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PII: S0008-6215(13)00088-8
DOI: http://dx.doi.org/10.1016/j.carres.2013.03.009
Reference: CAR 6420

To appear in: *Carbohydrate Research*

Received Date: 19 January 2013
Revised Date: 8 March 2013
Accepted Date: 12 March 2013

Please cite this article as: Szőcs, B., Tóth, M., Docsa, T., Gergely, P., Somsák, L., Synthesis of 2-(β-D-glucopyranosyl)-5-(substituted-amino)-1,3,4-oxa- and -thiadiazoles for inhibition of glycogen phosphorylase, *Carbohydrate Research* (2013), doi: http://dx.doi.org/10.1016/j.carres.2013.03.009

# Synthesis of 2-(β-D-glucopyranosyl)-5-(substituted-amino)-1,3,4-oxa- and -thiadiazoles for inhibition of glycogen phosphorylase

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**Abstract**

*O*-Perbenzoylated 4-phenyl-[*C*-(β-D-glucopyranosyl)formaldehyde]semicarbazone was prepared in the reaction of *O*-perbenzoylated β-D-glucopyranosyl cyanide and 4-phenylsemicarbazide in the presence of Raney-Ni. Acylation of *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde semicarbazone furnished the corresponding 4-acyl-[*C*-(β-D-glucopyranosyl)formaldehyde]semicarbazones. The reaction of *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde semicarbazone with the corresponding thiosemicarbazide resulted in *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde thiosemicarbazone and its 4-phenyl derivative. Acylation of *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde thiosemicarbazone provided the corresponding 4-acyl-2-acylamino-5-(β-D-glucopyranosyl)-$\Delta^2$-1,3,4-thiadiazolidines. Oxidative transformations of these precursors gave *O*-protected 2-(β-D-glucopyranosyl)-5-substituted-amino-1,3,4-oxa- and -thiadiazoles. The *O*-benzoyl protecting groups were removed under base-catalyzed transesterification conditions. The *C*-

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glucopyranosyl heterocyclic compounds proved inactive against rabbit muscle glycogen phosphorylase *b*, however, the semicarbazones showed moderate inhibition (best inhibitor was 4-phenyl-[C-(β-D-glucopyranosyl)formaldehyde]semicarbazone ($K_i$ = 29 μM).

**Keywords**

*C*-glycosyl-formaldehyde (thio)semicarbazone, *C*-glycosyl-1,3,4-oxadiazole, *C*-glycosyl-1,3,4-thiadiazole, glycogen phosphorylase, inhibitor

## 1. Introduction

Glycogen phosphorylase (EC 2.4.1.1) inhibitors (GPIs) have been considered as possible means for therapeutic intervention in type 2 diabetes and some other diseased states (e. g. early cardiac and cardiovascular disease in non-diabetics, cardiac arrhythmias, ischemic injuries, tumour growth) as rationalized in the recent review literature.[1-5] Among several compound classes[4,6] glucose derivatives are one of the most intensively investigated inhibitors.[5,7] The quoted review articles[5,7] provide the reader with a detailed description of the structure–activity relationships (SAR) of glucose analogue GPIs, therefore, only those features are summarized hereinafter which form the direct basis of our compound design. *N*-Acyl-β-D-glucopyranosylamines[8] (Chart 1, **I**: e. g. for R = 2-naphthyl $K_i$ measured against rabbit muscle GP*b* (RMGP*b*)[9] was 10-13 μM[8,10]), *N*-aryl-*N*'-β-D-glucopyranosyl ureas[4,11] **II** (R = 2-naphthyl: $K_i$ (RMGP*b*) 5.2 μM), as well as *N*-acyl-*N*'-β-D-glucopyranosyl urea derivatives[4,12] **III** (R = 2-naphthyl: $K_i$ (RMGP*b*) 0.35 μM) have been shown to inhibit the enzyme in the low micromolar range. As a part of a program to replace the NHCO moiety of the above compounds by non-classical bioisosteric heterocyclic linkers, among others we have carried out the synthesis of compounds **IA**.[13] Enzymatic tests as well as crystallographic studies revealed high similarity of the amide (see $K_i$ of **I** above) and the 1,2,3-triazole type (for **IA** R = 2-naphthyl: $K_i$ (RMGPb) 16 μM) inhibitors both in binding strength and structural features of the enzyme-inhibitor complexes.[10] Applying the isomeric oxadiazoles **B**, **D**, and **E** as linkers resulted in inhibitors of varying efficiency, whereby the 3-aryl-5-β-D-glucopyranosyl-1,2,4-oxadiazole (**IE** type) derivatives proved to be the most potent compounds (for the best inhibitor where R = 2-naphthyl the $K_i$ (RMGPb) was 2.4 μM).[14,15]

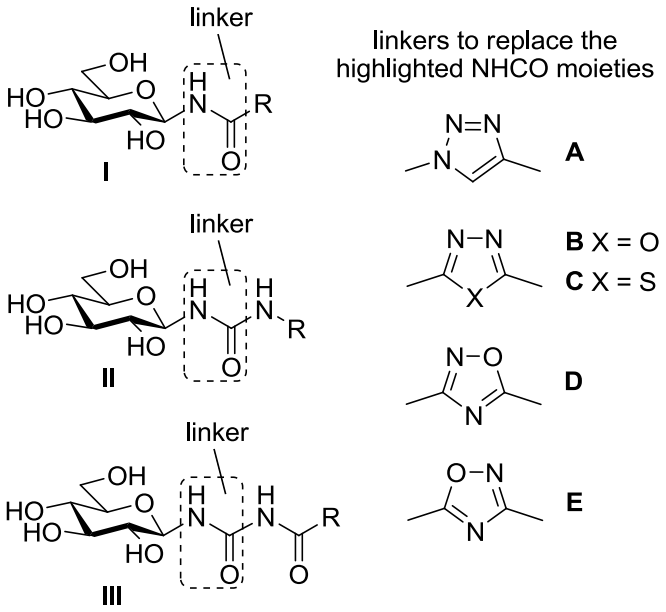



**Chart 1.**

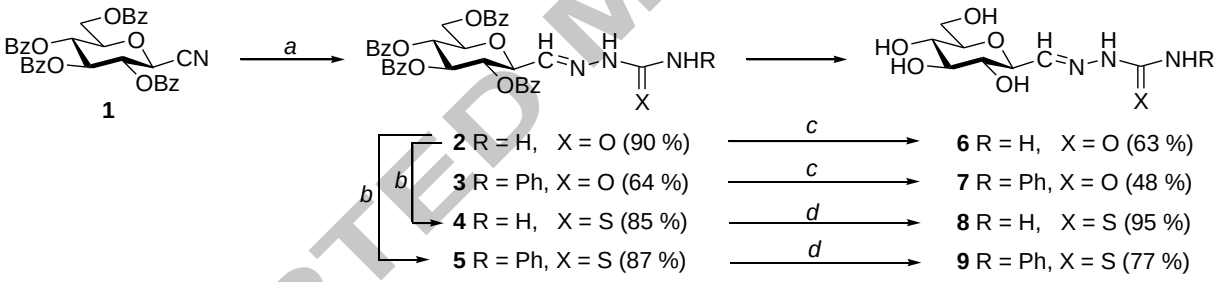
Herein we report on the synthesis and enzymatic test of compounds of type **II** and **III** with 1,3,4-oxadiazole **B** and 1,3,4-thiadiazole **C** as linkers representing bioisosteric replacements of NHCO moieties of *N*-substituted-*N*'-β-D-glucopyranosyl ureas. These studies contribute to an extension of SAR related to interactions of inhibitors in the β-channel of the enzyme which can accommodate aglycons of glucose analogue compounds and is lined with amino acid side chains of mixed character.[16]

## 2. Results and Discussion

For the formation of the heterocyclic parts of the target compounds oxidative ring closure of (thio)semicarbazones (similar to that applied for the syntheses of **IB**[15]) was envisaged as the key step. To this end, the protected *C*-(β-D-glucopyranosyl)formaldehyde semicarbazone **2** was prepared by a reaction of $NH_2C(=O)NHNH_2$ with *O*-perbenzoylated β-D-glucopyranosyl cyanide[17] **1** in the presence of Raney Ni and $NaH_2PO_2$ at 40 °C (Scheme 1) as described earlier.[18] *O*-Perbenzoylated 4-phenyl-[*C*-(β-D-glucopyranosyl)formaldehyde]semicarbazone **3**

was obtained in a similar way using $PhNHC(=O)NHNH_2$ as the trapping agent. Debenzoylation was performed by the Zemplén protocol to result in moderate yields of semicarbazones **6** and **7**.

In order to get thiosemicarbazones **4** and **5**, acid catalyzed transimination of **2** was carried out because the direct transformation of β-D-glucopyranosyl cyanide **1** into thiosemicarbazones failed. Thus, semicarbazone **2** was reacted with $NH_2C(=S)NHNH_2$ or $PhNHC(=S)NHNH_2$ in glacial AcOH at 70 °C to give the corresponding thiosemicarbazones **4** and **5**, respectively. Removal of the benzoyl protecting groups in **4** and **5** was carried out by LiOH in MeOH to give compounds **8** and **9**, respectively, in satisfactory yields.

