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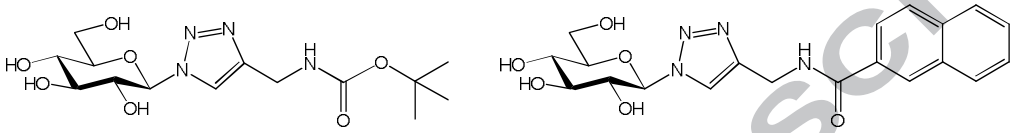
D. Goyard, T. Docsa, P. Gergely, J.-P. Praly, and S. Vidal*

Best inhibitors against RMGP*b* among 8 examples



Synthesis of 4-amidomethyl-1-glucosyl-1,2,3-triazoles and evaluation as glycogen phosphorylase inhibitors

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Abstract:

Glycogen phosphorylase (GP) appears as a key enzyme for the control of hyperglycaemia in the context of type 2 diabetes. In order to gain additional data for structure-activity studies of the inhibition of this enzyme, a series of eight GP inhibitor candidates were prepared from peracetylglucopyranosyl azide **1** by click-chemistry. The need for a *N*-Boc-protected propargylamine was identified in the CuAAC with azide **1** under Meldal's conditions, while Sharpless' conditions were better adapted to the CuAAC of azide **1** with propargyl bromide. Cycloaddition of Boc-propargylamine with azide **1** afforded the *N*-Boc precursor of a 4-aminomethyl-1-glucosyl-1,2,3-triazole which gave access to a series of eight amide and sulfonamide derivatives. After deacetylation, enzymatic studies revealed poor to moderate inhibitions towards this enzyme. The *N*-Boc-protected amine was the best inhibitor (IC_{50} = 620 µM) unexpectedly slightly better than the 2-naphthylamido substituted analogue (IC_{50} = 650 µM).

Keywords: Carbohydrate, Triazole, Click chemistry, Inhibitor, Glycogen phophorylase

1. Introduction

Glycogen phosphorylase[1,2] (GP) is an enzyme responsible for the depolymerization of glycogen and a contributor to hepatic glucose output to the blood stream. Hyperglycaemia can be linked to the activity of this enzyme and the tight control of GP activity appears as a promising strategy in the context of type 2 diabetes.[3-6] Glucose-based derivatives have been intensively studied and provided the most populated family of GP inhibitors.[7-11] While the best candidates displaying sub-micromolar activities for inhibition of the enzyme are spiro-anomeric-bicyclic carbohydrates,[12-19] a large set of heteroaromatic glucosides have also been investigated providing inhibitions in the low micromolar range.[20-28]

N-Acyl-β-D-glucopyranosylamines[29] (Figure 1, **A**) have been reported as good inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGP*b*), the unphosphorylated isoenzyme typically used for inhibition studies. The bioisosterism between the amide bond and the 1,2,3-triazole[30,31] moiety prompted the synthesis of 1-glucopyranosyl-4-aryl-1,2,3-triazoles[32,33] (Figure 1, **B**). The inhibition of both derivatives was in the micromolar range while in the case of *N*-acyl-*N*'-β-D-glucopyranosyl ureas with an additional amide bond (Figure 1, **C**) the inhibition was largely improved to reach sub-micromolar K_i values.[34]

We therefore decided to synthesize analogues of such triazoles **B** or ureas **C** identified as potent GP inhibitors. The corresponding analogues (Figure 1, **D**) can be constructed on a 1,2,3-triazole scaffold displaying a methylamino substituent for amidation with acyl or sulfonyl halides. Such molecular design provides a 1,2,3-triazole moiety as a surrogate of the first amide bond while the second amide bond is maintained. The methylene group between the triazole and amide functionalities can be seen as a flexible pivotal linkage providing a conformational mobility to the scaffold in order to better fit the binding pocket of the enzyme.

The substituents attached at the amine functionality were chosen in connection with the properties of the so-called β-channel.[1] This pocket is in close vicinity to the catalytic site of GP and capable of hydrophobic interactions with the heteroaromatic moieties attached at the β-anomeric position of the glucose residue. Amide bond were therefore generated with hydrophobic derivatives such as *t*-butyloxycarbamate (Boc), acetyl, and phenyl substituents but also with tyrosine, tosyl and hydrophilic phosphonate moieties.

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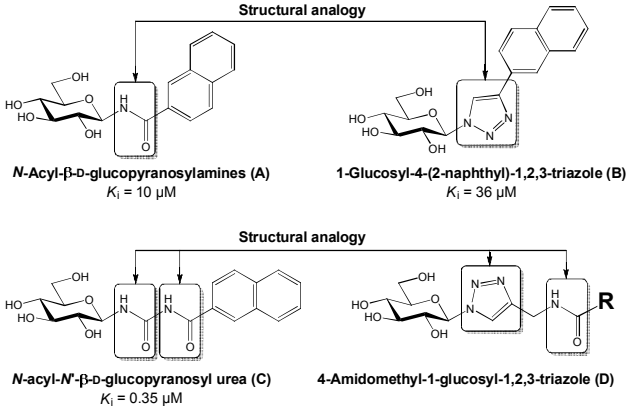


Figure 1. Structural analogy between amide- and triazole-containing GP inhibitors (K_i values are given against RMGP*b*)

