesised according to published procedures.

4.2. General procedure I for the preparation of 1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-substituted-1,2,3-triazoles (2a–f) (adapted from Ref. 44)

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**1**, 1 g, 2.7 mmol), the corresponding alkyne (2.7 mmol), $CuSO_4{\cdot}5H_2O$ (10 mg, 0.04 mmol) and L-ascorbic acid (100 mg, 0.57 mmol) were heated in water (15 mL) at 70 °C with vigorous stirring and monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction, the heterogeneous mixture was cooled to rt and then in an ice bath, the solid was filtered off and washed with water. The crude product was purified by crystallisation or column chromatography.

4.3. General procedure II for the preparation of 1-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-4-substituted-1,2,3-triazoles (5a–c), [1-(3′,4′,5′,7′-tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-ethoxycarbonyl-1,2,3-triazole]onamide (9b) and methyl [1-(3′,4′,5′,7′-tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-ethoxycarbonyl-1,2,3-triazole]onate (10b)

An azide (**4** or **7** or **8**, 2.7 mmol), the corresponding alkyne (2.7 mmol), $CuSO_4{\cdot}5H_2O$ (50 mg, 0.2 mmol) and L-ascorbic acid (100 mg, 0.57 mmol) were heated in water (1.5 mL/100 mg azide) at 70 °C with vigorous stirring and monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction, the heterogeneous mixture was cooled to rt and then in an ice bath, the solid was filtered off and washed with water. The crude product was purified by column chromatography.

4.4. General procedure III for the preparation of [1-(3′,4′,5′,7′-tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-substituted-1,2,3-triazole]onamides (9a,c,d)

[(3,4,5,7-Tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)azide] onamide (**7**, 100 mg, 0.15 mmol), the corresponding alkyne (0.3 mmol), $CuSO_4{\cdot}5H_2O$ (4 mg, 0.017 mmol) and L-ascorbic acid (8 mg, 0.045 mmol) were heated in DMSO (3 mL) at 70 °C and monitored by TLC (1:1 EtOAc–hexane). When the TLC showed no more change (conversions were incomplete), the mixture was cooled to rt, water (15 mL) was added, and extracted with diethyl ether (5 × 30 mL). The combined organic phase was dried, concentrated under diminished pressure, and the crude product was purified by column chromatography.

4.5. General procedure IV for the Zemplén-deacylation (3a,b*ii*,c,d–f, 6a,b*ii*,c, 11a,c,d)

An acetylated or benzoylated compound was dissolved in dry MeOH (5 mL/100 mg, a few drops of $CHCl_3$ were added in case of incomplete dissolution) and a catalytic amount of a NaOMe solution (~1 M in MeOH) was added. The mixture was kept at rt and monitored by TLC (7:3 $CHCl_3$–MeOH). When the starting material was consumed the mixture was neutralised with a cation exchange resin Amberlyst 15 (H^+ form), then the resin was filtered off and the solvent removed. If the residue was chromatographically not uniform, it was purified by column chromatography.

4.6. General procedure V for the deacylation of the glucose derivatives containing ester groups (3b*iii*, 6b*iii*, 11b, 12b)

An acetylated or benzoylated compound was dissolved in dry MeOH (5 mL/100 mg) and 1 M methanolic NaOH (2–4 equiv) was added. The reaction mixture was kept at rt and monitored by TLC (7:3 $CHCl_3$–MeOH). After completion of the reaction, the deposited crystalline product was filtered off and purified by column chromatography.

4.7. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-hydroxymethyl-1,2,3-triazole (2a)

From **1** (1 g, 2.68 mmol) and propargyl alcohol (0.16 mL, 2.70 mmol) according to General procedure **I**. Purified by recrystallisation from ethanol to yield 0.75 g (65%) white solid. Mp: 152–154 °C (lit.[32] mp: 150–151 °C); $[\alpha]_D = -29$ (*c* 0.22, $CHCl_3$); ^1H and ^{13}C NMR data correspond to the reported spectra.[32]

4.8. Ethyl 1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole-4-carboxylate (2b)

From **1** (1 g, 2.68 mmol) and ethyl propiolate (0.28 mL, 2.70 mmol) according to General procedure **I**. Purified by recrystallisation from ethanol to yield 1.12 g (89%) white solid. Mp: 172–174 °C; $[\alpha]_D = -62$ (*c* 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.40 (1H, s, triazole H), 5.98 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 5.49–5.41 (2H, m, H-2′, H-3′), 5.27 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, $J_{4',5'}$ 9.2 Hz, H-4′), 4.44 (2H, q, *J* 7.3 Hz, CH_2), 4.32 (1H, dd, $J_{6'a,6'b}$ 13.2 Hz, H-6′a), 4.17 (1H, dd, $J_{5',6'b}$ 2.6 Hz, H-6′b), 4.08 (1H, ddd, $J_{5',6'a}$ 5.3 Hz, H-5′), 2.10, 2.08, 2.04, 1.90 (12H, 4s, 4 × CH_3), 1.42 (3H, t, *J* 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 170.3, 169.7 169.2, 168.8 (CO), 160.1 (*C*OOEt), 140.8 (triazole C-4), 126.0 (triazole C-5), 85.7 (C-1′), 75.2, 72.2, 70.3, 67.4 (C-2′–C-5′), 61.5, 61.3 (C-6′, CH_2), 20.5, 20.4 (2), 19.9 (CH_3), 14.1 (CH_3). Anal. Calcd for $C_{19}H_{25}N_3O_{11}$ (471.42): C, 48.41; H, 5.35; N, 8.91; Found: C, 48.34; H, 5.40; N, 8.99.