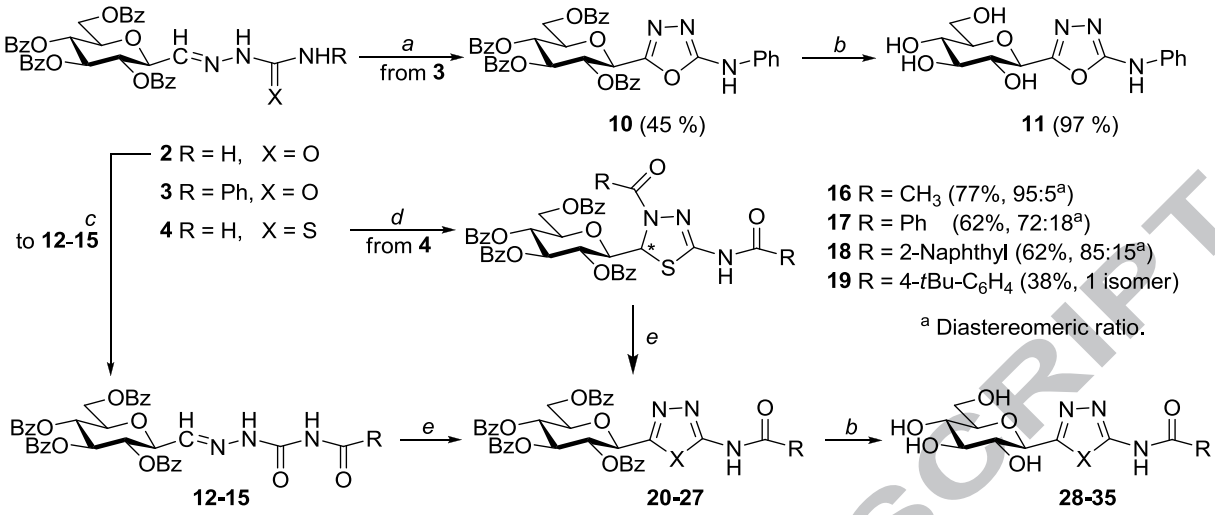



**Scheme 1.** Reagents and conditions: (a) $RNHC(=O)NHNH_2$, Raney Ni, $NaH_2PO_2$, $H_2O$, AcOH, pyridine, 40 °C; (b) $RNHC(=S)NHNH_2$, AcOH, 70 °C; (c) NaOMe, dry MeOH, 25 °C; (d) LiOH, dry MeOH, 0 °C.

To obtain precursors for compounds **IIIB** semicarbazone **2** was treated by acid chlorides in $CH_2Cl_2$ in the presence of $Et_3N$ to give *O*-perbenzoylated 4-acyl-[*C*-(β-D-glucopyranosyl)formaldehyde]semicarbazones **12-15** in satisfactory yields (Scheme 2). Under these conditions no reaction took place with thiosemicarbazone **3**. Acylation of **3** in dry pyridine at 80 °C resulted in the formation of 4-acyl-2-acylamino-5-(β-D-glucopyranosyl)-$\Delta^2$-

1,3,4-thiadiazolines **16-19** as inseparable mixtures of two diastereoisomers in good yields. This observation is in accord with literature experiences.[19]

Ring closing reactions of the precursors under oxidative conditions were studied next. Semicarbazone **3** was reacted with $Pb(OAc)_4$ in glacial AcOH at 70 °C to furnish *O*-perbenzoylated 2-phenylamino-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole **10** (Scheme 2). Trials to use other oxidizing agents such as $FeCl_3$ or PIDA failed, **3** was recovered in these reactions. Deprotection of **10** was achieved by the Zemplén method to give **11** in an excellent yield. Thiosemicarbazone **4** resisted to several oxidation reagents (PIDA, $Pb(OAc)_4$, $FeCl_3$, $Br_2$, $K_3Fe(CN)_6$). Semicarbazones **12-15** were reacted with PIDA in $CH_2Cl_2$ at rt to get *O*-perbenzoylated 2-acylamino-5-(β-D-glucopyranosyl)-1,3,4-oxadiazoles **20-23** in good yields (Scheme2). Thiadiazolines **16-19** were oxidized in a similar way to result in 1,3,4-thiadiazoles **24-27.** Debenzoylations were performed by the Zemplén protocol to give good and excellent yields of 1,3,4-oxadiazoles **28-31** and 1,3,4-thiadiazoles **32-35**.




| | | X = O | X = S | X = O | X = S |
|---|---|---|---|---|---|
| R = $CH_3$ | **12** (47 %) | **20** (50 %) | **24** (67 %) | **28** (41 %) | **32** (92 %) |
| R = Ph | **13** (70 %) | **21** (57 %) | **25** (68 %) | **29** (87 %) | **33** (68 %) |
| R = 2-Naphthyl | **14** (50 %) | **22** (69 %) | **26** (59 %) | **30** (93 %) | **34** (57 %) |
| R = 4-*t*Bu-$C_6H_4$ | **15** (55 %) | **23** (60 %) | **27** (84 %) | **31** (76 %) | **35** (72 %) |

**Scheme 2.** Reagents and conditions: (a) $Pb(OAc)_4$, AcOH, 70 °C; (b) NaOMe, dry MeOH, 25 °C; (c) RCOCl, $Et_3N$, dry $CH_2Cl_2$; (d) RCOCl, dry pyridine, 80 °C; (e) PIDA, $CH_2Cl_2$, 25 °C.

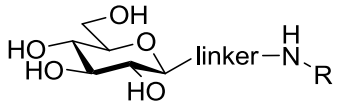
The deprotected compounds were tested for their inhibition potency against rabbit muscle glycogen phosphorylase *b* (RMGP*b*) according to the protocol described earlier.[20] The results are summarized in Table 1 also showing the inhibitory efficiency of some relevant reference compounds.

Replacement of the NHCO moiety in compound type **II** (entry 1) by a 1,3,4-oxadiazole ring (**11**) resulted in a loss of inhibition. A similar observation was made with compounds type **III** whereby on changing the NHCO group of the acylurea derivatives (entry 2) to either 1,3,4-oxadiazole (entry 3, **28-31**) or 1,3,4-thiadiazole (entry 4, **32-35**) the efficiency was lost. These findings resemble those obtained with compounds type **IB** in Chart 1 where 1,3,4-oxadiazole replacements in *N*-acyl-glucopyranosylamines resulted in practically inactive compounds.[15] It

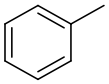
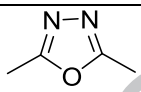
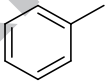
follows from these results that the 1,3,4-oxadiazole and 1,3,4-thiadiazole moieties cannot contribute to favourable interactions in the β-channel of RMGP*b*.

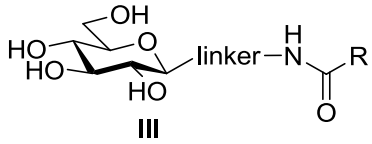
Interestingly, semicarbazones **6** and **7** (entry 6) and thiosemicarbazones **8** and **9** (entry 7), the "open chain" precursors of the target compounds of this work, showed week to moderate inhibition. Semicarbazones **6** and **7** are better inhibitors than the thiosemicarbazone counterparts **8** and **9**. Phenyl derivatives **7** and **9** are more efficient than the unsubstituted compounds **6** and **8**, respectively, and this is in agreement with the general trend to show stronger inhibition by those compounds which have a large(r) aromatic part in the aglycon.[4] A comparison of **7** (actually the best inhibitor in this study) to the biuret type inhibitor (entry 5) indicates no significant difference in the inhibition constants. This may reveal that interactions of the whole NHCO linker moiety or its carbonyl group has probably less significance in binding to the enzyme than those of the "second" NHCO unit.

**Table 1.** Inhibition of rabbit muscle glycogen phosphorylase *b* (RMGP*b*) by selected glucose derivatives and the new compounds ($K_i$ [μM])

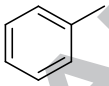
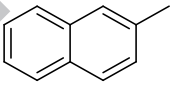
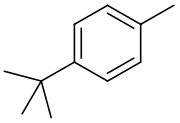
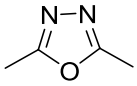
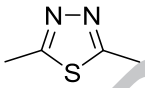


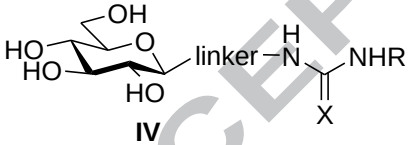
**II**

| Entry | linker | R | linker | R |
|---|---|---|---|---|
| 1 | NHCO |  |  |  |
| | | 18[4] | | **11** No inh.[a] |

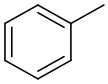


**III**

| | | R | | | |
|---|---|---|---|---|---|
| | linker | $CH_3$ |  |  |  |
| 2 | NHCO | 305[21] | 4.6[21] | 0.35[4] | 0.7[4] |
| 3 |  | **28** No inh.[a] | **29** No inh.[a] | **30** No inh.[a] | **31** No inh.[a] |
| 4 |  | **32** No inh.[a] | **33** No inh.[a] | **34** No inh.[a] | **35** No inh.[a] |



**IV**

| | | | R | |
|---|---|---|---|---|
| | linker | X | H |  |
| 5 | NHCO | O | - | 21[4] |
| 6 | CH=N | O | **6** 332[b] | **7** 29 |
| 7 | CH=N | S | **8** No inh. | **9** 300[b] |

[a]No inhibition at a tested concentration of 625 μM.

[b]Calculated from the $IC_{50}$ value by using a web-based tool.[22]

## 3. Conclusion

The reductive transformation of D-glycopyranosyl cyanides in the presence of acylhydrazines was extended to the preparation of new anhydro-aldose semicarbazone and thiosemicarbazone derivatives. Acylation of semicarbazones yielded the expected 4-acyl semicarbazones, while under similar conditions thiosemicarbazones gave *O*-peracylated 4-acyl-2-acylamino-5-(β-D-glucopyranosyl)-$\Delta^2$-1,3,4-thiadiazolines. Oxidation of the aforementioned precursors resulted in protected 2-(β-D-glucopyranosyl)-5-(substituted-amino)-1,3,4-oxa- and thiadiazoles, respectively. After *O*-deprotection enzyme kinetic measurements showed the 1,3,4-oxa- and -thiadiazoles to be inactive against rabbit muscle glycogen phosphorylase *b*. However, the precursor "open chain" 4-phenyl semicarbazone proved to be a low micromolar GPI, equipotent with a biuret derivative of similar chain length between the sugar and the aromatic part of the molecule. Replacement of the oxygen by a sulphur atom caused the loss of activity. This latter finding may indicate a difference in contribution to the binding of the two NHCO unites of *N*-acyl-*N'*-glucopyranosyl urea type inhibitors of glycogen phosphorylase.

