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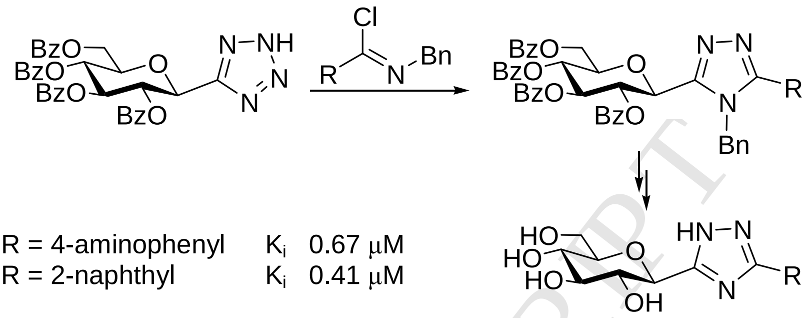
C-Glucopyranosyl-1,2,4-triazoles are novel skeletons to inhibit glycogen phosphorylase in the nanomolar range.



Best inhibitors of rabbit muscle glycogen phosphorylase *b*

R = 4-aminophenyl K_i 0.67 μM
R = 2-naphthyl K_i 0.41 μM

New synthesis of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles, nanomolar inhibitors of glycogen phosphorylase

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Abstract

O-Perbenzoylated 5-(β-D-glucopyranosyl)tetrazole was reacted with *N*-benzyl carboximidoyl chlorides to give the corresponding 4-benzyl-3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles. Removal of the *O*-benzoyl and *N*-benzyl protecting groups by base catalysed transesterification and catalytic hydrogenation, respectively, furnished a series of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles with aliphatic, mono- and bicyclic aromatic, and heterocyclic substituents in the 5-position. Enzyme kinetic studies revealed these compounds to inhibit rabbit muscle glycogen phosphorylase *b*: best inhibitors were the 5-(4-aminophenyl)- (K_i 0.67 μM) and the 5-(2-naphthyl)-substituted (K_i 0.41 μM) derivatives. This study uncovered the *C*-glucopyranosyl-1,2,4-triazoles as a novel skeleton for nanomolar inhibition of glycogen phosphorylase.

Keywords

1,2,4-Triazole, *C*-glucopyranosyl derivative, bioisoster, glycogen phosphorylase, inhibitor.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a severe disease with large economic consequences, which is significantly under-diagnosed and incompletely treated in the general population [1, 2]. Control of blood glucose levels is a key objective in treating diabetic patients, who are most often prescribed modification of diet and exercise, one or more oral hypoglycaemic agents, as well as insulin. In spite of the availability of different classes of hypoglycaemic drugs, current treatments are often unable to achieve an intensive degree of blood glucose control to reduce effectively the incidence and severity of diabetic complications [3].

Hepatic glucose output is elevated in type 2 diabetic patients and current evidence indicates that glycogenolysis (release of monomeric glucose from the glycogen polymer storage form) is an important contributor to the abnormally high production of glucose by the liver. Glycogen phosphorylase (GP) is the enzyme responsible for glycogen breakdown to produce glucose and related metabolites for energy supply [4]. Due to its key role in the modulation of glycogen metabolism, pharmacological inhibition of GP has been regarded as an effective therapeutic approach to treating diseases caused by abnormalities in glycogen metabolism, first of all T2DM [5-7], but also myocardial [8, 9] and cerebral [10, 11] ischemias and tumors [12-15]. Therefore, the study of glycogen phosphorylase inhibitors [16] (GPIs) is a continuing challenge for synthetic and medicinal chemistry [17, 18], computational chemistry [19], protein crystallography [5, 20], and physiology [21]. The biochemical and pharmacological background of this research has been thoroughly summarized in several reviews of the past decade, therefore, the reader is kindly referred to those papers [4, 22, 23].

Several structural classes of GP inhibitors have been reported [5, 17, 18, 24] whose binding sites identified in GP include the catalytic site, the purine inhibitory site, the allosteric site, the glycogen storage site, the new allosteric inhibitor site and the lately discovered benzimidazole-binding site. The most widely studied group of molecules is that of glucose derivatives [7, 25-35] which bind primarily to the active site of GP [36]. The best glucose analogue GPIs are glucopyranosylidene-spiro-heterocycles (K_i 0.16-0.63 μM) and *N*-acyl-*N'*-β-D-glucopyranosyl ureas (K_i 0.35-0.7 μM) exhibiting submicromolar inhibition [26] of rabbit muscle GP*b*, the prototype of GPs [20]. Glucopyranosylidene-spiro-thiohydantoin (K_i 29.8 μM against rat liver GP) was shown to exert considerable *in vivo* blood sugar diminishing activity [37], and an *N*-acyl-*N'*-β-D-glucopyranosyl urea derivative improved glucose tolerance and had remarkable effects in rearranging hepatic metabolism in diabetic mice [38].

N-Acyl-β-D-glucopyranosylamines (compounds **I** in Chart 1) were among the first synthetic glucose analogue inhibitors of GP [39] and several derivatives modified in the acyl groups were investigated [40-44]. In this series *N*-(2-naphthoyl)-β-D-glucopyranosylamine (**IC**) was the best inhibitor [41], which also served as a lead structure for bioisosteric replacements [45-48]. X-Ray crystallographic studies on several RMGP*b*-**I** complexes showed the presence of a H-bond between the amide NH and the main chain C=O of His377 (outline **X** in Chart 1), and the strong binding was attributed to a large extent to this interaction.

Inserting a 1,2,3-triazole ring in place of the NHCO moiety as in **II** revealed that **I** and **II** were equipotent inhibitors [49] and the structural features of the binding determined by X-ray crystallography were also very similar [42]. Oxadiazoles **III-V**, prepared in each possible variant [50, 51], showed that the constitution of the heterocycle had a strong bearing on the inhibition: the most efficient inhibitor among these compounds was 5-(β-D-glucopyranosyl)-3-(2-naphthyl)-1,2,4-oxadiazole (**IVC**) which had a similar efficiency to that of **IC**. Other studies with *C*-glucopyranosyl heterocycles showed that benzothiazole **VI** was much less efficient than benzimidazoles **VII** and **VIII** [33, 52]. An X-ray crystallographic study of the

RMGP*b*–**VII** complex revealed the presence of a specific H-bond between NH of the heterocycle and the main chain C=O of His377 [53] (outline **XI** in Chart 1), and the stronger binding of **VII** was explained by this interaction which cannot exist in the case of **VI**.

Based on these structure–activity relationships it was anticipated that *C*-glucopyranosyl 1,2,4-triazoles of type **IX**, non-classical bioisosteres of compounds **I-V**, could be more efficient GPIs. Very recently we have demonstrated in a preliminary communication that **IX** (R = 2-naphthyl, K_i 0.41 μM) indeed fulfills these expectations [54]. In this paper we disclose a new synthesis and structure-activity relationships of **IX** with a wide range of substituents R.

Chart 1.

In the literature *C*-glycopyranosyl-1,2,4-triazoles are represented by some 1,3,5-trisubstituted derivatives obtained from glycosyl cyanides with 1-aza-2-azoniaallene salts [56] or with hydrazonoyl chlorides in the presence of $Yb(OTf)_3$ [57]. 3-Glycopyranosyl-5-substituted-1,2,4-triazoles **IX** have been unknown until our very recent preliminary communication describing the synthesis of these compounds by acylation of N^1-tosyl-*C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidrazone followed by *N*- and/or *O*-deprotection [54]. However, this synthetic sequence was rather long (5-6 steps from the corresponding glucosyl cyanide) and complicated by the removal of the *N*-tosyl moiety from the heterocycle. Therefore, a more straightforward synthesis of the target compounds has been sought for and accomplished by the ring transformation of 5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)tetrazole.

2. Results and Discussion

2.1. Syntheses

To select a suitable synthetic pathway towards compounds **IX** a retrosynthetic analysis for the construction of the 1,2,4-triazole ring was carried out taking into account 1,3-dipolar cycloadditions (Scheme 1). It was envisaged that synthetic methods [58] for 1,3,5-trisubstituted-1,2,4-triazoles [59, 60] with a protecting group as the 1-substituent could be applied. Given the tautomeric nature of this heterocycle three *N*-protected isomers may exist whose disconnections **A** and **B** refer to cycloadditions between nitrilimines and nitriles. Following route **A** the known glucosyl cyanide and 2,5-disubstituted-tetrazoles or *N*-protected hydrazones or their halides would have been the necessary starting compounds, however, this possibility was ruled out due to the costly reagents and catalysts. For the analogous route **B** precursors of the intermediate *C*-glucosyl-nitrilimine would have been required which are unknown in the literature. Therefore, our attention turned to disconnection **C**, actually a variant of **B**, which needed the relatively easily available *C*-glucosyl-tetrazole and imidoyl-halides. The analogous disconnection **C'** (not shown in details) was also discarded because of the necessity to prepare a series of tetrazoles and lack of the glucose based precursor of the imidoyl-halide.

Scheme 1.

Syntheses of the target compounds were started by the preparation of *O*-protected *C*-glucopyranosyl-tetrazole **1** (Table 1) from 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl cyanide [61] according to our recent procedure [27]. *N*-Benzyl arenecarboxamides **2**, obtained from the corresponding acid chloride and benzylamine, were converted to imidoyl chlorides by $SOCl_2$ which were then reacted without purification with tetrazole **1** in a one-pot fashion to give 4-benzyl-1,2,4-triazole derivatives **3**. The *O*-benzoyl protecting groups were removed by the Zemplén method to give **4**. Subsequent catalytic hydrogenation gave fully deprotected *C*-glucopyranosyl-1,2,4-triazoles **6d-g,i,m,p,q**. Several *O*-perbenzoylated 3-glucopyranosyl-5-substituted derivatives **5** were obtained in an alternative synthetic pathway published recently [62], and these compounds were also converted to the corresponding unprotected **6a-d,h,j,l,n,q,r** by the Zemplén protocol. Amino compounds **6k** and **6o** were obtained from the corresponding nitro derivatives **6j** and **6n**, respectively, by catalytic hydrogenation.

Table 1.

2.2. Enzyme kinetic studies

The new compounds were assayed against rabbit muscle glycogen phosphorylase *b* as described in earlier publications [40, 63], and the results are collected in Table 2.

Compounds **6a-c** with aliphatic substituents proved weak inhibitors and were much less efficient than the corresponding „parent" amides **I** (shown in Chart 1; for R = CH_3: K_i 32 µM [39]; R = $C(CH_3)_3$: IC_{50} 7.5 mM [41]; R = CH_2OH: K_i 18 [42] or 20 [49] µM), however, the trend in the strength of inhibition remained the same (*t*-butyl derivatives were the less efficient followed by the methyl and hydroxymethyl compounds in both series).

Appending a phenyl substituent to the heterocycle as in **6d** resulted in a significantly better inhibitor. A comparison to the corresponding amide **I** (R = C_6H_5: K_i 81 [39] or 144 [40]) indicated more than an order of magnitude stronger inhibition by the triazole, and this strengthening was higher than those observed with the aliphatic amide-triazole pairs. Introduction of substituents in the 4-position of the phenyl ring brought about large changes in the inhibition. The 4-tolyl derivative **6e** was ~4 times better than **6d**, and comparing it to the relevant amide **I** (R = 4-CH_3-C_6H_4: IC_{50} 4.5 mM [41]) revealed a very large increase of the binding strength in favour of the triazole. The bulky 4-*t*-butyl substituent in **6f** caused a significant weakening of the inhibition. The 4-trifluoromethyl derivative **6g** proved also a weak inhibitor, and this was surprising especially in the light of the similar size of CH_3 (**6e**) and CF_3 (**6g**). The presence of a phenolic hydroxyl group in position 4 (**6h**) made again a good inhibitor, and the 4-methoxy compound **6i** proved slightly better and comparable to **6e**. Introduction of the 4-nitro substituent weakened the binding in comparison to **6d**, however, the 4-amino derivative **6k** was inhibiting in the submicromolar range. This may reveal the significance of a basic group in making contacts to the relevant parts of the enzyme. A carboxylic acid function in the 4-position (**6l**) was fully detrimental for the binding and this may be at least in part due to the size of this group (compare with the slightly acidic **6h**).

Multiple substitutions in the phenyl ring (**6m-p**) resulted in generally weaker inhibitors, although the importance of the basic substituents was corroborated by the diamino derivative **6o** showing the highest efficiency within this group of inhibitors.

The 2-naphthyl compound **6q** proved the best inhibitor of the whole series, and its nanomolar inhibition constant rendered this derivative among the most efficient glucose analogue inhibitors of GP. Comparing **6q** to the corresponding amide **I** (R = 2-naphthyl: K_i 10 [41] or 13 [42]) indicates a ~25-30-fold stronger binding for the triazole.

The 2-pyridyl moiety of **6r** was disadvantegous for the inhibition (a similar tendency was observed in the *N*-acyl-*N'*-β-D-glucopyranosyl urea series [24]).

A comparison of the inhibitory potency of these triazole derivatives clearly shows them to be superior to the corresponding oxadiazoles (**III-V** in Chart 1), as well. For the directly comparable pairs of 1,2,4-triazoles **6** and the best 1,2,4-oxadiazoles **IV** the increase of the efficiency is in the 9-29-fold range for the phenyl and 2-naphthyl substituted derivatives, respectively.

Further studies to understand the binding peculiarities of this series of GPIs by molecular dockings and X-ray crystallography are in progress and will be disclosed in due course.

Table 2.

3. Conclusion

A new synthetic sequence has been elaborated for the preparation of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles by converting 5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)tetrazole with *N*-benzyl carboximidoyl chlorides into *O*-perbenzoylated 4-benzyl-3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles and subsequent *O*- and *N*-deprotection. These triazole derivatives with aliphatic, phenyl, substituted phenyl, 2-naphthyl, and 2-pyridyl substituents in the 5-position were evaluated as inhibitors of rabbit muscle glycogen phosphorylase *b*. Compounds with aliphatic groups exhibited weak inhibition, while several phenyl derivatives were low micromolar inhibitors. Nanomolar inhibition was observed for the 5-(4-aminophenyl)- and the 5-(2-naphthyl)-substituted compounds of the series rendering these derivatives to be among the best glucose derived GPIs with similar efficiency as those of glucopyranosylidene-spiro-heterocycles and *N*-acyl-*N’*-β-D-glucopyranosyl ureas.

4. Experimental

4.1. General methods

Melting points were measured 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 360 (360/90 MHz for ^{1}H/ ^{13}C) spectrometer. Chemical shifts are referenced to Me_4Si (^{1}H), or to the residual solvent signals (^{13}C). Mass spectra were recorded on a Bruker Micro TOF-Q mass spectrometer. Microanalyses were performed on an Elementar Vario Micro Cube. 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. 5-(2',3',4',6'-Tetra-*O*-benzoyl-β-D-glucopyranosyl)tetrazole [27] (**1**) and 5-substituted-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazoles [62] **5a,b,d,j,n,q,r,t,u** were prepared according to published procedures.

4.2. General procedure I for the synthesis of *N*-benzyl-arenecarboxamides (2)

In a flame dried three necked bottle, equipped with a $CaCl_2$ tube, benzylamine (1 mL, 9.16 mmol) and TEA (1.53 mL, 11 mmol, 1.2 equiv.) was dissolved in the appropriate anhydrous solvent (5 mL, CH_2Cl_2, THF or toluene, depending on the solubility of acid chloride). To this stirred mixture a solution (in 5 mL anhydrous CH_2Cl_2, THF or toluene) of an acid chloride (9.16 mmol, 1 equiv.) was added dropwise at 0°C. The mixture was slowly allowed to reach rt, stirred for 2 hours, then diluted, and extracted with water. The organic phase was dried over $MgSO_4$, the solvent was evaporated, and the crude product was crystallised from EtOH.

Yields of the synthesized derivatives: *N*-benzyl-benzamide [65] (**2d**, 64 %), *N*-benzyl-4-methylbenzamide [66] (**2e**, 81 %), *N*-benzyl-4-*tert*-butylbenzamide [67] (**2f**, 97 %), *N*-benzyl-4-trifluoromethylbenzamide [68] (**2g**, 76 %), *N*-benzyl-4-methoxybenzamide [66] (**2i**, 67 %), *N*-benzyl-4-nitrobenzamide [69] (**2j**, 77 %), *N*-benzyl-3,5-dimethylbenzamide [67] (**2m**, 81 %), *N*-benzyl-3,4,5-trimethoxybenzamide [70] (**2p**, 98 %), *N*-benzyl-naphthalene-2-carboxamide [71] (**2q**, 74 %), *N*-benzyl-(4-benzyloxycarbonyl)-benzamide (**2s**, 56%, mp: 127-129 °C). Physical as well as NMR data of the title compounds are in agreement with those reported in the cited literature.

4.3. General procedure II for the synthesis of 4-benzyl-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles (3)

An *N*-benzyl-arenecarboxamide (**2**, 4.63 mmol, 3 equiv.) was dissolved in thionyl chloride (20 mL), and refluxed for 2 hours. After distilling off the excess of thionyl chloride under diminished pressure, 20 mL of anhydrous toluene was evaporated from the residue. 5-(2',3',4',6'-Tetra-*O*-benzoyl-β-D-glucopyranosyl)tetrazole[27, 52] (**1**, 1.54 mmol, 1 equiv.) and anhydrous toluene or xylene (20 mL) were added, the mixture was heated to reflux temperature, and the reaction was monitored by TLC (1:1 EtOAc-hexane). After total consumption of the tetrazole the solvent was removed and the residue was purified by column chromatography.

4.4. General procedure III for removal of *O*-acyl protecting groups by the Zemplén protocol

An *O*-acylated 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) (or with acetic acid), then the resin was filtered off and the solvent removed. The residue was purified by column chromatography.

4.5. General procedure IV for the removal of benzyl protecting groups

A benzylated compound (0.5 mmol) was dissolved in anhydrous MeOH (25 mL), 10% Pd(C) (20 mg) was added, and H_2 gas was bubbled through the reaction mixture at 50°C. After disappearance of the starting material (monitored by TLC, 7:3 $CHCl_3$-MeOH) the reaction mixture was filtered through a pad of celite, the solvent was evaporated, and the residue was purified by column chromatography.

4.6. 4-Benzyl-5-phenyl-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3d)

From tetrazole **1** (2.00 g, 3.08 mmol) and *N*-benzyl-benzamide (**2d**, 1.95 g, 9.25 mmol) in toluene according to General procedure **II**. Reaction time: 16 hours. Purified by column chromatography (1:1 EtOAc-hexane) to yield 1.73 g (69 %) colourless syrup. R_f: 0.15 (1:1 EtOAc-hexane); $[\alpha]_D$ = −25 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.95-6.97 (30H, m aromatics), 5.99-5.96 (2 x 1H, m, H-2' and/or H-3' and/or H-4'), 5.67 (1H, pseudo t, *J* = 10.6, 9.3 Hz, H-2' or H-3' or H-4'), 5.63 (1H, d, *J* = 15.9 Hz, $PhCH_2$), 5.53 (1H, d, *J* = 15.9 Hz, $PhCH_2$), 5.16 (1H, d, *J* = 9.3 Hz, H-1'), 4.49 (1H, dd, *J* = 12.2, 2.4 Hz, H-6'a), 4.33 (1H, dd, *J* = 12.2, 5.4 Hz, H-6'b), 4.19 (1H, ddd, *J* = 9.6, 5.4, 2.4 Hz, H-5'); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.9, 165.7, 165.1, 164.8 (CO), 156.7, 149.8 (triazole C-3, C-5), 135.4-126.2 (aromatics), 76.8, 73.8, 73.2, 70.0, 69.1 (C-1' – C-5'), 62.9 (C-6'), 48.1 (Ph*C*H_2). Anal: Calcd for $C_{49}H_{39}N_3O_9$ (813.85): C, 72.31; H, 4.83; N, 5.16. Found: C, 72.47; H, 4.88; N, 5.03.