4.9. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-phenyl-1,2,3-triazole (2c)

From **1** (1 g, 2.68 mmol) and phenylacetylene (0.30 mL, 2.70 mmol) according to General procedure **I**. Purified by recrystallisation from ethanol to yield 0.74 g (58%) white solid. Mp: 214–216 °C (lit.[44] mp 198–202 °C, lit.[39] mp 213–215 °C, lit.[58] mp 218 °C); $[\alpha]_D = -123$ (*c* 0.2, $CHCl_3$) (lit.[44] $[\alpha]_D = -86$ (*c* 1.0, CH_2Cl_2),

lit.[58] $[\alpha]_D = -65$ (*c* 0.95 $CHCl_3$)); ^1H and ^{13}C NMR data correspond to the reported spectra.[44,39]

4.10. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(2-naphthyl)-1,2,3-triazole (2d)

From **1** (0.35 g, 0.94 mmol) and 2-naphthylacetylene (0.14 g, 0.94 mmol) according to General procedure **I**. Purified by column chromatography (1:2 EtOAc–hexane) to yield 0.35 g (71%) white solid. Mp: 262–263 °C; $[\alpha]_D = -194$ (*c* 0.25, DMSO); ^1H NMR (DMSO-d_6): δ (ppm) 9.12 (1H, s, triazole H), 8.44 (1H, s, aromatic), 8.05–7.95 (4H, m, aromatics), 7.59–7.55 (2H, m, aromatics), 6.47 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 5.73, 5.65, 5.22 (3 × 1H, 3pseudot, *J* 9.2 Hz in each, H-2′, H-3′, H-4′), 4.46 (1H, ddd, $J_{4',5'}$ 9.2 Hz, $J_{5',6'a}$ 5.3 Hz, H-5′), 4.20 (1H, dd, $J_{6'a,6'b}$ 13.2 Hz, H-6′a), 4.13 (1H, dd, $J_{5',6'b}$ 2.6 Hz, H-6′b), 2.07, 2.03, 2.00, 1.84 (12H, 4s, 4 × CH_3); ^{13}C NMR (DMSO-d_6): δ (ppm) 170.0, 169.5 169.4, 168.6 (CO), 146.9 (triazole C-4), 133.0, 132.7, 128.6, 128.0, 127.7, 127.4, 126.7, 126.3, 123.7, 123.5, 120.7 (aromatics, triazole C-5), 83.9 (C-1′), 73.2, 72.0, 70.3, 67.5 (C-2′–C-5′), 61.8 (C-6′), 20.5, 20.4, 20.2, 19.9 (CH_3). Anal. Calcd for $C_{26}H_{27}N_3O_9$ (525.52): C, 59.42; H, 5.18; N, 8.00. Found: C, 59.51; H, 5.10; N, 8.12.

4.11. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(1-naphthyl)-1,2,3-triazole (2e)

From **1** (0.35 g, 0.94 mmol) and 1-naphthylacetylene (0.14 g, 0.94 mmol) according to General procedure **I**. Purified by column chromatography (1:2 EtOAc–hexane) to yield 0.33 g (67%) white solid. Mp: 217–219 °C; $[\alpha]_D = -103$ (*c* 0.22, DMSO); ^1H NMR (DMSO-d_6): δ (ppm) 8.99 (1H, s, triazole H), 8.34 (1H, s, aromatic), 8.00 (2H, m, aromatics), 7.76 (1H, m, aromatic), 7.60–7.58 (3H, m, aromatics), 6.48 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 5.85, 5.65, 5.24 (3 × 1H, 3pseudot, *J* 9.2 Hz in each, H-2′, H-3′, H-4′), 4.45 (1H, ddd, $J_{4',5'}$ 9.2 Hz, $J_{5',6'a}$ 5.3 Hz, $J_{5',6'b}$ 2.6 Hz, H-5′), 4.20–4.15 (2H, m, H-6′a, H-6′b), 2.05, 2.01, 1.99, 1.86 (12H, 4s, 4 × CH_3); ^{13}C NMR (DMSO-d_6): δ (ppm) 170.0, 169.5 169.4, 168.7 (CO), 145.9 (triazole C-4), 133.5, 130.1, 128.9, 128.5, 127.3, 127.0, 126.8, 126.1, 125.5, 125.0, 123.1 (aromatics, triazole C-5), 84.0 (C-1′), 73.2, 71.9, 70.4, 67.5 (C-2′–C-5′), 61.7 (C-6′), 20.5, 20.4, 20.2, 19.9 (CH_3). Anal. Calcd for $C_{26}H_{27}N_3O_9$ (525.52): C, 59.42; H, 5.18; N, 8.00. Found: C, 59.30; H, 5.09; N, 8.15.

4.12. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-benzyl-1,2,3-triazole (2f)

From **1** (1 g, 2.68 mmol) and 3-phenyl-1-propyne (0.34 mL, 2.70 mmol) according to General procedure **I**. Purified by recrystallisation from ethanol to yield 1.26 g (96%) white solid. Mp: 175–177 °C; $[\alpha]_D = -36$ (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 7.45–7.23 (6H, m, aromatics, triazole H), 5.88 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 5.39–5.42 (2H, m, H-2′, H-3′), 5.24 (1H, pseudot, $J_{3',4'}$ 9.2, Hz, $J_{4',5'}$ 9.2 Hz, H-4′), 4.28 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, H-6′a), 4.14–4.09 (3H, m, H-6′b, CH_2), 3.99 (1H, ddd, $J_{5',6'a}$ 5.3 Hz, $J_{5',6'b}$ 2.6 Hz, H-5′), 2.05 (6H, s, 2 × CH_3), 2.01, 1.85 (6H, 2s, 2 × CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 170.4, 169.8, 169.2, 168.8 (CO), 148.2 (triazole C-4), 138.4, 128.5, 128.5,128.5, 128.5, 126.5 (aromatics), 119.7 (triazole C-5), 85.5 (C-1′), 74.9, 72.5, 70.1, 67.6 (C-2′–C-5′), 61.4 (C-6′), 31.9 (CH_2), 20.4 (2), 19.9 (2) (CH_3). Anal. Calcd for $C_{23}H_{27}N_3O_9$ (489.49): C, 56.44; H, 5.56; N, 8.58. Found: C, 56.28; H, 5.64; N, 8.39.

4.13. 1-(β-D-Glucopyranosyl)-4-hydroxymethyl-1,2,3-triazole (3a)

From **2a** (0.25 g, 0.58 mmol) according to General procedure **IV**. Yield: 0.13 g (82%) white solid. Mp: 156–158 °C (lit.[32] mp: 162–163 °C); $[\alpha]_D = -5$ (*c* 0.16, H_2O); ^1H NMR (D_2O): δ (ppm) 8.18 (1H, s, triazole H), 5.73 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 4.74 (2H, s, CH_2), 4.00 (1H, pseudot, $J_{2',3'}$ 9.2 Hz, H-2′), 3.90 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'a}$ <1 Hz, H-6′a), 3.80–3.59 (4H, m, H-3′, H-4′, H-5′, H-6′b); ^{13}C NMR (D_2O): δ (ppm) 147.7 (triazole C-4), 123.9 (triazole C-5), 88.0 (C-1′), 79.5, 76.6, 72.9, 69.6 (C-2′–C-5′), 61.0 (C-6′), 55.2 (CH_2). Anal. Calcd for $C_9H_{15}N_3O_6$ (261.24): C, 41.38; H, 5.79; N, 16.09. Found: C, 41.25; H, 5.86; N, 16.17.