## 4. Experimental

### 4.1. General methods

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker 360 (360/90 MHz for $^1$H/$^{13}$C) or Bruker 400 (400/100 MHz for $^1$H/$^{13}$C) spectrometers. Chemical shifts are referenced to TMS as the internal reference ($^1$H), or to the residual solvent signals ($^{13}$C). Microanalyses were performed on an Elementar vario Micro cube. ESI-MS were recorded with a Thermo Scientific LTQ XL instrument. TLC was performed on DC-Alurolle Kieselgel 60 $F_{254}$

(Merck). TLC plates were visualized under UV light, and by gentle heating with a commercially available heat gun without any charring reagent. For column chromatography Kieselgel 60 (Merck, particle size (0.063-0.200mm) was applied. Organic solutions were dried over anhydrous $MgSO_4$, and concentrated under diminished pressure at 40-50 °C (water bath).

**4.2. 4-Phenyl-[*C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde]semicarbazone (3)**

Raney Ni (3.53 g, from an aqueous suspension, Merck) was added at rt to a vigorously stirred solution of pyridine (14 mL), $H_2O$ (9 mL), and AcOH (9 mL). Then, $NaH_2PO_2$ (1.76 g, 20.0 mmol), (2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl) cyanide[17] (**1**, 1.50 g, 2.48 mmol), and $PhNHC(=O)NHNH_2$ (0.75 g, 4.96 mmol) were added to the mixture. The reaction mixture was stirred heated at 40 °C. When the reaction was complete (TLC, 1:2 EtOAc–hexane) the insoluble materials were filtered off with suction, and washed with EtOAc (3 x 15 mL). The organic layer of the filtrate was separated, washed with 10% HCl (2 x 15 mL), saturated $NaHCO_3$ solution (3 x 20 mL), $H_2O$ (2 x 15 mL), dried, and concentrated under reduced pressure. Traces of pyridine were removed by repeated co-evaporations with toluene. The crude product was purified by column chromatography (2:3 EtOAc–hexane) to yield 1.17 g (64%) of **3** as a white amorphous product. $[\alpha]_D$ = +33 (*c* 0.52, $CHCl_3$); $R_f$ : 0.44 (1:1 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 10.36 (1H, s, N*H*), 8.20 (1H, s, NH), 8.05-7.02 (26H, m, Ar, CH=N), 6.08, 6.03, 5.77 (3H, 3 pt, $J$ = 9.2, 9.5 Hz in each, H-2, H-3, H-4), 4.67 (1H, dd, $J_{6a,6b}$ = 12.7 Hz, H-6a), 4.53 (1H, dd, $J_{1,CH=N}$ = 4.1 Hz, $J_{1,2}$ = 9.1 Hz, H-1), 4.40 (1H, dd, H-6b), 4.25 (1H, ddd, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 4.5 Hz, $J_{4,5}$ = 9.9 Hz, H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) δ (ppm) 166.0, 165.8, 165.0 (CO), 153.7 (NHCONH), 138.0 (CH=N), 136.5-119.4

(Ar), 76.3, 76.2, 74.3, 69.3 (C-1–C-5), 63.0 (C-6). Anal. Calcd. for $C_{42}H_{35}N_3O_{10}$ (741.74): C, 68.01, H, 4.76; N, 5.67. Found: C, 69.00; H, 4.83; N, 5.62.

### 4.3. *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde thiosemicarbazone (4)

*C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde semicarbazone[18] (**2**, 1.50 g, 2.25 mmol) was dissolved in glacial AcOH (65 mL) and then $NH_2C(=S)NHNH_2$ (0.83 g, 9.05 mmol) was added. The mixture was stirred and heated at 70 °C. The reaction was monitored by TLC (1:1 EtOAc-hexane). When the reaction was complete, the reaction mixture was diluted with $H_2O$ (200 mL), and extracted with EtOAc (4 x 20 mL), and washed with $NaHCO_3$ (3 x 25 mL), and $H_2O$ (1 x 20 mL). The organic phase was dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (1:1 EtOAc–hexane) to give 1.30 g (85%) of **4** as a yellow amorphous product **4**. $[\alpha]_D$ = +11 (*c* 0.35, $CHCl_3$); $R_f$ : 0.33 (1:2 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 9.94 (1H, s, NH), 8.07-7.10 (21H, m, Ar, CH=N), 6.34 (1H, s, $J$ = 2.4 Hz, N*H*), 5.98, 5.87, 5.71 (3H, 3 pt, $J$ = 9.5, 9.8 Hz in each, H-2, H-3, H-4), 4.66 (1H, dd, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.49-4.43 (2H, m, H-1, H-6b), 4.22 (1H, ddd, $J_{5,6a}$ = 2.9 Hz, $J_{5,6b}$ = 5.0 Hz, $J_{4,5}$ = 9.9 Hz, H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 179.2 (CS), 166.1, 165.9, 165.8, 165.1 (CO), 139.2 (CH=N), 133.7-128.3 (Ar), 76.9, 76.4, 73.9, 69.6, 69.1 (C-1–C-5), 62.9 (C-6). Anal. Calcd. for $C_{36}H_{31}N_3O_9S$ (681.71): C, 63.43, H, 4.58; N, 6.16; S, 4.70. Found: C, 63.54; H, 4.67; N, 6.09; S, 4.78.

**4.4. 4-Phenyl-[C-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde]thiosemicarbazone (5)**

*C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde semicarbazone[18] (**2**, 1.00 g, 1.50 mmol) was dissolved in glacial AcOH (43 mL) and then $PhNHC(=S)NHNH_2$ (0.83 g, 9.05 mmol) was added. The mixture was stirred and heated at 70 °C. The reaction was monitored by TLC (1:1 EtOAc–hexane). When the reaction was complete, the reaction mixture was diluted with $H_2O$ (150 mL), and extracted with EtOAc (4 x 15 mL), and washed with $NaHCO_3$ (3 x 20 mL), and $H_2O$ (1 x 15 mL). The organic phase was dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (1:1.5 EtOAc–hexane) to yield 1.00 g (87%) of **5** as a yellow amorphous product. $[\alpha]_D$ = +7 (*c* 0.33, $CHCl_3$); $R_f$: 0.55 (1:1 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 10.74 (1H, s, NH), 9.19 (1H, s, NH), 8.04-7.18 (26H, m, Ar, CH=N), 6.09-5.99 (2H, m, H-2 and/or H-3 and/or H-4), 5.76 (1H, 1 pt, $J$ = 9.3 Hz, H-2 or H-3 or H-4), 4.66 (1H, dd, $J_{5,6a}$ = 2.4 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.54 (1H, dd, $J_{1,\,CH=N}$ = 4.0 Hz, $J_{1,2}$ = 9.2 Hz, H-1), 4.49 (1H, dd, $J_{5,6b}$ = 5.3 Hz, H-6b), 4.26-4.22 (1H, m, H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 176.0 (CS), 166.0, 165.2, 165.2, 164.9 (CO), 138.1 (CH=N), 137.6-124.5 (Ar), 76.0, 76.1, 74.1, 69.33, 69.1 (C-1–C-5), 62.8 (C-6). Anal. Calcd. for $C_{42}H_{35}N_3O_9S$ (757.81): C, 66.57, H, 4.66; N, 5.54; S, 4.23. Found: C, 66.63; H, 4.72; N, 5.58; S, 4.29.

**4.5. 2-Phenylamino-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole (10)**

Semicarbazone **3** (0.20 g, 0.27 mmol) was dissolved in glacial AcOH (3 mL). Then $Pb(OAc)_4$ (0.18 g, 0.40 mmol) was added, and the mixture was stirred and heated at 70 °C. The reaction was monitored by TLC (1:2 EtOAc–hexane). When the reaction was complete, the reaction mixture was diluted with $H_2O$ (15 mL), and extracted with EtOAc (3 x 6ml). The organic phase was dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was

purified by column chromatography (1:2 EtOAc–hexane) to yield 90 mg (45%) of **10** as a white amorphous product. $[\alpha]_D = -17$ (*c* 0.21, $CHCl_3$); $R_f$ : 0.41 (1:2 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 8.87 (1H, s, NH), 8.02-7.00 (25H, m, Ar), 6.08, 5.93, 5.83 (3H, 3 pt, $J$ = 9.5, 9.7 Hz in each, H-2, H-3, H-4), 5.13 (1H, d, $J_{1,2}$ = 9.9 Hz, H-1), 4.65 (1H, dd, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.51 (1H, dd, $J_{5,6b}$ = 5.2 Hz, H-6b) 4.40-4.30 (1H, m, H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.1, 165.7, 165.1, 164.9 (CO), 161.2, 154.8 (C-oxadiazole), 137.4-117.8 (Ar), 76.8, 73.6, 71.9, 70.1, 69.1 (C-1–C-5), 63.0 (C-6). Anal. Calcd. for $C_{42}H_{33}N_3O_{10}$ (739.73): C, 68.19, H, 4.50; N, 5.68. Found: C, 68.25; H, 4.59; N, 5.61.

### 4.6. General procedure I for the synthesis of *O*-perbenzoylated 4-acyl-[*C*-(β-D-glucopyranosyl)formaldehyde]semicarbazones

*C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde semicarbazone[18] (**2**, 0.10 g, 0.15 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL), and then $Et_3N$ (0.063 mL, 0.45 mmol) and an RCOCl (0.45 mmol) were added. The mixture was stirred and heated at 40 °C. The reaction was monitored by TLC (1:1 EtOAc–hexane). When the reaction was complete, the solvent was evaporated, and the residue was purified by column chromatography.