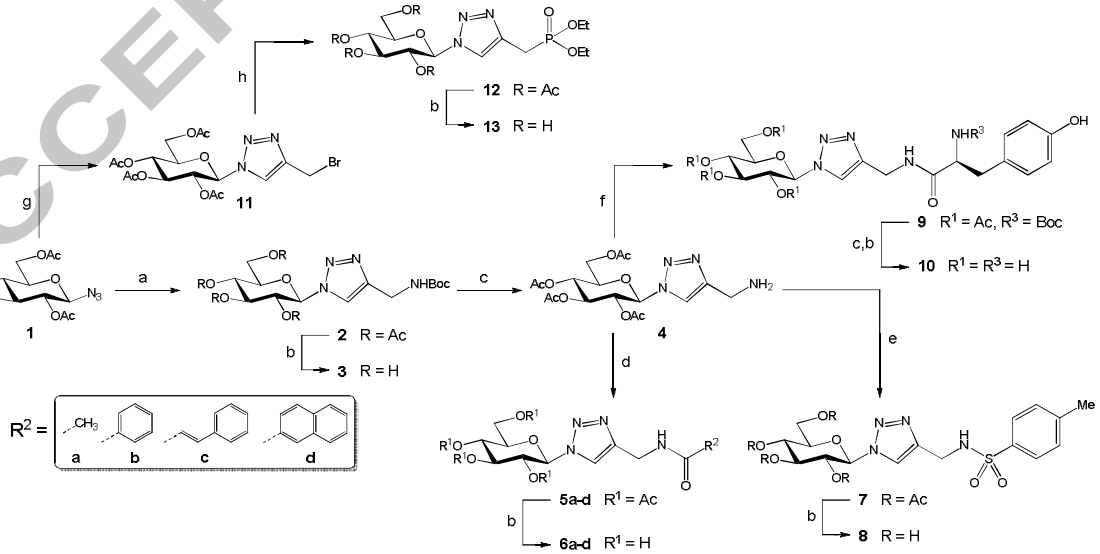
2. Results and discussion

2.1. Synthesis

The synthesis of the target glucose-based inhibitors of GP was performed by 1,3-dipolar cycloaddition of a propargylamine derivative with peracetylglucopyranosyl azide **1** (Scheme 1). The development of Cu(I)-catalyzed azide-alkyne cycloaddition[35] (CuAAC) reactions in organic chemistry was boosted after the discovery of reliable and powerful catalysis with Cu(I) species by Meldal[36] and Sharpless[37] following the pioneering discovery on such 1,3-dipolar cycloadditions by Huisgen.[38] Although this reaction is now intensively used, its outcome sometimes differs from the typical result expected, leading to 5-halogenated 1,2,3-triazoles or even 5,5'-*bis*-triazoles under certain conditions.[39,27]

In various investigations,[40-44] propargylamine has been used as a dipolarophile affording in good to excellent yields 4-aminomethyl-triazoles of interest. Attempted cycloaddition performed with propargylamine and the azido derivative **1** did not afford cleanly the expected triazole but instead a complex mixture containing partially deacetylated compounds most probably through aminolysis of the acetate protecting groups in **1** by propargylamine. Even though reacetylation of the crude mixture could be envisaged for the recovery of the target compound, this strategy was not further investigated. Fortunately, carbamoylation of propargylamine as the *t*-butyloxycarbamate (Boc) derivative allowed for a clean and high yielding (95%) cycloaddition with azide **1** to afford the desired Boc-protected amine **2**[45] (Scheme 1). This compound was deacetylated under Zemplén conditions to afford compound **3** as a GP inhibitor candidate.

The Boc-protected amine **2** was converted quantitatively by acidic cleavage to the free amine **4** suitable for further functionalization with acyl chlorides (Scheme 1, R^2COCl) affording the acetylated amides **5a-d** which were deprotected to the GP inhibitors candidates **6a-d**. The amine **4** was also converted to the sulfonamide derivative **7** using *p*-toluenesulfonyl chloride TsCl and subsequent deacetylation afforded derivative **8**. The sulfonamide **8** was synthesized in order to take advantage of hydrophobic contact in the β-channel of GP and also to have potential additional contacts with the sulfonamide group and the side chain amino acids of the enzyme. Finally, the Boc-protected tyrosine amino acid was conjugated to amine **4** under standard conditions to afford the desired amide **9**. The phenol moiety of tyrosine did not require a protecting group and was compatible with the amide bond formation. Subsequent one-pot deprotection of the carbamate then acetate protecting groups afforded derivative **10**.



Scheme 1. a) HC≡CCH_2NHBoc, CuI, *i*$PrNEt_2$, DMF, 70°C, 4 h; b) MeONa, MeOH, rt, 16 h; c) CH_2Cl_2/TFA (10:1), rt, 4 h; d) R^2COCl, Et_3N, CH_2Cl_2, rt, 4 h; e) TsCl, Et_3N, CH_2Cl_2, rt, 4 h; f) BocTyrOH, EDCI, HOBt, CH_2Cl_2/DMF (2:1), –10°C, 2 h then rt, 16 h; g) HC≡CCH_2Br, $CuSO_4$, sodium ascorbate, *t*$BuOH/H_2O$ (1:1), rt, 16 h; h) $P(OEt)_3$, 140°C (μW), 1 h.

In order to expand our family/library of triazole-based analogues, the reaction of propargyl bromide with the azido derivative **1** was investigated.[42] When performed under Meldal's conditions (CuI, *i*PrNEt$_2$), a complex reaction mixture was obtained probably due to the decomposition of propargyl bromide and also decomposition of the desired cycloadduct. Application of Sharpless' conditions ($CuSO_4$, sodium ascorbate) afforded the desired 4-bromomethyl-1,2,3-triazole **11** in excellent yield (85%). Deacetylation with sodium methoxide in methanol (Zemplén conditions) led to a complex mixture of decomposed and partially deprotected compounds probably due to the substitution of the bromide atom in the presence of sodium methoxide. Therefore, we did not investigate further this approach but decided to take advantage of the bromomethyl group to synthesize a phosphonate analogue. Arbuzov reaction of the brominated derivative **11** with triethylphosphite under microwaves activation allowed for the rapid formation of the acetylated phosphonate **12** which was subsequently converted to phosphonate **13** as a GP inhibitor candidate. Although the preparation of the phosphonate **12** was quite simple and high yielding, only one example has been reported in the literature using a different synthetic strategy for a similar phosphonate on a triazole scaffold.[46]

To summarize, the need for a Boc-protected propargylamine was identified in the CuAAC with azide **1** under Meldal's conditions, while Sharpless' conditions were better adapted to the CuAAC with propargyl bromide. The CuAAC route from azide **1** led in few steps to a series of eight GP inhibitor candidates evaluated to gain additional data for structure-activity studies of the inhibition of this enzyme.

2.2. Enzymatic studies

The eight inhibitor candidates have been assayed *in vitro*[10] for their inhibitory properties towards RMGP*b* (Table 1), the model enzyme used for the study of GP due to its high similarity (97%) to human isoforms and with complete conservation (100%) at the catalytic site.[2]

Although compound **2** was just an intermediate in the synthetic route to the target compounds, its Boc-protected derivative **3** was considered as a GP inhibitor candidate. Indeed, compared to the other compounds tested (Table 1), an unexpected but significant inhibition (IC_{50} = 620 µM) was observed for the Boc-amine derivative **3**, even though it remained below the expected levels (Figure 1). The high hydrophobicity of the *t*-butyl substituent present in the Boc-protected amine is most probably responsible for hydrophobic interactions in the β-channel of the enzyme's catalytic site.

The 4-amidomethyl-1-glucosylated 1,2,3-triazoles **6a-d** displayed IC_{50} values in the high micromolar range. The acetyl group of compound **6a** is most probably too small to fit and interact with the amino acids in the β-channel thus providing only 40% inhibition at 5 mM. As they displayed an aromatic group, compounds **6b** and **6c** showed improved inhibitory properties although with IC_{50} values in the mM range. As observed for several glucose-based GP inhibitors,[10] the best aromatic pharmacophore was almost consistently the 2-naphthyl moiety and compound **6d** displayed the best IC_{50} value (650 µM) in the 4-amidomethyl-1,2,3-triazole series.