4.14. Methyl 1-(β-D-glucopyranosyl)-1,2,3-triazole-4-carboxylate (3b*ii*)

From **2b** (0.26 g, 0.55 mmol) according to General procedure **IV**. Purified by column chromatography (8:2 $CHCl_3$–MeOH) to yield 0.11 g (70%) colourless syrup. R_f: 0.44 (7:3 $CHCl_3$–MeOH); $[\alpha]_D = +4$ (*c* 0.22, H_2O); ^1H NMR (D_2O): δ (ppm) 8.77 (1H, s, triazole H), 5.81 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 4.00 (1H, pseudot, $J_{2',3'}$ 9.2 Hz, H-2′), 3.90 (3H, s, OMe), 3.80 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'a}$ <1 Hz, H-6′a), 3.76–3.69 (3H, m, H-3′, H-5′, H-6′b), 3.62 (1H, pseudot, $J_{3',4'}$ 9.2, Hz, $J_{4',5'}$ 9.2 Hz, H-4′). ^{13}C NMR (D_2O): δ (ppm) 162.2 (CO), 139.5 (triazole C-4), 128.9 (triazole C-5), 87.9 (C-1′), 79.2, 76.0, 72.5, 69.0 (C-2′–C-5′), 60.6 (C-6′), 52.9 (OMe). Anal. Calcd for $C_{10}H_{15}N_3O_7$ (289.25): C, 41.53; H, 5.23; N, 14.53. Found: C, 41.43; H, 5.33; N, 14.45.

4.15. Sodium 1-(β-D-glucopyranosyl)-1,2,3-triazole-4-carboxylate (3b*iii*)

From **2b** (0.25 g, 0.53 mmol) according to General procedure **V**. Yield 0.09 g (55%) white solid. Mp: 198–201 °C; $[\alpha]_D = -12$ (*c* 0.18, H_2O); ^1H NMR (D_2O): δ (ppm) 8.37 (1H, s, triazole H), 5.67 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 3.93 (1H, pseudot, $J_{2',3'}$ 9.2 Hz, H-2′), 3.84 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'a}$ <1 Hz, H-6′a), 3.76–3.52 (4H, m, H-3′, H-4′, H-5′, H-6′b); ^{13}C NMR (D_2O): δ (ppm) 167.8 (CO), 145.8 (triazole C-4), 127.0 (triazole C-5), 88.3 (C-1′), 79.6, 76.6, 72.9, 69.6 (C-2′–C-5′), 61.1 (C-6′).

4.16. 1-(β-D-Glucopyranosyl)-1,2,3-triazole-4-carboxamide (3b*iv*)

Compound **2b** (0.8 g, 1.7 mmol) was stirred in dry methanolic NH_3 (6 mL) at rt for 1 day. After completion of the reaction (monitored by TLC 7:3 $CHCl_3$–MeOH), the solvent was removed to give white crystalline product. Yield: 0.40 g (86%). Mp: 227–229 °C (lit.[59] mp 232 °C); $[\alpha]_D = -3$ (*c* 0.19, DMSO) (lit.[59] $[\alpha]_D = +2$ (*c* 0.5, H_2O)); ^1H NMR (D_2O): δ (ppm) 8.64 (1H, s, triazole H), 5.79 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 3.99 (1H, pseudot, $J_{2',3'}$ 9.2 Hz, H-2′), 3.87 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'a}$ 5.3 Hz, H-6′a), 3.78–3.67 (3H, m, H-3′, H-5′, H-6′b), 3.60 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, $J_{4',5'}$ 9.2 Hz, H-4′). (DMSO-d_6): δ (ppm) 7.05 (1H, s, CONH_2), 6.66 (1H, s, CONH_2). ^{13}C NMR (D_2O): δ (ppm) 164.1 (CO), 142.1 (triazole C-4), 126.9 (triazole C-5), 87.8 (C-1′), 79.2, 76.0, 72.5, 69.1 (C-2′–C-5′), 60.6 (C-6′). Anal. Calcd for $C_9H_{14}N_4O_6$ (274.24): C, 39.42; H, 5.15; N, 20.43. Found: C, 39.34; H, 5.05; N, 20.55.

4.17. 1-(β-D-Glucopyranosyl)-4-phenyl-1,2,3-triazole (3c)

From **2c** (0.25 g, 0.53 mmol) according to General procedure **IV**. Yield: 0.14 g (89%) white solid. Mp: 229–231 °C (lit.[39] Mp: 228–230 °C, lit.[58] mp 234 °C); $[\alpha]_D = -69$ (*c* 0.24, DMSO) (lit.[58] $[\alpha]_D = 0$ (*c* 1, water)); ^1H and ^{13}C NMR data correspond to the reported spectra.[39]

4.18. 1-(β-D-Glucopyranosyl)-4-(2-naphthyl)-1,2,3-triazole (3d)

From **2d** (0.16 g, 0.30 mmol) according to General procedure **IV**. Yield: 0.08 g (72%) white solid. Mp: 212–214 °C; $[\alpha]_D = -26$ (*c* 0.21,

DMSO); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.98 (1H, s, triazole H), 8.47 (1H, s, aromatic), 8.01–7.92 (4H, m, aromatics), 7.53 (2H, m, aromatics), 5.62 (1H, d, $J_{1',2'}$ 7.9 Hz, H-1′), 5.50 (1H, d, J 4.0 Hz, OH), 5.38 (1H, d, J 2.6 Hz, OH), 5.22 (1H, d, J 4.0 Hz, OH), 4.68 (1H, t, OH), 3.84–3.29 (6H, m, H-2′, H-3′, H-4′, H-5′, H-6′a, H-6′b). ^{13}C NMR (DMSO-d_6): δ (ppm) 146.3 (triazole C-4), 133.1, 132.5, 128.5, 128.0, 127.9, 127.7, 126.6, 126.1, 123.6, 123.4 (aromatics), 120.8 (triazole C-5), 87.7 (C-1′), 79.9, 76.8, 72.2, 69.6 (C-2′–C-5′), 60.7 (C-6′). Anal. Calcd for $C_{18}H_{19}N_3O_5$ (357.37): C, 60.50; H, 5.36; N, 11.76. Found: C, 60.61; H, 5.31; N, 11.82.