#### 4.6.1. 4-Acetyl-[*C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde]semicarbazone (12)

From **2** (0.19 g, 0.29 mmol) and AcCl (62 μL, 0.87 mmol) according to General procedure I (Section 4.6.). Purified by column chromatography (1:1.5 EtOAc–hexane) to yield 91 mg (47%) of **12** as a yellow amorphous product. $[\alpha]_D = +8$ (*c* 0.35, $CHCl_3$); $R_f$ : 0.37 (1:1 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 9.83 (1H, s, NH), 8.10-7.80 (8H, m, Ar), 7.58-7.18 (14H, m, Ar, CH=N, NH), 6.00, 5.73, 5.66 (3H, 3 pt, $J$ = 9.6, 9.7 Hz in each, H-2, H-3,

H-4), 4.65 (1H, dd, $J_{5,6a}$ = 1.8 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.52-4.37 (2H, m, H-1, H-6b), 4.28-4.17 (1H, m, H-5), 1.91 (3H, s, $CH_3$). $^{13}$C NMR ($CDCl_3$, 360 MHz) δ (ppm) 173.8, 166.1, 165.8, 165.3, 165.1, 158.4 (CO, NHCO, NHCONH), 140.5 (CH=N), 133.4-128.2 (Ar), 77.7, 76.2, 73.7, 70.2, 69.3 (C-1–C-5), 63.0 (C-6), 19.7 ($CH_3$). Anal. Calcd. for $C_{38}H_{33}N_3O_{11}$ (707.68): C, 64.49, H, 4.70; N, 5.94. Found: C, 64.59; H, 4.79; N, 5.86.

**4.6.2. 4-Benzoyl-[C-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde]semicarbazone (13)**

From **2** (0.10 g, 0.15 mmol) and BzCl (53 μL, 0.45 mmol) according to General procedure I (Section 4.6.). Purified by column chromatography (1:1.5 EtOAc–hexane) to yield 81 mg (70%) of **13** as a yellow amorphous product. $[\alpha]_D$ = –61 (*c* 0.18, $CHCl_3$); $R_f$ : 0.51 (1:1 EtOAc–hexane); $^1$H NMR ($CD_3CN$, 360 MHz) $\delta$ (ppm) 10.28 (1H, bs, NH), 8.06-7.30 (27H, m, Ar, CH=N, NH), 6.06, 5.80, 5.73 (3H, 3 pt, *J* = 9.5, 9.8 Hz in each, H-2, H-3, H-4), 4.70-4.65 (1H, m, H-5), 4.59 (2H, dd, $J_{5,6a}$ = 2.4 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.53 (1H, dd, $J_{5,6b}$ = 4.1 Hz, H-6b), 4.42 (1H, d, $J_{1,2}$ = 9.1 Hz, H-1). $^{13}$C NMR ($CD_3CN$, 360 MHz) $\delta$ (ppm) 166.7, 166.4, 166.1, 166.0, 164.5 (CO, NHCO, NHCONH), 145.9 (CH=N) 134.5-118.2 (Ar), 78.6, 76.5, 75.1, 71.5, 70.0 (C-1–C-5), 63.7 (C-6). Anal. Calcd. for $C_{43}H_{35}N_3O_{11}$ (769.75): C, 67.09, H, 4.58; N, 5.46. Found: C, 67.01; H, 4.50; N, 5.55.

**4.6.3. 4-(2-Naphthoyl)-[C-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde]semicarbazone (14)**

From **2** (0.20 g, 0.30 mmol) and 2-naphthoyl chloride (172 mg, 0.90 mmol) according to General procedure I (Section 4.6.). Purified by column chromatography (1:3,5 EtOAc–toluene) to yield 123 mg (50%) of **14** as a yellow amorphous product. $[\alpha]_D$ = –134 (*c* 0.16, $CHCl_3$); $R_f$: 0.43 (1:3.5 EtOAc–toluene); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 9.79 (1H, bs,

NH), 8.18-7.23 (29H, m, Ar, CH=N, NH), 6.06, 5.77, 5.65 (3H, 3 pt, $J$ = 8.7 Hz, 9.3 Hz in each, H-2, H-3, H-4), 4.73-4.58 (2H, m, H-1, H-6a), 4.48 (1H, dd, $J_{5,6b}$ = 4.9 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6b), 4.32-4.19 (1H, m, H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.1, 165.7, 165.3, 164.3 (CO, NHCO, NHCONH), 145.1 (CH=N), 134.8-123.8 (Ar), 78.5, 76.3, 73.6, 70.8, 69.4 (C-1–C-5), 63.2 (C-6). Anal. Calcd. for $C_{47}H_{37}N_3O_{11}$ (819.81): C, 68.86, H, 4.55; N, 5.13. Found: C, 68.97; H, 4.65; N, 5.20.

#### 4.6.4. 4-(4-*tert*-Butylbenzoyl)-[C-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde]semicarbazone (15)

From **2** (0.10 g, 0.15 mmol) and 4-*tert*-butylbenzoyl chloride (88 μL, 0.45 mmol) according to General procedure I (Section 4.6.). Purified by column chromatography (1:2 EtOAc–hexane) to yield 68 mg (55%) of **15** as a yellow amorphous product. $[\alpha]_D$ = +41 (*c* 0.52, $CHCl_3$); $R_f$ : 0.27 (1:2 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 9.66 (1H, bs, NH), 8.01-7.21 (26H, m, Ar, CH=N, NH), 6.06, 5.77, 5.64 (3H, 3 pt, $J$ = 8.6, 9.3 Hz in each, H-2, H-3, H-4), 4.76-4.56 (2H, m, H-1, H-6a), 4.49 (1H, dd, $J_{5,6b}$ = 4.9 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6b), 4.32-4.18 (1H, m, H-5), 1.26 (9H, s, $CH_3$). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.0, 165.9, 165.6, 165.2 (CO, NHCO, NHCONH), 144.6 (CH=N), 155.4, 133.4-125.2 (Ar), 78.6, 76.2, 73.6, 70.8, 69.3 (C-1–C-5), 63.2 (C-6), 34.7 (C*t*Bu), 30.9 ($CH_3$). Anal. Calcd. for $C_{47}H_{43}N_3O_{11}$ (825.86): C, 68.35, H, 5.25; N, 5.09. Found: C, 68.44; H, 5.36; N, 5.16.

### 4.7. General procedure II for the synthesis of 4-acyl-2-acylamino-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-$\Delta^2$-1,3,4-thiadiazolines

*C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde thiosemicarbazone (**4**, 0.10 g, 0.14 mmol) was dissolved in dry pyridine (5 mL) and then RCOCl (0.44 mmol) was added. The mixture was stirred and heated at 80 °C. The reaction was monitored by TLC (1:2

EtOAc–hexane). When the reaction was complete, the solvent was evaporated, and the residue was purified by column chromatography.

**4.7.1. 2-Acetamido-4-acetyl-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-$\Delta^2$-1,3,4-thiadiazoline** (**16**)

From **4** (0.20 g, 0.28 mmol) and AcCl (60 μL, 0.84 mmol) according to General procedure II (Section 4.7.). Purified by column chromatography (1:2 EtOAc–toluene) to yield 170 mg (77%) of **16** as a white amorphous product. $[\alpha]_D = -178$ (*c* 0.35, $CHCl_3$); $R_f$ : 0.30 (1:2 EtOAc–toluene); ESI-MS (positive mode) m/z: 766.25 $[M+H]^+$. Anal. Calcd. for $C_{40}H_{35}N_3O_{11}S$ (765.78): C, 62.74, H, 4.61; N, 5.49; S, 4.19. Found: C, 62.71; H, 4.65; N, 5.46; S, 4.15.

major isomer: $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 9.43 (1H, s, NH), 8.10-7.11 (20H, m, Ar), 6.05-5.96 (2H, m, H-2 or H-3 or H-4, CH-thiadiazoline), 5.68, 5,56 (2H, 2 pt, *J* = 9.8 Hz in each, H-2 and/or H-3 and/or H-4), 4.53-4.42 (3H, m, H-6a, H-6b, H-1), 4.15-4.08 (1H, m, H-5), 1.99, 1.93 (6H, 2 s, $CH_3$). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 169.0, 166.0, 165.6, 165.0 (CO, NHCO), 147.4 (Cq-thiadiazoline), 133.6-125.1 (Ar), 76.0, 75.2, 73.5, 69.1, 66.3 (C-1–C-5), 69.1 (CH-thiadiazoline), 62.4 (C-6), 22.6, 21.5 ($CH_3$).

minor isomer: $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 9.14 (1H, s, NH), 5.84, 5.43 (2H, 2 pt, *J* = 9.5, 9.7 Hz in each, H-2 and/or H-3 and/or H-4).

**4.7.2. 2-Benzamido-4-benzoyl-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-$\Delta^2$-1,3,4-thiadiazoline** (**17**)

From **4** (0.50 g, 0.74 mmol) and BzCl (258 μL, 2.22 mmol) according to General procedure II (Section 4.7.). Purified by column chromatography (1:2 EtOAc–hexane) to yield 400 mg

(62%) of **17** as a yellow amorphous product. $[\alpha]_D = -295$ (*c* 0.16, $CHCl_3$); $R_f$: 0.34 (1:2 EtOAc–hexane). ESI-MS (positive mode) m/z: 890.33 $[M+H]^+$. Anal. Calcd. for $C_{50}H_{39}N_3O_{11}S$ (889.92): C, 67.48, H, 4.42; N, 4.72; S, 3.60. Found: C, 67.42; H, 4.45; N, 5.71; S, 3.63.

major isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 9.26 (1H, s, NH) 8.05-7.10 (30H, m, Ar), 6.34 (1H, s, CH-thiadiazoline), 6.02 (1H, pt, $J$ = 9.5 Hz, H-2 or H-3 or H-4), 5.72-5.60 (2H, m, H-2 and/or H-3 and/or H-4), 4.62 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.54 (1H, dd, $J_{5,6a}$ = 5.3 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.48 (1H, dd, $J_{5,6b}$ = 1.9 Hz, H-6b), 4.17-4.11 (1H, m, H-5). $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 166.6, 166.2, 165.7, 165.7, 165.1, 165.0 (CO, NHCO), 148.4 (Cq-thiadiazoline) 133.7-127.3 (Ar), 76.5, 75.9, 73.7, 69.2, 67.7 (C-1–C-5), 69.1 (CH-thiadiazoline), 62.6 (C-6).

minor isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 9.10 (1H, s, NH), 6.63 (1H, s, CH-thiadiazoline), 6.09, 5.90 (2H, 2 pt, $J$ = 9.5 Hz in each, H-2 and/or H-3 and/or H-4), 4.72 (1H, d, $J_{1,2}$ = 9.1 Hz, H-1), 4.67 (1H, dd, $J_{5,6a}$ = 2.3 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.41 (1H, dd, $J_{5,6b}$ = 4.9 Hz, H-6b), 4.26-4.20 (1H, m, H-5). $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 76.1, 74.8, 68.6 (C-1–C-5), 60.3 (C-6).