4.7. 4-Benzyl-5-(4-methylphenyl)-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3e)

From tetrazole **1** (0.50 g, 0.77 mmol) and *N*-benzyl-4-methylbenzamide (**2e**, 0.52 g, 2.31 mmol) in *m*-xylene according to General procedure **II**. Reaction time: 3 hours. Purified by column chromatography (1:1 EtOAc-hexane) to yield 0.32 g (49 %) brownish foam. R_f: 0.20 (1:1 EtOAc-hexane); $[\alpha]_D = -4$ (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.97-6.98 (29H, m, aromatics), 6.04, 5.98, 5.68 (3 x 1H, 3 pseudo t, *J* = 9.5, 9.5 Hz in each, H-2', H-3', H-4'), 5.50 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.31 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.13 (1H, d, *J* = 9.5 Hz, H-1'), 4.48 (1H, dd, *J* = 12.4, 2.6 Hz, H-6'a), 4.34 (1H, dd, *J* = 12.4, 5.4 Hz, H-6'b), 4.20 (1H, ddd, *J* = 9.8, 5.4, 2.6 Hz, H-5'), 2.33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.7, 165.0, 164.6 (CO), 156.7, 149.7 (triazole C-3, C-5), 140.2, 135.4, 133.4-123.6 (aromatics), 76.6, 73.8, 73.0, 69.9, 69.0 (C-1' – C-5'), 62.8 (C-6'), 47.9 (Ph*C*H_2), 21.3 (CH_3). Anal: Calcd for $C_{50}H_{41}N_3O_9$ (827.88): C, 72.54; H, 4.99; N, 5.08. Found: C, 72.65; H, 4.88; N, 5.20.

4.8. 4-Benzyl-5-(4-*tert*-butylphenyl)-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3f)

From tetrazole **1** (0.70 g, 1.08 mmol) and *N*-benzyl-4-*tert*-butylbenzamide (**2f**, 0.93 g, 3.23 mmol) in *m*-xylene according to General procedure **II**. Reaction time: 3 hours. Purified by column chromatography (1:1 EtOAc-hexane) to yield 0.57 g (61 %) yellow solid. Mp: 231-233 °C; R_f: 0.28 (1:1 EtOAc-hexane); $[\alpha]_D = -43$ (c 0.37, $CHCl_3$);^{1}H NMR ($CDCl_3$) δ (ppm): 7.97-7.00 (29H, m, aromatics), 6.00, 5.97, 5.65 (3 x 1H, 3 pseudo t, *J* = 9.6, 9.6 Hz in each, H-2', H-3', H-4'), 5.51 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.33 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.11 (1H, d, *J* = 9.6 Hz, H-1'), 4.49 (1H, dd, *J* =12.2, 1.9 Hz, H-6'a), 4.32 (1H, dd, *J* =12.2, 5.3 Hz, H-6'b), 4.17 (1H, ddd, *J* =9.6, 5.2, 1.9 H-5'), 1.29 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.9, 165.7, 165.1, 164.7 (CO), 156.7, 153.4 (triazole C-3, C-5), 149.7, 135.5, 133.5-123.7 (aromatics), 76.7, 73.9, 73.1, 69.9, 69.1 (C-1' – C-5'), 62.9 (C-6'), 48.0 (Ph*C*H_2), 34.2 (*C*(CH_3)$_3$), 31.1 (C(*C*H_3)$_3$). Anal: Calcd for $C_{53}H_{47}N_3O_9$ (869.95): C, 73.17; H, 5.45; N, 4.83. Found: C, 73.11; H, 5.36; N, 4.91.

4.9. 4-Benzyl-5-(4-trifluoromethylphenyl)-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3g)

From tetrazole **1** (0.60 g, 0.93 mmol) and *N*-benzyl-4-trifluoromethylbenzamide (**2g**, 0.78 g, 2.78 mmol) in toluene according to General procedure **II**. Reaction time: 16 hours. Purified by column chromatography (1:4 → 1:1 EtOAc-hexane) to yield 0.72 g (88 %) white solid. Mp: 213-215 °C; $[\alpha]_D$ = −26 (c 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.94-6.95 (29H, m, aromatics), 6.06-5.98 (2 x 1H, m, H-2' and/or H-3' and/or H-4'), 5.70 (1H, pseudo t, *J* = 9.2, 9.2 Hz, H-2' or H-3' or H-4'), 5.60 (1H, d, *J* = 16.4 Hz, PhCH_2), 5.29 (1H, d, *J* = 16.4 Hz, PhCH_2), 5.21 (1H, d, *J* = 8.8 Hz, H-1'), 4.50 (1H, dd, *J* = 12.3, < 1 Hz, H-6'a), 4.34 (1H, dd, *J* = 12.3, 4.8 Hz, H-6'b), 4.23 (1H, ddd, *J* = 9.2, 4.8, < 1 Hz, H-5'); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.7, 165.1, 164.8 (CO), 155.4, 150.3 (triazole C-3, C-5), 134.9-125.0 (aromatics), 132.0 (q, $^2J_{(C, F)}$ = 34.6 Hz, *C*-CF_3), 123.5 (q, $^1J_{(C, F)}$ = 271.3 Hz, *C*F_3), 76.8, 73.7, 73.2, 69.9, 68.9 (C-1' – C-5'), 62.7 (C-6'), 48.2 (Ph*C*H_2). Anal: Calcd for $C_{50}H_{38}F_3N_3O_9$ (881.85): C, 68.10; H, 4.34; N, 4.77. Found: C, 68.23; H, 4.41; N, 4.63.

4.10. 4-Benzyl-5-(4-methoxyphenyl)-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3i)

From tetrazole **1** (1.0 g, 1.54 mmol) and *N*-benzyl-4-methoxybenzamide (**2i**, 1.12 g, 4.64 mmol) in *m*-xylene according to General procedure **II**. Purified by column chromatography (1:1 → 2:1 EtOAc-hexane) to yield 0.81 g (62 %) white amorphous solid. R_f: 0.45 (2:1

EtOAc-hexane); $[\alpha]_D$ = −19 (c 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.98-6.98 (27H, m, aromatics); 6.87 (2H, d, *J* = 8.8 Hz, aromatics), 6.06-5.91 (2 x 1H, m, H-2' and/or H-3' and/or H-4'), 5.65 (1H, pseudo t, *J* = 9.6, 9.6 Hz, H-2' or H-3' or H-4'), 5.50 (1H, d, *J* =16.6 Hz, $PhCH_2$), 5.29 (1H, d, *J* = 16.6 Hz, $PhCH_2$), 5.18 (1H, d, *J* = 9.6, H-1'), 4.48 (1H, dd, *J* = 12,3, 2.6 Hz, H-6'a), 4.32 (1H, dd, *J* = 12,3 and 5.4 Hz, H-6'b), 4.19 (1H, ddd, *J* = 9.6, 5.4, 2.6 Hz, H-5'), 3.79 (3H, s, OMe); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.0, 165.8, 165.2, 164.8 (CO), 161.1 (MeOPh C-4), 156.7, 149.7 (triazole C-3, C-5), 135.5-126.1, 118.8, 114.2 (2) (aromatics), 76.7, 73.9, 73.2, 70.0, 69.1 (C-1' – C-5'), 63.0 (C-6'), 55.3 (OMe), 48.1 (Ph*C*H_2). Anal: Calcd for $C_{50}H_{41}N_3O_{10}$ (843.87): C, 71.16; H, 4.90; N, 4.98. Found: C, 71.08; H, 5.01; N, 4.91.

4.11. 4-Benzyl-5-(4-nitrophenyl)-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3j)

From tetrazole **1** (0.50 g, 0.77 mmol) and *N*-benzyl-4-nitrobenzamide (**2j**, 0.59 g, 2.31 mmol) in toluene according to General procedure **II**. Reaction time: 16 hours. Purified by column chromatography (1:1 EtOAc-hexane) to yield 0.25 g (38 %) yellow syrup. R_f: 0.28 (1:1 EtOAc-hexane); $[\alpha]_D$ = −41 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 8.18 (2H, d, *J* = 8.5 Hz, aromatics), 7.92-7.19 (25H, m, aromatics), 6.95 (2H, d, *J* = 6.9 Hz, aromatics), 6.05, 6.00, 5.72 (3 x 1H, 3 pseudo t, *J* = 9.5, 9.5 Hz in each, H-2', H-3', H-4'), 5.66 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.31 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.26 (1H, d, *J* = 9.4 Hz, H-1'), 4.51 (1H, dd, *J* = 12.1, < 1 Hz, H-6'a), 4.35 (1H, dd, *J* = 12.1, 5.1 Hz, H-6'b), 4.27 (1H, ddd, *J* = 9.5, 5.1, 2.2 Hz, H-5'); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.6, 165.1, 164.9 (CO), 154.6, 150.7 (triazole C-3, C-5), 148.6, 134.6-123.7 (aromatics), 76.8, 73.6, 73.2, 70.1, 68.9 (C-1' – C-5'), 62.7 (C-6'), 48.4 (Ph*C*H_2). Anal: Calcd for $C_{49}H_{38}N_4O_{11}$ (858.85): C, 68.52; H, 4.46; N, 6.52. Found: C, 68.64; H, 4.52; N, 6.43.

4.12. 4-Benzyl-5-(3,5-dimethylphenyl)-3-(2’,3’,4’,6’-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3m)

From tetrazole **1** (1.0 g, 1.54 mmol) and *N*-benzyl-3,5-dimethylbenzamide (**2m**, 1.11 g, 4.64 mmol) in *m*-xylene according to General procedure **II**. Reaction time: 3 hours. Purified by column chromatography (1:1 → 2:1 EtOAc-hexane) to yield 0.85 g (66 %) white solid. Mp: 225-227 °C; R_f: 0.28 (1:1 EtOAc-hexane); $[\alpha]_D$ = −19 (c 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.98-7.00 (28H, m, aromatics), 6.12, 6.05, 5.75 (3 x 1H, 3 pseudo t, *J* = 9.5, 9.3 Hz in each, H-2’, H-3’, H-4’), 5.50 (1H, d, *J* = 16.4 Hz, $PhCH_2$), 5.32 (1H, d, *J* = 16.4 Hz, $PhCH_2$), 5.22 (1H, d, *J* = 9.6 Hz, H-1’), 4.52 (1H, dd, *J* = 12.5, 2.6 Hz, H-6’a), 4.39 (1H, dd, *J* = 12.6, 5.2 Hz, H-6’b), 4.26 (1H, ddd, *J* = 9.5, 5.2, 2.6 Hz, H-5’), 2.19 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.6, 165.5, 164.9, 164.5 (CO), 156.7, 149.6 (triazole C-3, C-5), 138.0 (2), 135.3-126.0 (aromatics), 76.4, 73.8, 72.6, 69.8, 68.8 (C-1’ – C-5’), 62.6 (C-6’), 47.9 (Ph*C*H_2), 20.9 (2 x CH_3). Anal: Calcd for $C_{51}H_{43}N_3O_9$ (841.90): C, 72.76; H, 5.15; N, 4.99. Found: C, 72.69; H, 5.07; N, 4.86.

4.13. 4-Benzyl-5-(3,4,5-trimethoxyphenyl)-3-(2’,3’,4’,6’-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3p)

From tetrazole **1** (0.50 g, 0.77 mmol) and *N*-benzyl-3,4,5-trimethoxybenzamide (**2p**, 0.7 g, 2.31 mmol) in *m*-xylene according to General procedure **II**. Reaction time: 8 hours. Purified by column chromatography (3:2 EtOAc-hexane) to yield 0.45 g (65 %) pale yellow syrup. R_f: 0.15 (3:2 EtOAc-hexane); $[\alpha]_D$ = −33 (c 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.96-7.00 (25H, m, aromatics), 6.62 (2H, s, aromatics), 6.10-5.99 (2 x 1H, m, H-2’ and/or H-3’ and/or H-4’), 5.70 (1H, pseudo t, *J* = 9.3, 9.3 Hz, H-2’ or H-3’ or H-4’), 5.55 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 5.31 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 5.22 (1H, d, *J* = 9.3 Hz, H-1’), 4.45 (1H, dd, *J* =

10.8, < 1 Hz, H-6’a), 4.32-4.24 (2 x 1H, m, H-6’b, H-5’), 3.83 (3H, s, OMe), 3.59 (6H, s, 2 x OMe); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.7, 165.0, 164.7 (CO), 156.5, 153.2, 150.0 (triazole C-3, C-5, 3,4,5-$(MeO)_3$Ph C-3, C-5), 135.7-121.5, 106.1 (2) (aromatics), 76.7, 73.8, 73.1, 70.0, 68.9 (C-1’ – C-5’), 62.8 (C-6’), 60.8 (OMe), 55.8 (2 x OMe), 48.1 (Ph*C*H_2). Anal: Calcd for $C_{52}H_{45}N_3O_{12}$ (903.93): C, 69.09; H, 5.02; N, 4.65. Found: C, 69.19; H, 4.96; N, 4.51.

4.14. 4-Benzyl-5-(2-naphthyl)-3-(2’,3’,4’,6’-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3q)

From tetrazole **1** (0.60 g, 0.93 mmol) and *N*-benzyl-naphthalene-2-carboxamide (**2q**, 0.73 g, 2.78 mmol) in toluene according to General procedure **II**. Reaction time: 3 hours. Purified by column chromatography (1:1 → 3:2 EtOAc-hexane) to yield 0.41 g (52 %) pale yellow amorphous solid. R_f: 0.25 (1:1 EtOAc-hexane); $[\alpha]_D = -33$ (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.96-7.01 (32H, m, aromatics), 6.08, 6.02, 5.70 (3 x 1H, 3 pseudo t, *J* = 9.3, 9.3 Hz in each, H-2’, H-3’, H-4’), 5.58 (1H, d, *J* = 15.9 Hz, PhCH_2), 5.38 (1H, d, *J* = 15.9 Hz, PhCH_2), 5.19 (1H, d, *J* = 9.3 Hz, H-1’), 4.49 (1H, dd, *J* = 11.9, 2.6 Hz, H-6’a), 4.35 (1H, dd, *J* = 11.9, 5.3 Hz, H-6’b), 4.23 (1H, ddd, *J* = 9.3, 5.3, 2.6 Hz, H-5’); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.7, 165.0, 164.7 (CO), 156.6, 149.9 (triazole C-3, C-5), 135.4-123.9 (aromatics), 76.7, 73.8, 73.0, 69.9, 69.0 (C-1’ – C-5’), 62.8 (C-6’), 48.2 (Ph*C*H_2). Anal: Calcd for $C_{53}H_{41}N_3O_9$ (863.91): C, 73.68; H, 4.78; N, 4.86. Found: C, 73.80; H, 4.69; N, 4.97.

4.15. 4-Benzyl-5-(4-benzyloxycarbonylphenyl)-3-(2’,3’,4’,6’-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (3s)

From tetrazole **1** (0.30 g, 0.46 mmol) and *N*-benzyl-(4-benzyloxycarbonyl)-benzamide (**2s**, 0.48 g, 1.39 mmol) in *m*-xylene according to General procedure **II**. Reaction time: 3 hours.

Purified by column chromatography (1:4 → 1:1 EtOAc-hexane) to yield 0.30 g (69 %) brownish foam. R_f: 0.23 (1:1 EtOAc-hexane); $[\alpha]_D = -26$ (c 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 8.07-6.94 (34H, m, aromatics), 6.01-5.99 (2 x 1H, m, H-2' and/or H-3' and/or H-4'), 5.68 (1H, pseudo t, *J* = 9.4, 8.6 Hz, H-2' or H-3' or H-4'), 5.57 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.35 (2H, s, $PhCH_2$), 5.29 (1H, d, *J* = 16.5 Hz, $PhCH_2$), 5.18 (1H, d, *J* = 9.2 Hz, H-1'), 4.49 (1H, dd, *J* = 12.3, 2.0 Hz, H-6'a), 4.33 (1H, dd, *J* = 12.3, 5.3 Hz, H-6'b), 4.20 (1H, ddd, *J* = 9.5, 5.3, 2.0 Hz, H-5'); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.7, 165.5, 165.0, 164.8 (CO), 155.8, 150.3 (triazole C-3, C-5), 135.6-126.0 (aromatics), 76.8, 73.7, 73.2, 70.0, 68.9 (C-1' – C-5'), 67.0 (COO*CH₂*Ph), 62.8 (C-6'), 48.2 (Ph*CH₂*). Anal: Calcd for $C_{57}H_{45}N_3O_{11}$ (947.98): C, 72.22; H, 4.78; N, 4.43. Found: C, 72.28; H, 4.91; N, 4.34.

4.16. 4-Benzyl-3-(β-D-glucopyranosyl)-5-phenyl-1,2,4-triazole (4d)

From triazole **3d** (0.82 g, 1.00 mmol) according to General procedure **III**. Reaction time: 4 days. Purified by column chromatography (9:1 → 4:1 $CHCl_3$-MeOH) to yield 0.29 g (73 %) pale yellow syrup. R_f: 0.55 (7:3 $CHCl_3$-MeOH); $[\alpha]_D = -15$ (c 0.60, MeOH); ^1H NMR (D_2O) δ (ppm): 7.50-6.94 (10H, m, aromatics), 5.31 (2H, s, $PhCH_2$), 4.48 (1H, d, *J* = 10.6 Hz, H-1'), 3.98 (1H, pseudo t, *J* = 9.3, 9.3 Hz, H-2' or H-3' or H-4'), 3.67-3.47 (4 x 1H, m, H-6'a, H-6'b, H-2' and/or H-3' and/or H-4'), 3.34 (1H, m, H-5'); ^{13}C NMR (D_2O) δ (ppm): 156.9, 153.2 (triazole C-3, C-5), 135.2, 131.2, 129.3 (2), 129.1 (2), 129.0 (2), 128.3, 126.4 (2), 125.4 (aromatics), 80.3, 77.2, 72.1, 71.8, 69.4 (C-1' – C-5'), 60.8 (C-6'), 47.6 (Ph*CH₂*). Anal: Calcd for $C_{21}H_{23}N_3O_5$ (397.42): C, 63.46; H, 5.83; N, 10.57. Found: C, 63.32; H, 5.75; N, 10.68.