Besides the replacement of the carbonyl (-CO-) with a sulfonyl group (-SO_2-), the sulfonamide **8** differs from the benzamide **6b** with the presence of a methyl substituent on the phenyl ring. The poor inhibition (30%) observed at 5 mM highlights the negative effect of the sulfamide moiety (maybe due to unfavorable structural constraints) and possibly the negative influence of the methyl group.

Attachment of amino acids to amine intermediate **4** might create additional and positive interactions between the chosen amino acid and the enzyme's catalytic site. Since aromatic groups are usually the best pharmacophores, tyrosine appeared a suitable choice but no inhibition was observed at 5 mM for compound **10**. The amino acid probably does not fit into the catalytic site of GP probably due to size, structure or properties.

Finally, phosphonate **13** did not display any inhibition at a maximum concentration of 5 mM.

Table 1. Enzyme kinetic studies of the eight inhibitor candidates (IC_{50}) against RMGP*b*

Inhibitor	IC_{50} (µM)
3	620
6a	40% inhibition at 5 000[a]
6b	1 400
6c	2 100
6d	650
8	30% inhibition at 5 000[a]
10	no inhibition at 5 000[a]
13	no inhibition at 5 000[a]

[a] Percentage of inhibition observed at 5 mM.

The evaluation of eight GP inhibitor candidates highlighted that the structural design was limited to only a small series of 4-amidomethyl-1-glucosyl-1,2,3-triazoles while several other structural moieties (sulfamido, amino acid or phosphonate) proved detrimental. To our surprise, the inhibitory properties of the Boc-amine protected intermediate **3** were the best in this study although with an IC_{50} value in the high µM range.

Although the present study reveals a novel series of potential GP inhibitors, the poor to moderate inhibition measured did not prompt for the detailed study of their interactions at the catalytic site of the enzyme through soaking experiments with the crystallized enzyme. The presence of these inhibitors at the catalytic site of the enzyme cannot be proved but only assumed in similarity to almost all glucose-based GP inhibitors identified so far.[10] Similarly, docking experiments and calculations for the interpretation of the possible modes of binding in the catalytic site of the enzyme could be performed but only with more active inhibitors. *In silico* studies are now in progress in order to identify pharmacophores providing a better inhibition. The synthesis and biological evaluation of such GP inhibitor candidates will then be performed.

3. Conclusion

Cycloaddition of Boc-propargylamine with peracetylated glucosyl azide afforded the precursor of a 4-aminomethyl-1-glucosyl-1,2,3-triazole which was converted into various amido derivatives. The eight potential GP inhibitors obtained revealed by enzymatic studies poor to moderate inhibitions towards this enzyme. The best inhibitor displayed an IC_{50} value of 620 µM and was actually a Boc-protected amine derivative which performed almost equally to the 2-naphthylamido substituted inhibitor (IC_{50} = 650 µM).

4. Experimental Section

General methods. All reagents were obtained from commercial sources and used without further purification. Dichloromethane was distilled over CaH_2 and methanol over Mg/I_2. All reactions were performed under an argon atmosphere. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 F_{254} (Merck). TLC plates were inspected by UV light (λ = 254 nm) and developed by treatment with a mixture of 10% H_2SO_4 in EtOH/H_2O (1:1 v/v) followed by heating. Silica gel column chromatography was performed with silica gel Si 60 (40–63 µm). NMR spectra were recorded at 293 K using a Bruker 400 MHz spectrometer. Chemical shifts are referenced relative to deuterated solvent residual peaks. The following abbreviations are used to explain the observed multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet and bs, broad singlet. Complete signal assignments were based on 1D and 2D NMR (COSY, HSQC and HMBC correlations). High resolution (HR-ESI-QToF) mass spectra were recorded using a Bruker MicroToF-Q II XL spectrometer. Optical rotation was measured using a Perkin Elmer polarimeter at 20°C and values are given in 10^{-1} deg.cm^2.g^{-1}.

General procedure A for the coupling of amine 4 with acyl and tosyl chlorides. To a solution of amine **4** (100 mg, 0.23 mmol, 1 eq.) in anhydrous CH_2Cl_2 (5 mL) was added Et_3N (0.5 mL) and acyl or tosyl chloride (0.46 mmol, 2 eq.). The mixture was stirred at r.t. for 4 h, concentrated *in vacuo* and purified over silica gel chromatography (PE/EtOAc 3:7) to afford products **5a-d** and **7**.

General procedure B for the Zemplén deacetylation. To a suspension of acetylated compound (1 eq.) in dry MeOH (5 mL/0.2 mmol), was added MeONa (0.4 eq.). If the acetylated compound was not soluble in MeOH, CH_2Cl_2 was added in order to reach reasonable solubility. The mixture was stirred at r.t. for 16 h, neutralized with Amberlite IR 120 resin, filtrated and concentrated *in vacuo* to afford the corresponding *O*-unprotected compounds in quantitative yields.

***tert*-Butyl {[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}carbamate (2)**[45]

To a suspension of azide **1** (3.99 g, 10.70 mmol, 1 eq.), *tert*-butyl prop-2-yn-1-ylcarbamate (1.99 g, 12.84 mmol, 1.2 eq.) and CuI (0.408 g, 2.14 mmol, 0.2 eq.) in anhydrous DMF (50 mL) was added DIPEA (13.26 mL, 80.25 mmol, 7.5 eq.). The mixture was stirred at 70°C for 4 h, cooled down to r.t. and concentrated *in vacuo*. The crude product was purified over silica gel chromatography (CH_2Cl_2/EtOAc 9:1 then 8:2) to afford **2** as a white powder (5.364 g, 95%).

mp = 199-200°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.34 (CH_2Cl_2/EtOAc 8:2); $\mathbf{[\alpha]_D^{20}}$ = – 21 (c 1, $CHCl_3$); **^{1}H NMR** (CD_3OD, 300 MHz) δ 7.79 (br s, 1H, H-5'), 5.86 (d, 1H, *J* = 8.3 Hz, H-1), 5.37-5.46 (m, 2H, H-2, H-3), 5.23 (pdd, 1H, *J* = 9.7 Hz, H-4), 5.10 (br s, 1H, NH), 4.28 (dd, 1H, *J* = 12.6, 4.9 Hz, H-6a), 4.13 (dd, 1H, *J* = 12.6, 1.9 Hz, H-6b), 3.99 (ddd, 1H, *J* = 10.0, 4.8, 2.0 Hz, H-5), 2.07, 2.06, 2.0, 1.86 (4s, 12H, acetyl), 1.44 (s, 9H, *t*Bu); **HRMS** [ESI+] *m/z* $[M+H]^+$ calcd for $C_{22}H_{32}N_4NaO_{11}$ 551.1960; found 551.1948