**4.7.3. 2-(2-Naphthamido)-4-(2-naphtoyl)-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-$\Delta^2$-1,3,4-thiadiazoline** (**18**)

From **4** (0.50 g, 0.74 mmol) and 2-naphthoyl chloride (423 mg, 2.22 mmol) according to General procedure II (Section 4.7.). Purified by column chromatography (1:2 EtOAc–hexane) to yield 450 mg (62%) of **18** as a yellow amorphous product. $[\alpha]_D = -318$ (*c* 0.16, $CHCl_3$); $R_f$: 0.43 (1:8 EtOAc–toluene). ESI-MS (positive mode) m/z: 990.33 $[M+H]^+$. Anal. Calcd. for

$C_{58}H_{43}N_3O_{11}S$ (989.26): C, 70.36, H, 4.38; N, 4.24; S, 3.24. Found: C, 70.32; H, 4.36; N, 4.21; S, 3.27.

major isomer: $^1$H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.30 (1H, s, NH) 8.36-6.84 (34H, m, Ar), 6.36 (1H, d, CH-thiadiazoline), 5.96 (1H, pt, $J$ = 9.5 Hz, H-2 or H-3 or H-4), 5.70-5.61 (2H, m, H-2 and/or H-3 and/or H-4), 4.60 (1H, dd, $J_{1,CH}$ = 1.4 Hz, $J_{1,2}$ = 9.9 Hz, H-1), 4.52 (1H, dd, $J_{6a,6b}$ = 12.2 Hz, H-6a,), 4.46 (1H, dd, H-6b), 3.97 (1H, ddd, $J_{5,6b}$ = 2.7 Hz, $J_{5,6a}$ = 4.9 Hz, $J_{4,5}$ = 9.7 Hz, H-5). $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 169.7, 166.5, 166.3, 165.8, 165.7, 165.0 (CO, NHCO), 148.1 (Cq-thiadiazoline), 135.3-123.5 (Ar), 76.4, 75.8, 73.7, 69.1, 68.0 (C-1–C-5), 69.1 (CH-thiadiazoline), 62.5 (C-6).

minor isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 6.68 (1H, d, CH-thiadiazoline), 6.13, 5.89 (2H, 2 pt, $J$ = 9.5 Hz in each, H-2 and/or H-3 and/or H-4), 4.76 (1H, dd, $J_{1,CH}$ =2.5 Hz, $J_{1,2}$ =9.8 Hz, H-1), 4.65 (1H, dd, $J_{6a,6b}$ =12.3 Hz, H-6a), 4.19 (1H, ddd, $J_{5,6a}$ =2.8 Hz, $J_{5,6b}$ =4.6 Hz, $J_{4,5}$ = 9.6 Hz, H-5). $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm) 167.3, 166.2, 165.4, 164.9 (CO, NHCO), 148.7 (Cq-thiadiazoline), 76.1, 75.4, 74.8, 68.5, 67.8 (C-1–C-5), 63.0 (C-6).

**4.7.4. 2-(4-*tert*-Butylbenzamido)-4-(4-*tert*-butylbenzoyl)-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-$\Delta^2$-1,3,4-thiadiazoline (19)**

From **4** (0.15 g, 0.22 mmol) and 4-*tert*-butylbenzoyl chloride (129 μL, 0.66 mmol) according to General procedure II (Section 4.7.). Purified by column chromatography (1:4 EtOAc–hexane) to yield 83 mg (38%) of **19** as a yellow amorphous product. $[\alpha]_D$ = –378 (*c* 0.18, $CHCl_3$); $R_f$ : 0.48 (1:2 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 8.71 (1H, s, NH), 8.01-7.14 (28H, m, Ar), 6.36 (1H, d, $J$ = 1.4 Hz, CH-thiadiazoline), 6.01, 5.65, 5.64 (3H, 3 pt, $J$ = 9.5 Hz in each, H-2, H-3, H-4), 4.64-4.55 (2H, m, H-6a, H-1), 4.42 (1H, dd, $J_{6a,6b}$ = 12.0 Hz, H-6b), 4.14 (1H, ddd, $J_{5,6b}$ = 2.0 Hz, $J_{5,6a}$ = 5.7 Hz, $J_{4,5}$ = 9.5 Hz, H-5), 1.36

(9H, bs, $CH_3$), 1.31 (9H, s, $CH_3$). $^{13}C$ NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.4, 166.3, 165.8, 165.8, 165.2, 164.7 (CO, NHCO), 156.9, 154.3 (Cq-phenyl), 145.9 (Cq-thiadiazoline), 133.7-124.7 (Ar), 76.6, 76.0, 73.8, 69.3, 67.8, (C-1–C-5), 69.1 (CH-thiadiazoline), 62.8 (C-6), 35.2, 34.9 (Cq), 31.2, 31.1 ($CH_3$). ESI-MS (positive mode) m/z: 1002.33 $[M+H]^+$. Anal. Calcd. for $C_{58}H_{55}N_3O_{11}S$ (1002.14): C, 69.51, H, 5.53; N, 4.19; S, 3.20. Found: C, 69.54; H, 5.56; N, 4.16; S, 3.25.

### 4.8. General procedure III for the synthesis of 2-acylamino-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazoles and -thiadiazoles

A 4-acyl-[*C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formaldehyde]semicarbazone (**12-15**, 0.03 mmol) or a 2-acylamino-4-acyl-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-thiadiazoline (**16-19**, 0.03 mmol) was dissolved in $CH_2Cl_2$ (1 mL). Then PIDA (1.1 equiv.) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC (1:1 EtOAc–hexane). When the reaction was complete, the solvent was evaporated and the residue was purified by column chromatography.

#### 4.8.1. 2-Acetamido-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole (20)

From **12** (0.16 g, 0.23 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:3 EtOAc–hexane) to yield 81 mg (50%) of **20** as a white amorphous product. $[\alpha]_D = -2$ (*c* 0.25, $CHCl_3$); $R_f$ : 0.38 (1:3 EtOAc–toluene); $^1H$ NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 8.03-7.22 (21H, m, Ar, NH), 6.08, 5.86, 5.84 (3H, 3 pt, $J$ = 9.7 Hz in each H-2, H-3, H-4), 5.18 (1H d, $J_{1,2}$ = 9.8 Hz, H-1), 4.71-4.60 (1H, dd, $J_{5,6a}$ < 1 Hz, H-6a), 4.52 (1H, dd, $J_{5,6b}$ = 4.3 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6b), 4.40-4.30 (1H, m, H-5), 2.53 (1H, s, $CH_3$). $^{13}C$ NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.0, 165.6, 165.2, 165.0, 164.8, 160.9 (CO, NHCO, C-oxadiazole), 133.5-128.3 (Ar), 76.9, 73.4, 71.8, 70.3, 68.9 (C-1–C-5), 62.9 (C-6),

11.0 ($CH_3$). Anal. Calcd. for $C_{38}H_{31}N_3O_{11}$ (705.67): C, 64.68, H, 4.43; N, 5.95. Found: C, 64.60; H, 4.51; N, 5.86.

**4.8.2. 2-Benzamido-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole (21)**

From **13** (0.084 g, 0.11 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:3 EtOAc–hexane) to yield 70 mg (57%) of **21** as a white amorphous product. $[\alpha]_D = -205$ (*c* 0.4, $CHCl_3$); $R_f$ : 0.68 (1:1 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 8.06-7.26 (26H, m, Ar, NH), 6.11, 6.02, 5.88 (3H, 3 pt, $J$ = 9.5, 9.8 Hz in each H-2, H-3, H-4), 5.28 (1H d, $J_{1,2}$ = 9.8 Hz, H-1), 4.71 (1H, dd, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.54 (1H, dd, H-6b) 4.39 (1H, ddd, $J_{5,6a}$ = 2.4 Hz, $J_{5,6b}$ = 5.2 Hz, $J_{4,5}$ = 9.4 Hz , H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.0, 165.9, 165.6, 165.1, 164.8, 160.9 (CO, NHCO, C-oxadiazole), 133.5-123.3 (Ar), 77.0, 73.5, 71.8, 70.2, 69.0 (C-1–C-5), 62.9 (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, 67.35; H, 4.42; N, 5.40.

**4.8.3. 2-(2-Naphthamido)-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole (22)**

From **14** (0.28 g, 0.34 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:6 EtOAc–toluene) to yield 192 mg (69%) of **22** as a yellow amorphous product. $[\alpha]_D = -121$ (*c* 0.16, $CHCl_3$); $R_f$.: 0.58 (1:3.5 EtOAc-toluene); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 8.52 (1H, s, NH), 8.11-7.10 (27H, m, Ar), 6.18, 6.11, 5.95 (3H, 3 pt, $J$ = 9.7 Hz in each, H-2, H-3 , H-4), 5.27 (1H, d, $J_{1,2}$ = 9.5 Hz, H-1), 4.70 (1H, dd, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.54 (1H, dd, H-6b) 4.39 (1H, ddd, $J_{5,6a}$ = 2.7 Hz, $J_{5,6b}$ = 4.3 Hz, $J_{4,5}$ = 9.5 Hz, H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.0, 165.9, 165.6, 164.8, 161.1 (CO, NHCO, C-oxadiazole), 134.7-120.5 (Ar), 77.0, 73.6, 71.9, 70.3, 69.1 (C-1–C-5), 63.0 (C-6). Anal.

Calcd. for $C_{47}H_{35}N_3O_{11}$ (817.79): C, 69.03, H, 4.31; N, 5.14. Found: C, 69.11; H, 4.41; N, 5.05.