4.19. 1-(β-D-Glucopyranosyl)-4-(1-naphthyl)-1,2,3-triazole (3e)

From **2e** (0.16 g, 0.30 mmol) according to General procedure **IV**. Yield: 0.10 g (95%) colourless syrup. R_f: 0.35 (8:2 $CHCl_3$–MeOH); $[\alpha]_D$ = −22 (*c* 0.21, MeOH); ^{1}H NMR (CD_3OD): δ (ppm) 8.48 (1H, s, triazole H), 8.20–8.17 (1H, m, aromatic), 7.87–7.85 (2H, m, aromatics), 7.63–7.61 (1H, m, aromatic), 7.49–7.44 (3H, m, aromatics), 5.75 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 4.05 (1H, pseudot, $J_{2',3'}$ 9.2 Hz, H-2′), 3.91 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'a}$ <1 Hz, H-6′a), 3.73 (1H, dd, $J_{5',6'b}$ 5.3 Hz, H-6′b), 3.68–3.55 (3H, m, H-3′, H-4′, H-5′). ^{13}C NMR (CD_3OD): δ (ppm) 147.5 (triazole C-4), 135.3, 132.3, 130.3, 129.5, 128.5, 127.8, 127.2, 126.4, 126.2 (aromatics), 124.5 (triazole C-5), 89.8 (C-1′), 81.1, 78.4, 74.0, 70.8 (C-2′–C-5′), 62.3 (C-6′). Anal. Calcd for $C_{18}H_{19}N_3O_5$ (357.37): C, 60.50; H, 5.36; N, 11.76. Found: C, 60.42; H, 5.25; N, 11.69.

4.20. 1-(β-D-Glucopyranosyl)-4-benzyl-1,2,3-triazole (3f)

From **2f** (0.25 g, 0.51 mmol) according to General procedure **IV**. Yield: 0.16 g (95%) colourless syrup. R_f: 0.39 (8:2 $CHCl_3$–MeOH); $[\alpha]_D$ = −18 (*c* 0.23, DMSO); ^{1}H NMR (CD_3OD): δ (ppm) 7.89 (1H, s, triazole H), 7.26–7.19 (5H, m, aromatics), 5.56 (1H, d, $J_{1',2'}$ 9.2 Hz, H-1′), 4.05 (2H, s, CH_2), 3.87–3.84 (2H, m, H-2′, H-6′a,), 3.69 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'b}$ <1 Hz, H-6′b), 3.54–3.48 (3H, m, H-3′, H-4′, H-5′). ^{13}C NMR (DMSO-d_6): δ (ppm) 145.9 (triazole C-4), 139.5, 128.6 (2), 128.4 (2), 126.2 (aromatics), 121.4 (triazole C-5), 87.6 (C-1′), 79.9, 76.7, 72.2, 69.7 (C-2′–C-5′), 60.8 (C-6′), 31.3 (CH_2). Anal. Calcd for $C_{15}H_{19}N_3O_5$ (321.34): C, 56.07; H, 5.96; N, 13.08. Found: C, 55.92; H, 6.09; N, 12.95.

4.21. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-glucopyranosyl)-4-hydroxymethyl-1,2,3-triazole (5a)

From **4** (1 g, 2.68 mmol) and propargyl alcohol (0.16 mL, 2.70 mmol) according to General procedure **II**. Purified by column chromatography (3:1 EtOAc–hexane) to yield 0.41 g (36%) colourless syrup. R_f: 0.18 (3:1 EtOAc–hexane); $[\alpha]_D$ = +236 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ (ppm) 7.77 (1H, s, triazole H), 6.41 (1H, d, $J_{1',2'}$ 5.3 Hz, H-1′), 6.28 (1H, pseudot, $J_{3',4'}$ 10.6 Hz, H-3′), 5.35 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 5.28 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′), 4.84 (2H, s, CH_2) 4.36 (1H, ddd, $J_{5',6'a}$ 4.0 Hz, H-5′), 4.27 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, H-6′a), 4.01 (1H, dd, $J_{5',6'b}$ 2.6 Hz, H-6′b), 3.72 (1H, s, CH_2OH), 2.08 (6H, s, 2 × CH_3), 2.04, 1.89 (6H, 2s, 2 × CH_3); ^{13}C NMR($CDCl_3$): δ (ppm) 170.4, 170.1 169.7, 169.6 (CO), 147.3 (triazole C-4), 124.2 (triazole C-5), 81.3 (C-1′), 70.9, 70.3, 69.5, 67.8 (C-2′–C-5′), 61.1 (C-6′), 55.9 (CH_2), 20.6 (2), 20.3, 20.2 (CH_3). Anal. Calcd for $C_{17}H_{23}N_3O_{10}$ (429.39): C, 47.55; H, 5.40; N, 9.79. Found: C, 47.40; H, 5.47; N, 9.64.

4.22. Ethyl 1-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,2,3-triazole-4-carboxylate (5b)

From **4** (1 g, 2.70 mmol) and ethyl propiolate (0.28 mL, 2.70 mmol) according to General procedure **II**. Purified by column chromatography (4:6 EtOAc–hexane) to yield 0.91 g (72%) white solid. Mp: 145–147 °C; $[\alpha]_D$ = +227 (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ (ppm) 8.20 (1H, s, triazole H), 6.42 (1H, d, $J_{1',2'}$ 6.6 Hz, H-1′), 6.21 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, H-3′), 5.34 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 5.27 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′), 4.43 (2H, q, J 7.3 Hz, CH_2), 4.31 (1H, ddd, $J_{5',6'a}$ 4.0 Hz, H-5′), 4.25 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, H-6′a), 4.00 (1H, dd, $J_{5',6'b}$ 2.6 Hz, H-6′b), 2.08 (6H, s, 2 × CH_3), 2.04, 1.88 (6H, 2s, 2 × CH_3), 1.43 (3H, t, J 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 170.4, 170.0, 169.6, 169.5 (CO), 160.2 (*C*OOEt), 139.8 (triazole C-4), 129.6 (triazole C-5), 81.9 (C-1′), 71.4, 70.0, 69.5, 67.6 (C-2′–C-5′), 61.6, 61.1 (C-6′, CH_2), 20.6 (3), 20.2 (CH_3), 14.2 (CH_3). Anal. Calcd for $C_{19}H_{25}N_3O_{11}$ (471.42): C, 48.41; H, 5.35; N, 8.91. Found: C, 48.60; H, 5.22; N, 8.83.