4.17. 4-Benzyl-3-(β-D-glucopyranosyl)-5-(4-methylphenyl)-1,2,4-triazole (4e)

From triazole **3e** (0.52 g, 0.63 mmol) according to General procedure **III**. Reaction time: 2 days. Purified by column chromatography (9:1 → 4:1 $CHCl_3$-MeOH) to yield 0.25 g (94 %)

colourless syrup. R_f: 0.35 (4:1 $CHCl_3$-MeOH); $[\alpha]_D = -4$ (c 0.50, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.34-7.23 (7H, m, aromatics), 7.00 (2H, d, *J* = 6.6 Hz, aromatics), 5.41 (1H, d, *J* = 16.9 Hz, $PhCH_2$), 5.34 (1H, d, *J* = 16.9 Hz, $PhCH_2$), 4.34 (1H, d, *J* = 9.7 Hz, H-1'), 3.92 (1H, pseudo t, *J* = 9.1, 8.9 Hz, H-2' or H-3' or H-4'), 3.75 (1H, dd, *J* = 12.0, < 1 Hz, H-6'a), 3.63-3.54 (2H, m, H-6'b, H-2' or H-3' or H-4') 3.43-3.72 (2H, m, H-2' or H-3' or H-4', H-5'), 2.34 (3H, s, CH_3); ^{13}C NMR (CD_3OD) δ (ppm): 157.4, 155.0 (triazole C-3, C-5), 142.4, 136.9, 130.7 (2), 130.1 (2), 130.0 (2), 129.2, 127.5(2), 124.7 (aromatics), 82.5, 79.3, 74.2, 73.6, 71.1 (C-1' – C-5'), 62.7 (C-6'), 47.7 (Ph*C*H_2), 21.5 (CH_3). Anal: Calcd for $C_{22}H_{25}N_3O_5$ (411.45): C, 64.22; H, 6.12; N, 10.21. Found: C, 64.37; H, 6.19; N, 10.10.

4.18. 4-Benzyl-3-(β-D-glucopyranosyl)-5-(4-*tert*-butylphenyl)-1,2,4-triazole (4f)

From triazole **3f** (0.49 g, 0.56 mmol) according to General procedure **III**. Reaction time: 1 day. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.25 g (98 %) yellow syrup. R_f: 0.31 (4:1 $CHCl_3$-MeOH); $[\alpha]_D = -3$ (c 0.31, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.45 (2H, d, *J* = 8.3 Hz, aromatics), 7.35 (2H, d, *J* =8.3 Hz, aromatics), 7.23 (3H, m, aromatics), 6.99 (2H, d, *J* = 6.4 Hz, aromatics), 5.40 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 5.33 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 4.31 (1H, d, *J* = 9.7 Hz, H-1'), 3.89 (1H, pseudo t, *J* = 9.4, 9.0 Hz, H-2' or H-3' or H-4'), 3.74 (1H, dd, *J* = 12.1, 2.6 Hz, H-6'a), 3.56 (1H, dd, *J* = 12.1, 5.3 Hz, H-6'b), 3.41-3.34 (2H, m, H-2' and/or H-3' and/or H-4'), 3.25 (1H, ddd, *J* = 9.8, < 1 Hz, H-5'), 1.27 (9H, s, $C(CH_3)_3$), ^{13}C NMR (CD_3OD) δ (ppm): 157.3, 155.4, 155.1 (triazole C-3, C-5, 4-tBuPh C-4), 136.9-124.7 (aromatics), 82.5, 79.3, 74.2, 73.6, 71.1 (C-1' – C-5'), 62.7 (C-6'), 48.7 (Ph*C*H_2), 35.8 (*C*$(CH_3)_3$), 31.6 (C(*C*$H_3)_3$). Anal: Calcd for $C_{25}H_{31}N_3O_5$ (453.53): C, 66.21; H, 6.89; N, 9.27. Found: C, 66.27; H, 6.78; N, 9.39.

4.19. 4-Benzyl-3-(β-D-glucopyranosyl)-5-(4-trifluoromethylphenyl)-1,2,4-triazole (4g)

From triazole **3g** (0.50 g, 0.57 mmol) according to General procedure **III**. Reaction time: 4 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.16 g (61 %) white crystals. Mp: 208-210 °C; $[\alpha]_D$ = −18 (c 0.48, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.77-7.05 (9H, m, aromatics), 5.51 (1H, d, *J* = 16.9 Hz, PhCH_2), 5.45 (1H, d, *J* = 16.9 Hz, PhCH_2), 4.48 (1H, d, *J* = 9.3 Hz, H-1'), 3.99 (1H, m, H-2' or H-3' or H-4'), 3.82 (1H, dd, *J* = 11.7, < 1 Hz, H-6'a), 3.65 (1H, dd, *J* = 11.7, < 1 Hz, H-6'b), 3.47-3.37 (3 x 1H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (CD_3OD) δ (ppm): 156.0, 155.6 (triazole C-3, C-5), 136.6 (aromatics), 133.4 (q, $^2J_{(C, F)}$ = 31.7 Hz, *C*-CF_3), 131.7-127.0 (aromatics), 125.2 (q, $^1J_{(C, F)}$ = 271.3 Hz, *C*F_3), 82.5, 79.3, 74.2, 73.6, 71.1 (C-1' – C-5'), 62.7 (C-6'), 48.9 (Ph*C*H_2). Anal: Calcd for $C_{22}H_{22}F_3N_3O_5$ (465.42): C, 56.77; H, 4.76; N, 9.03. Found: C, 56.69; H, 4.71; N, 9.14.

4.20. 4-Benzyl-3-(β-D-glucopyranosyl)-5-(4-methoxyphenyl)-1,2,4-triazole (4i)

From triazole **3i** (0.80 g, 0.95 mmol) according to General procedure **III**. Reaction time: 3 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.23 g (68 %) yellow syrup. R_f: 0.33 (4:1 $CHCl_3$-MeOH). $[\alpha]_D$ = −14 (c 0.35, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.37 (2H, d, *J* = 8.8 Hz, aromatics), 7.32-7.20 (3H, m, aromatics), 7.05-6.99 (2H, m, aromatics), 6.96 (2H, d, *J* =8.8 Hz, aromatics), 5.42 (1H, d, *J* = 16.8 Hz, PhCH_2), 5.35 (1H, d, *J* = 16.8 Hz, PhCH_2), 4.35 (1H, d, *J* = 9.6 Hz, H-1'), 3.84 (1H, pseudo t, *J* = 10.8 Hz, 9.6 Hz, H-2' or H-3' or H-4'), 3.78 (3H, s, OMe), 3,77 (1H, dd, *J* = 12.4, 2.3 Hz, H-6'a), 3.61 (1H, dd, *J* = 12.4, 5.3 Hz, H-6'b), 3.41-3.29 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (CD_3OD) δ (ppm): 163.0 (4-MeOPh C-4), 157.2, 154.9 (triazole C-3, C-5), 136.9, 131.6 (2), 130.1 (2), 129.1, 127.5 (2), 119.5, 115.5 (2) (aromatics), 82.4, 79.3, 74.2, 73.6, 71.1 (C-1' – C-5'), 62.6 (C-6') 55.9 (OMe), 48.6 (Ph*C*H_2). Anal: Calcd for $C_{22}H_{25}N_3O_6$ (427.45): C, 61.82; H, 5.90; N, 9.83. Found: C, 61.87; H, 6.02; N, 9.75.

4.21. 4-Benzyl-3-(β-D-glucopyranosyl)-5-(4-nitrophenyl)-1,2,4-triazole (4j)

From triazole **3j** (0.23 g, 0.27 mmol) according to General procedure **III**. Reaction time: 6 hours. The product precipitated from the reaction mixture and was used after filtration without further purification. Yield: 0.11 g (91 %), pale yellow needles. Mp: 153-155 °C; $[\alpha]_D$ = −20 (c 0.50, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 8.29 (2H, d, *J* = 8.6 Hz, aromatics), 7.75 (2H, d, *J* = 8.6 Hz, aromatics), 7.28 (3H, m, aromatics), 7.05 (2H, d, *J* = 6.3 Hz, aromatics), 5.54 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 5.48 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 4.48 (1H, d, *J* = 9.7 Hz, H-1'), 3.98 (1H, pseudo t, *J* = 8.9, 8.9 Hz, H-2' or H-3' or H-4'), 3.82 (1H, dd, *J* = 11.9, < 1 Hz, H-6'a), 3.65 (1H, dd, *J* = 12.0, 5.4 Hz, H-6'b), 3.50-3.43 (2 x 1H, m, H-2' and/or H-3' and/or H-4'), 3.72 (1H, m, H-5'); ^{13}C NMR (CD_3OD) δ (ppm): 155.9, 155.5 (triazole C-3, C-5), 150.4, 136.5, 133.9, 131.4 (2), 130.2 (2), 129.3, 127.7 (2), 125.0 (2) (aromatics), 82.6, 79.4, 74.2, 73.7, 71.2 (C-1' – C-5'), 62.7 (C-6'), 49.0 ($PhCH_2$). Anal: Calcd for $C_{21}H_{22}N_4O_7$ (442.42): C, 57.01; H, 5.01; N, 12.66. Found: C, 56.87; H, 5.11; N, 12.54.

4.22. 4-Benzyl-5-(3,5-dimethylphenyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole (4m)

From triazole **3m** (0.64 g, 0.76 mmol) according to General procedure **III**. Reaction time: 3 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.20 g (62 %) of yellow syrup. R_f: 0.66 (7:3 $CHCl_3$-MeOH); $[\alpha]_D$ = −8 (c 0.69, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.25-6.95 (8H, m, aromatics), 5.36 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 5.29 (1H, d, *J* = 16.8 Hz, $PhCH_2$), 4.38 (1H, d, *J* = 9.7 Hz, H-1'), 3.96 (1H, pseudo t, *J* = 9.3, 8.9 Hz, H-2' or H-3' or H-4'), 3.76 (1H, dd, *J* = 12.2, 1.4 Hz, H-6'a), 3.60 (1H, dd, *J* = 12.2, 5.4 Hz, H-6'b), 3.48-3.40 (2H, m, H-2' and/or H-3' and/or H-4'), 3.33-3.28 (1H, m, H-5'), 2.18 (6H, s, 2 x CH_3); ^{13}C NMR (CD_3OD) δ (ppm): 157.7, 155.2 (triazole C-3, C-5), 140.2 (2), 137.2, 133.4, 130.3 (2), 129.4, 128.0 (2), 127.9 (2), 127.6 (aromatics), 82.7, 79.5, 74.4, 73.8, 71.3 (C-1' – C-5'), 62.9 (C-6’), 49.1 (Ph*C*H$_2$), 21.6 (2 x CH$_3$). Anal: Calcd for $C_{23}H_{27}N_3O_5$ (425.48): C, 64.93; H, 6.40; N, 9.88. Found: C, 65.02; H, 6.47; N, 9.74.

4.23. 4-Benzyl-3-(β-D-glucopyranosyl)-5-(3,4,5-trimethoxyphenyl)-1,2,4-triazole (4p)

From triazole **3p** (0.42 g, 0.46 mmol) according to General procedure **III**. Reaction time: 6 hours. Purified by column chromatography (9:1 → 4:1CHCl$_3$-MeOH) to yield 0.20 g (91 %) colourless syrup. R$_f$: 0.42 (4:1 CHCl$_3$-MeOH); $[\alpha]_D = -17$ (c 0.53, MeOH); ^{1}H NMR (CD$_3$OD) δ (ppm): 7.38-7.28 (3H, m, aromatics), 7.12 (2H, d, *J* = 7.3 Hz, aromatics), 6.69 (2H, s, aromatics), 5.50 (1H, d, *J* = 17.1 Hz, PhCH$_2$), 5.42 (1H, d, *J* = 17.1 Hz, PhCH$_2$), 4.45 (1H, d, *J* = 9.6 Hz, H-1’), 4.00 (1H, pseudo t, *J* = 8.6, 9.6 Hz, H-2’ or H-3’ or H-4’), 3.80 (1H, dd, *J* = 12.0, < 1 Hz, H-6’a), 3.77 (4H, m, H-6’b, 1 x OMe), 3.63 (7H, m, H-6’b, 2 x OMe), 3.50-3.43 (2 x 1H, m, H-2’ and/or H-3’ and/or H-4’), 3.63 (1H, m, H-5’); ^{13}C NMR (CD$_3$OD) δ (ppm): 157.2, 155.2 (triazole C-3, C-5), 154.9 (2), 141.0, 137.4, 130.2 (2), 129.1, 127.4 (2), 122.8, 107.5 (2) (aromatics), 82.5, 79.3, 74.2, 73.6, 71.1 (C-1’ – C-5’), 62.8 (C-6’), 61.1 (OMe), 56.6 (2 x OMe), 48.8 (Ph*C*H$_2$). Anal: Calcd for $C_{24}H_{29}N_3O_8$ (487.50): C, 59.13; H, 6.00; N, 8.62. Found: C, 59.22; H, 6.09; N, 8.49.

4.24. 4-Benzyl-3-(β-D-glucopyranosyl)-5-(2-naphthyl)-1,2,4-triazole (4q)

From triazole **3q** (0.50 g, 0.58 mmol) according to General procedure **III**. Reaction time: 3 hours. Purified by column chromatography (9:1 CHCl$_3$-MeOH) to yield 0.22 g (85 %) white crystals. Mp: 243-245 °C; $[\alpha]_D = -19$ (c 0.51, MeOH); ^{1}H NMR (DMSO-d$_6$) δ (ppm): 8.03-7.02 (12H, m, aromatics), 5.48 (1H, d, *J* = 16.9 Hz, PhCH$_2$), 5.42 (1H, d, *J* = 16.9 Hz, PhCH$_2$), 4.35 (1H, d, *J* = 9.3 Hz, H-1’), 3.86 (1H, pseudo t, *J* = 9.3, 9.3 Hz, H-2’ or H-3’ or H-4’), 3.62 (1H, dd, *J* = 11.9, < 1 Hz, H-6’a), 3.42 (1H, dd, *J* = 11.9, 5.3 Hz, H-6’b), 3.31-3.17 (3 x 1H, m, H-2’ and/or H-3’ and/or H-4’, H-5’); ^{13}C NMR (DMSO-d$_6$) δ (ppm): 154.3, 153.3 (triazole C-3, C-5), 136.1-124.6 (aromatics), 81.2, 78.0, 72.3, 71.4, 69.8 (C-1' – C-5'), 61.0 (C-6'), 46.8 (Ph*C*H_2). Anal: Calcd for $C_{25}H_{25}N_3O_5$ (447.48): C, 67.10; H, 5.63; N, 9.39. Found: C, 67.02; H, 5.74; N, 9.27.

4.25. 5-(4-Carboxyphenyl)-3-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (5l)

Triazole **3s** (0.56 g, 0.59 mmol) was dissolved in anhydrous EtOAc (35 mL), 10% Pd(C) (55 mg) was added and H_2 was bubbled through the reaction mixture at 50°C. After disappearance of the starting material (6 hours, monitored by TLC, 1:1 EtOAc-hexane) the reaction was filtered through a pad of celite, the solvent was evaporated, and the residue was purified by column chromatography (EtOAc) to yield 0.34 g (75 %) colourless syrup. R_f: 0.58 (1:3 AcOH-toluene); $[\alpha]_D = -33$ (c 0.48, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 8.02-7.12 (24H, m, aromatics), 6.24 (1H, pseudo t, *J* = 9.5, 9.5 Hz, H-3'), 6.08 (1H, pseudo t, *J* = 9.6, 9.5 Hz, H-2'), 5.95 (1H, pseudo t, *J* = 9.5, 9.5 Hz, H-4'), 5.38 (1H, d, *J* = 9.9 Hz, H-1'), 4.66-4.58 (3H, m, H-6'a, H-6'b, H-5'); ^{13}C NMR (CD_3OD) δ (ppm): 169.2 (*C*OOH), 167.6, 167.2, 166.7, 166.4 (CO), 134.7-127.4 (aromatics), 77.7 (C-5'), 75.7 (C-3'), 74.8 (C-1'), 73.1 (C-2'), 71.1 (C-4'), 64.6 (C-6'). Anal: Calcd for $C_{43}H_{33}N_3O_{11}$ (767.74): C, 67.27; H, 4.33; N, 5.47. Found: C, 67.14; H, 4.47; N, 5.39.

4.26. 3-(β-D-Glucopyranosyl)-5-methyl-1,2,4-triazole[54] (6a)

From triazole **5a** [62] (0.25 g, 0.38 mmol) according to General procedure **III**. Reaction time: 3 days. Purified by column chromatography (7:3 $CHCl_3$-MeOH) to yield 0.07 g (73 %) colourless syrup. R_f: 0.55 (1:1 $CHCl_3$-MeOH); $[\alpha]_D = +21$ (c 0.36, MeOH); ^{1}H NMR (D_2O) δ (ppm): 4.36 (1H, d, *J* = 9.2 Hz, H-1'), 3.82 (1H, dd, *J* = 11.9, < 1 Hz, H-6'a), 3.68-3.63 (2H, m, H-2' or H-3' or H-4', H-6'b), 3.56-3.43 (3H, m, H-2' and/or H-3' and/or H-4', H-5'), 2.36

(3H, s, CH_3); ^{13}C NMR (D_2O) δ (ppm): 159.6, 156.2 (triazole C-3, C-5), 80.8, 77.7, 75.3, 73.1, 70.1 (C-1' – C-5'), 61.5 (C-6'), 11.4 (CH_3). Anal: Calcd for $C_9H_{15}N_3O_5$ (245.23): C, 44.08; H, 6.17; N, 17.13. Found: C, 44.19; H, 6.23; N, 17.01.

4.27. 5-(*tert*-Butyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole (6b)

From triazole **5b** [62] (0.25 g, 0.36 mmol) according to General procedure **III**. Reaction time: 2 days. (The mixture was neutralised with acetic acid.) Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.10 g (98 %) colourless syrup. R_f: 0.51 (7:3 $CHCl_3$-MeOH); $[\alpha]_D$ = –6 (c 0.25, MeOH); ^1H NMR (CD_3OD) δ (ppm): 4.33 (1H, d, *J* = 8.6 Hz, H-1'), 3.82 (1H, dd, *J* = 11.9, 2.5 Hz, H-6'a), 3.69-3.64 (2H, m, H-2' or H-3' or H-4', H-6'b), 3.50-3.40 (3H, m, H-2' and/or H-3' and/or H-4', H-5'), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (CD_3OD) δ (ppm): 166.6, 162.1 (triazole C-3, C-5), 82.2, 79.3, 76.9, 74.2, 71.2 (C-1' – C-5'), 62.8 (C-6'), 33.3 ($\mathit{C}(CH_3)_3$) 29.6 ($C(\mathit{CH}_3)_3$). Anal: Calcd for $C_{12}H_{21}N_3O_5$ (287.31): C, 50.16; H, 7.37; N, 14.63. Found: C, 50.09; H, 7.52; N, 14.57.

4.28. 3-(β-D-Glucopyranosyl)-5-hydroxymethyl-1,2,4-triazole[54] (6c)

From triazole **5t** [62] (0.18 g, 0.25 mmol) according to General procedure **III**. Reaction time: 5 days. (The mixture was neutralised with acetic acid.) Purified by column chromatography (3:2 $CHCl_3$-MeOH) to yield 0.06 g (93 %) colourless syrup. R_f: 0.38 (1:1 $CHCl_3$-MeOH); $[\alpha]_D$ = –3 (c 0.42, MeOH); ^1H NMR (CD_3OD) δ (ppm): 4.67 (2H, s, CH_2), 4.35 (1H, d, *J* = 9.2 Hz, H-1'), 3.83 (1H, dd, *J* = 12.3, < 1 Hz, H-6'a), 3.68-3.59 (2H, m, H-2' or H-3' or H-4', H-6'b), 3.49-3.40 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (CD_3OD) δ (ppm): 160.5, 160.4 (triazole C-3, C-5), 82.2, 79.2, 76.3, 74.4, 71.2 (C-1' – C-5'), 62.8 (C-6'), 57.4 (CH_2). Anal: Calcd for $C_9H_{15}N_3O_6$ (261.23): C, 41.38; H, 5.79; N, 16.09. Found: C, 41.31; H, 5.91; N, 16.23.