**4.8.4. 2-(4-*tert*-Butylbenzamido)-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole (23)**

From **15** (0.09 g, 0.11 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:3 EtOAc–hexane) to yield 80 mg (60%) of **23** as a colourless amorphous product. $[\alpha]_D = -82$ (*c* 1.50, $CHCl_3$); $R_f$ : 0.29 (1:3 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 8.05-7.20 (25H, m, Ar, NH), 6.11, 6.02 , 5.88 (3H, 3 pt, $J$ = 9.5, 9.7 Hz in each, H-2, H-3, H-4), 5.28 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.70 (1H, dd, $J_{6a,6b}$ = 12.4 Hz , H-6a), 4.54 (1H, dd, H-6b), 4.40 (1H, ddd, $J_{5,6a}$ = 2.3 Hz, $J_{5,6b}$ = 5.3 Hz, $J_{4,5}$ = 9.7 Hz, H-5), 1.34 (9H, s, $CH_3$). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 166.0, 165.9, 165.6, 165.1, 164.8, 161.1 (CO, NHCO, C-oxadiazole), 155.6, 133.5-120.5 (Ar), 77.0, 73.6, 71.8, 70.2, 69.1 (C-1–C-5), 63.0 (C-6), 35.0 (Cq-*t*Bu), 31.0 ($CH_3$). Anal. Calcd. for $C_{47}H_{41}N_3O_{11}$ (823.84): C, 68.52, H, 5.02; N, 5.10. Found: C, 68.61; H, 5.11; N, 5.18.

**4.8.5. 2-Acetamido-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-thiadiazole (24)**

From **16** (0.17 g, 0.22 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:2 EtOAc–toluene) to yield 106 mg (67%) of **24** as a white amorphous product. $[\alpha]_D = -81$ (*c* 0.25, $CHCl_3$); $R_f$ : 0.42 (1:2 EtOAc–toluene); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ (ppm) 8.09-7.13 (21H, m, Ar, NH), 6.09, 5.81, 5.74 (3H, 3 pt, $J$ = 9.6, 9.8 Hz in each, H-2, H-3, H-4), 5.25 (1H, d, $J_{1,2}$ = 9.6 Hz, H-1), 4.70 (1H, dd, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.53 (1H, dd, H-6b), 4.36 (1H, ddd, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 4.8 Hz, $J_{4,5}$ = 9.5 Hz, H-5), 1.82 (3H, s, $CH_3$). $^{13}$C NMR ($CDCl_3$, 360 MHz) δ (ppm) 168.8, 166.1, 165.7, 165.1, 164.7 (CO, NHCO, C-thiadiazole), 133.5-128.4 (Ar), 76.9, 76.0, 73.5, 71.7, 69.2 (C-1–C-5), 62.9

(C-6). ESI-MS (positive mode) m/z: 722.33 $[M+H]^+$. Anal. Calcd. for $C_{38}H_{31}N_3O_{10}S$ (721.76): C, 63.24, H, 4.33; N, 5.82; S,4.44. Found: C, 63.21; H, 4.35; N, 5.84; S, 4.41.

**4.8.6. 2-Benzamido-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-thiadiazole (25)**

From **17** (0.09 g, 0.10 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:3 EtOAc–hexane) to yield 54 mg (68%) of **25** as a white amorphous product. $[\alpha]_D$ = –111 (*c* 0.20, $CHCl_3$); $R_f$ : 0.21 (1:2 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 8.20-7.26 (26H, m, Ar, NH), 6.12, 5.86, 5.77 (3H, 3 pt, *J* = 9.5, 9.8 Hz in each, H-2, H-3, H-4), 5.32 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.70 (1H, dd, $J_{6a,6b}$ = 12.4 Hz , H-6a), 4.55 (1H, dd, H-6b) 4.40 (1H, ddd, $J_{5,6a}$ = 2.7 Hz, $J_{5,6b}$ = 5.0 Hz, $J_{4,5}$ = 9.7 Hz , H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.2, 165.7, 165.1, 165.0, 164.9, 162.5, 161.1 (CO, NHCO, C-thiadiazole), 133.3-128.3 (Ar), 77.0, 76.3, 73.6, 72.2, 69.2, (C-1–C-5), 63.1 (C-6). Anal. Calcd. for $C_{43}H_{33}N_3O_{10}S$ (783.8): C, 65.89, H, 4.24; N, 5.36; S,4.09. Found: C, 65.94; H, 4.35; N, 5.28; S, 4.01.

**4.8.7. 2-(2-Naphthamido)-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-thiadiazole (26)**

From **18** (0.20 g, 0.20 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:6 EtOAc–toluene) to yield 100 mg (59%) of **26** as a yellow amorphous product. $[\alpha]_D$= –205 (*c* 0.16, $CHCl_3$); $R_f$ : 0.39 (1:6 EtOAc–toluene); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 8.71 (s, 1H, NH), 8.12-7.11 (27H, m, Ar), 6.15, 5.91, 5.80 (3H, 3pt, *J* = 9.6 Hz in each, H-2, H-3, H-4), 5.35 (1H, d, $J_{1,2}$ = 9.7 Hz, H-1), 4.70 (1H, dd, $J_{6a,6b}$ = 12.3 Hz , H-6a), 4.57 (1H, dd, H-6b), 4.41 (1H, ddd, $J_{5,6a}$ = 2.0 Hz, $J_{5,6b}$ = 4.9 Hz, $J_{4,5}$ = 9.4 Hz, H-5). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.1, 165.7, 165.2, 165.1, 165.0, 162.5, 160.9 (CO, NHCO, C-thiadiazole), 135.5-124.2 (Ar), 76.9, 76.3, 73.6, 72.3, 69.3 (C-1–C-5),

63.1 (C-6). ESI-MS (positive mode) m/z: 834.33 $[M+H]^+$. Anal. Calcd. for $C_{47}H_{35}N_3O_{10}S$ (833.86): C, 67.70, H, 4.23; N, 5.04; S, 3.85. Found: C, 67.81; H, 4.15; N, 5.12; S, 3.76.

#### 4.8.8. 2-(4-*tert*-Butylbenzamido)-5-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-thiadiazole (27)

From **19** (0.17 g, 0.17 mmol) according to General procedure III (Section 4.8.). Purified by column chromatography (1:3 EtOAc–hexane) to yield 120 mg (84%) of **27** as a white amorphous product. $[\alpha]_D$ = –179 (*c* 0.20, $CHCl_3$); $R_f$ : 0.20 (1:3 EtOAc–hexane); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 8.05-7.22 (25H, m, Ar, NH), 6.12, 5.86, 5.80 (3H, 3 pt, $J$ = 9.5, 9.7 Hz in each, H-2, H-3, H-4), 5.31 (1H, d, $J_{1,2}$ = 9.6 Hz, H-1), 4.68 (1H, dd, $J_{5,6a}$ < 1 Hz, $J_{6a,6b}$ = 12.2 Hz , H-6a), 4.54 (1H, dd, $J_{5,6b}$ = 5.0 Hz, H-6b), 4.43-4.35 (1H, m, H-5), 1.38 (9H, s, $CH_3$). $^{13}$C NMR ($CDCl_3$, 360 MHz) $\delta$(ppm) 166.1, 165.8, 165.2, 165.0, 164.8, 161.8, 160.9 (CO, NHCO, C-thiadiazole), 156.9, 133.5-125.8 (Ar), 76.9, 76.3, 73.7, 72.2, 69.4 (C-1–C-5), 63.2 (C-6), 31.9 (Cq-*t*Bu), 31.1 ($CH_3$). ESI-MS (positive mode) m/z: 840.42 $[M+H]^+$. Anal. Calcd. for $C_{47}H_{41}N_3O_{10}S$ (839.91): C, 67.21, H, 4.92; N, 5.00; S, 3.82. Found: C, 67.31; H, 4.83; N, 5.09; S, 3.91.

### 4.9. Preparation for the test compounds

#### 4.9.1. General procedure IV for the Zemplén debenzoylation

An *O*-perbenzoylated compound (100 mg) was dissolved in dry MeOH (1 mL) and a solution of NaOMe (1 M in MeOH) was added to the solution in a catalytic amount. The reaction mixture was kept at rt. When the reaction was complete (TLC, 7:3 $CHCl_3$–MeOH) the solution was neutralized with a cation exchange resin Amberlyst 15 ($H^+$ form). The resin was filtered off with suction, the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography.

#### 4.9.2. General procedure V for the removal of *O*-benzoyl protecting groups

An *O*-perbenzoylated compound (100 mg) was dissolved in dry MeOH (14 mL) and LiOH (16 equiv.) was added. The reaction mixture was stirred at 0 °C. When the reaction was complete (TLC, 7:3 $CHCl_3$–MeOH) the solution was neutralized with a cation exchange resin Amberlyst 15 ($H^+$ form). After filtration and removal of the solvent, the residue was purified by column chromatography.

#### 4.9.3. *C*-(β-D-glucopyranosyl)formaldehyde semicarbazone (6)

From **2** (0.17 g, 0.26 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (8:5 $CHCl_3$–methanol) to yield 40 mg (63%) of **6** as a white amorphous product. $[\alpha]_D$ = +32 (*c* 0.30, DMSO); $R_f$ : 0.17 (2:1 $CHCl_3$–methanol); $^1$H NMR (MeOD, 360 MHz) $\delta$(ppm) 7.19 (1H, s, CH=N), 3.88-3.72 (2H, m, H-1, H-2 or H-3 or H-4), 3.70-3.52 (1H, m, H-6a), 3.50-3.22 (4H, m, H-2 and/or H-3 and/or H-4, H-5, H-6b). $^{13}$C NMR (MeOD, 360 MHz) $\delta$(ppm) 160.1 (NHCONH), 143.2 (CH=N), 81.8, 80.2, 79.4, 73.4, 71.4 (C-1–C-5), 62.7 (C-6). Anal. Calcd. for $C_{84}H_{15}N_3O_6$ (249.22): C, 38.55, H, 6.07; N, 16.86. Found: C, 38.63; H, 6.12; N, 16.93.