4.23. 1-(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-glucopyranosyl)-4-phenyl-1,2,3-triazole (5c)

From **4** (0.2 g, 0.54 mmol) and phenylacetylene (0.06 mL, 0.54 mmol) according to General procedure **II**. Purified by column chromatography (1:2 EtOAc–hexane) to yield 0.10 g (39%) white solid. Mp: 193–195 °C; $[\alpha]_D$ = +282 (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ (ppm) 8.04 (1H, s, triazole H), 7.87–7.85 (2H, m, aromatics), 7.49–7.38 (3H, m, aromatics), 6.48 (1H, d, $J_{1',2'}$ 6.6 Hz, H-1′), 6.34 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, H-3′), 5.39 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 5.30 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′), 4.39 (1H, ddd, $J_{5',6'a}$ 4.0 Hz, H-5′), 4.28 (1H, dd, $J_{6'a,6'b}$ 11.9 Hz, H-6′a), 4.06 (1H, dd, $J_{5',6'b}$ 2.6 Hz, H-6′b), 2.08 (6H, s, 2 × CH_3), 2.06, 1.89 (6H, 2s, 2 × CH_3); ^{13}C NMR (CDCl3): δ (ppm) 170.6, 170.2, 169.7 (2) (CO), 147.1 (triazole C-4), 129.2, 128.8 (2), 128.5, 125.5 (2) (aromatics), 121.9 (triazole C-5), 81.2 (C-1′), 70.8, 70.3, 69.5, 67.8 (C-2′–C-5′), 61.1 (C-6′), 20.3 (3), 20.0 (CH_3). Anal. Calcd for $C_{22}H_{25}N_3O_9$ (475.46): C, 55.58; H, 5.30; N, 8.84. Found: C, 55.45; H, 5.18; N, 9.01.

4.24. 1-(α-D-Glucopyranosyl)-4-hydroxymethyl-1,2,3-triazole (6a)

From **5a** (0.1 g, 0.23 mmol) according to General procedure **IV**. Yield 0.04 g (72%) pale yellow syrup. R_f: 0.44 (1:1 $CHCl_3$–MeOH); $[\alpha]_D$ = +82 (*c* 0.20, H_2O); ^{1}H NMR (D_2O): δ (ppm) 8.10 (1H, s, triazole H), 6.26 (1H, d, $J_{1',2'}$ 5.3 Hz, H-1′), 4.70 (2H, s, CH_2), 4.38 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, H-3′), 4.09 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 3.73–3.64 (3H, m, H-5′, H-6′a, H-6′b), 3.54 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′); ^{13}C NMR (D_2O): δ (ppm) 146.3 (triazole C-4), 126.3 (triazole C-5), 85.3 (C-1′), 75.4, 73.3, 70.4, 69.5 (C-2′–C-5′), 60.5 (C-6′), 54.6 (CH_2). Anal. Calcd for $C_9H_{15}N_3O_6$ (261.24): C, 41.38; H, 5.79; N, 16.09. Found: C, 41.25; H, 5.88; N, 16.17.

4.25. Methyl 1-(α-D-glucopyranosyl)-1,2,3-triazole-4-carboxylate (6b*ii*)

From **5b** (0.25 g, 0.53 mmol) according to General procedure **IV**. Yield 0.14 g (93%) white solid. Mp: 174–176 °C; $[\alpha]_D$ = +68 (*c* 0.21, H_2O); ^{1}H NMR (D_2O): δ (ppm) 8.69 (1H, s, triazole H), 6.32 (1H, d, $J_{1',2'}$ 5.3 Hz, H-1′), 4.36 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, H-3′), 4.10 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 3.91 (1H, s, OMe), 3.79–3.67 (3H, m, H-5′, H-6′a, H-6′b), 3.57 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′); ^{13}C NMR (D_2O): δ (ppm) 162.9 (CO), 139.2 (triazole C-4), 132.0 (triazole C-5), 86.4 (C-1′), 76.3, 73.6, 70.8, 69.9 (C-2′–C-5′), 61.0 (C-6′), 51.4 (OMe). Anal. Calcd for $C_{10}H_{15}N_3O_7$ (289.25): C, 41.53; H, 5.23; N, 14.53. Found: C, 41.41; H, 5.32; N, 14.60.

4.26. Sodium 1-(α-D-glucopyranosyl)-1,2,3-triazole-4-carboxylate (6b*iii*)

From **5b** (0.4 g, 0.85 mmol) according to General procedure **V**. Purified by column chromatography (3:7 $CHCl_3$–MeOH) to yield 0.12 g (47%) white solid. Mp: 190–192 °C; $[\alpha]_D$ = +143 (*c* 0.19,

H_2O); ^1H NMR (D_2O): δ (ppm) 8.33 (1H, s, triazole H), 6.25 (1H, d, $J_{1',2'}$ 6.6 Hz, H-1′), 4.38 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, H-3′), 4.07 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 3.74–3.63 (3H, m, H-5′, H-6′a, H-6′b), 3.54 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′); ^{13}C NMR (D_2O): δ (ppm) 168.1 (CO), 144.7 (triazole C-4), 129.9 (triazole C-5), 85.7 (C-1′), 75.8, 73.6, 70.8, 69.9 (C-2′–C-5′), 60.9 (C-6′).

4.27. 1-(α-D-Glucopyranosyl)-1,2,3-triazole-4-carboxamide (6b*iv*)

5b (0.4 g, 0.85 mmol) was stirred in dry methanolic NH_3 (4 mL) at rt for 1 day. After completion of the reaction (monitored by TLC 7:3 $CHCl_3$–MeOH), the solvent was removed to give white crystalline product. Yield: 0.19 g (81%). Mp: 219–221 °C $[\alpha]_D$ = +208 (*c* 0.21, H_2O)); ^1H NMR (D_2O): δ (ppm) 8.59 (1H, s, triazole H), 6.34 (1H, d, $J_{1',2'}$ 5.3 Hz, H-1′), 4.40 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, H-3′), 4.14 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 3.81–3.67 (3H, m, H-5′, H-6′a, H-6′b), 3.60 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′); (DMSO-d_6): δ (ppm) 7.90 (1H, s, CONH_2), 7.50 (1H, s, CONH_2). ^{13}C NMR (D_2O): δ (ppm) 164.7 (CO), 141.7 (triazole C-4), 130.1 (triazole C-5), 86.2 (C-1′), 76.1, 73.6, 70.8, 69.9 (C-2′–C-5′), 60.9 (C-6′). Anal. Calcd for $C_9H_{14}N_4O_6$ (274.24): C, 39.42; H, 5.15; N, 20.43. Found: C, 39.51; H, 5.23; N, 20.31.