***tert*-Butyl {[1-(β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}carbamate (3)**

Prepared according to general procedure B. White foam; $\mathbf{R_f}$ = 0.18 (EtOAc/MeOH 8:2); $\mathbf{[\alpha]_D^{20}}$ = + 2 (c 0.5, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 8.04 (s, 1H, H-5'), 5.60 (d, 1H, *J* = 9.1 Hz, H-1), 4.33 (s, 2H, C*H*$_2$NH), 3.86-3.92 (m, 2H, H-2, H-6a), 3.72 (dd, 1H, *J* = 12.2, 5.2 Hz, H-6b), 3.57-3.60 (m, 2H, H-3, H-5), 3.51 (pdd, 1H, *J* = 9.0 Hz, H-4), 1.44 (s, 9H, *t*Bu); **^{13}C NMR** (CD_3OD, 100 MHz) δ 158.3 (C=O), 147.2 (C-4'), 123.2 (C-5'), 89.5 (C-1), 81.0 (C-5), 80.5 (C, *t*Bu), 78.4 (C-3), 74.0 (C-2), 70.8 (C-4), 62.3 (C-6), 36.6 (CH_2NH), 28.7 (CH_3, *t*Bu); **HRMS** [ESI+] *m/z* $[M+Na]^+$ calcd for $C_{20}H_{22}N_4NaO_6$ 437.1432; found 434.1430

[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methanamine (4)

To a solution of **2** (5.00 g, 9.47 mmol, 1 eq.) in anhydrous CH_2Cl_2 (50 mL) was added TFA (5 mL). The reaction was stirred at r.t. for 4 h and concentrated *in vacuo*. The crude product was purified over silica gel chromatography (CH_2Cl_2/MeOH/Et_3N 79:20:1) to afford **4** as a white foam in a quantitative yield.

$\mathbf{R_f}$ = 0.31 (EtOAc/MeOH 8:2); $\mathbf{[\alpha]_D^{20}}$ = – 12 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (s, 1H, H-5'), 5.86 (d, 1H, *J* = 8.8 Hz, H-1), 5.37-5.44 (m, 2H, H-2, H-3), 5.21 (pdd, 1H, *J* = 9.6 Hz, H-4), 4.27 (dd, 1H, *J* = 12.6, 4.9 Hz, H-6a), 4.11 (dd, 1H, *J* = 12.6, 1.8 Hz, H-6b), 3.99 (ddd, 1H, *J* = 10.1, 4.8, 1.9 Hz, H-5), 3.96 (br s, 2H, C*H*$_2$NH$_2$), 2.05, 2.04, 2.00, 1.85 (4s, 12H, acetyl); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.8, 170.0, 169.5, 169.1 (4C, C=O), 150.3 (C-4'), 119.2 (C-5'), 85.7 (C-1), 75.1 (C-5), 72.7 (C-3), 70.4 (C-2), 67.8 (C-4), 61.6 (C-6), 37.8 (CH_2NH_2), 20.8, 20.6, 20.6, 20.3 (4CH_3, acetyl); **HRMS** [ESI+] *m/z* $[M+H]^+$ calcd for $C_{17}H_{25}N_4O_9$ 429.1616; found 429.1599

***N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}acetamide (5a)**

Prepared according to general procedure A. White powder (101 mg, 92%); **mp** = 200-201°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.12 (EtOAc/PE/EtOAc 8:2); $[\alpha]_D^{20}$ = – 14 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H, H-5'), 6.40 (br s, 1H, NH), 5.85 (d, 1H, *J* = 9.1 Hz, H-1), 5.38-5.45 (m, 2H, H-2, H-3), 5.24 (pdd, 1H, *J* = 9.8 Hz, H-4), 4.55 (dd, 1H, *J* = 15.3, 4.9 Hz, C*H*$_2$NH), 4.47 (dd, 1H, *J* = 15.3, 4.6 Hz, C*H*$_2$NH), 4.29 (dd, 1H, *J* = 12.7, 4.8 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.6, 1.9 Hz, H-6b), 4.00 (ddd, 1H, *J* = 10.1, 4.8, 2.0 Hz, H-5), 2.08, 2.06, 2.02, 2.01 1.87 (5s, 15H, acetyl); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.7, 170.4, 170.1, 169.5, 169.0 (5C, C=O), 145.4 (C-4'), 121.1 (C-5'), 86.0 (C-1), 75.3 (C-5), 72.7 (C-3), 70.5 (C-2), 67.7 (C-4), 61.6 (C-6), 35.0 (CH_2NH), 23.2, 20.8, 20.7, 20.6, 20.3 (5CH_3, acetyl); **HRMS** [ESI+] *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{26}N_4NaO_{10}$ 493.1541; found 493.1523

***N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}benzamide (5b)**

Prepared according to general procedure A. White powder (109 mg, 89%); **mp** = 189-190°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.32 (PE/EtOAc 3:7); $[\alpha]_D^{20}$ = – 27 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.89 (s, 1H, H-5'), 7.78-7.80 (m, 2H, H-Ar), 7.47-7.51 (m, 1H, H-Ar), 7.40-7.43 (m, 2H, H-Ar), 6.96 (br s, 1H, NH), 5.86 (d, 1H, *J* = 8.7 Hz, H-1), 5.39-5.47 (m, 2H, H-2, H-3), 5.24 (pdd, 1H, *J* = 9.6 Hz, H-4), 4.76 (dd, 1H, *J* = 15.2, 5.4 Hz, C*H*$_2$NH), 4.69 (dd, 1H, *J* = 15.1, 5.3 Hz, C*H*$_2$NH), 4.29 (dd, 1H, *J* = 12.6, 4.8 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.6, 1.8 Hz, H-6b), 4.00 (ddd, 1H, *J* = 10.1, 4.8, 2.0 Hz, H-5), 2.06, 2.05, 2.02, 1.85 (4s, 12H, acetyl); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.7, 170.1, 169.5, 169.0, 167.6 (5C, C=O), 145.5 (C-4'), 134.1 (134.1 C-Ar), 131.8 (CH-Ar), 128.7 (2CH-Ar), 127.2 (2CH-Ar), 121.3 (C-5'), 85.9 (C-1), 75.3 (C-5), 72.8 (C-3), 70.5 (C-2), 67.7 (C-4), 61.6 (C-6), 35.5 (CH_2NH), 20.8, 20.7, 20.7, 20.3 (4CH_3, acetyl); **HRMS** [ESI+] *m*/*z* $[M+Na]^+$ calcd for $C_{24}H_{28}N_4NaO_{10}$ 555.1698; found 555.1676