#### 4.9.4. 4-Phenyl-[C-(β-D-glucopyranosyl)formaldehyde]semicarbazone (7)

From **3** (0.20 g, 0.27 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (4:1 $CHCl_3$–methanol) to yield 42 mg (48%) of **7** as a white amorphous product. $[\alpha]_D$ = +52 (*c* 0.43, DMSO); $R_f$ : 0.23 (4:1 $CHCl_3$–methanol); $^1$H NMR (MeOD, 360 MHz) $\delta$(ppm) 7.46 (2H, d, $J$ = 7.9 Hz, Ar), 7.30-7.17 (3H, m, Ar, CH=N), 7.01 (1H, t, $J$ = 7.3 Hz, Ar), 3.91-3.79 (2H, m, H-1, H-2 or H-3 or H-4), 3.65 (1H, dd, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 11.4 Hz, H-6a), 3.42-3.21 (4H, m, H-2 and/or H-3 and/or H-4, H-5, H-6b), $^{13}$C

NMR (MeOD, 360 MHz) $\delta$(ppm) 155.9 (NHCONH), 143.3 (CH=N), 139.7, 129.8, 124.5, 121.3 (Ar), 82.0, 80.2, 79.5, 73.5, 71.5 (C-1–C-5), 62.8 (C-6). Anal. Calcd. for $C_{14}H_{19}N_3O_6$ (325.32): C, 51.69, H, 5.89; N, 12.92. Found: C, 51.79; H, 5.98; N, 12.85.

#### 4.9.5. *C*-(β-D-glucopyranosyl)formaldehyde thiosemicarbazone (8)

From **4** (0.16 g, 0.24 mmol) according to General procedure V (Section 4.9.2.). Purified by column chromatography (3:1 $CHCl_3$–methanol) to yield 60 mg (95%) of **8** as a white amorphous product. $[\alpha]_D$ = +6 (*c* 2.00, DMSO); $R_f$ : 0.24 (3:1 $CHCl_3$–methanol); $^1$H NMR (MeOD, 360 MHz) $\delta$(ppm) 7.39 (1H, s, CH=N), 3.92-3.81 (2H, m, H-1, H-2 or H-3 or H-4), 3.68 (1H, dd, $J_{5,6a}$ = 3.1 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.52-3.32 (4H, m, H-2 and/or H-3 and/or H-4, H-5, H-6b). $^{13}$C NMR (MeOD, 360 MHz) $\delta$(ppm) 180.0 (NHCSNH), 145.5 (CH=N), 81.7, 79.8, 79.0, 73.2, 71.4 (C-1–C-5), 62.7 (C-6). Anal. Calcd. for $C_8H_{15}N_3O_5S$ (265.29): C, 36.22, H, 5.70; N, 15.84; S, 12.09. Found: C, 36.12; H, 5.81; N, 15.92; S, 12.17.

#### 4.9.6. 4-Phenyl-[*C*-(β-D-glucopyranosyl)formaldehyde]thiosemicarbazone (9)

From **5** (0.20 g, 0.26 mmol) according to General procedure V (Section 4.9.2.). Purified by column chromatography (7:1 $CHCl_3$–methanol) to yield 70 mg (77%) of **9** as a yellow amorphous product. $[\alpha]_D$ = +33 (*c* 0.13, MeOH); $R_f$ : 0.40 (3:1 $CHCl_3$–methanol); $^1$H NMR (MeOD, 360 MHz) $\delta$(ppm) 7.61 (2H, d, *J* = 7.8 Hz, Ar), 7.42-7.30 (3H, m, Ar, CH=N), 7.21 (1H, t, *J* = 7.4 Hz, Ar), 3.97-3.82 (2H, m, H-1, H-2 or H-3 or H-4), 3.71 (1H, dd, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), 3.48-3.33 (4H, m, H-2 and/or H-3 and/or H-4, H-5, H-6b). $^{13}$C NMR (MeOD, 360 MHz) $\delta$(ppm) 178.3 (NHCSNH), 144.7 (CH=N), 140.1, 129.4, 126.8, 126.2 (Ar), 82.0, 80.1, 79.5, 73.4, 71.5 (C-1–C-5), 62.8 (C-6). Anal. Calcd. for $C_{13}H_{19}N_3O_5S$ (341.38): C, 49.26, H, 5.61; N, 12.31; S, 9.39. Found: C, 49.19; H, 5.70; N, 12.39; S, 9.29.

**4.9.7. 2-Phenylamino-5-(β-D-glucopyranosyl)-1,3,4-oxadiazole (11)**

From **10** (0.16 g, 0.22 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (7:1 $CHCl_3$–methanol) to yield 68 mg (97%) of **11** as a white amorphous product. $[\alpha]_D$ = +14 (*c* 0.21, DMSO); $R_f$ : 0.24 (7:1 $CHCl_3$–methanol); $^1$H NMR (MeOD, 360 MHz) $\delta$ (ppm) 7.49 (2H, d, *J* = 8.0 Hz, Ar), 7.33 (2H, t, *J* = 7.6 Hz, Ar), 7.03 (1H, t, *J* = 7.3 Hz, Ar), 4.44 (1H, d, $J_{1,2}$ = 9.9 Hz, H-1), 3.93-3.85 (1H, m, H-6a), 3.77-3.65 (2H, m, H-2 or H-3 or H-4, H-6b), 3.55-3.37 (3H, m, H-2 and/or H-3 and/or H-4, H-5). $^{13}$C NMR (MeOD, 360 MHz) $\delta$ (ppm) 162.4, 159.2 (C-oxadiazole), 139.6, 130.2, 123.8, 118.8 (Ar), 82.6, 79.1, 74.6, 73.2, 71.3 (C-1–C-5), 62.8 (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, 52.11; H, 5.39; N, 13.11.

**4.9.8. 2-Acetamido-5-(β-D-glucopyranosyl)-1,3,4-oxadiazole (28)**

From **20** (0.18 g, 0.62 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (5:1 $CHCl_3$–methanol) to yield 30 mg (41%) of **28** as a white amorphous product. $[\alpha]_D$ = +38 (*c* 0.15, $H_2O$); $R_f$ : 0.28 (3:1 $CHCl_3$–methanol); $^1$H NMR ($D_2O$+MeOD, 360 MHz) $\delta$ (ppm) 4.69 (1H, d, $J_{1,2}$ = 9.9 Hz, H-1), 3.91 (1H, dd, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 3.82-3.70 (2H, m, H-2 or H-3 or H-4, H-6b), 3.66-3.57 (2H, m, H-2 or H-3 or H-4, H-5), 3.52 (1H, pt, *J* = 9.2 Hz, H-2 or H-3 or H-4), 2.57 (3H, s, $CH_3$). $^{13}$C NMR ($D_2O$+MeOD, 360 MHz) $\delta$ (ppm) 166.6 (NHCO, C-oxadiazole), 163.8 (C-oxadiazole), 80.4, 76.6, 72.3, 71.5, 69.2 (C-1–C-5), 62.7 (C-6), 10.0 ($CH_3$). Anal. Calcd. for $C_{10}H_{15}N_3O_7$ (289.24): C, 41.52, H, 5.23; N, 14.53. Found: C, 41.59; H, 5.29; N, 14.62.

**4.9.9. 2-Benzamido-5-(β-D-glucopyranosyl)-1,3,4-oxadiazole (30)**

From **21** (0.15 g, 0.43 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (8:1 $CHCl_3$–methanol) to yield 60 mg (87%) of **29** as a white

amorphous product. $[\alpha]_D$ = +11 (*c* 0.13, DMSO); $R_f$ : 0.26 (3:1 $CHCl_3$–methanol); $^1$H NMR (MeOD, 360 MHz) $\delta$(ppm) 8.07 (2H, d, *J* = 7.2 Hz, Ar), 7.65-7.50 (3H, m, Ar), 4.66 (1H d, $J_{1,2}$ = 9.8 Hz, H-1), 3.93 (1H, dd, $J_{5,6a}$ = 1.4 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 3.85 (1H, pt, *J* = 9.0 Hz, H-2 or H-3 or H-4), 3.74 (1H, dd, $J_{5,6b}$ = 5.2 Hz, H-6b) 3.60-3.43 (3H, m, H-2 and/or H-3 and/or H-4, H-5,). $^{13}$C NMR (MeOD, 360 MHz) $\delta$(ppm) 166.8 (NHCO, C-oxadiazole), 165.6 (C-oxadiazole), 133.4, 130.4, 128.0, 124.6 (Ar), 82.8, 79.0, 74.6, 73.4, 71.2 (C-1–C-5), 62.7 (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, 51.20; H, 4.93; N, 12.06.

**4.9.10. 2-(2-Naphthamido)-5-(β-D-glucopyranosyl)-1,3,4-oxadiazole (30)**

From **22** (0.16 g, 0.40 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (8:1 $CHCl_3$–methanol) to yield 73 mg (93%) of **30** as a white amorphous product. $[\alpha]_D$ = +13 (*c* 0.10, DMSO); $R_f$ : 0.13 (8:1 $CHCl_3$–methanol); $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$(ppm) 7.81 (1H, bs, Ar), 7.35-7.10 (4H, m, Ar), 6.82 (2H, bs, Ar), 3.87 (1H, d, $J_{1,2}$ = 9.6 Hz, H-1), 3.15-3.02 (2H, m, H-2 or H-3 or H-4, H-6a,), 2.97-2.87 (1H, m, H-6b), 2.80-2.64 (3H, m, H-2 and/or H-3 and/or H-4, H-5,). $^{13}$C NMR (DMSO-$d_6$, 360 MHz) $\delta$(ppm) 164.8 (NHCO, C-oxadiazole), 164.2 (C-oxadiazole), 134.4-120.5 (Ar), 81.9, 77.3, 72.9, 71.8, 69.9 (C-1–C-5), 61.0 (C-6). Anal. Calcd. for $C_{19}H_{19}N_3O_7$ (401.37): C, 56.86, H, 4.77; N, 10.47. Found: C, 56.79; H, 4.88; N, 10.38.