4.29. 3-(β-D-Glucopyranosyl)-5-phenyl-1,2,4-triazole[54] (6d)

A) From triazole **4d** (0.20 g, 0.50 mmol) according to General procedure **IV**. Reaction time: 4 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.13 g (85 %) colourless syrup.

B) From triazole **5d** [62] (0.25 g, 0.35 mmol) according to General procedure **III**. Reaction time: 3 days. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.07 g (62 %) colourless syrup. R_f: 0.48 (7:3 $CHCl_3$-MeOH); $[\alpha]_D$ = +31 (c 0.20, H_2O); ^{1}H NMR (D_2O) δ (ppm): 7.66 (2H, d, *J* = 7.9 Hz, aromatics), 7.38-7.36 (3H, m, aromatics), 4.45 (1H, d, *J* = 9.2 Hz, H-1'), 3.87 (1H, dd, J = 11.9, < 1 Hz, H-6'a), 3.77-3.69 (2H, m, H-2' or H-3' or H-4', H-6'b), 3.64-3.54 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (D_2O) δ (ppm): 159.1, 157.8 (triazole C-3, C-5), 130.9, 129.3 (2), 126.9, 126.5 (2) (aromatics), 80.2, 77.2, 74.7, 72.8, 69.5 (C-1' – C-5'), 61.0 (C-6'). Anal: Calcd for $C_{14}H_{17}N_3O_5$ (307.30): C, 54.72; H, 5.58; N, 13.67. Found: C, 54.85; H, 5.45; N, 13.54.

4.30. 3-(β-D-Glucopyranosyl)-5-(4-methylphenyl)-1,2,4-triazole (6e)

From triazole **4e** (0.20 g, 0.49 mmol) according to General procedure **IV**. Reaction time: 3 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.14 g (90 %) white foam. R_f: 0.51 (7:3 $CHCl_3$-MeOH); $[\alpha]_D$ = +6 (c 0.45, MeOH); ^{1}H NMR (D_2O) δ (ppm): 7.31 (2H, d, *J* = 7.9 Hz, aromatics), 6.93 (2H, d, *J* = 7.9 Hz, aromatics), 4.36 (1H, d, *J* = 9.5 Hz, H-1'), 3.83 (1H, dd, *J* = 11.9, < 1 Hz, H-6'a), 3.72 (1H, dd, *J* = 11.9, 3.1 Hz, H-6'b), 3.66 (1H, pseudo t, *J* = 9.2, 8.9 Hz, H-2' or H-3' or H-4'), 3.59-3.50 (3H, m, H-2' and/or H-3' and/or H-4', H-5'), 2.06 (3H, s, CH_3); ^{13}C NMR (D_2O) δ (ppm): 159.5, 157.5 (triazole C-3, C-5), 141.9, 130.0 (2), 126.6 (2), 123.8 (aromatics), 80.5, 77.6, 75.2, 73.3, 69.9 (C-1' – C-5'), 61.4

(C-6'), 21.1 (CH_3). Anal: Calcd for $C_{15}H_{19}N_3O_5$ (321.33): C, 56.07; H, 5.96; N, 13.08. Found: C, 55.98; H, 5.85; N, 12.96.

4.31. 5-(4-*tert*-Butylphenyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole[54] (6f)

From triazole **4f** (0.20 g, 0.44 mmol) according to General procedure **IV**. Reaction time: 3 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.13 g (79 %) colourless syrup. R_f: 0.22 (4:1 $CHCl_3$-MeOH); $[\alpha]_D$ = +8 (c 0.55, DMSO); ^{1}H NMR (CD_3OD) δ (ppm): 7.90 (2H, d, *J* = 8.0, aromatics), 7.51 (2H, d, *J* = 8.0, aromatics), 4.48 (1H, d, *J* = 9.5 Hz, H-1'), 3.90 (1H, dd, *J* = 11.5, < 1 Hz, H-6'a), 3.77-3.73 (2H, m, H-2' or H-3' or H-4', H-6'b), 3.59-3.51 (3H, m, H-2' and/or H-3' and/or H-4', H-5'), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR (CD_3OD) δ (ppm): 161.6, 158.1 (triazole C-3, C-5), 154.7, 127.4 (2), 126.9 (2) (aromatics), 82.0, 79.1, 76.3, 74.3, 71.1 (C-1' – C-5'), 62.6 (C-6'), 35.7 ($\mathit{C}(CH_3)_3$), 31.6 ($C(\mathit{C}H_3)_3$). Anal: Calcd for $C_{18}H_{25}N_3O_5$ (363.41): C, 59.49; H, 6.93; N, 11.56. Found: C, 59.60; H, 6.84; N, 11.47. MS-ESI (*m/z*): 386.169 $[M+Na]^+$

4.32. 3-(β-D-Glucopyranosyl)-5-(4-trifluoromethylphenyl)-1,2,4-triazole (6g)

From triazole **4g** (85 mg, 0.18 mmol) according to General procedure **IV**. Reaction time: 1.5 hours. Purified by column chromatography (9:1 $CHCl_3$-MeOH) to yield 52 mg (77 %) white amorphous solid. R_f: 0.20 (4:1 $CHCl_3$-MeOH); $[\alpha]_D$ = +13 (c 0.52, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 8.09 (2H, br s, aromatics), 7.66 (2H, br s, aromatics), 4.40 (1H, d, *J* = 7.2 Hz, H-1'), 3.80 (1H, dd, *J* = 10.7, < 1 Hz, H-6'a), 3.66-3.20 (5H, m, H-2', H-3', H-4', H-5', H-6'b); ^{13}C NMR (CD_3OD) δ (ppm): 160.2, 159.1 (triazole C-3, C-5), 134.9, 132.3 (q, $^2J_{(C, F)}$ = 34.6 Hz, *C*-CF_3), 127.9 (2), 126.8 (2) (aromatics), 125.6 (q, $^1J_{(C, F)}$ = 271.3 Hz, $\mathit{C}F_3$), 82.3, 79.2, 75.9, 74.6, 71.2 (C-1' – C-5'), 62.7 (C-6'). Anal: Calcd for $C_{15}H_{16}F_3N_3O_5$ (375.30): C, 48.00; H, 4.30; N, 11.20. Found: C, 48.12; H, 4.35; N, 11.07.

4.33. 3-(β-D-Glucopyranosyl)-5-(4-hydroxyphenyl)-1,2,4-triazole (6h)

From triazole **5u** [62] (0.57 g, 0.73 mmol) according to General procedure **III**. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.16 g (67%) white solid. Mp: 172-174 °C; $[\alpha]_D$ = +14 (c 0.35, DMSO); ^{1}H NMR (CD_3OD) δ (ppm): 7.69 (2H, d, *J* = 8.2 Hz, aromatics), 6.79 (2H, d, *J* = 8.5 Hz, aromatics), 4.38 (1H, d, *J* = 9.6 Hz, H-1') 3.82 (1H, d, *J* = 11.0, < 1 Hz, H-6'a), 3.68-3.64 (2H, m, H-2' or H-3' or H-4', H-6'b), 3.53-3.41 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (CD_3OD) δ (ppm): 162.1, 160.6, 157.6 (triazole C-3, C-5, 4-HOPh C-4), 129.2 (2), 126.9, 116.8 (2) (aromatics), 82.0, 79.2, 76.5, 74.4, 71.2 (C-1' – C-5'), 62.7 (C-6'). Anal: Calcd for $C_{14}H_{17}N_3O_6$ (323.30): C, 52.01; H, 5.30; N, 13.00. Found: C, 51.93; H, 5.41; N, 13.12.

4.34. 3-(β-D-Glucopyranosyl)-5-(4-methoxyphenyl)-1,2,4-triazole (6i)

From triazole **4i** (0.24 g, 0.55 mmol) according to General procedure **IV**. Purified by column chromatography (7:3 $CHCl_3$-MeOH) to yield 0.18 g (95 %) colourless syrup. R_f: 0.52 (7:3 $CHCl_3$-MeOH); $[\alpha]_D$ = +12 (c 0.41, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.82 (2H, d, *J* = 8.3 Hz, aromatics), 6.92 (2H, d, *J* = 8.3 Hz, aromatics), 4.46 (1H, d, *J* = 9.5 Hz, H-1'), 3.86 (1H, dd, *J* = 12.1, < 1 Hz, H-6'), 3.75 (5H, m, H-2' and/or H-3' and/or H-4', H-6'b, OMe), 3.60-3.50 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (CD_3OD) δ (ppm): 162.6 (4-MeOPh C-4), 160.1, 159.1 (triazole C-3, C-5), 129.0 (2), 121.5, 115.3 (2) (aromatics), 82.0, 79.1, 76.3, 74.3, 71.1 (C-1' – C-5'), 62.7 (C-6'), 55.9 (OMe). Anal: Calcd for $C_{15}H_{19}N_3O_6$ (337.33): C, 53.41; H, 5.68; N, 12.46. Found: C, 53.55; H, 5.63; N, 12.56.

4.35. 3-(β-D-Glucopyranosyl)-5-(4-nitrophenyl)-1,2,4-triazole (6j)

From triazole **5j** [62] (0.65 g, 0.85 mmol) according to General procedure **III**. Reaction time: 1 day. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.22 g (75 %) pale yellow solid. Mp: 166-169 °C; $[\alpha]_D$ = +20 (c 1.3, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.34 (2H, d, *J* = 8.2 Hz, aromatics), 8.26 (2H, d, *J* = 7.8 Hz, aromatics), 5.15, 5.10, 4.57 (4H, 3 br s, OH), 4.34 (1H, d, *J* = 9.7 Hz, H-1'), 3.71 (1H, dd, *J* = 11.7, 5.4 Hz, H-6'a), 3.63 (1H, pseudo t, *J* = 9.2, 9.0 Hz, H-2' or H-3' or H-4'), 3.46-3.28 (3H, m, H-2' and/or H-3'and/or H-4', H-5', H-6'b), 3.18 (1H, pseudo t, *J* = 9.0, 8.9 Hz, H-2' or H-3' or H-4'); ^{13}C NMR (DMSO-d_6) δ (ppm): 158.2, 157.0 (triazole C-3, C-5), 147.5, 136.7, 126.8 (2), 124.2 (2) (aromatics), 81.6, 77.9, 74.0, 72.5, 70.0 (C-1' – C-5'), 61.2 (C-6'). Anal: Calcd for $C_{14}H_{16}N_4O_7$ (352.30): C, 47.73; H, 4.58; N, 15.90. Found: C, 47.81; H, 4.62; N, 15.78. MS-ESI (*m/z*): 375.093 $[M+Na]^+$.

4.36. 5-(4-Aminophenyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole (6k)

Triazole **6j** (0.10 g, 0.28 mmol) was dissolved in dry MeOH (3 mL), and 0.01g Pd-C (10%) was added. The reaction mixture was stirred at rt under hydrogen atmosphere for one hour. After completion of the transformation monitored by TLC (1:1 $CHCl_3$-MeOH) Pd-C was filtrated through a pad of celite, the solvent was evaporated in vacuo and the residue was purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.09 g (94 %) amorphous yellow product. R_f: 0.59 (1:1 $CHCl_3$-MeOH); $[\alpha]_D$ = +9 (c 1.46, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.64 (2H, d, *J* = 8.0 Hz, aromatics), 6.60 (2H, d, *J* = 8.0 Hz, aromatics), 5.51 (2H, br s, NH_2), 4.98, 4.79, 4.53 (4H, 3 br s, OH), 4.13 (1H, d, *J* = 9.2 Hz, H-1'), 3.70-3.64 (2H, m, H-2'or H-3' or H-4', H-6'a), 3.42-3.16 (4H, m, H-2' and/or H-3' and/or H-4', H-5', H-6'b); ^{13}C NMR (DMSO-d_6) δ (ppm): 161.3, 155.0 (triazole C-3, C-5), 150.3, 127.1 (2), 114.7, 113.6 (2) (aromatics), 81.4, 78.3, 75.7, 72.4, 70.2 (C-1' – C-5'), 61.3 (C-6'). Anal:

Calcd for $C_{14}H_{18}N_4O_5$ (322.32): C, 52.17; H, 5.63; N, 17.38. Found: C, 52.21; H, 5.55; N, 17.26. MS-ESI (*m/z*): 345.118 $[M+Na]^+$.

4.37. 5-(4-Carboxyphenyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole (6l)

From triazole **5l** (0.24 g, 0.32 mmol) according to General procedure **III**. Reaction time: 5 days. Purified by column chromatography (1:1 $CHCl_3$-MeOH) to yield 0.10 g (86 %) yellowish syrup. R_f: 0.55 (1:1:1 toluene-AcOH-MeOH); $[\alpha]_D$ = +6 (c 0.54, MeOH); ^1H NMR (DMSO-d_6) δ (ppm): 8.10-8.04 (4H, m, aromatics), 4.33 (1H, d, *J* = 9.7 Hz, H-1'), 3.74-3.65 (2H, m, H-2' and/or H-3' and/or H-4', H-6'a), 3.47 (1H, ddd, *J* = 8.9, 5.3, < 1 Hz, H-5'), 3.37-3.25 (2H, m, H-2' and/or H-3' and/or H-4', H-6'b), 3.20 (1H, pseudo t, *J* = 9.0, 8.9 Hz, H-2' or H-3' or H-4'); ^{13}C NMR (DMSO-d_6) δ (ppm): 168.7 (*C*OOH), 158.4, 157.8 (triazole C-3, C-5), 134.1, 133.1, 129.9 (2), 125.7 (2) (aromatics), 81.6, 78.1, 74.5, 72.6, 70.2 (C-1' – C-5'), 61.3 (C-6'). Anal: Calcd for $C_{15}H_{17}N_3O_7$ (351.31): C, 51.28; H, 4.88; N, 11.96. Found: C, 51.15; H, 4.96; N, 11.89.

4.38. 5-(3,5-Dimethylphenyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole (6m)

From triazole **4m** (0.14 g, 0.34 mmol) according to General procedure **IV**. Reaction time: 3 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.11 g (98 %) colourless syrup. R_f: 0.54 (3:1 $CHCl_3$-MeOH); $[\alpha]_D$ = +12 (c 0.57, MeOH); ^1H NMR (CD_3OD) δ (ppm): 7.48 (2H, s, aromatics), 6.99 (1H, s, aromatic), 4.43 (1H, d, *J* = 9.6 Hz, H-1'), 3.85 (1H, dd, *J* = 12.0, 1.3 Hz, H-6'a), 3.73-3.68 (2H, m, H-2' or H-3' or H-4', H-6'b,), 3.56-3.40 (3H, m, H-2'and/or H-3'and/or H-4', H-5'), 2.25 (6H, s, 2 x CH_3); ^{13}C NMR (CD_3OD) δ (ppm): 162.2, 157.6 (triazole C-3, C-5), 139.7 (2), 132.7, 128.0, 125.2 (2) (aromatics), 82.0, 79.1, 76.2, 74.3, 71.1 (C-1' – C-5'), 62.7 (C-6'), 21.3 (2 x CH_3). Anal:

Calcd for $C_{16}H_{21}N_3O_5$ (335.36): C, 57.30; H, 6.31; N, 12.53. Found: C, 57.41; H, 6.24; N, 12.41.

4.39. 5-(3,5-Dinitrophenyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole (6n)

From triazole **5n** [62] (0.52 g, 0.63 mmol) according to General procedure **III**. Reaction time: 3 day. Purified by column chromatography (7:3 $CHCl_3$-MeOH) to yield 0.18 g (72%) white solid. Mp: 203-205 ºC; $[\alpha]_D$ = –21 (c 0.11, DMSO); ^{1}H NMR (DMSO-d_6-D_2O) δ (ppm): 9.02 (2H, s, aromatics), 8.83 (1H, s, aromatic), 4.37 (1H, d, *J* = 9.8 Hz, H-1'), 3.69 (1H, dd, *J* = 11.9, < 1 Hz, H-6'a), 3.58 (1H, pseudo t, *J* = 9.1, 9.1 Hz, H-2' or H-3' or H-4'), 3.47 (1H, dd, *J* = 11.9, 5.6 Hz, H-6'b), 3.35-3.30 (2H, m, H-2' or H-3' or H-4', H-5'), 3.22 (1H, pseudo t, *J* = 9.1, 9.1 Hz, H-2' or H-3' or H-4'); ^{13}C NMR (DMSO-d_6) δ (ppm): 162.2, 157.3 (triazole C-3, C-5), 148.5 (2), 137.7, 124.1 (2), 115.5 (aromatics), 80.8, 77.9, 75.8, 73.2, 70.5 (C-1' – C-5'), 61.3 (C-6'). Anal: Calcd for $C_{14}H_{15}N_5O_9$ (397.30): C, 42.32; H, 3.81; N, 17.63. Found: C, 42.39; H, 3.93; N, 17.56.

4.40. 5-(3,5-Diaminophenyl)-3-(β-D-glucopyranosyl)-1,2,4-triazole (6o)

Triazole **6n** (0.07 g, 0.18 mmol) was dissolved in dry MeOH (10 mL), and 0.015g Pd-C (10%) was added. The reaction mixture was stirred at rt under hydrogen atmosphere for one hour. After completion of the transformation monitored by TLC (1:1 $CHCl_3$-MeOH) Pd-C was filtrated through a pad of celite, the solvent was evaporated in vacuo and the residue was purified by column chromatography (1:1 $CHCl_3$-MeOH) to yield 0.04 g (72 %) amorphous brownish product. R_f: 0.33 (1:1 $CHCl_3$-MeOH); ^{1}H NMR (DMSO-d_6-D_2O) δ (ppm): 6.49 (2H, d, *J* = 2.0 Hz, aromatics), 5.84 (1H, t, *J* = 2.0, aromatic), 4.16 (1H, d, *J* = 9.9 Hz, H-1'), 3.65 (1H, dd, *J* = 12.6, < 1 Hz, H-6'a), 3.57 (1H, pseudo t, *J* = 9.9, 9.2 Hz, H-2' or H-3' or H-4'), 3.42 (1H, dd, *J* = 12.6, 4.9 Hz, H-6'b), 3.32-3.17 (3H, m, H-2' and/or H-3' and/or H-4', H-5’); ^{13}C NMR (DMSO-d_6) δ (ppm): 159.7, 158.8 (triazole C-3, C-5), 149.6 (2), 130.6, 102.3 (2), 102.1 (aromatics), 81.2, 78.2, 75.4, 73.1, 70.3 (C-1’ – C-5’), 61.5 (C-6’). Anal: Calcd for $C_{14}H_{19}N_5O_5$ (337.33): C, 49.85; H, 5.68; N, 20.76. Found: C, 49.99; H, 5.75; N, 20.64.