***N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}cinnamamide (5c)**

Prepared according to general procedure A. White powder (122 mg, 95%); **mp** = 172-173°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.23 (PE/EtOAc 3:7); $[\alpha]_D^{20}$ = – 16 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.85 (s, 1H, H-5'), 7.64 (d, 1H, *J* = 15.6 Hz, Csp^{2}H), 7.48-7.50 (m, 2H, H-Ar), 7.3-7.37 (m, 3H, H-Ar), 6.51 (br s, 1H, NH), 6.44 (d, 1H, *J* = 15.6 Hz, Csp^{2}H), 5.86 (d, 1H, *J* = 8.8 Hz, H-1), 5.39-5.47 (m, 2H, H-2, H-3), 5.24 (pdd, 1H, *J* = 9.6 Hz, H-4), 4.71 (dd, 1H, *J* = 15.4, 5.8 Hz, C*H*$_2$NH), 4.62 (dd, 1H, *J* = 15.4, 5.4 Hz, C*H*$_2$NH), 4.29 (dd, 1H, *J* = 12.6, 4.9 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.6, 1.9 Hz, H-6b), 4.00 (ddd, 1H, *J* = 10.1, 4.8, 2.0 Hz, H-5), 2.07, 2.06, 2.02, 1.87 (4s, 12H, acetyl); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.7, 170.1, 169.5, 169.0 (5C, C=O), 145.5 (C-4'), 141.6 (Csp^2), 134.8 (C-Ar), 130.0 (CH-Ar), 129.0 (2CH-Ar), 128.0 (2CH-Ar), 121.1 (C-5'), 120.3 (Csp^2), 85.9 (C-1), 75.3 (C-5), 72.3 (C-3), 70.5 (C-2), 67.7 (C-4), 61.6 (C-6), 35.2 (CH_2NH), 20.8, 20.7, 20.7, 20.3 (4CH_3, acetyl); **HRMS** [ESI+] *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{30}N_4NaO_{10}$ 581.1854; found 581.1843

***N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}-2-naphthamide (5d)**

Prepared according to general procedure A. White powder (123 mg, 92%); **mp** = 108-109°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.13 (EtOAc/PE 4:6); $[\alpha]_D^{20}$ = – 27 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (s, 1H, H-Ar), 7.97 (s, 1H, H-5'), 7.80-7.87 (m, 4H, H-Ar), 7.47-7.55 (m, 2H, H-Ar), 7.36 (t, 1H, *J* = 5.3 Hz, NH), 5.88 (d, 1H, *J* = 8.9 Hz, H-1), 5.47 (pdd, 1H, *J* = 9.3 Hz, H-2), 5.42 (pdd, 1H, *J* = 9.2 Hz, H-3), 5.25 (pdd, 1H, *J* = 9.6 Hz, H-4), 4.82 (dd, 1H, *J* = 15.2, 5.8 Hz, C*H*$_2$NH), 4.74 (dd, 1H, *J* = 15.2, 5.5 Hz, C*H*$_2$NH), 4.28 (dd, 1H, *J* = 12.6, 4.8 Hz, H-6a), 4.13 (dd, 1H, *J* = 12.6, 1.9 Hz, H-6b), 4.00 (ddd, 1H, *J* = 10.1, 4.8, 2.0 Hz, H-5), 2.05, 2.04, 2.01, 1.83 (4s, 12H, acetyl); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.7, 170.1, 169.5, 168.9 (5C, C=O), 145.6 (C-4'), 134.9 (C-Ar), 132.7 (C-Ar), 131.2 (C-Ar), 129.1 (CH-Ar), 128.5 (CH-Ar), 127.8 (2CH-Ar), 127.8 (CH-Ar), 126.8 (CH-Ar), 123.7 (CH-Ar), 121.5 (C-5'), 85.9 (C-1), 75.2 (C-5), 72.7 (C-3), 70.5 (C-2), 67.7 (C-4), 61.6 (C-6), 35.5 (CH_2NH), 20.8, 20.7, 20.6, 20.3 (4CH_3, acetyl); **HRMS** [ESI+] *m*/*z* $[M+Na]^+$ calcd for $C_{28}H_{30}N_4NaO_{10}$ 605.1854; found 605.1845

***N*-{[1-(β-D-Glucopyranosyl)-1,2,3-triazol-4-yl]methyl}acetamide (6a)**

Prepared according to general procedure B. Colorless oil; $\mathbf{R_f}$ = 0.14 (CH_2Cl_2/MeOH 8:2); $[\alpha]_D^{20}$ = + 1 (c 1, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 8.55 (br s, 1H, NH), 8.07 (s, 1H, H-5'), 5.58 (d, 1H, *J* = 9.2 Hz, H-1), 4.44 (s, 2H, C*H*$_2$NH), 3.85-3.90 (m, 2H, H-2, H-6a), 3.70 (dd, 1H, *J* = 12.2, 5.4 Hz, H-6b), 3.54-3.63 (m, 2H, H-3, H-5), 3.49 (pdd, 1H, *J* = 9.2 Hz, H-4), 1.97 (s, 3H, CH_3); **^{13}C NMR** (CD_3OD, 100 MHz) δ 173.3 (C=O), 146.3 (C-4'), 123.5 (C-5'), 89.6 (C-1), 81.1 (C-5), 78.4 (C-3), 74.0 (C-2), 70.9 (C-4), 62.4 (C-6), 35.6 (CH_2NH), 22.5 (CH_3); **HRMS** [ESI+] *m*/*z* $[M+Na]^+$ calcd for $C_{11}H_{18}N_4NaO_6$ 325.1119; found 325.1113

***N*-{[1-(β-D-Glucopyranosyl)-1,2,3-triazol-4-yl]methyl}benzamide (6b)**

Prepared according to general procedure B. Colorless oil; $\mathbf{R_f}$ = 0.19 (EtOAc/MeOH 8:2); $[\alpha]_D^{20}$ = + 4 (c 1, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 8.13 (s, 1H, H-5'), 7.85 (d, 2H, *J* = 7.8 Hz, H-Ar), 7.54 (t, 1H, *J* = 7.3 Hz, H-Ar), 7.46 (t, 2H, *J* = 7.5 Hz, H-Ar), 5.60 (d, 1H, *J* = 9.2 Hz, H-1), 4.66 (s, 2H, C*H*$_2$NH), 3.85-3.91 (m, 2H, H-2, H-6a), 3.70 (dd, 1H, *J* = 12.6, 5.6 Hz, H-6b), 3.55-3.59 (m, 2H, H-3, H-5), 3.49 (pdd, 1H, *J* = 9.1 Hz, H-4); **^{13}C NMR** (CD_3OD, 100 MHz) δ 170.1 (C=O), 146.5 (C-4'), 135.2 (C-Ar), 132.9 (CH-Ar), 129.6 (2CH-Ar), 128.4 (2CH-Ar), 123.6 (C-5'), 89.6 (C-1), 81.1 (C-5), 78.4 (C-3), 74.0 (C-2), 70.9 (C-4), 62.3 (C-6), 36.1 (*C*H$_2$NH); **HRMS** [ESI+] *m*/*z* $[M+Na]^+$ calcd for $C_{16}H_{20}N_4O_6$ 387.1275; found 387.1277

