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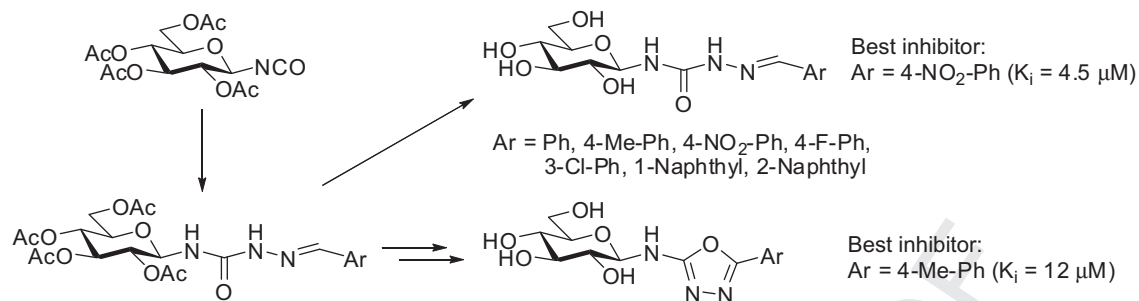
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Graphical abstract

Synthesis of 2-(β -D-glucopyranosylamino)-5-substituted-1,3,4-oxadiazoles for inhibition of glycogen phosphorylase

pp xxx-xxx

Marietta Tóth*, Béla Szócs, Tímea Kaszás, Tibor Docsa, Pál Gergely, László Somsák*



Highlights

- Preparation of aromatic aldehyde 4-(β -D-glucopyranosyl)semicarbazones.
- Synthesis of 2-(β -D-glucopyranosylamino)-5-substituted-1,3,4-oxadiazoles.
- Low micromolar inhibitors of glycogen phosphorylase.



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Synthesis of 2-(β -D-glucopyranosylamino)-5-substituted-1,3,4-oxadiazoles for inhibition of glycogen phosphorylase

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ARTICLE INFO

Article history:

Received 13 March 2013

Received in revised form 18 April 2013

Accepted 18 April 2013

Available online xxxxx

Keywords:

Semicarbazone

1,3,4-Oxadiazole

 β -D-Glucopyranosyl derivatives

Glycogen phosphorylase

Inhibitor

ABSTRACT

Aromatic aldehyde 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazones were synthesized by the addition of different hydrazones onto O-peracetylated β -D-glucopyranosyl isocyanate. Oxidative transformations of these precursors gave O-protected 2-(β -D-glucopyranosylamino)-5-substituted-1,3,4-oxadiazoles. Removal of the O-acetyl protecting groups under Zemplén conditions gave test compounds to show low micromolar inhibition against rabbit muscle glycogen phosphorylase *b*. Best inhibitors of these series were 4-(β -D-glucopyranosyl)semicarbazones of 4-fluorobenzaldehyde (K_i = 4.5 μ M), 2-naphthaldehyde (K_i = 5.5 μ M) and 2-(β -D-glucopyranosylamino)-5-(4-methylphenyl)-1,3,4-oxadiazole (K_i = 12 μ M).

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1. Introduction

Inhibition of glycogen phosphorylase (GP) can be a new therapeutic method for the treatment of type 2 diabetes mellitus, and potential application of GP inhibitors (GPIs) in some other diseased states, such as early cardiac and cardiovascular disorders in non-diabetics, cardiac arrhythmias, ischemic injuries, and tumor growth was also proposed.^{1–5} A large array of compounds was shown to have inhibitory effect against GP under in vitro conditions.^{4,6} Among these molecules glucose derivatives are the most intensively investigated GPIs, and detailed studies can be found in the literature on their structure–activity relationships (SAR).^{5,7} Some glucose derived GPIs had in vivo hypoglycaemic⁸ and other interesting physiological effects.⁹

Widely studied glucose analogue GPIs are derivatives of β -D-glucopyranosylamine, such as *N*-acyl- β -D-glucopyranosylamines^{10–13} (**I** in Chart 1, e.g., K_i = 10–13 μ M^{11,14} against rabbit muscle GPb (RMGPb)¹⁵ for R = 2-naphthyl), *N*-aryl-*N'*- β -D-glucopyranosyl ureas⁴ (**II**, e.g., K_i = 5.2 μ M (RMGPb) for R = 2-naphthyl), as well as *N*-acyl-*N'*- β -D-glucopyranosyl urea derivatives^{4,16} (**III**, e.g., K_i = 0.35 μ M (RMGPb) for R = 2-naphthyl) which inhibited the enzyme in or below the low micromolar range. Micromolar efficiency was reported also for 4-(β -D-glucopyranosyl)thiosemicarbazones of aromatic aldehydes^{17,18} (**IV** X = S, e.g., IC₅₀ = 5.7 μ M (RMGPb)

for Ar = 4-fluorophenyl). Compounds **V**, in which the sugar and the aromatic parts are interchanged in comparison to **IV**, have very recently been shown to be GPIs (K_i = 29 μ M for **V** X = O, and K_i = 300 μ M for **V** X = S against RMGPb).¹⁹