4.41. 3-(β-D-Glucopyranosyl)-5-(3,4,5-trimethoxyphenyl)-1,2,4-triazole (6p)

From triazole **4p** (0.18 g, 0.37 mmol) according to General procedure **IV**. Reaction time: 3 hours. Purified by column chromatography (9:1 $CHCl_3$-MeOH) to yield 0.14 g (92 %) colourless syrup. R_f: 0.37 (4:1 $CHCl_3$-MeOH); $[\alpha]_D$ = +5 (c 0.44, MeOH); ^{1}H NMR (D_2O) δ (ppm): 6.64 (2H, s, aromatics), 4.57 (1H, d, *J* = 9.3 Hz, H-1’), 4.05 (1H, dd, *J* = 11.9, < 1 Hz, H-6’a), 3.92 (1H, dd, *J* = 11.9, < 1 Hz, H-6’b), 3.88-3.72 (4H, m, H-2’, H-3’, H-4’, H-5’), 3.65-3.64 (9H, m, 3 x OMe); ^{13}C NMR (D_2O) δ (ppm): 159.8, 157.4 (triazole C-3, C-5), 152.6 (2), 138.3, 122.7, 103.2 (2) (aromatics), 80.5, 77.5, 75.0, 73.4, 70.0 (C-1’ – C-5’), 61.5 (C-6’), 61.2 (OMe), 56.1 (2 x OMe). Anal: Calcd for $C_{17}H_{23}N_3O_8$ (397.38): C, 51.38; H, 5.83; N, 10.57. Found: C, 51.25; H, 5.94; N, 10.64.

4.42. 3-(β-D-Glucopyranosyl)-5-(2-naphthyl)-1,2,4-triazole[54] (6q)

A) From triazole **4q** (0.10 g, 0.23 mmol) according to General procedure **IV**. Reaction time: 3 hours. Purified by column chromatography (4:1 $CHCl_3$-MeOH) to yield 0.07 g (90 %) colourless syrup.

B) From triazole **5q** [62] (0.27 g, 0.35 mmol) according to General procedure **III**. Reaction time: 3 days. Purified by column chromatography (9:1 $CHCl_3$-MeOH) to yield 0.10 g (81 %) colourless syrup. Compound characterization data were identical with those reported in our preliminary communication [54].

4.43. 3-(β-D-Glucopyranosyl)-5-(2-pyridyl)-1,2,4-triazole (6r)

From triazole **5r** [62] (0.31 g, 0.43 mmol) according to General procedure **III**. Reaction time: 3.5 hours. Purified by column chromatography (7:3 $CHCl_3$-MeOH) to yield 0.05 g (40 %) colourless syrup. R_f: 0.36 (1:1 $CHCl_3$-MeOH); $[\alpha]_D$ = +30 (c 0.22, H_2O); ^{1}H NMR (D_2O) δ (ppm): 8.49 (1H, d, *J* = 4.0 Hz, Py), 7.85-7.78 (2H, m, Py), 7.41-7.38 (1H, m, Py), 4.57 (1H, d, *J* = 9.2 Hz, H-1'), 3.94 (1H, dd, *J* = 11.9, < 1 Hz, H-6'a), 3.83-3.76 (2H, m, H-2' or H-3' or H-4', H-6'b), 3.70-3.57 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (D_2O) δ (ppm): 158.5, 156.8 (triazole C-3, C-5), 149.4, 145.3, 138.3, 125.5, 122.0 (Py), 80.0, 76.8, 74.3, 72.5, 69.3 (C-1' – C-5'), 60.7 (C-6'). Anal: Calcd for $C_{13}H_{16}N_4O_5$ (308.29): C, 50.65; H, 5.23; N, 18.17. Found: C, 50.77; H, 5.10; N, 18.29. MS-ESI (*m/z*): 331.100 $[M+Na]^+$, 639.217 $[2M+Na]^+$, 309.118 $[M+H]^+$.

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Supplementary data

^{1}H and ^{13}C NMR spectra of representative compounds.

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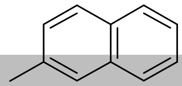
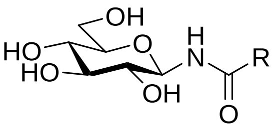
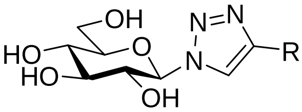
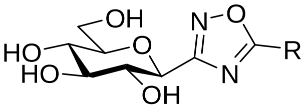
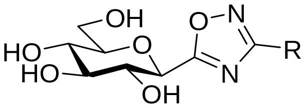
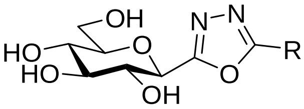
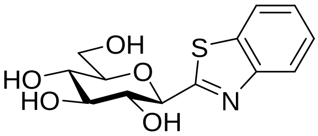
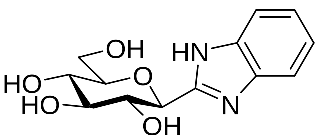
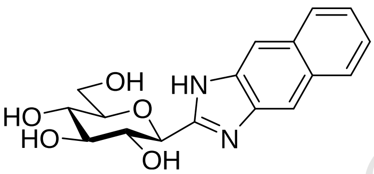
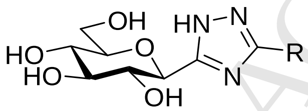
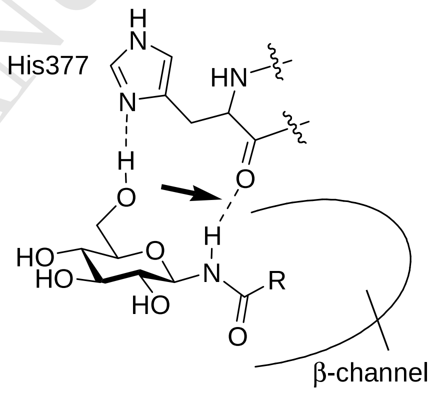
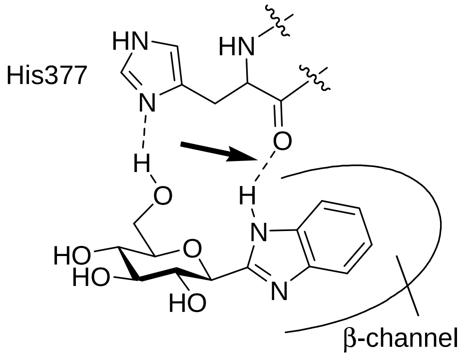
	R = CH_3 **A**	 **B**	 **C**
 **I**	32 [39]	81 [39] 144 [40]	10 [41] 13 [42]
 **II**	-	151 [42] 162 [49]	16 [42] 36 [49]
 **III**	No inh. [50]	10 % at 625 μM [50]	38 [50]
 **IV**	-	27 [55] 64 [51]	12* [51]
 **V**	212 [52] 145 [53]	10 % at 625 μM [51]	10 % at 625 μM [51]
 **VI**	229 [52] 76 [53]		
 **VII**	11 [52] 9 [53]		
 **VIII**	2.1 [33]		
 **IX**	target compounds		



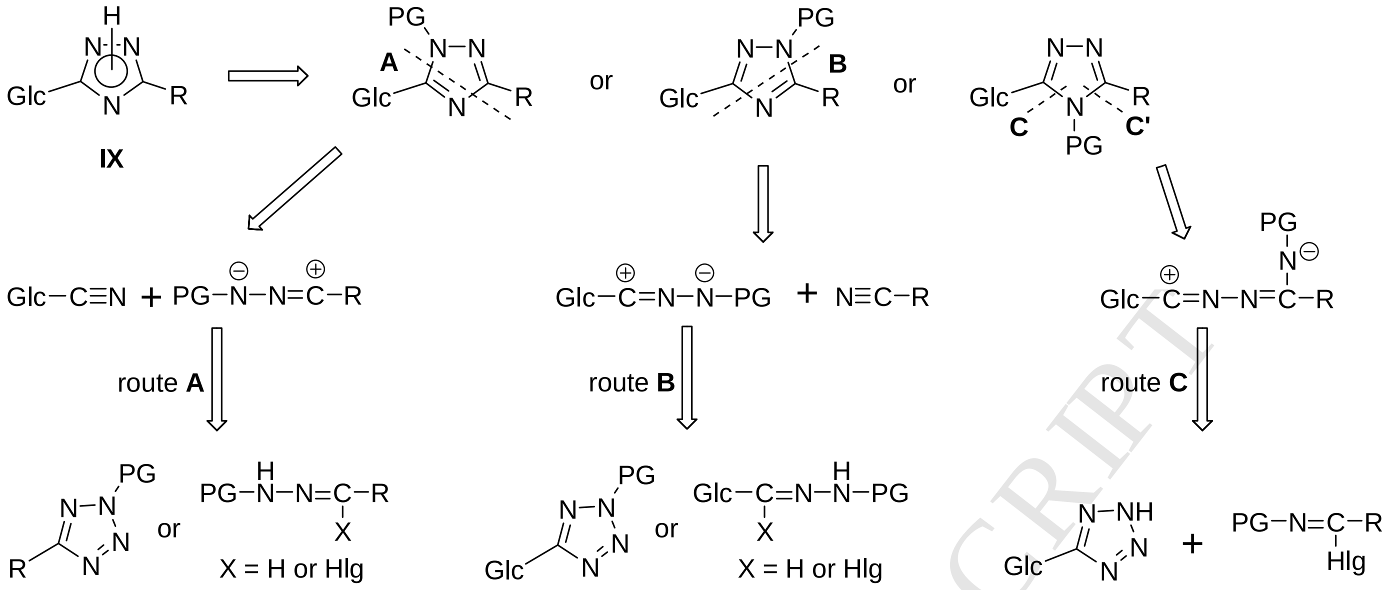
X



XI

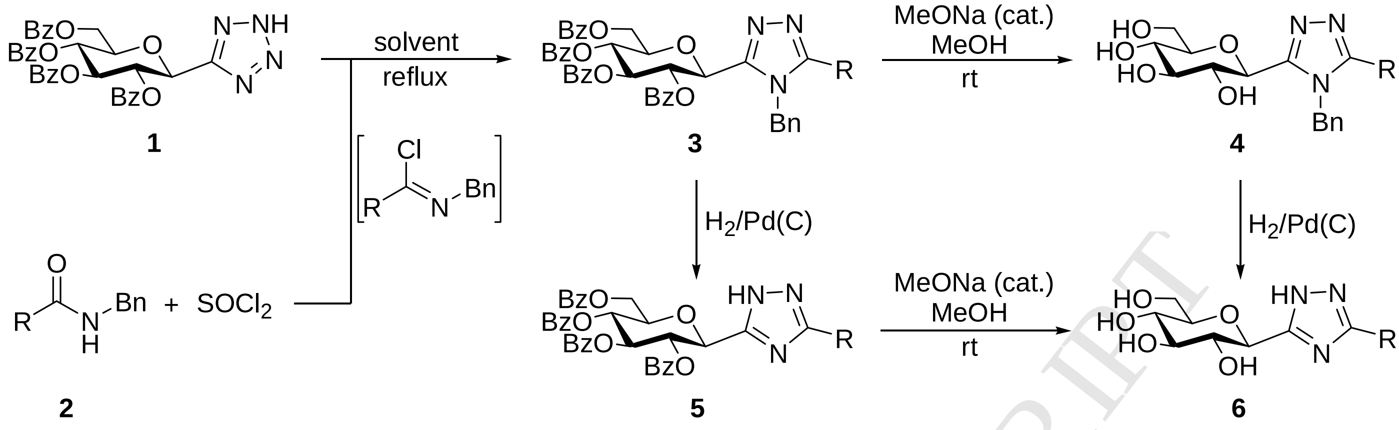
*A K_i value of 2.4 μM was measured by N. G. Oikonomakos et al. (unpublished results in ref. [51])

Chart 1. Glycogen phosphorylase inhibitors (GPIs, K_i [μM] against rabbit muscle GP*b*, **I-VIII**); synthetic targets of this study (**IX**); outline of binding of glucose analogues at the active site of GP highlighting important H-bonds to His377 and interactions in the so-called β-channel for *N*-acyl-β-D-glucopyranosylamine type inhibitors (**X**) and 2-β-D-glucopyranosyl benzimidazole (**XI**) as observed by X-ray crystallography.



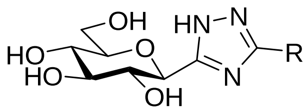
Scheme 1. Retrosynthetic analysis of the target compounds **IX** based on 1,3-dipolar cycloadditions (Glc = *O*-protected β-D-glucopyranosyl residue, PG = protecting group).

Table 1. Synthesis of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles

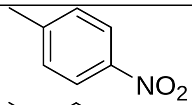
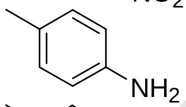
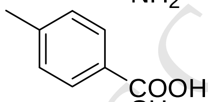
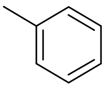
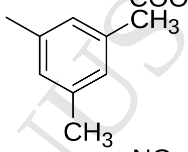
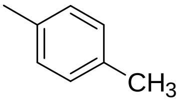
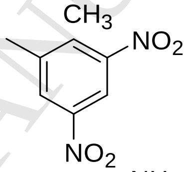


	R	Yield (%)			
		3 (solvent)	**4**	**5**	**6**
a	CH_3	-	-	see ref. [62]	73 (from **5a**)
b	$C(CH_3)_3$	-	-	see ref. [62]	98 (from **5b**)
c	CH_2OH	-	-	-	93 (from **5t**)
d	C_6H_5	69 (toluene)	73	see ref. [62]	85 (from **4d**) 62 (from **5d**)
e	C_6H_4-4-CH_3	49 (*m*-xylene)	94	-	90 (from **4e**)
f	C_6H_4-4-$C(CH_3)_3$	61 (*m*-xylene)	98	-	79 (from **4f**)
g	C_6H_4-4-CF_3	88 (toluene)	61	-	77 (from **4g**)
h	C_6H_4-4-OH	-	-	-	67 (from **5u**)
i	C_6H_4-4-OCH_3	62 (*m*-xylene)	68	-	95 (from **4i**)
j	C_6H_4-4-NO_2	38 (toluene)	91	see ref. [62]	75 (from **5j**)
k	C_6H_4-4-NH_2	-	-	-	94 (from **6j**)
l	C_6H_4-4-COOH	-	-	75 (from **3s**)	86 (from **5l**)
m	C_6H_3-3,5-$(CH_3)_2$	66 (*m*-xylene)	62	-	98 (from **4m**)
n	C_6H_3-3,5-$(NO_2)_2$	-	-	see ref. [62]	72 (from **5n**)
o	C_6H_3-3,5-$(NH_2)_2$	-	-	-	72 (from **6n**)
p	C_6H_2-3,4,5-$(OCH_3)_3$	65 (*m*-xylene)	91	-	92 (from **4p**)
q	$C_{10}H_7$ (2-naphthyl)	52 (toluene)	85	see ref. [62]	90 (from **4q**) 81 (from **5q**)
r	C_5H_4N (2-pyridyl)	-	-	see ref. [62]	40 (from **5r**)
s	C_6H_4-4-COOBn	69 (*m*-xylene)	-	-	-
t	CH_2OCOCH_3	-	-	see ref. [62]	-
u	C_6H_4-4-$OCOCH_3$	-	-	see ref. [62]	-

Table 2. Inhibition of rabbit muscle glycogen phosphorylase *b* by 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles (**6**)



6

<table>
<tr><th></th><th>R</th><th>K_i [µM]</th><th></th><th>R</th><th>K_i [µM]</th></tr>
<tr><td>a</td><td>$-CH_3$</td><td>499</td><td>j</td><td></td><td>33.5</td></tr>
<tr><td>b</td><td>$-C(CH_3)_3$</td><td>no inh.
at 625 µM</td><td>k</td><td></td><td>0.67</td></tr>
<tr><td>c</td><td>$-CH_2OH$</td><td>105</td><td>l</td><td></td><td>no inh.
at 625 µM</td></tr>
<tr><td>d</td><td></td><td>7</td><td>m</td><td></td><td>39.7</td></tr>
<tr><td>e</td><td></td><td>1.7</td><td>n</td><td></td><td>no inh.
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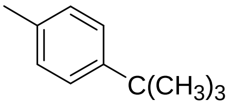
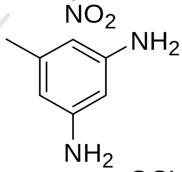
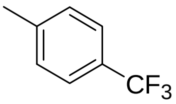
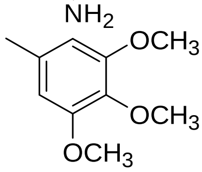
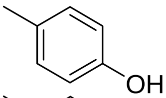
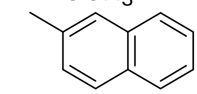
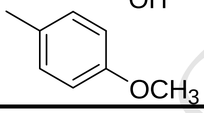
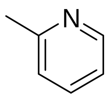
<tr><td>f</td><td></td><td>778</td><td>o</td><td></td><td>14</td></tr>
<tr><td>g</td><td></td><td>111</td><td>p</td><td></td><td>518*</td></tr>
<tr><td>h</td><td></td><td>2.9</td><td>q</td><td></td><td>0.41</td></tr>
<tr><td>i</td><td></td><td>1.9</td><td>r</td><td></td><td>707</td></tr>
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*Calculated from the IC_{50} value by using a web-based tool [64].

Legends:

Chart 1. Glycogen phosphorylase inhibitors (GPIs, K_i [μM] against rabbit muscle GP*b*, **I-VIII**); synthetic targets of this study (**IX**); outline of binding of glucose analogues at the active site of GP highlighting important H-bonds to His377 and interactions in the so-called β-channel for *N*-acyl-β-D-glucopyranosylamine type inhibitors (**X**) and 2-β-D-glucopyranosyl benzimidazole (**XI**) as observed by X-ray crystallography.

Scheme 1. Retrosynthetic analysis of the target compounds **IX** based on 1,3-dipolar cycloadditions (Glc = *O*-protected β-D-glucopyranosyl residue, PG = protecting group).

Highlights

- New synthesis of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles.
- Carboximidoylation of *O*-protected 5-(β-D-glucopyranosyl)tetrazole.
- New nanomolar inhibitors of glycogen phosphorylase.