***N*-{[1-(β-D-Glucopyranosyl)-1,2,3-triazol-4-yl]methyl}cinnamamide (6c)**

Prepared according to general procedure B. White foam; $\mathbf{R_f}$ = 0.13 (CH_2Cl_2/MeOH 85:15); $[\alpha]_D^{20}$ = + 7 (c 1, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 8.13 (s, 1H, H-5'), 7.57 (d, 1H, *J* = 15.7 Hz, Csp^2-H), 7.53-7.55 (m, 2H, H-Ar), 7.35-7.40 (m, 3H, H-Ar), 6.64 (d, 1H, *J* = 15.8 Hz, Csp2-H), 5.62 (d, 1H, *J* = 9.2 Hz, H-1), 4.58 (s, 2H, NH), 3.86-3.94 (m, 2H, H-2, H-6a), 3.72 (dd, 1H, *J* = 12.1, 5.1 Hz, H-6b), 3.58-3.62 (m, 2H, H-3, H-5), 3.52 (pdd, 1H, *J* = 9.0 Hz, H-4); **^{13}C NMR** (CD_3OD, 100 MHz) δ 168.5 (CONH), 146.2 (C-4'), 142.2 (Csp^2), 136.1 (C-Ar), 130.1 (CH-Ar), 129.9 (2CH-Ar), 128.9 (2CH-Ar), 123.6 (C-5'), 121.4 (Csp^2), 89.5 (C-1), 81.0 (C-5), 78.4 (C-3), 74.0 (C-2), 70.8 (C-4), 62.3 (C-6), 35.7 (CH_2NH); HRMS [ESI+] *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{22}N_4NaO_6$ 413.1436; found 413.1429

***N*-{[1-(β-D-Glucopyranosyl)-1,2,3-triazol-4-yl]methyl}naphthamide (6d)**

Prepared according to general procedure B. Colorless oil; $\mathbf{R_f}$ = 0.21 (EtOAc/MeOH 8:2); $[\alpha]_D^{20}$ = + 1 (c 1, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 8.55 (s, 1H, NH), 8.41 (s, 1H, H-Ar), 8.16 (s, 1H, H-5'), 7.90-7.98 (m, 4H, H-Ar), 7.54-7.61 (m, 2H, H-Ar), 5.60 (d, 1H, *J* = 9.2 Hz, H-1), 4.72 (s, 2H, C*H*$_2$NH), 3.90 (pdd, 1H, *J* = 9.1 Hz, H-2), 3.86 (dd, 1H, *J* = 12.2, 1.9 Hz, H-6a), 3.70 (dd, 1H, *J* = 12.2, 5.4 Hz, H-6b), 3.56 (pdd, 1H, *J* = 8.8 Hz, H-3), 3.54-3.58 (m, 1H, H-5), 3.49 (pdd, 1H, *J* = 9.2 Hz, H-4); **^{13}C NMR** (CD_3OD, 100 MHz) δ 170.2 (C=O), 146.6 (C-4'), 136.4 (C-Ar), 134.0 (C-Ar), 132.5 (C-Ar), 130.1 (CH-Ar), 129.4 (CH-Ar), 129.0 (CH-Ar), 128.9 (CH-Ar), 128.8 (CH-Ar), 127.9 (CH-Ar), 124.9 (CH-Ar), 123.7 (C-5'), 89.6 (C-1), 81.1 (C-5), 78.5 (C-3), 74.0 (C-2), 70.9 (C-4), 62.4 (C-6), 36.2 (CH_2NH); **HRMS** [ESI+] *m/z* $[M+Na]^+$ calcd for $C_{20}H_{22}N_4NaO_6$ 437.1432; found 434.1430

***N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}-*p*-toluenesulfonamide (7)**

Prepared according to general procedure A. White powder (126 mg, 94%); **mp** = 205-206°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.35 (PE/EtOAc 4:6); $[\alpha]_D^{20}$ = – 19 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.73-7.75 (m, 3H, H-5', H-Ar), 7.30 (d, 2H, *J* = 8.0 Hz, H-Ar), 5.85 (d, 1H, *J* = 8.6 Hz, H-1), 5.48 (br s, 1H, NH), 5.36-5.44 (m, 2H, H-2, H-3), 5.23 (pdd, 1H, *J* = 9.5 Hz, H-4), 4.28 (dd, 1H, *J* = 12.7, 4.8 Hz, H-6a), 4.22 (s, 2H, C*H*$_2$NH), 4.15 (dd, 1H, *J* = 12.5, 1.2 Hz, H-6b), 4.01 (ddd, 1H, *J* = 10.1 4.8, 1.2 Hz, H-5), 2.42 (s, 3H, CH_3), 2.06, 2.05, 2.01, 1.82 (4s, 12H, acetyl); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.7, 170.1, 169.5, 169.0 (4C, C=O), 144.7 (C-4'), 143.8 (C-Ar), 136.5 (C-Ar), 129.9 (2CH-Ar), 127.3 (2CH-Ar), 121.2 (C-5'), 85.8 (C-1), 75.1 (C-5), 72.7 (C-3), 70.5 (C-2), 67.7 (C-4), 61.6 (C-6), 38.7 (CH_2NH), 21.6 (CH_3), 20.8, 20.6, 20.6, 20.2 (4CH_3, acetyl); **HRMS** [ESI+] *m/z* $[M+H]^+$ calcd for $C_{24}H_{31}N_4O_{11}S$ 583.1705 ; found 583.1695

***N*-{[1-(β-D-Glucopyranosyl)-1,2,3-triazol-4-yl]methyl}-*p*-toluenesulfonamide (8)**

Prepared according to general procedure B. White foam; $\mathbf{R_f}$ = 0.21 (CH_2Cl_2/MeOH 85:15); $[\alpha]_D^{20}$ = + 3 (c 1, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.95 (s, 1H, H-5'), 7.74 (d, 2H, *J* = 8.2 Hz, H-Ar), 7.38 (d, 2H, *J* = 8.2 Hz, H-Ar), 5.56 (d, 1H, *J* = 9.2 Hz, H-1), 4.15 (s, 2H, C*H*$_2$NH), 3.88 (dd, 1H, *J* = 12.2, 1.5 Hz, H-6a), 3.83 (pdd, 1H, *J* = 9.2 Hz, H-2), 3.72 (dd, 1H, *J* = 12.2, 5.3 Hz, H-6b), 3.54-3.62 (m, 2H, H-3, H-5), 3.49 (pdd, 1H, *J* = 9.2 Hz, H-4), 2.43 (s, 3H, CH_3); **^{13}C NMR** (CD_3OD, 100 MHz) δ 145.7 (C-4'), 144.9 (C-Ar), 138.5 (C-Ar), 130.9 (2CH-Ar), 128.1 (2CH-Ar), 123.8 (C-5'), 89.5 (C-1), 81.0 (C-5), 78.4 (C-3), 74.0 (C-2), 70.8 (C-4), 62.3 (C-6), 39.1 (CH_2NH), 21.5 (CH_3); **HRMS** [ESI+] *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}N_4O_7S$ 415.1286; found 415.1290