4.28. 1-(α-D-Glucopyranosyl)-4-phenyl-1,2,3-triazole (6c)

From **5c** (0.075 g, 0.16 mmol) according to General procedure **IV**. Yield 0.04 g (75%) white solid. Mp: 195–197 °C; $[\alpha]_D$ = +143 (*c* 0.23, H_2O); ^1H NMR (D_2O–CD_3OD): δ (ppm) 8.38(1H, s, triazole H), 7.74–7.72 (2H, m, aromatics), 7.44–7.33 (3H, m, aromatics), 6.25 (1H, d, $J_{1',2'}$ 6.6 Hz, H-1′), 4.39 (1H, pseudot, $J_{3',4'}$ 9.2 Hz, H-3′), 4.06 (1H, dd, $J_{2',3'}$ 9.2 Hz, H-2′), 3.73–3.65 (3H, m, H-5′, H-6′a, H-6′b), 3.52 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′); ^{13}C NMR (D_2O–CD_3OD): δ (ppm) 147.6 (triazole C-4), 130.3, 130.2 (2), 129.9, 126.8 (2) (aromatics), 125.0 (triazole C-5), 86.3 (C-1′), 76.4, 74.2, 71.4, 70.4 (C-2′–C-5′), 61.4 (C-6′). Anal. Calcd for $C_{14}H_{17}N_3O_5$ (307.31): C, 54.72; H, 5.58; N, 13.67. Found: C, 54.80; H, 5.74; N, 13.55.

4.29. [1-(3′,4′,5′,7′-Tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-hydroxymethyl-1,2,3-triazole]onamide (9a)

From **7** (0.1 g, 0.15 mmol) and propargyl alcohol (18 μL, 0.30 mmol) according to General procedure **III**. Purified by column chromatography (6:4 EtOAc–hexane) to yield 0.041 g (conversion: 51%, yield: 75%) white solid. Mp: 112–114 °C; $[\alpha]_D$ = +0.2 (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.04–7.22 (21H, m, aromatics + triazole H), 7.09 (1H, s, CONH_2), 6.53 (1H, s, CONH_2), 6.34 (1H, pseudot, $J_{4',5'}$ 7.9 Hz, H-4′), 6.17 (1H, d, $J_{3',4'}$ 7.9 Hz, H-3′), 5.87 (1H, pseudot, $J_{5',6'}$ 7.9 Hz, H-5′), 5.08 (1H, ddd, $J_{6',7a'}$ 2.6 Hz, $J_{6',7b'}$ 4.0 Hz, H-6′), 4.82 (1H, dd, $J_{7'a,7'b}$ 11.9 Hz, H-7′a), 4.53–4.49 (3H, m, H-7′b + CH_2), 3.61 (1H, s, CH_2OH). ^{13}C NMR ($CDCl_3$): δ (ppm) 166.2 (2), 165.1, 164.9, 164.4 (CO), 147.6 (triazole C-4), 133.7–128.2 (aromatics), 120.9 (triazole C-5), 89.4 (C-2′), 73.7, 72.1, 71.1, 68.3 (C-3′–C-6′), 62.5 (C-7′), 55.7 (CH_2). Anal. Calcd for $C_{38}H_{32}N_4O_{11}$ (720.70): C, 63.33; H, 4.48; N, 7.77. Found: C, 63.21; H, 4.55; N, 7.70.

4.30. [1-(3′,4′,5′,7′-Tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-ethoxycarbonyl-1,2,3-triazole]onamide (9b)

From **7** (0.7 g, 1.07 mmol) and ethyl propiolate (0.11 mL, 1.07 mmol) according to General procedure **II**. Purified by column chromatography (1:2 EtOAc–hexane) to yield 0.28 g (conversion: 63%, yield: 56%) pale yellow syrup. R_f: 0.31 (1:1 EtOAc–hexane); $[\alpha]_D$ = −70 (*c* 0.17, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.56 (1H, s, triazole H), 8.09–7.23 (20H, m, aromatics), 7.08 (1H, s, CONH_2), 6.58 (1H, s, CONH_2), 6.33 (1H, pseudot, $J_{4',5'}$ 7.9 Hz, H-4′), 6.19 (1H, d, $J_{3',4'}$ 7.9 Hz, H-3′), 5.89 (1H, pseudot, $J_{5',6'}$ 10.6 Hz, H-5′), 5.20 (1H, ddd, $J_{6',7a'}$ 2.6 Hz, H-6′), 4.89 (1H, dd, $J_{7'a,7'b}$ 11.9 Hz, H-7′a), 4.57 (1H, dd, $J_{6',7b'}$ 4.0 Hz, H-7′b), 4.32 (2H, q, *J* 7.3 Hz, CH_2), 1.32 (3H, t, *J* 7.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 166.1, 165.6, 165.0, 164.9, 164.2, 159.9 (CO), 139.9 (triazole C-4), 133.8–128.0 (aromatics), 126.6 (triazole C-5), 89.6 (C-2′), 74.1, 72.2, 70.9, 68.0 (C-3′–C-6′), 62.3, 61.4 (C-7′, CH_2), 14.1 (CH_3). Anal. Calcd for $C_{40}H_{34}N_4O_{12}$ (762.74): C, 62.99; H, 4.49; N, 7.35. Found: C, 63.08; H, 4.57; N, 7.21.