SUPPORTING INFORMATION

New synthesis of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles, nanomolar inhibitors of glycogen phosphorylase

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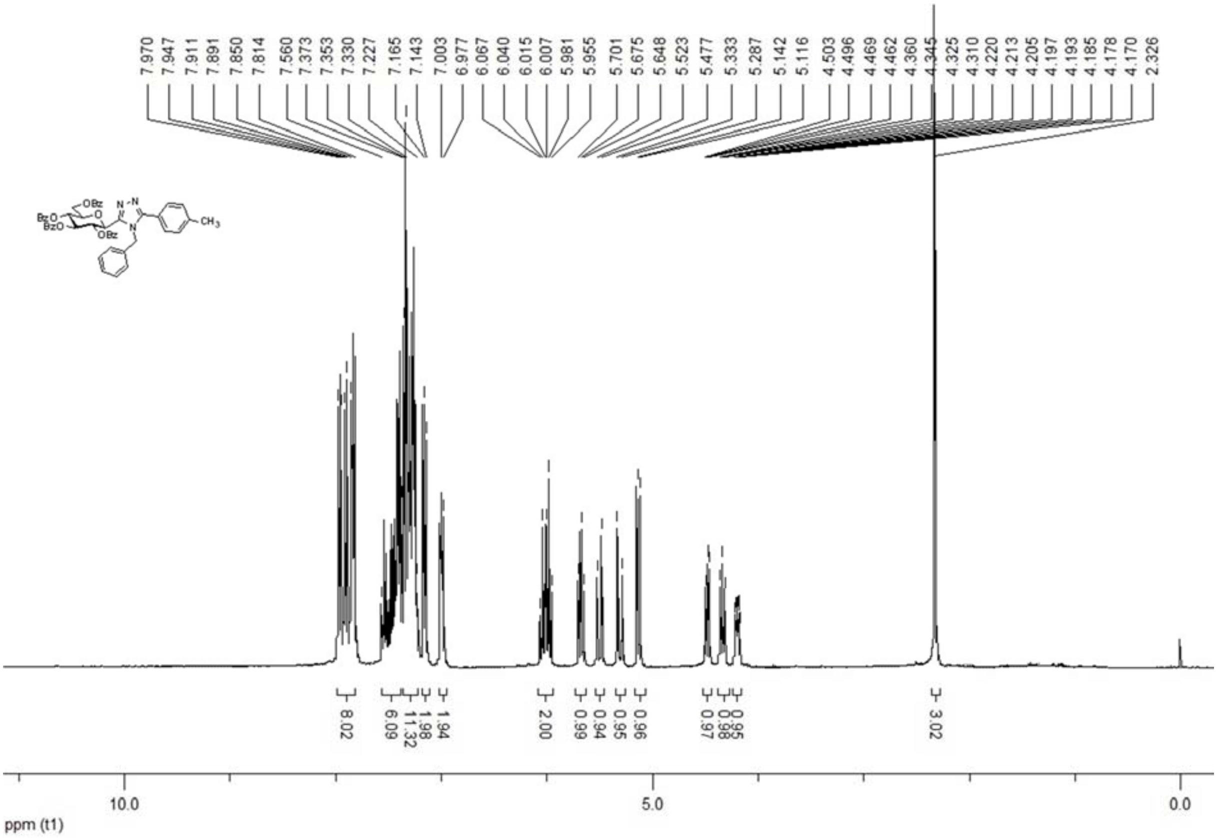
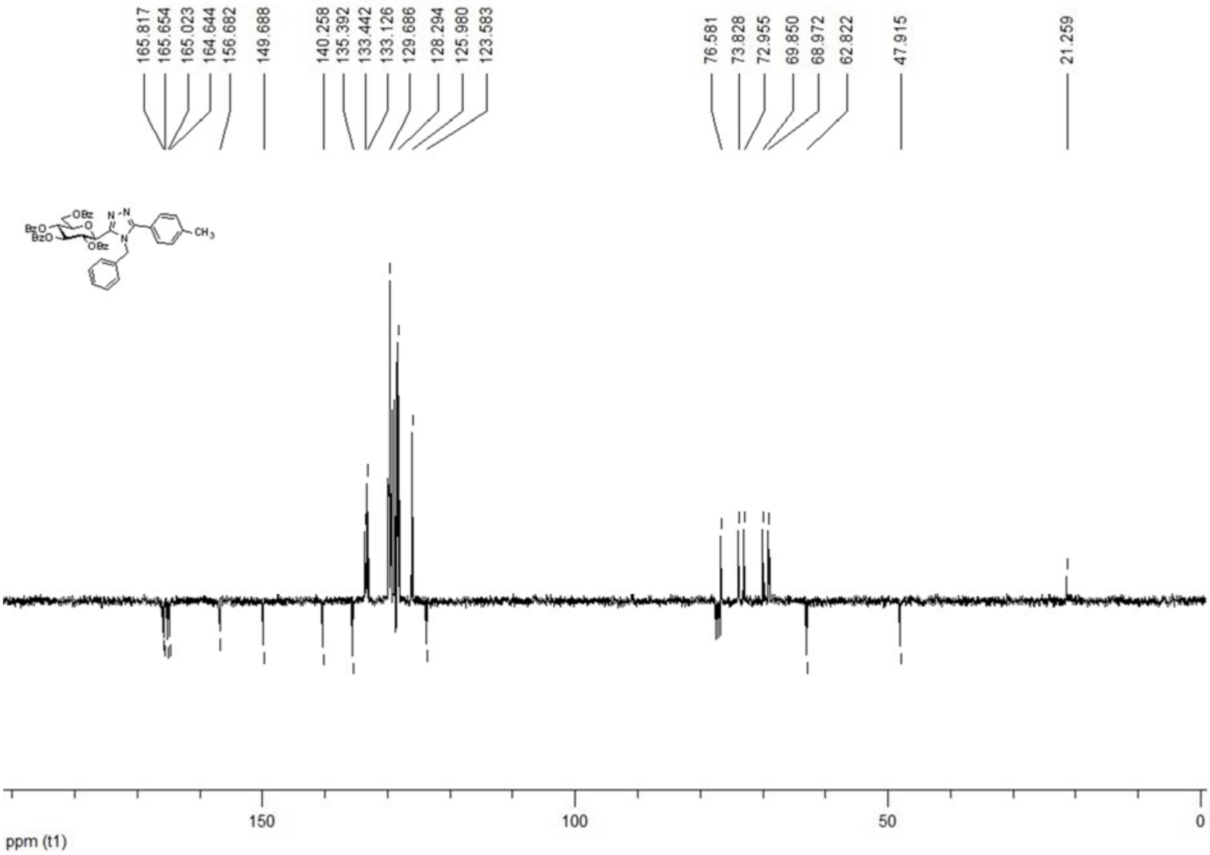
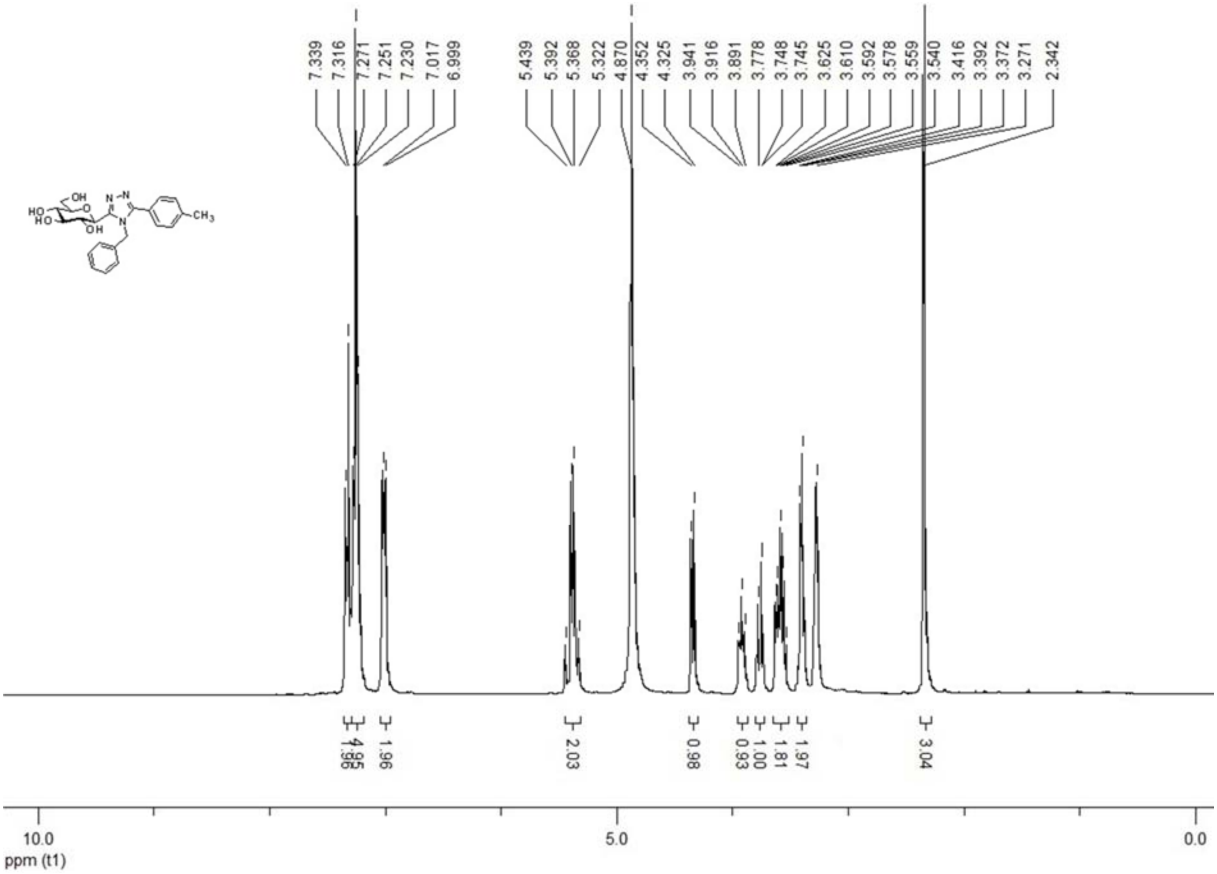
^{1}H and ^{13}C NMR spectra for selected compounds.

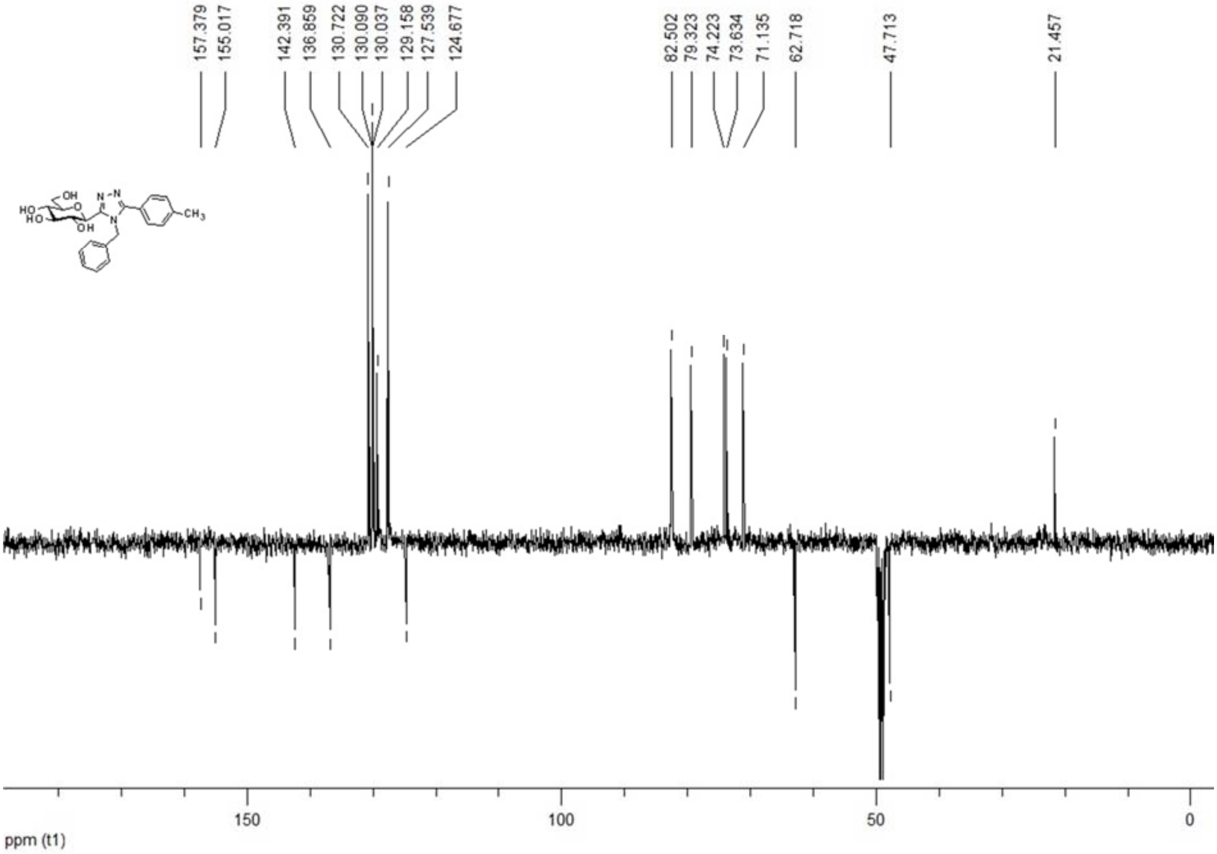
[*]Corresponding author – tel.: +3652512900 ext 22348, fax: +3652512744, e-mail: somsak@tigris.unideb.hu



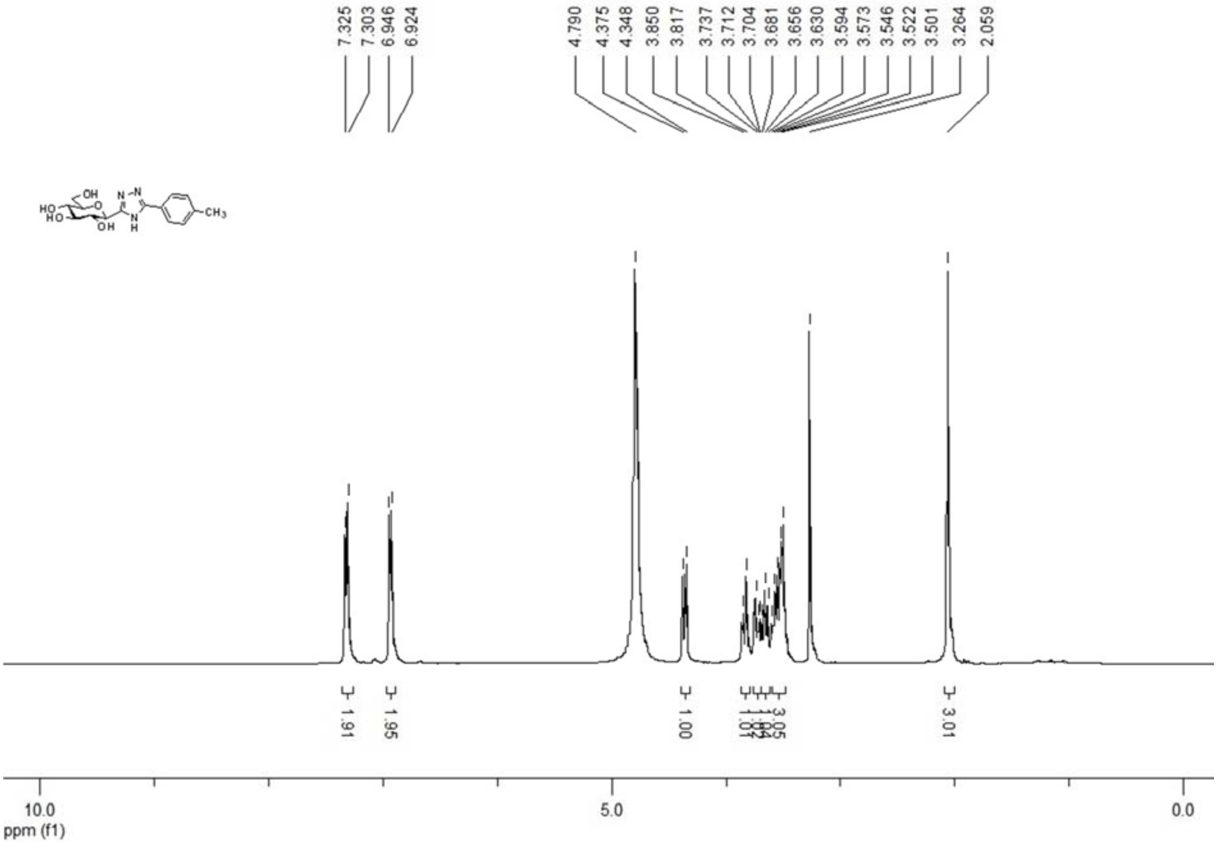


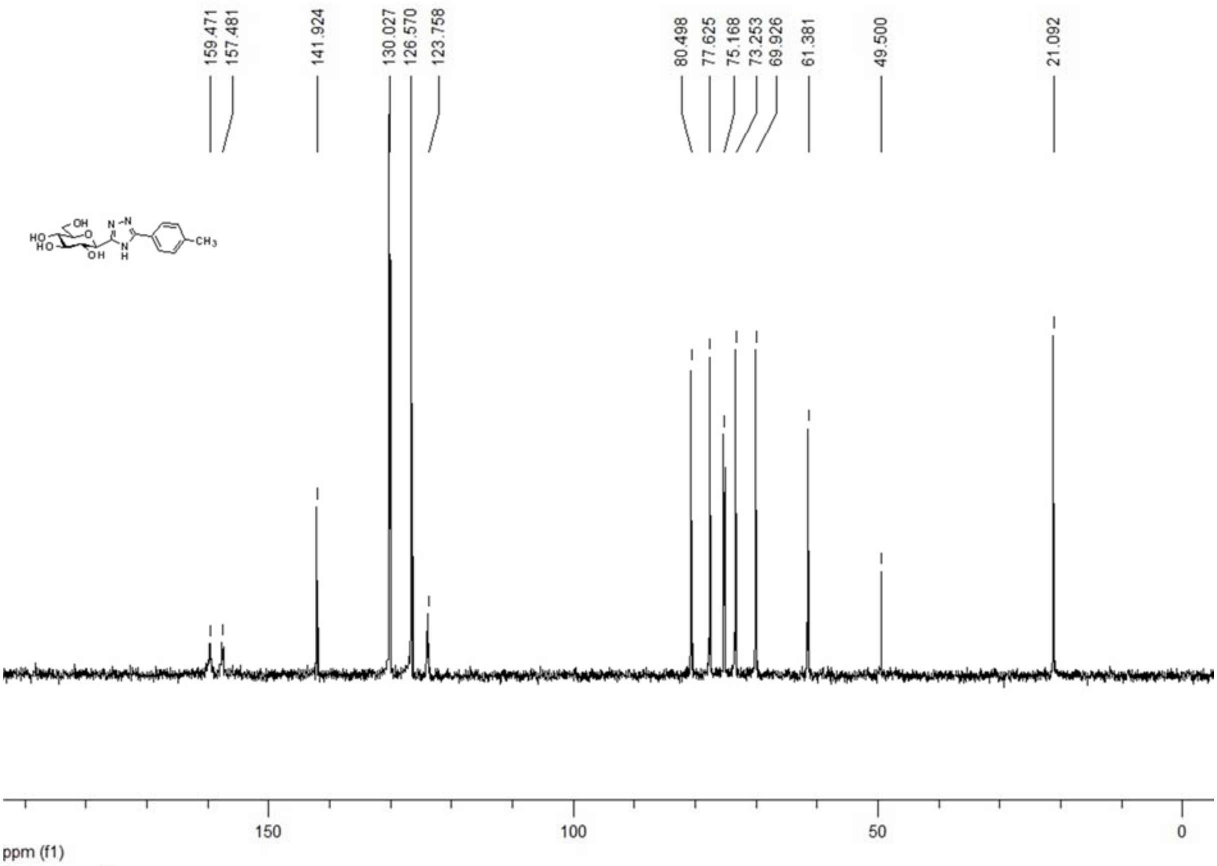
[1]H and [13]C NMR spectra of compound **3e** in $CDCl_3$.