Replacement of the NHCO moiety by 1,2,3-triazole (a non-classical bioisosteric heterocyclic linker **A**) in molecules **I** resulted in effective GP inhibitors²⁰ (**IA**, e.g., K_i = 16 μ M (RMGPb) for R = 2-naphthyl). Enzymatic tests and crystallographic studies have shown high similarity of the amide (**I**) and the 1,2,3-triazole (**IA**) type molecules both in binding strength and structural features of the enzyme–inhibitor complexes.¹⁴ Replacement of the NHCO moiety with isomeric oxadiazoles **B**, **C**, and **D** resulted in inhibitors **IB–D** with varying efficiency. Among these molecules the 3-aryl-5- β -D-glucopyranosyl-1,2,4-oxadiazoles **IC** proved to be the most effective compounds (e.g., K_i = 2.4 μ M (RMGPb) for R = 2-naphthyl).^{21,22} Bioisosteric replacement studies were also carried out with compounds **III**.^{13,19,23}

As part of a program to systematically replace NHCO moieties of GPIs **I–III** by heterocyclic bioisosteres, herein we report on the syntheses and enzymatic tests of a series of 2-(β -D-glucopyranosylamino)-5-substituted-1,3,4-oxadiazoles **IIB**.

For the construction of 1,3,4-oxadiazole rings from acyclic precursors acidic treatment of *N,N'*-diacyl- (or *N*-acyl-*N'*-thioacyl)-hydrazines as well as oxidative cyclization of acylhydrazones were the most frequently used procedures, and both methods were applied for the syntheses of 2-amino-5-substituted-1,3,4-oxadiazoles, too.²⁴ 2-Glycosylamino-5-substituted-1,3,4-oxadiazoles are also known and have been synthesized from glycosyl isothiocyanates either by the addition of acid hydrazides followed by ring

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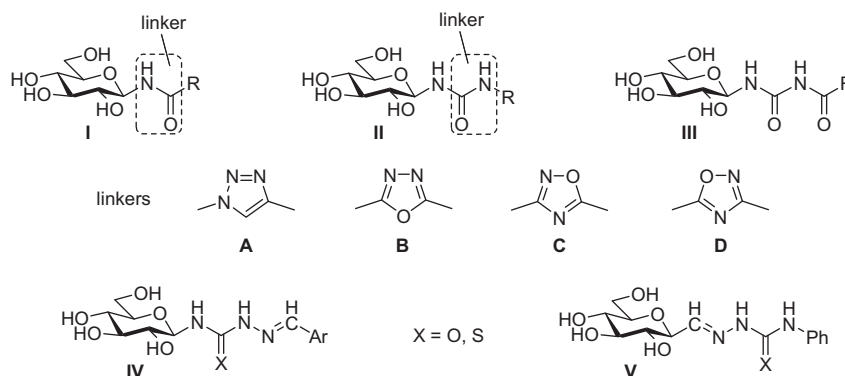


Chart 1.

closure of the resulting 1-acyl-4-glycosyl-thiosemicarbazides^{25–27} or by chlorination to give intermediate glycosyl isocyanide dichlorides to be cyclized with acid hydrazides.²⁸

In this work we investigated the synthesis of compounds **IIB** from aldehyde 4-glycosyl-semicarbazones (cf. O-protected **IV** X = O in Chart 1), a route which, to the best of our knowledge, has not yet been applied to obtain 2-glycosylamino-1,3,4-oxadiazoles. On the other hand, the preparation of semicarbazones **IV** (X = O) gave the opportunity to compare their GPI properties to the corresponding thiosemicarbazones **IV** (X = S).