4.31. [1-(3′,4′,5′,7′-Tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-phenyl-1,2,3-triazole]onamide (9c)

From **7** (0.1 g, 0.15 mmol) and phenylacetylene (33 μL, 0.30 mmol) according to General procedure **III**. Purified by column chromatography (1:2 EtOAc–hexane) to yield 0.07 g (conversion: 73%, yield: 83%) white solid. Mp: 193–195 °C; $[\alpha]_D$ = −198 (*c* 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.22 (1H, s, triazole H), 8.13–7.12 (26H, m, aromatics + CONH_2), 6.33–6.29 (2H, m, H-4′ + CONH_2), 6.24 (1H, d, $J_{3',4'}$ 7.9 Hz, H-3′), 5.92 (1H, pseudot, $J_{4',5'}$ 7.9 Hz, $J_{5',6'}$ 9.2 Hz, H-5′), 5.29 (1H, ddd, $J_{6',7a'}$ 2.6 Hz, H-6′), 5.00 (1H, dd, $J_{7'a,7'b}$ 13.2 Hz, H-7′a), 4.54 (1H, dd, $J_{6',7'b}$ 4.0 Hz, H-7′b); ^{13}C NMR ($CDCl_3$): δ (ppm) 166.4, 166.2, 165.0, 164.9, 164.2 (CO), 147.6 (triazole C-4), 133.7–125.7 (aromatics), 118.6 (triazole C-5), 89.4 (C-2′), 74.0, 72.2, 71.0, 68.9 (C-3′–C-6′), 62.2 (C-7′). Anal. Calcd for $C_{43}H_{34}N_4O_{10}$ (766.77): C, 67.36; H, 4.47; N, 7.31. Found: C, 67.25; H, 4.39; N, 7.42.

4.32. [1-(3′,4′,5′,7′-Tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-(2-naphthyl)-1,2,3-triazole]onamide (9d)

From **7** (0.1 g, 0.15 mmol) and 2-naphthylacetylene (0.047 g, 0.30 mmol) according to General procedure **III**. Purified by column chromatography (4:6 EtOAc–hexane) to yield 0.068 g (Conversion: 63%, Yield: 87%) white solid. Mp: 242–243 °C; $[\alpha]_D$ = −289 (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.34 (1H, s, triazole H), 8.15–7.14 (28H, m, aromatics + CONH_2), 6.36–6.28 (3H, m, H-3′, H-4′ + CONH_2), 5.94 (1H, pseudot, $J_{4',5'}$ 7.9 Hz, $J_{5',6'}$ 9.2 Hz, H-5′), 5.31 (1H, ddd, $J_{6',7a'}$ 2.6 Hz, H-6′), 5.03 (1H, dd, $J_{7'a,7'b}$ 11.9 Hz, H-7′a), 4.57 (1H, dd, $J_{6',7'b}$ 4.0 Hz, H-7′b). ^{13}C NMR ($CDCl_3$): δ (ppm) 166.5, 166.2, 165.0, 164.9, 164.2 (CO), 147.6 (triazole C-4), 133.7–123.6 (aromatics), 118.9 (triazole C-5), 89.5 (C-2′), 74.0, 72.3, 71.1, 68.2 (C-3′–C-6′), 62.3 (C-7′). Anal. Calcd for $C_{47}H_{36}N_4O_{10}$ (816.83): C, 69.11; H, 4.44; N, 6.86. Found: C, 69.25; H, 4.51; N, 6.97.

4.33. Methyl [1-(3′,4′,5′,7′-tetra-*O*-benzoyl-β-D-*gluco*-hept-2-ulopyranosyl)-4-ethoxycarbonyl-1,2,3-triazole]onate (10b)

From **8** (0.6 g, 0.88 mmol) and ethyl propiolate (0.09 mL, 0.88 mmol) according to General procedure **II**. Purified by column chromatography (1:3 EtOAc–hexane) to yield 0.36 g (Conversion: 74%, Yield: 70%) pale yellow syrup. R_f: 0.29 (1:2 EtOAc–hexane); $[\alpha]_D$ = +46 (*c* 0.24, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.54 (1H, s, triazole H), 8.08–7.23 (20H, m, aromatics), 6.47 (1H, pseudot, $J_{4',5'}$ 9.2 Hz, H-4′), 6.39 (1H, d, $J_{3',4'}$ 7.9 Hz, H-3′), 5.91 (1H, pseudot, $J_{5',6'}$ 9.2 Hz, H-5′), 4.93 (1H, ddd, $J_{6',7a'}$ 2.6 Hz, H-6′), 4.87 (1H, dd, $J_{7'a,7'b}$ 11.9 Hz, H-7′a), 4.59 (1H, dd, $J_{6',7b'}$ 4.0 Hz, H-7′b), 4.37 (2H, q, *J* 7.3 Hz, CH_2), 3.88 (3H, s, OMe), 1.35 (3H, t, *J* 7.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 165.8, 164.9, 164.8, 164.3, 164.1, 160.0 (CO), 139.5 (triazole C-4), 133.4–128.1 (aromatics), 126.2 (triazole C-5), 89.7 (C-2′), 73.9, 71.3, 70.7, 68.0 (C-3′–C-6′), 62.1, 61.2 (C-7′, CH_2), 54.0 (OMe), 14.0 (CH_3). Anal. Calcd for $C_{41}H_{35}N_3O_{13}$ (777.75): C, 63.32; H, 4.54; N, 5.40. Found: C, 63.45; H, 4.59; N, 5.32.

4.34. [1-(β-D-*Gluco*-hept-2-ulopyranosyl)-4-hydroxymethyl-1,2,3-triazole]onamide (11a)

From **9a** (0.14 g, 0.19 mmol) according to General procedure **IV**. Purified by column chromatography (7:3 $CHCl_3$–MeOH) to yield 0.04 g (68%) colourless syrup. R_f: 0.40 (1:1 $CHCl_3$–MeOH); $[\alpha]_D$ = +124 (*c* 0.17, H_2O); ^1H NMR (D_2O): δ (ppm) 8.27 (1H, s, triazole H), 4.72 (1H, s, CH_2), 4.01 (1H, d, $J_{3',4'}$ 10.6 Hz, H-3′), 3.92–3.81 (3H, m, H-6′, H-7′a, H-7′b), 3.80–3.65 (2H, m, H-4′, H-5′). ^{13}C NMR (D_2O): δ (ppm) 168.7 (CO), 147.4 (triazole C-4), 123.0 (triazole C-5), 90.3 (C-2′), 78.1, 76.1, 74.3, 69.2 (C-3′–C-6′), 60.9 (C-7′), 55.3 (CH_2). Anal. Calcd for $C_{10}H_{16}N_4O_7$ (304.26): C, 39.48; H, 5.30; N, 18.41. Found: C, 39.41; H, 5.41; N, 18.50.