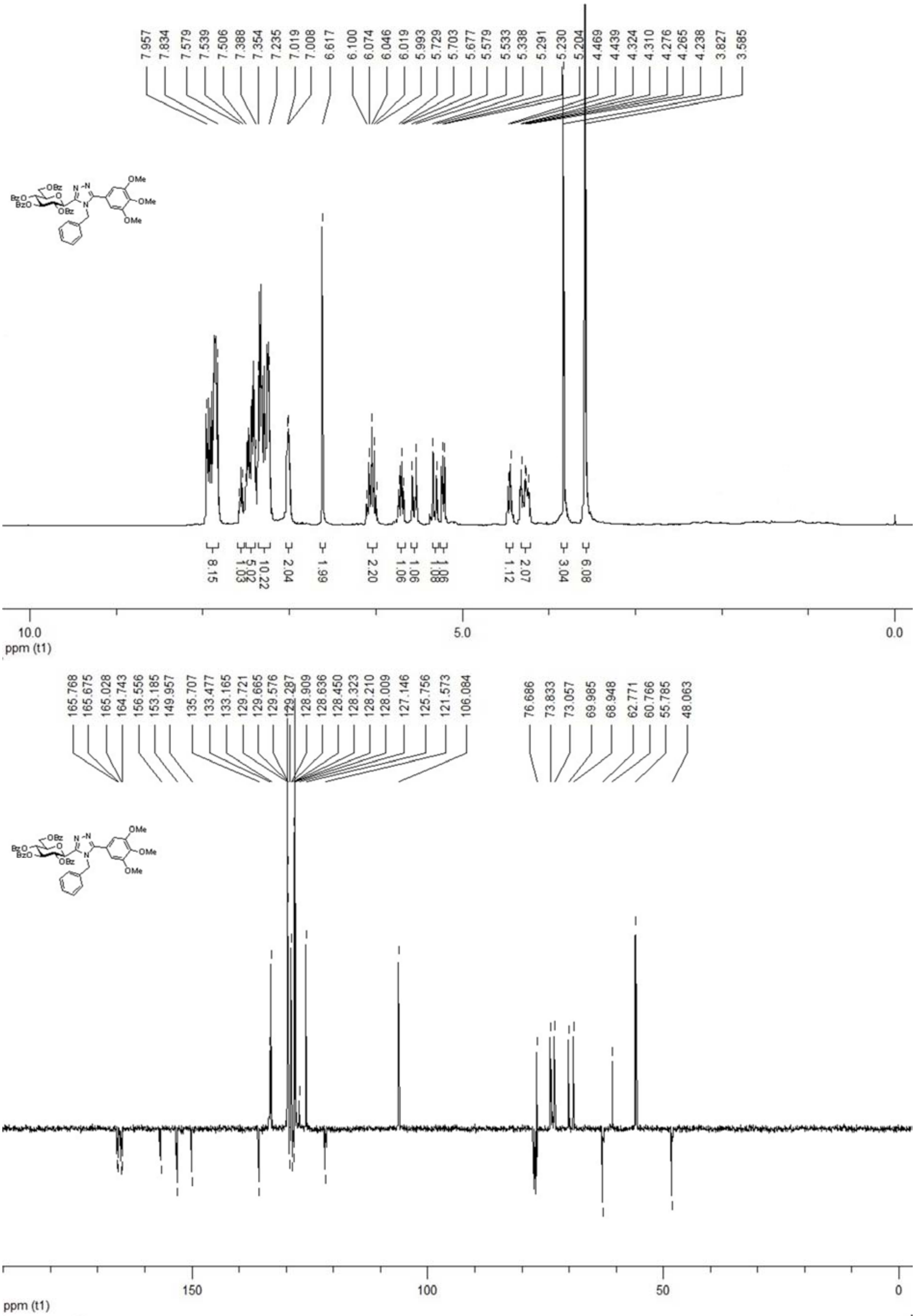


[1]H and [13]C NMR spectra of compound **4e** in CD_3OD.

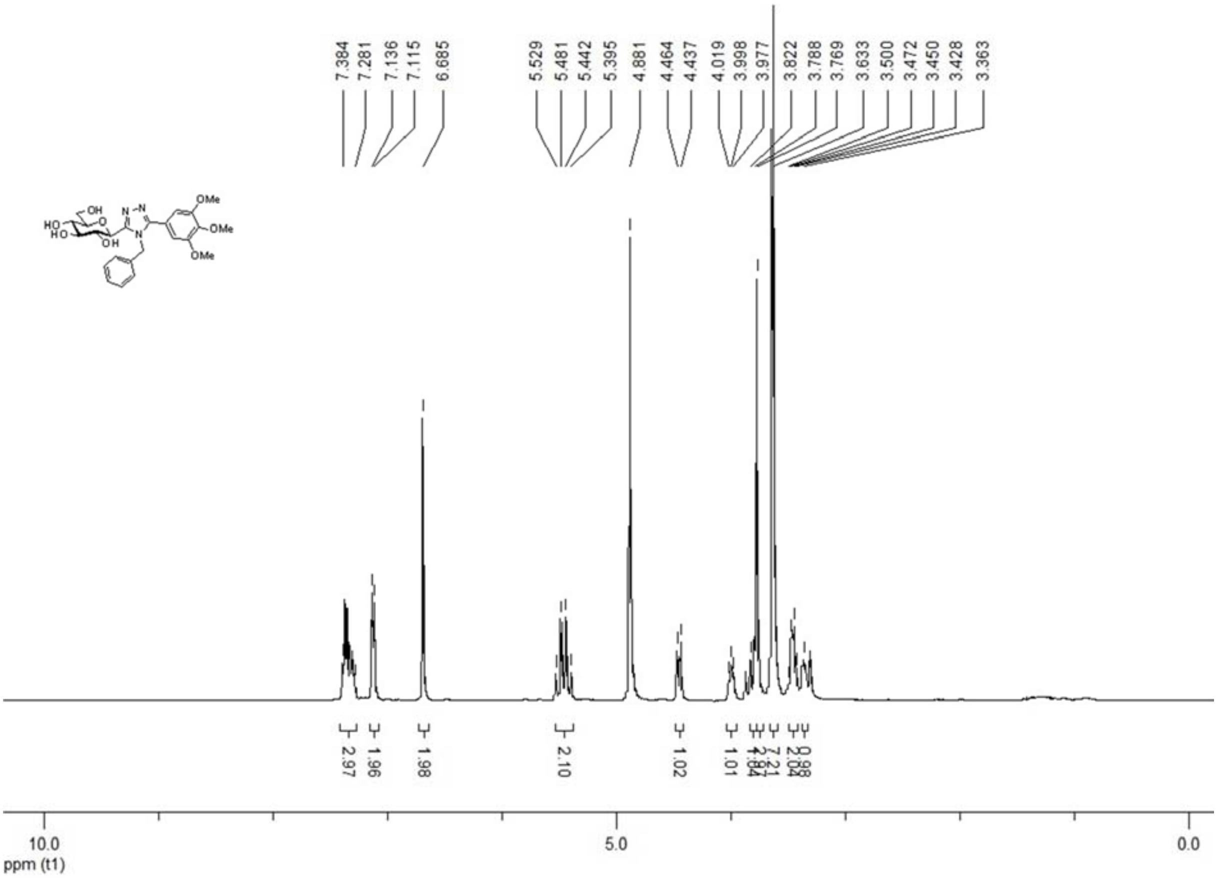


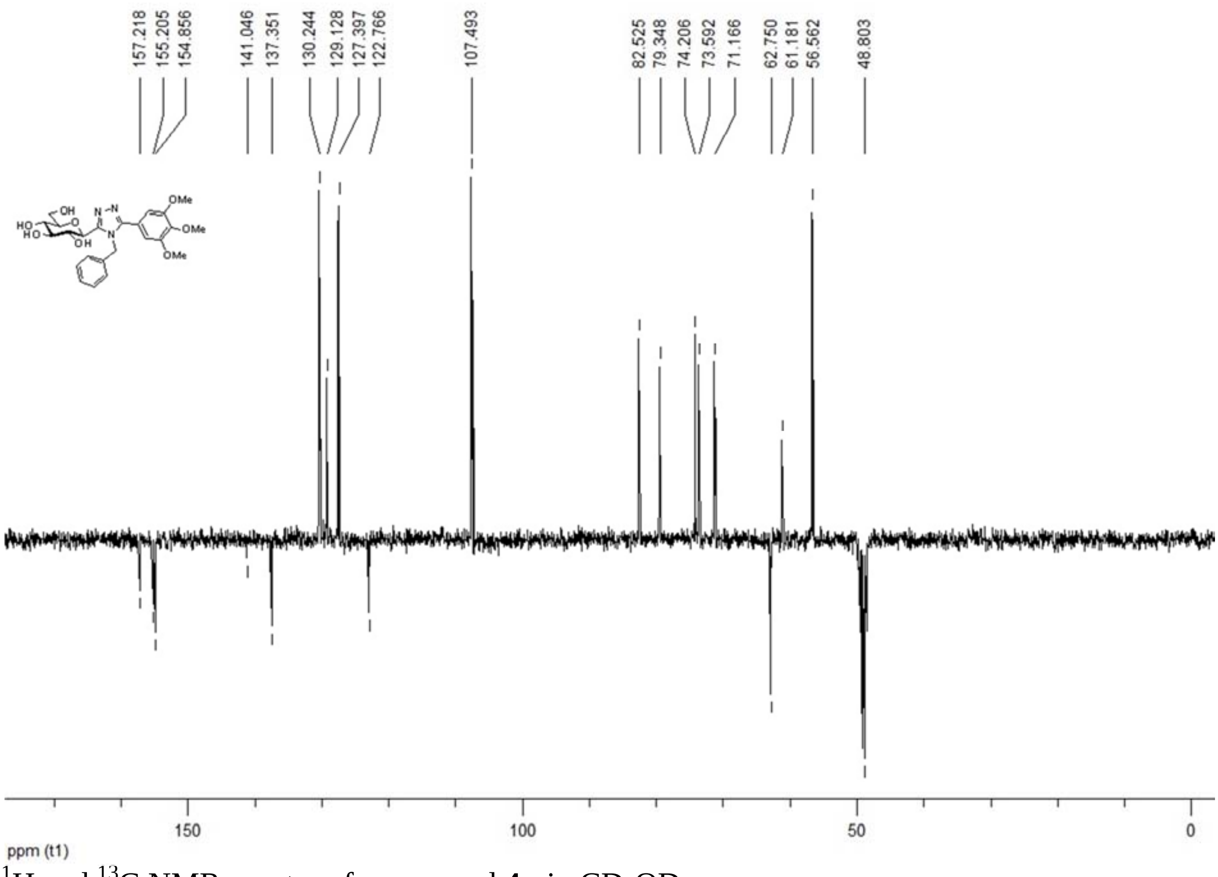


^{1}H and ^{13}C NMR spectra of compound **6e** in D_2O.

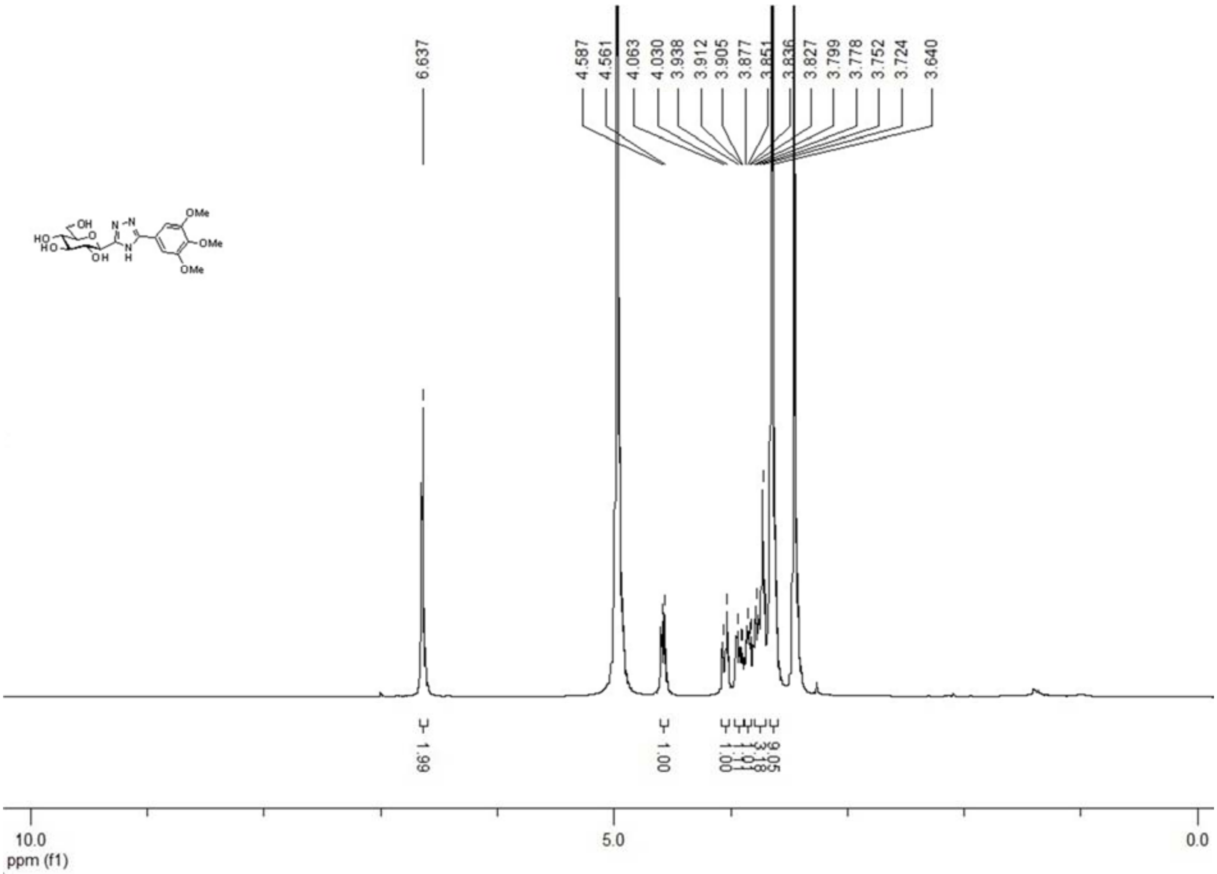


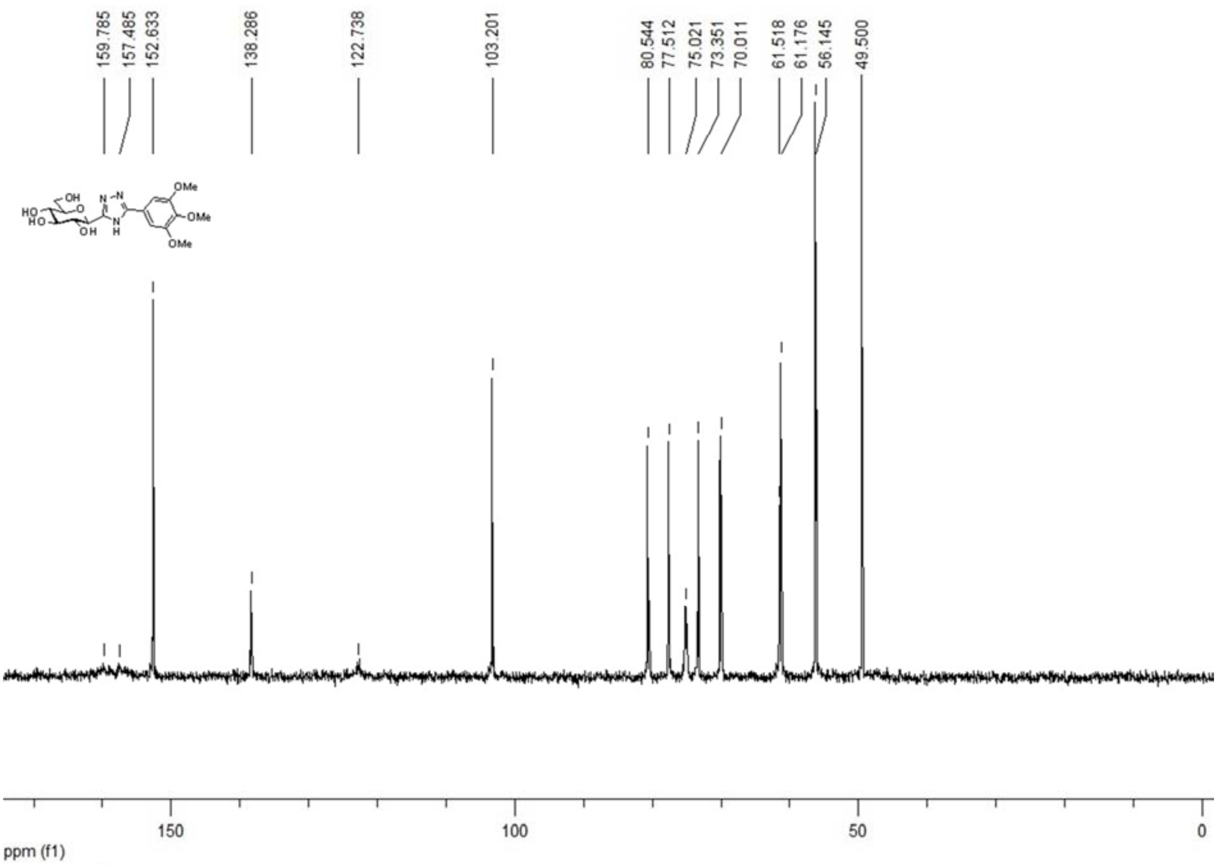
[1]H and [13]C NMR spectra of compound **3p** in $CDCl_3$.