***N*-{[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}-*N*-(*tert*-butoxycarbonyl)-L-tyrosinamide (9)**

To a solution of Boc-Tyrosine (394 mg, 1.40 mmol, 3 eq) in a 1:1 mixture of anhydrous DMF and CH_2Cl_2 (10 mL) at –10°C under Ar was added HOBt (254 mg, 1.88 mmol, 4 eq.) and EDCI (360 mg, 1.88 mmol, 4 eq.). The mixture was stirred at –10°C for 40 min. and then a solution of amine **4** (200 mg, 0.47 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) was added dropwise over 60 min. using a syringe pump. The mixture was then allowed to warm up to r.t., stirred for an additional 16 h and concentrated *in vacuo*. The crude material was diluted with EtOAc (50 mL), washed with aqueous solutions of HCl 1N (2×20 mL), saturated $NaHCO_3$ (2×20 mL), H_2O (2×20 mL) and brine (2×20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified over silica gel chromatography (PE/EtOAc 3:7) to afford **9** as a white foam (276 mg, 85%).

$\mathbf{R_f}$ = 0.39 (EtOAc/PE 8:2); $[\alpha]_D^{20}$ = – 41 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.54 (s, 1H, H-5'), 6.92 (d, 2H, *J* = 7.8 Hz, H-Ar), 6.69 (d, 2H, *J* = 8.2 Hz, H-Ar), 5.88 (d, 1H, *J* = 9.0 Hz, H-1), 5.48 (pdd, 1H, *J* = 9.3 Hz, H-2), 5.42 (pdd, 1H, *J* = 9.3 Hz, H-3), 5.31 (pdd, 1H, *J* = 9.6 Hz, H-4), 5.23 (d, 1H, *J* = 7.3 Hz, C*H*NH), 4.43 (br s, 2H, C*H*$_2$NH), 4.33 (dd, 1H, *J* = 12.6, 4.9 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.6, 1.9 Hz, H-6b), 4.05 (ddd, 1H, *J* = 9.9, 4.8, 2.0 Hz, H-5), 3.04 (dd, 1H, *J* = 13.6, 5.2 Hz, C*H*$_2$Ph), 2.86 (dd, 1H, *J* = 13.6, 7.9 Hz, C*H*$_2$Ph), 2.07, 2.06, 2.03, 1.85 (4s, 12H, acetyl), 1.41 (s, 9H, *t*Bu); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.7 (CONH), 170.9, 170.2, 169.6, 169.2 (4C, acetyl), 155.5 (CO_2*t*Bu), 155.3 (C-Ar), 145.3 (C-4'), 130.6 (2CH-Ar), 128.0 (C-Ar), 121.3 (C-5'), 115.7 (2CH-Ar), 85.8 (C-1), 80.4 (C, tBu), 75.2 (C-5), 72.9 (C-3), 70.4 (C-2), 67.8 (C-4), 61.8 (C-6), 56.1 (CHNH), 38.0 (CH_2Ph) 34.8 (CH_2NH), 28.4 (3CH_3, *t*Bu), 20.8, 20.7, 20.7, 20.3 (4CH_3, acetyl); **HRMS** [ESI+] *m/z* $[M+H]^+$ calcd for $C_{31}H_{42}N_5O_{13}$ 692.2774; found 692.2769

***N*-{[1-(β-D-Glucopyranosyl)-1,2,3-triazol-4-yl]methyl}-L-tyrosinamide (10)**

To a solution of **9** (60 mg, 0.10 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) was added TFA (1 mL). The mixture was stirred at r.t. for 4 h and concentrated *in vacuo*. The product was then suspended in anhydrous MeOH (10 mL) and MeONa (2.2 mg, 0.04 mmol, 0.4 eq.) was added. The mixture was stirred at r.t. for 16 h and concentrated *in vacuo*. The crude product was purified by C_{18} reverse phase silica gel chromatography (H_2O/MeOH 10:0 then 1:1) to afford **10** as a white foam.

$[\alpha]_D^{20}$ = + 11 (c 1, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.70 (s, 1H, H-5'), 6.99 (d, 2H, *J* = 8.5 Hz, H-Ar), 6.71 (d, 2H, *J* = 8.5 Hz, H-Ar), 5.55 (d, 1H, *J* = 9.2 Hz, H-1), 4.45 (d, 1H, *J* = 15.4 Hz, C*H*NH), 4.37 (d, 1H, *J* = 15.4 Hz, C*H*NH), 3.88-3.92 (m, 2H, H-2, H-6a), 3.73 (dd, 1H, *J* = 12.1, 5.3 Hz, H-6b), 3.51-3.61 (m, 4H, H-3, H-4, H-5, C*H*NH_2), 2.87 (dd, 1H, *J* = 13.4, 7.1 Hz, C*H*$_2$-Ph), 2.79 (dd, 1H, *J* = 13.5, 6.7 Hz, C*H*$_2$-Ph); **^{13}C NMR** (CD_3OD, 100 MHz) δ 176.3 (CONH), 157.3 (C-Ar), 146.1 (C-4'), 131.5 (2CH-Ar), 129.1 (C-Ar), 123.5 (C-5'), 116.4 (2CH-Ar), 89.5 (C-1), 81.1 (C-5), 78.5 (C-3), 73.9 (C-2), 70.9 (C-4), 62.4 (C-6), 57.8 (CHNH_2), 41.3 (*C*H_2-Ph), 35.5 (CH_2NH); **HRMS** [ESI+] *m/z* $[M+Na]^+$ calcd for $C_{18}H_{25}N_5O_7$ 423.1755; found 423.1750

4-Bromomethyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (11)

A mixture of azide **1** (2.00 g, 5.36 mmol, 1 eq.), propargyl bromide (0.924 mL, 10.72 mmol, 2 eq.), $CuSO_4$•H_2O (267 mg, 1.07 mmol, 0.2 eq.) and sodium ascorbate (2.123 g, 10.72 mmol, 2 eq.) in *t*BuOH/H_2O (20 mL, 1:1) was stirred at r.t. for 16 h and concentrated *in vacuo*. The crude mixture was filtered through Celite and washed with EtOAc. The solid was discarded and the filtrate was concentrated *in vacuo* and purified over silica gel chromatography (PE/EtOAc 6:4) to afford **11** as a white powder (2.243 g, 85%).