2. Results and discussion

2.1. Syntheses

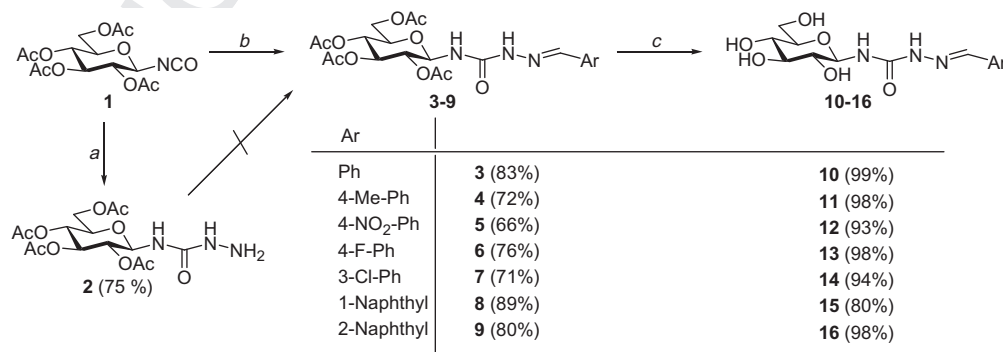
For the formation of the target oxadiazoles oxidative ring closure of aromatic aldehyde 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazones (similar to that applied for the syntheses of 2-aryl-5-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-1,3,4-oxadiazoles²²) was envisaged as the key step. To this end, O-peracetylated 4-(β -D-glucopyranosyl)semicarbazide **2** was prepared (Scheme 1) by the reaction of glucopyranosyl isocyanate **1**²⁹ (obtained from the corresponding glucopyranosylamine³⁰) with hydrazine reagents under different reaction conditions (reagents: $\text{NH}_2\text{NH}_2\cdot\text{HCl}$, $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$; solvents: dry pyridine, dry CH_2Cl_2 , and 1 equiv Et_3N). The best yield (75%) was achieved with $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$ in dry CH_2Cl_2 in the presence of Et_3N . In each of the above reactions bis-glucopyranosyl urea was also isolated in various amounts which could be due to the presence of traces of water in the mixtures.³¹

In order to get semicarbazones **3–9** condensation of semicarbazide **2** with the proper aldehydes was planned. However, reactions of **2** with 2-naphthaldehyde in dry EtOH or dry toluene in the presence of catalytic amounts of either AcOH or CF_3COOH

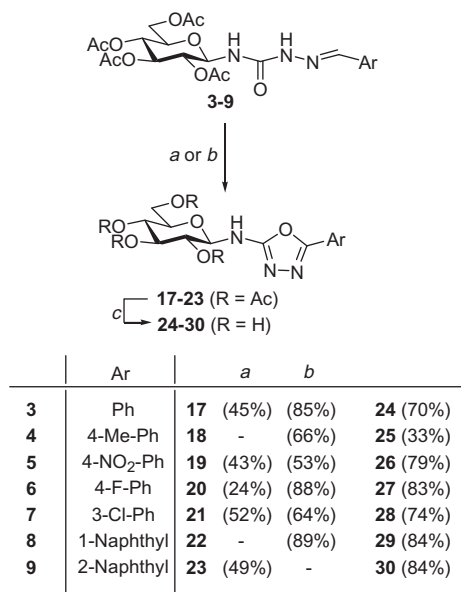
at reflux temperature resulted in complex reaction mixtures. Therefore, β -D-glucopyranosyl isocyanate **2** was reacted with aldehyde hydrazones³² in boiling dry dioxane to result in the target molecules **3–9** in good yields. Debenzoylations were performed by the Zemplén protocol to give excellent yields of semicarbazones **10–16**.

Ring closing reactions of the precursors under oxidative conditions were studied next. Semicarbazones **3**, **5–7**, and **9** were reacted with phenyliodonium diacetate (PIDA) in CH_2Cl_2 at rt (Scheme 2) to furnish the corresponding O-peracetylated 2-(β -D-glucopyranosylamino)-5-substituted-1,3,4-oxadiazoles **17**, **19–21**, and **23**, respectively, in moderate yields. Application of $\text{Pb}(\text{OAc})_4$ as the oxidizing agent in glacial AcOH at 80 °C resulted in better yields for 1,3,4-oxadiazoles **17–22** (compare yields under conditions a and b in Scheme 2). Debenzoylations were performed by the Zemplén protocol to give mostly good yields of 1,3,4-oxadiazoles **24–30** (Scheme 2).