4.35. Sodium [1-(β-D-*gluco*-hept-2-ulopyranosyl)onamide]-1,2,3-triazole-4-carboxylate (11b)

From **9b** (0.25 g, 0.33 mmol) according to General procedure **V**. Purified by column chromatography (3:7 $CHCl_3$–MeOH) to yield 0.075 g (67%) white solid. Mp: 275–278 °C; $[\alpha]_D$ = +76 (*c* 0.24, H_2O); ^1H NMR (D_2O): δ (ppm) 8.48 (1H, s, triazole H), 3.99 (1H, d, $J_{3',4'}$ 9.2 Hz, H-3′), 3.91–3.87 (2H, m, H-6′, H-7′a), 3.82 (1H, dd, $J_{7'a,7'b}$ 13.2 Hz, $J_{6',7'b}$ 2.6 Hz, H-7′b), 3.73–3.63 (2H, m H-4′, H-5′). ^{13}C NMR (D_2O): δ (ppm) 168.5, 167.7 (CO), 145.5 (triazole C-4), 126.0 (triazole C-5), 90.3 (C-2′), 78.0, 76.1, 74.2, 69.1 (C-3′–C-6′), 60.8 (C-7′).

4.36. [1-(β-D-*Gluco*-hept-2-ulopyranosyl)-4-phenyl-1,2,3-triazole]onamide (11c)

From **9c** (0.23 g, 0.30 mmol) according to General procedure **IV**. Purified by column chromatography (8:2 $CHCl_3$–MeOH) to yield 0.097 g (92%) colourless syrup. R_f: 0.22 (8:2 $CHCl_3$–MeOH); $[\alpha]_D$ = +85 (*c* 0.20, H_2O); ^1H NMR (D_2O): δ (ppm) 8.44 (1H, s, triazole H), 7.63–7.59 (2H, m, aromatics), 7.35–7.31 (3H, m, aromatics), 4.02 (1H, d, $J_{3',4'}$ 9.2 Hz, H-3′), 3.92–3.79 (3H, m, H-6′, H-7′a, H-7′b), 3.72 (1H, pseudot, *J* 9.2, 9.2 Hz, H-4′ or H-5′), 3.65 (1H, pseudot, *J* 9.2, 9.2 Hz, H-4′ or H-5′); ^{13}C NMR (D_2O): δ (ppm) 168.6 (CO), 148.1 (triazole C-4), 129.8 (2), 129.7, 129.4, 126.4 (2) (aromatics), 120.9 (triazole C-5), 90.3 (C-2′), 78.2, 76.1, 74.4, 69.3 (C-3′–C-6′), 61.0 (C-7′). Anal. Calcd for $C_{15}H_{18}N_4O_6$ (350.33): C, 51.43; H, 5.18; N, 15.99. Found: C, 51.34; H, 5.11; N, 16.07.

4.37. [1-(β-D-*Gluco*-hept-2-ulopyranosyl)-4-(2-naphthyl)-1,2,3-triazole]onamide (11d)

From **9d** (0.24 g, 0.29 mmol) according to General procedure **IV**. Purified by column chromatography (8:2 $CHCl_3$–MeOH) to yield 0.096 g (81%) white solid. Mp: 220–222 °C; $[\alpha]_D$ = +66 (*c* 0.23, MeOH); ^1H NMR (CD_3OD): δ (ppm) 8.79 (1H, s, triazole H), 8.34 (1H, s, aromatic), 7.93–7.85 (4H, m, aromatics), 7.49–7.47 (2H, m, aromatics), 4.10 (1H, d, $J_{3',4'}$ 9.2 Hz, H-3′), 3.97 (1H, dd, $J_{7a',7b'}$ 13.2 Hz, $J_{6',7'a}$ <1 Hz, H-7′a), 3.86–3.76 (3H, m, H-4′ or H-5′, H-6′, H-7′b), 3.66 (1H, pseudot, *J* 9.2, 9.2 Hz, H-4′ or H-5′); ^{13}C (CD_3OD): δ (ppm) 169.3 (CO), 148.7 (triazole C-4), 135.1, 134.8, 129.8, 129.2, 128.9, 127.6, 127.4, 125.6, 125.5, 124.7 (aromatics), 121.3 (triazole C-5), 90.8 (C-2′), 79.5, 77.5, 76.0, 70.4 (C-3′–C-6′), 62.2 (C-7′). Anal. Calcd for $C_{19}H_{20}N_4O_6$ (400.39): C, 57.00; H, 5.03; N, 13.99. Found: C, 56.88; H, 5.11; N, 13.90.

4.38. [1-(β-D-*Gluco*-hept-2-ulopyranosyl)-4-carboxylato-1,2,3-triazole]onic acid disodium salt (12b)

From **10b** (0.26 g, 0.33 mmol) according to General procedure **V**. Purified by column chromatography (3:7 $CHCl_3$–MeOH) to yield 0.04 g (35%) white solid. Mp: 230–232 °C; $[\alpha]_D$ = +49 (*c* 0.21, H_2O); ^1H NMR (D_2O): δ (ppm) 8.39 (1H, s, triazole H), 3.89–3.82 (4H, m, H-3′, H-6′, H-7′a, H-7′b), 3.68–3.63 (2H, m, H-4′, H-5′). ^{13}C NMR (D_2O): δ (ppm) 170.2, 168.0 (CO), 145.0 (triazole C-4), 126.2 (triazole C-5), 90.8 (C-2′), 77.6, 76.5, 75.3, 69.3 (C-3′–C-6′), 60.9 (C-7′).

4.39. Enzymology

Glycogen phosphorylase *b* was prepared from rabbit skeletal muscle according to the method of Fischer and Krebs,[60] using dithiothreitol instead of L-cysteine, and recrystallised at least three times before use. Kinetic experiments were performed in the direction of glycogen synthesis as described previously.[61] Kinetic data for the inhibition of rabbit skeletal muscle glycogen phosphorylase were collected using different concentrations of α-D-glucose-1-phosphate (2–20 mM), constant concentrations of glycogen (1% w/v) and AMP (1 mM), and various concentrations of inhibitors. Inhibitors were dissolved in dimethyl sulfoxide (DMSO) and diluted in the assay buffer (50 mM triethanolamine, 1 mM EDTA and 1 mM dithiothreitol) so that the DMSO concentration in the assay should be lower than 1%. The enzymatic activities were presented in the form of double-reciprocal plots (Lineweaver–Burk) applying a nonlinear data analysis program. The inhibitor constants (K_i) were determined by Dixon plots, by replotting the slopes from the Lineweaver–Burk plots against the inhibitor concentrations.[15,49] The means of standard errors for all calculated kinetic parameters averaged to less than 10%.

Acknowledgement

This work was supported by the Hungarian Scientific Research Fund (Grants: OTKA 61336, 68578, and 77712).

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