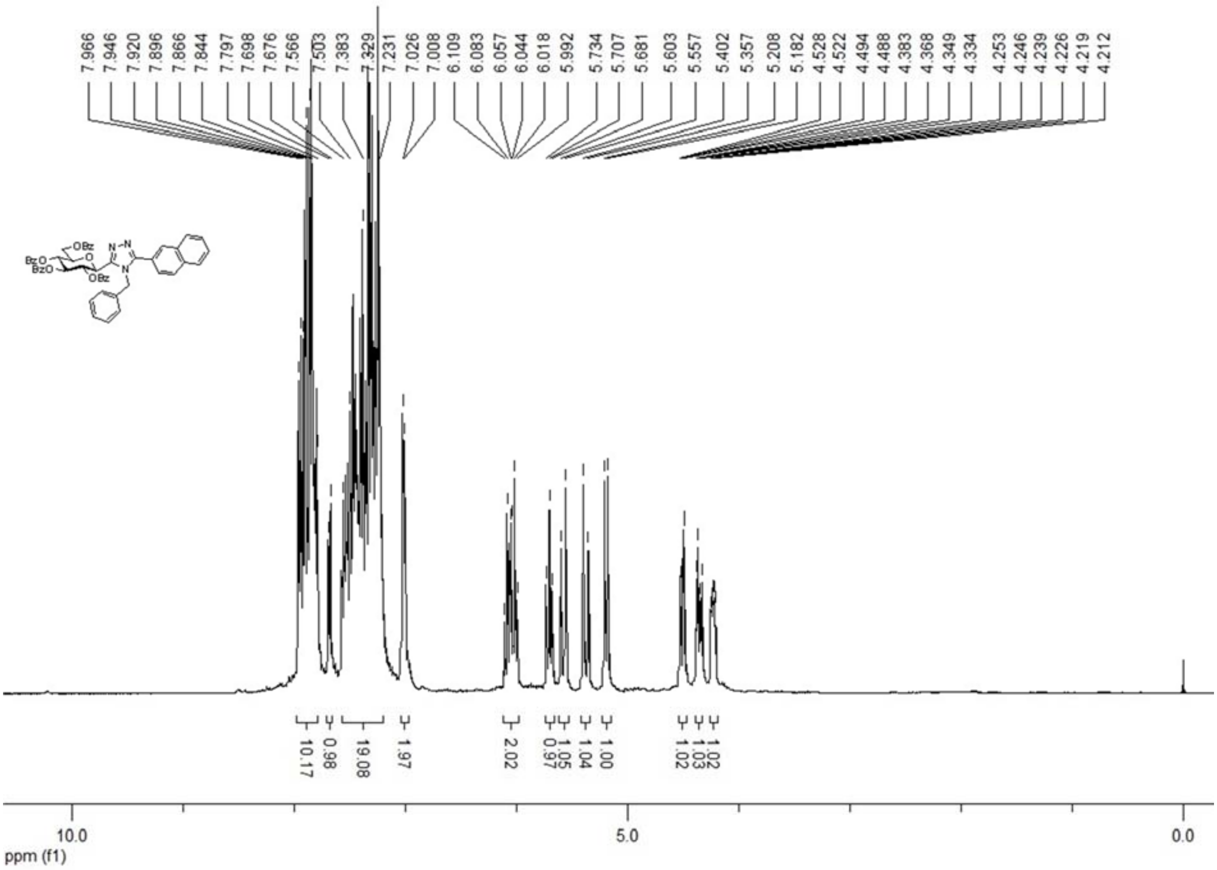


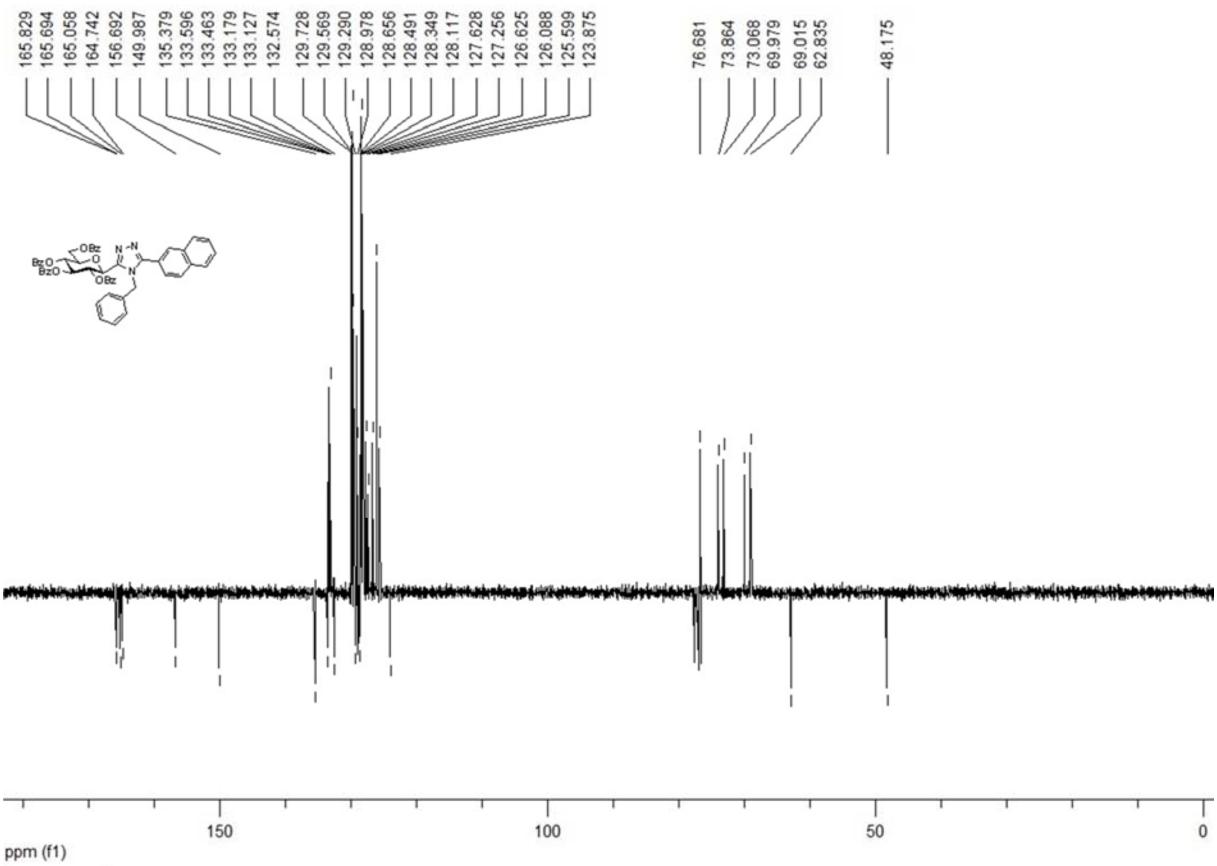
[1]H and [13]C NMR spectra of compound **4p** in CD_3OD.



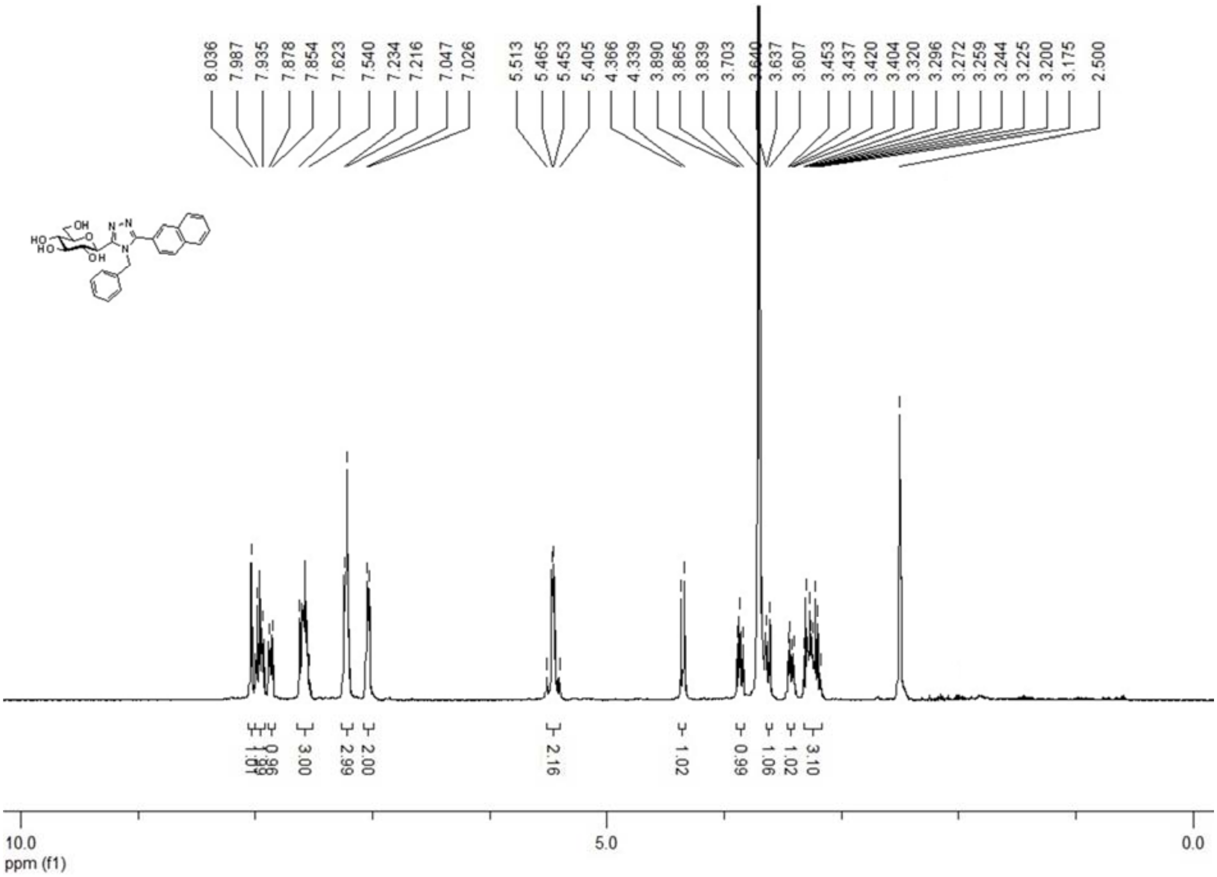


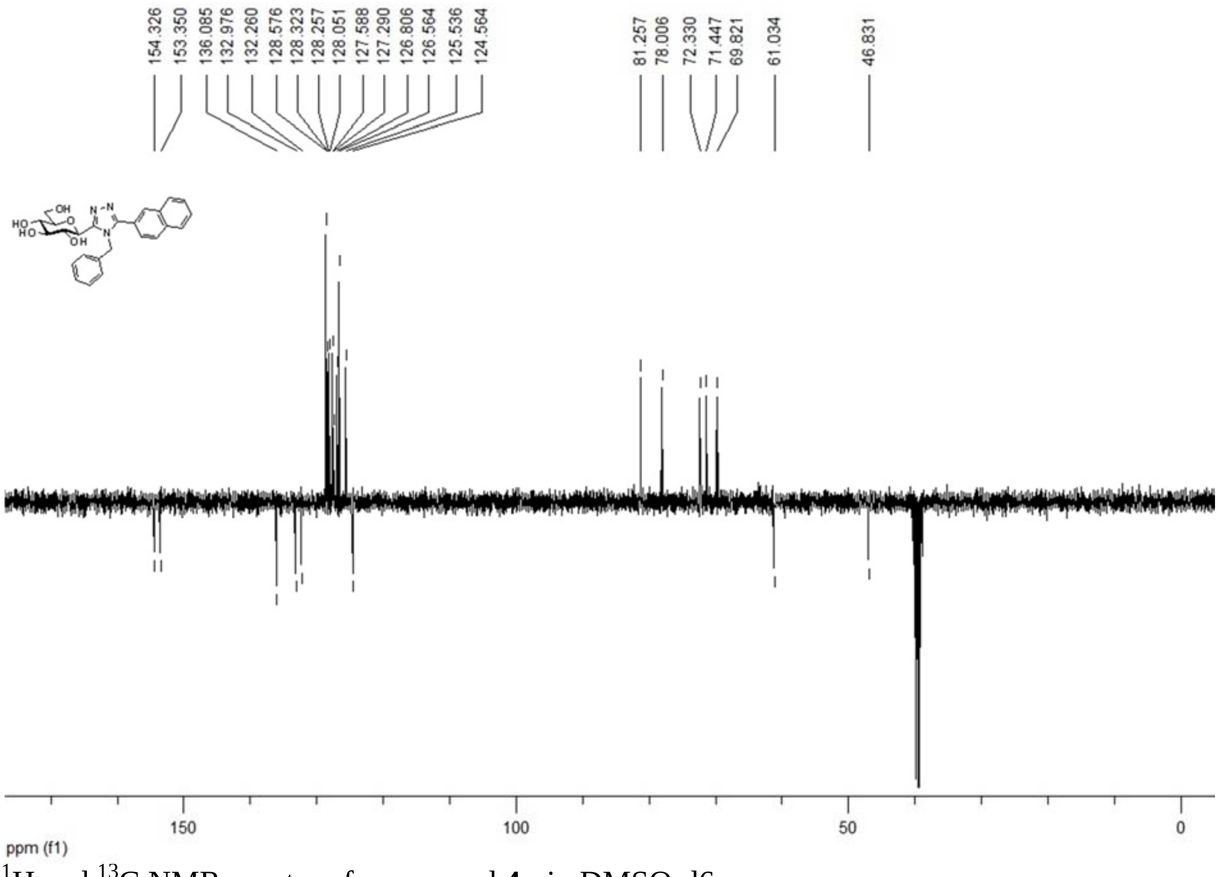
[1]H and [13]C NMR spectra of compound **6p** in D_2O.



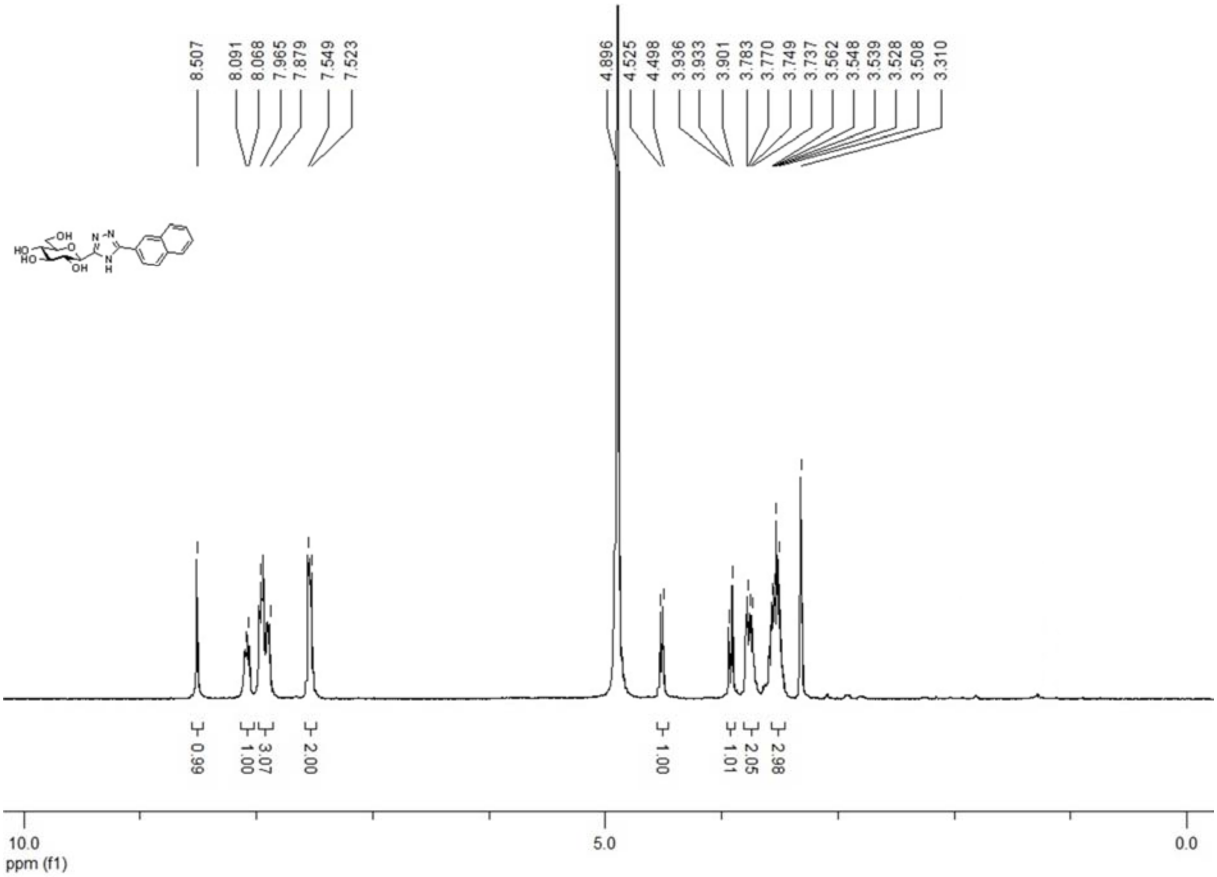


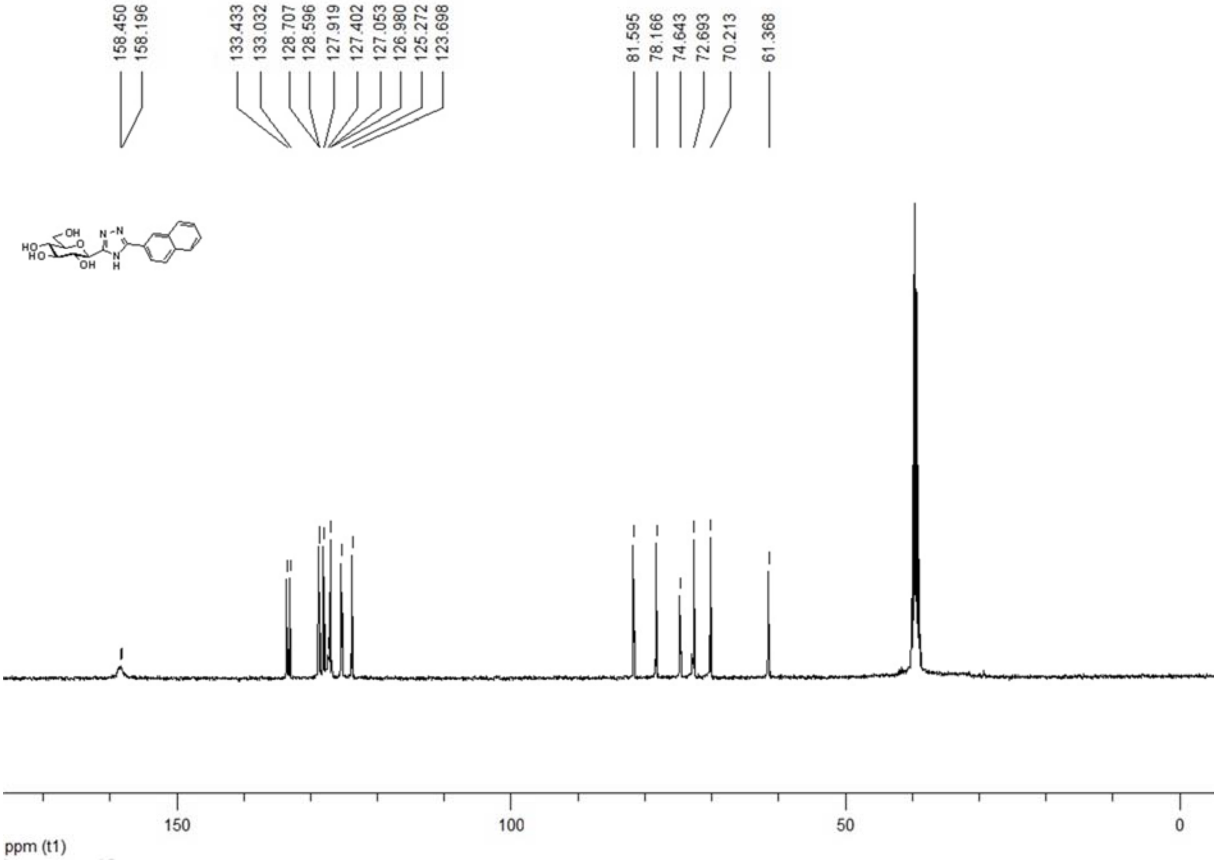
[1]H and [13]C NMR spectra of compound **3q** in $CDCl_3$.





[1]H and [13]C NMR spectra of compound **4q** in DMSO-d6.





[1]H and [13]C NMR spectra of compound **6q** in CD_3OD and DMSO-d6, respectively.