**4.9.11. 2-(4-*tert*-Butylbenzamido)-5-(β-D-glucopyranosyl)-1,3,4- oxadiazole (31)**

From **23** (0.15 g, 0.37 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (7:1 $CHCl_3$–methanol) to yield 56 mg (76%) of **31** as a white amorphous product. $[\alpha]_D$ = +13 (*c* 0.29, DMSO); $R_f$ : 0.30 (7:1 $CHCl_3$–methanol); $^1$H NMR (MeOD, 360 MHz) $\delta$(ppm) 7.99 (2H, d, *J* = 8.2 Hz, Ar), 7.62 (2H, d, *J* = 8.2 Hz, Ar), 4.66

(1H, d, $J_{1,2}$ = 9.8 Hz, H-1), 3.92 (1H, m, H-6a), 3.84 (1H, pt, $J$ = 9.1 Hz, H-2 or H-3 or H-4), 3.72 (1H, dd, $J_{5,6b}$ = 4.6 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 3.62-3.42 (3H, m, H-2 and/or H-3 and/or H-4, H-5), 1.37 (9H, s, $CH_3$). $^{13}$C NMR (MeOD, 360 MHz) $\delta$ (ppm) 167.0 (NHCO, C-oxadiazole), 165.4 (C-oxadiazole), 157.3, 127.9, 127.4, 121.8 (Ar), 82.9, 79.1, 74.6, 73.4, 71.3 (C-1–C-5), 62.8 (C-6), 36.0 (Cq-*t*Bu), 31.5 ($CH_3$). Anal. Calcd. for $C_{19}H_{25}N_3O_7$ (407.42): C, 56.01, H, 6.18; N, 10.31. Found: C, 56.12; H, 6.27; N, 10.21.

**4.9.12. 2-Acetamido-5-(β-D-glucopyranosyl)-1,3,4-thiadiazole (32)**

From **24** (0.18 g, 0.59 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (8:1 $CHCl_3$–methanol) to yield 70 mg (92%) of **32** as a white amorphous product. $[\alpha]_D$ = +25 (*c* 0.27, DMSO); $R_f$ : 0.12 (8:1 $CHCl_3$–methanol); $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$ (ppm) 4.48 (1H, d, $J_{1,2}$ = 9.0 Hz, H-1), 3.69 (1H, dd, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 11.6 Hz, H-6a), 3.47-3.27 (4H, m, H-2, H-3, H-4, H-6b), 3.22-3.18 (1H, m, H-5), 2.19 (3H, s, $CH_3$). $^{13}$C NMR (DMSO-$d_6$, 360 MHz) $\delta$ (ppm) 168.5 (NHCO), 162.8, 158.9 (C-thiadiazole), 81.5, 77.6, 76.7, 74.5, 69.9 (C-1–C-5), 61.1 (C-6), 22.3 ($CH_3$). Anal. Calcd. for $C_{10}H_{15}N_3O_6S$ (305.31): C, 39.34, H, 4.95; N, 13.76; S, 10.50. Found: C, 39.25; H, 4.86; N, 13.65; S, 10.59.

**4.9.13. 2-Benzamido-5-(β-D-glucopyranosyl)-1,3,4-thiadiazole (33)**

From **25** (0.11 g, 0.30 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (8:1 $CHCl_3$–methanol) to yield 35 mg (68%) of **33** as a white amorphous product. $[\alpha]_D$ = +9 (*c* 0.20, DMSO); $R_f$ : 0.13 (8:1 $CHCl_3$–methanol); $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$ (ppm) 8.09 (2H, d, $J$ = 7.5 Hz, Ar), 7.66 (1H, pt, $J$ = 7.2 Hz, Ar), 7.56 (2H, pt, $J$ = 7.5 Hz, Ar), 4.54 (1H, d, $J_{1,2}$ = 8.7 Hz, H-1), 3.76-3.66 (1H, m, H-6a), 3.45 (1H, dd, $J_{5,6b}$ = 6.0 Hz, $J_{6a,6b}$ = 11.9 Hz , H-6b), 3.40-3.29 (3H, m, H-2 and/or H-3 and/or H-4,

H-5), 3.20 (1H, t, *J* = 8.7 Hz, H-2 or H-3 or H-4). $^{13}$C NMR (DMSO-$d_6$, 360 MHz) $\delta$(ppm) 165.5 (NHCO), 163.4, 160.2 (C thiadiazole), 133.2, 131.6, 128.9, 128.5 (Ar), 81.7, 77.6, 76.9, 74.6, 70.0 (C-1–C-5), 61.2 (C-6). ESI-MS (positive mode) m/z: 368.08 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{17}N_3O_6S$ (367.38): C, 49.04, H, 4.66; N, 11.44; S, 8.73. Found: C, 49.13; H, 4.75; N, 11.53; S, 8.62.

**4.9.14. 2-(2-Naphthamido)-5-(β-D-glucopyranosyl)-1,3,4-thiadiazole (34)**

From **26** (0.14 g, 0.34 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (7:1 $CHCl_3$–methanol) to yield 40 mg (57%) of **34** as a white amorphous product. $[\alpha]_D$ = +10 (*c* 1.10, DMSO); $R_f$ : 0.32 (7:1 $CHCl_3$–methanol); $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$(ppm) 8.81 (1H, bs, Ar), 8.15-8.00 (4H, m, Ar), 7.72-7.60 (2H, m, Ar), 4.55 (1H, d, $J_{1,2}$ = 8.9 Hz, H-1), 3.76-3.68 (1H, m, H-6a), 3.40-3.30 (4H, m, H-2 and/or H-3 and/or H-4, H-5, H-6b), 3.21 (1H, pt, *J* = 8.9 Hz, H-2 or H-3 or H-4). $^{13}$C NMR (DMSO-$d_6$, 360 MHz) $\delta$(ppm) 165.5 (NHCO), 163.2, 160.0 (C-thiadiazole), 134.9-122.8 (Ar), 81.6, 77.6, 76.8, 74.5, 69.9 (C-1–C-5), 61.1 (C-6). Anal. Calcd. for $C_{19}H_{19}N_3O_6S$ (417.44): C, 54.67, H, 4.59; N, 10.07; S,7.68. Found: C, 54.56; H, 4.68; N, 10.01; S, 7.78.

**4.9.15. 2-(4-*tert*-Butylbenzamido)-5-(β-D-glucopyranosyl)-1,3,4-thiadiazole (35)**

From **27** (0.18 g, 0.43 mmol) according to General procedure IV (Section 4.9.1.). Purified by column chromatography (7:1 $CHCl_3$–methanol) to yield 60 mg (66%) of **35** as a white amorphous product. $[\alpha]_D$ = +9 (*c* 1.00, DMSO); $R_f$ : 0.36 (7:1 $CHCl_3$–methanol); $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$(ppm) 8.07 (2H, d, *J* = 8.2 Hz, Ar), 7.59 (2H, d, *J* = 8.2 Hz, Ar), 4.55 (1H, d, $J_{1,2}$ = 8.6 Hz, H-1), 3.78-3.70 (1H, m, H-6a), 3.48 (1H, dd, $J_{5,6b}$ = 5.9 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6b), 3.41-3.30 (3H, m, H-2 and/or H-3 and/or H-4, H-5), 3.22 (1H, pt, *J* = 8.7 Hz, H-2 or H-3 or H-4), 1.33 (9H, s, $CH_3$). $^{13}$C NMR (DMSO-$d_6$, 360 MHz) $\delta$(ppm) 165.1 (NHCO),

163.3, 160.0 (C-thiadiazole), 156.3, 128.7, 128.4, 125.7 (Ar), 81.7, 77.6, 76.9, 74.5, 70.0 (C-1–C-5), 61.2 (C-6), 35.0 (Cq-*t*Bu), 31.0 ($CH_3$). Anal. Calcd. for $C_{19}H_{25}N_3O_6S$ (423.48): C, 53.89, H, 5.95; N, 9.92; S, 7.57. Found: C, 53.97; H, 6.02; N, 9.99; S, 7.50.

**Acknowledgement**

This work was supported by the Hungarian Scientific Research Fund (OTKA CK77712, CNK80709), TÁMOP 4.2.1./B-09/1/KONV-2010-0007 and TÁMOP-4.2.2./B-10/1-2010-0024 projects implemented through the New Hungary Development Plan, co-financed by the European Social Fund, and Bolyai Janos Research Fellowships (to MT and TD).

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**Synthesis of 2-(β-D-glucopyranosyl)-5-(substituted-amino)-1,3,4-oxa- and -thiadiazoles for inhibition of glycogen phosphorylase**

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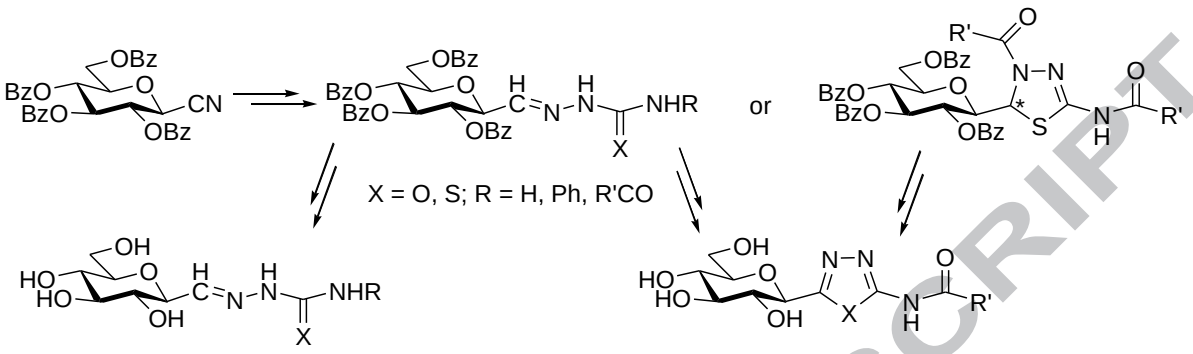


X = O, S; R = H, Ph

Best inhibitior: X = O; R = Ph ($K_i$ = 29 μM).

X = O, S; R' = $CH_3$, Ph, 2-Naphthyl, 4-*t*Bu-$C_6H_4$

No inhibition at 625 μM.

Highlights

- Preparation of new anhydro-aldose semicarbazones and thiosemicarbazones.
- Synthesis of 2-acylamino- or 2-arylamino-5-(β-D-glucopyranosyl)-1,3,4-oxa- and -thiadiazoles.
- Low micromolar inhibitor of glycogen phosphorylase.