Structural elucidation of the new compounds was based on NMR spectra. The β -D-anomeric configuration was indicated by the 8.1–9.9 Hz coupling constants between 1-H and 2-H protons in the $^4\text{C}_1$ conformation of each compound. Coupling of 1-H and N(4)H (9.2–9.8 Hz) could be observed in the spectra of semicarbazones **3–9** only. For the oxadiazoles **17–23** 1-H and NH appeared as doublets and singlets, respectively, probably because of a specific dihedral angle between these protons resulting in a very small coupling constant. A ^1H spectrum of semicarbazone **5** recorded immediately (~ 5 min) after dissolution showed the presence of one compound only. A NOE difference spectrum obtained by irradiation of the N(2)H signal gave positive NOE for the signal of $\text{CH}=\text{N}$ (7.86 ppm) and N(4)H (7.25 ppm) indicating E configuration of the $\text{C}=\text{N}$ double bond. After 72 h the ^1H spectrum of **5** exhibited two sets of signals as a result of E/Z isomerisation ($\sim 1:1$ ratio, characteristic chemical shifts (δ , ppm) for the E isomer: 10.10 (N(2)H), 7.86 ($\text{CH}=\text{N}$), 7.25 (N(4)H); for the Z isomer: 8.62 (N(2)H), 7.41 ($\text{CH}=\text{N}$),



Scheme 1. Reagents and conditions: (a) $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$, dry CH_2Cl_2 , Et_3N , rt; (b) $\text{ArCH}=\text{N}-\text{NH}_2$, dry dioxane, reflux; (c) NaOMe, dry MeOH, rt.



Scheme 2. Reagents and conditions: (a) PIDA, CH₂Cl₂, rt; (b) Pb(OAc)₄, AcOH, 80 °C; (c) NaOMe, dry MeOH, rt.

7.15 (N(4)H). These upfield shifts for the Z isomer are in accord with literature experiences for semicarbazones,³³ however, contrast those for O-peracetylated 4-(β-D-glucopyranosyl)thiosemicarbazones where the N(2)H signals were reported to appear at 10.1 (E) and 14.6 (Z) ppm.¹⁷

2.2. Enzyme inhibition studies

The kinetic parameters (inhibition potency against rabbit muscle glycogen phosphorylase *b* (RMGPb)) of the deprotected compounds were determined according to the protocol described earlier.³⁴ The results are summarized in Table 1 showing the inhibitory efficiency of some relevant reference compounds, as well.

Type IV semicarbazones **10–16**, the 'open chain' precursors of the target compounds of this work, proved low micromolar inhibitors with the practically equipotent 4-nitrophenyl (**12**) and 2-naphthyl (**16**) compounds as the best ones. The strong binding of **16** fits the general trend observed with several glucose derivatives exhibiting most efficient inhibition with large hydrophobic groups in the aglycons.⁴ A comparison to the structurally related thiosemicarbazone counterparts would be possible for the pairs **12–31**, **13–32**, and **14–33**, however, the reported inhibition data¹⁸ for the sulfur containing compounds **31–33** are IC₅₀ values not directly comparable with the inhibitor constants. Nevertheless, it is interesting to note that the tendency is different in the two series: within semicarbazones the 4-nitrophenyl (**12**) compound while within the thiosemicarbazones the 4-fluorophenyl (**32**) derivative proved ~4 to 6 times stronger inhibitors than the next best ones **14** and **33**, respectively.

A comparison of inhibition of **10** to that of the biuret type compound **37**,⁴ having the same number of atoms between the sugar and the aromatic ring, indicates the latter to be a ~twice better inhibitor than the former one. This may underline the importance of both carbonyl units in the binding. On the other hand, **10** binds ~15-fold stronger than **38**⁴ with two C=O moieties but also having a rotatable CH₂ unit in place of NH, thereby emphasizing that the rigidity of **10** makes an important contribution to the binding.

A further comparison of **10** to type V compound **39**,¹⁹ wherein the semicarbazone linker is formally reversed between the carbohydrate ring and the phenyl group, shows a moderate strengthening of the inhibition that may refer to the higher

contribution of the second carbonyl unit to the binding. This is corroborated by the smaller decrease caused by the change **37**→**39** than that of **37**→**10**. A formal reversal of the thiosemicarbazone linker as in **40**¹⁹ makes a very large decrease in the binding strength most probably because the thiocarbonyl in the position of the 'second amide' moiety is much less suitable to make strong interactions to the enzyme.