mp = 153-154°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.52 (PE/EtOAc 1:1); $[\alpha]_D^{20}$ = – 22 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.82 (s, 1H, H-5'), 5.86 (d, 1H, *J* = 9.2 Hz, H-1), 5.40-5.43 (m, 2H, H-2, H-3), 5.23 (pdd, 1H, *J* = 9.8 Hz, H-4), 4.55 (s, 2H, CH_2Br), 4.30 (dd, 1H, *J* =

12.7, 5.0 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.6, 2.0 Hz, H-6b), 4.00 (ddd,1H, *J* = 10.1, 5.0, 2.0 Hz, H-5), 2.08, 2.06, 2.0, 1.88 (4s, 12H, acetyl); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.6, 70.0, 169.5, 169.1 (4C, C=O), 145.5 (C-4'), 121.3 (C-5'), 85.9 (C-1), 75.4 (C-5), 72.6 (C-3), 70.4 (C-2), 67.8 (C-4), 61.6 (C-6), 21.1 (CH_2Br), 20.8, 20.7, 20.7, 20.3 ($4CH_3$, acetyl); **HRMS** [ESI+] *m/z* $[M+Na]^+$ calcd for $C_{17}H_{22}BrN_3NaO_9$ 514.0437; found 514.0432

Diethyl {[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}phosphonate (12)

A solution of **11** (100 mg, 0.20 mmol, 1 eq.) in triethylphosphite (5 mL) was heated at 140°C under microwave conditions for 60 min, allowed to cool down to r.t. and concentrated *in vacuo*. The crude mixture was purified over silica gel chromatography (PE/EtOAc 1:1 then 3:7) to afford **12** as a white powder (96 mg, 86%).

mp = 132-133°C (CH_2Cl_2/PE); $\mathbf{R_f}$ = 0.09 (EtOAc/PE 113); $\mathbf{[\alpha]_D^{20}}$ = – 18 (c 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81 (d, 1H, *J* = 2.2 Hz, H-5'), 5.83 (d, 1H, *J* = 9.0 Hz, H-1), 5.37-5.45 (m, 2H, H-2, H-3), 5.23 (pdd, 1H, *J* = 9.7 Hz, H-4), 4.29 (dd, 1H, *J* = 12.6, 4.9 Hz, H-6a), 4.04-4.15 (m, 5H, H-6b, C*H*$_2$CH$_3$), 3.98 (ddd, 1H, *J* = 10.1, 4.8, 2.0 Hz, H-5), 3.31 (d, 2H, *J* = 20.5 Hz, CH_2P), 2.08, 2.05, 2.02, 1.86 (4s, 12H, acetyl), 1.30 (t, 3H, *J* = 6.3 Hz, CH_2CH_3), 1.26 (t, 3H, *J* = 6.3 Hz, CH_2CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 170.7, 170.1, 169.5, 168.9 (4C, C=O), 139.5 (d, *J* = 6.8 Hz, C-4'), 121.2 (d, *J* = 4.2 Hz, C-5'), 85.9 (C-1), 75.2 (C-5), 72.8 (C-3), 70.4 (C-2), 67.7 (C-4), 62.6 (d, *J* = 3.4 Hz, CH_2CH_3), 62.5 (d, *J* = 3.3 Hz, CH_2CH_3), 61.6 (C-6), 24.3 (d, *J* = 142.9 Hz, CH_2P), 20.8, 20.7, 20.7, 20.2 ($4CH_3$, acetyl), 16.5 (d, *J* = 5.8 Hz, CH_2CH_3), 16.4 (d, *J* = 5.9 Hz, CH_2CH_3); **HRMS** [ESI+] *m/z* $[M+Na]^+$ calcd for $C_{21}H_{32}N_3NaO_{12}P$ 572.1616; found 572.1601

Diethyl {[1-(β-D-glucopyranosyl)-1,2,3-triazol-4-yl]methyl}phosphonate (13)

Prepared according to general procedure B. White powder; **mp** = 132-133°C (MeOH/CH_2Cl_2); $\mathbf{R_f}$ = 0.25 (EtOAc/MeOH 8:2); $\mathbf{[\alpha]_D^{20}}$ = + 4 (c 1, MeOH); **^{1}H NMR** (CD_3OD, 400 MHz) δ 8.10 (d, 1H, *J* = 2.6 Hz, H-5'), 5.60 (d, 1H, *J* = 9.2 Hz, H-1), 4.07-4.15 (m, 4H, C*H*$_2$CH$_3$), 3.86-3.91 (m, 2H, H-2, H-6a), 3.72 (dd, 1H, *J* = 12.2, 5.4 Hz, H-6b), 3.48-3.60 (m, 3H, H-3, H-4, H-5), 3.40 (d, 2H, *J* = 20.6 Hz, CH_2P), 1.31 (m, 6H, CH_2CH_3); **^{13}C NMR** (CD_3OD, 100 MHz) δ 139.3 (d, *J* = 8.2 Hz, C-4'), 124.2 (d, *J* = 5.2 Hz, C-5'), 89.6 (C-1), 81.1 (C-5), 78.4 (C-3), 74.0 (C-2), 70.9 (C-4), 64.1 (d, *J* = 3.8 Hz, CH_2CH_3), 64.0 (d, *J* = 3.8 Hz, CH_2CH_3), 62.4 (C-6), 24.1 (d, *J* = 143.0 Hz, CH_2P), 16.7 (d, *J* = 6.0 Hz, 2×CH_2CH_3); **HRMS** [ESI+] *m/z* $[M+Na]^+$ calcd for $C_{13}H_{25}N_3O_8P$ 382.1374; found 382.1367

Glycogen phosphorylase inhibition measurements (IC_{50} values). Glycogen phosphorylase *b* was prepared from rabbit skeletal muscle according to the method of Fischer and Krebs,[47] using dithiothreitol instead of L-cysteine, and recrystallized at least three times before use with a specific activity of 55 U/mg protein. Kinetic experiments were performed in the direction of glycogen synthesis as described previously.[14] 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 inhibitor. Inhibitor was dissolved in dimethyl sulfoxide (DMSO) and diluted in the assay buffer (50 mM triethanolammine, 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 means of standard errors for all calculated kinetic parameters averaged to less than 10%. IC_{50} values were determined in the presence of 4 mM α-D-glucose-1-phosphate, 1 mM AMP, 1% glycogen, and varying concentrations of the inhibitor.

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Supplementary Material

Supplementary data (^{1}H and ^{13}C NMR for all new compounds) associated with this article can be found, in the online version, at doi:xxxxxxxxxxxxxx.

Highlights

1) Glycogen phosphorylase is a target enzyme for the regulation of glycaemia in the context of type 2 diabetes.
2) Synthesis of 4-amidomethyl-1-glucosyl-1,2,3-triazoles was achieved from the condensation of glucosyl azide and Boc-protected propargyl amine.
3) Inhibition of GP was in the high micromolar range for the designed inhibitors.
4) The Boc-carbamate group could be identified as a potential pharmacophore for the inhibition of GP.