Replacement of the NHCO moiety in compounds type II by the 1,3,4-oxadiazole ring (compounds type IIB: **24–30**) resulted in moderate GPIs. For the phenyl and 1-naphthyl substituted pairs **34–24** and **35–29** there is no significant change in the binding strength. Substitution in the 4-position of the aromatic ring (**25–27**) resulted in a small and unspecific increase of the efficiency, while the 3-chloro replacement (**28**) made a somewhat weaker inhibitor. Based on these results one could argue that the 1,3,4-oxadiazole is an acceptable bioisosteric replacement of the NHCO moiety in this system. However, this argument is weakened by the ~5 times worse inhibition of **30** as compared to **36** for which a speculative explanation can be that the large and rigid aglycon is unable to find an accommodable position in the binding site of the enzyme.

3. Conclusion

Reaction of O-peracetylated β-D-glucopyranosyl isocyanate with different hydrazones gave the corresponding aldehyde 4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)semicarbazones in good yields. Oxidation of these compounds by PIDA or more advantageously by Pb(OAc)₄ resulted in 2-(β-D-glucopyranosylamino)-5-substituted-1,3,4-oxadiazoles. Zemplén deacetylation furnished test compounds which proved low micromolar inhibitors against RMGPb. Structure–activity considerations allow to estimate the relative contribution to the binding by carbonyl and thiocarbonyl groups of N-acyl-N'-glucopyranosyl urea type GPIs, and raise the possibility of applying 1,3,4-oxadiazoles as bioisosteric replacements of NHCO moieties.

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 ¹H/¹³C) or Bruker 400 (400/100 MHz for ¹H/¹³C) spectrometers. Chemical shifts are referenced to TMS as the internal reference (¹H), or to the residual solvent signals (¹³C). Microanalyses were performed on an Elementar vario Micro cube. ESIMS were recorded with a Bruker micrOTOF-Q instrument. TLC was performed on DC-Alurolle Kieselgel 60 F₂₅₄ (Merck). TLC plates were visualized under UV light, and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was applied. Organic solutions were dried over anhydrous MgSO₄, and concentrated under diminished pressure at 40–50 °C (water bath). Aldehyde hydrazones were obtained from the corresponding aldehydes and H₂NNH₂·H₂O according to a literature procedure.³²

4.2. General procedure I for the synthesis of aromatic aldehyde 4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)semicarbazones (3–9)

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl isocyanate²⁹ (**1**, 0.22 g, 0.59 mmol) was added to the solution of an aldehyde hydrazone (0.27 g, 1.80 mmol) in dry dioxane (5 mL). The reaction mixture was stirred at reflux temperature for 24 h. When the reaction

Table 1

Inhibition of rabbit muscle glycogen phosphorylase *b* (RMGPb) by selected glucose derivatives and the new compounds (K_i [μ M])

Ar							
		X = O	X = S				
	10	38	—	34	18 ⁴	24	20
	11	136	—	—	—	25	12
	12	4.5	31	25.7 ¹⁸ (IC ₅₀)	—	26	15
	13	48	32	5.7 ¹⁸ (IC ₅₀)	—	27	14
	14	30	33	23.2 ¹⁸ (IC ₅₀)	—	28	33
	15	124	—	35	350 ⁴ (IC ₅₀)	29	315 (IC ₅₀)
	16	5.5	—	36	5.2 ⁴	30	27
	37 X = NH 38 X = CH ₂	21 ⁴ 600 ⁴			39 X = O 40 X = S	29 ¹⁹ 300 ¹⁹	

was complete (TLC 1:1 EtOAc/hexane) the reaction mixture was filtered with suction, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography.

4.3. General procedure II for the synthesis of 5-aryl-2-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosylamino)-1,3,4-oxadiazoles (**17–23**)

An aldehyde 4-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)semicarbazone (**3–9**, 0.03 mmol/mL) was dissolved in CH₂Cl₂, then PIDA (1.1 equiv) was added, and the mixture was stirred at rt. When the reaction was complete (TLC, 1:1 EtOAc/hexane) the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography.

4.4. General procedure III for the synthesis of 5-aryl-2-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosylamino)-1,3,4-oxadiazoles (**17–23**)

An aldehyde 4-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)semicarbazone (**3–9**, 0.03 mmol/mL) was dissolved in glacial AcOH, then Pb(OAc)₄ (1 equiv) was added, and the mixture was stirred at 80 °C. The reaction was monitored by TLC (1:1 EtOAc/hexane). When the reaction was complete, the reaction mixture was diluted with H₂O (10 mL), and washed with EtOAc (3 \times 6 mL). The organic layer was separated, dried, and the solvent

was evaporated under reduced pressure. The residue was purified by column chromatography.

4.5. General procedure IV for the removal of *O*-acetyl protecting groups

An *O*-peracetylated compound (100 mg) was dissolved in dry MeOH (1 mL) and a solution of NaOMe (0.1 M in MeOH) was added to the solution in a catalytic amount. The reaction mixture was stirred at rt. When the reaction was complete (TLC, 3:1 CHCl₃/MeOH) the solution was neutralized with a cation exchange resin Amberlyst 15 (H⁺ form). The resin was filtered off with suction and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography.

4.6. 4-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)semicarbazide (**2**)

NH₂NH₂·HOAc (97%, 26.6 mg, 0.28 mmol) was added to the solution of 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl isocyanate²⁹ (**1**, 0.10 g, 0.27 mmol) and Et₃N (39 μ L, 0.28 mmol) in dry CH₂Cl₂ (2 mL). The reaction mixture was stirred at rt. When the reaction was complete (TLC 5:1 EtOAc/hexane) the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: 5:1 EtOAc/hexane) to give 81 mg (75%) of **2** as a white amorphous product. [α]_D -4 (c 0.50, DMSO); *R*_f = 0.27 (5:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 9.28, 6.82,

6.53, 6.27 (4H, 4 s, NH), 5.32, 5.14, 5.07, 4.97 (4H, 4 pt, $J = 8.9$, 9.6 Hz in each, H-1, H-2, H-3, H-4), **4.31–4.12** (2H, m, H-6a, H-6b), **3.85–3.83** (1H, m, H-5), 2.08, 2.07, 2.04 (12H, 3 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.0, 169.4, 169.3, 169.2 (CO), 157.2 (NHCONH), 78.5, 72.8, 71.7, 70.4, 67.9 (C-1 to C-5), 61.7 (C-6), 20.5, 20.3 (CH₃). Anal. Calcd for C₁₅H₂₃N₃O₁₀ (405.36): C, 44.44; H, 5.72; N, 10.37. Found: C, 44.58; H, 5.84; N, 10.26.

4.7. Benzaldehyde 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazone (3)

From isocyanate **1** (0.10 g, 0.27 mmol) and benzaldehyde hydrazone (0.064 g, 0.54 mmol) according to General procedure I (Section 4.2). Purified by column chromatography (1:1 EtOAc/hexane) to yield 110 mg (83%) of **3** as a white amorphous product. $[\alpha]_D^{25}$ -61 (c 0.99, CHCl₃); R_f: 0.58 (5:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 9.47 (1H, br s, NH), 7.77 (1H, s, CH=N), 7.70–7.66 (2H, m, Ar), 7.43–7.40 (3H, m, Ar), 7.16 (1H, d, $J_{1,NH} = 9.5$ Hz, NH), 5.39, 5.28, 5.15, 5.13 (4H, 4 pt, $J = 9.5$, 9.7 Hz in each, H-1, H-2, H-3, H-4), 4.38 (1H, dd, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.12 (1H, dd, H-6b), 3.92 (1H, ddd, $J_{5,6a} = 4.1$ Hz, $J_{5,6b} = 1.8$ Hz, $J_{4,5} = 10.1$ Hz, H-5), 2.08, 2.05, 2.04, 2.03 (12H, 4 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.7, 170.5, 170.0, 169.5 (CO), 155.7 (NHCONH), 142.6 (CH=N), 133.6, 130.0, 128.7, 127.1 (Ar), 79.3, 73.2, 72.8, 70.3, 68.2 (C-1 to C-5), 61.6 (C-6), 20.7, 20.6 (CH₃). Anal. Calcd for C₂₂H₂₇N₃O₁₀ (493.46): C, 53.55; H, 5.51; N, 8.52. Found: C, 53.46; H, 5.61; N, 8.60.

4.8. 4-Methylbenzaldehyde 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazone (4)

From isocyanate **1** (0.40 g, 1.07 mmol) and 4-methylbenzaldehyde hydrazone (0.29 g, 2.14 mmol) according to General procedure I (Section 4.2). Purified by column chromatography (1:1 EtOAc/hexane) to yield 390 mg (72%) of **4** as a white amorphous product. $[\alpha]_D^{25}$ -50 (c 0.86, CHCl₃); R_f: 0.66 (5:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 9.21 (1H, br s, NH), 7.71 (1H, s, CH=N), 7.56 (2H, d, $J = 8.0$ Hz, Ar), 7.27–7.20 (2H, m, Ar), 7.13 (1H, d, $J_{1,NH} = 9.5$ Hz, NH), 5.37, 5.26, 5.14, 5.12 (4H, 4 pt, $J = 9.5$ Hz in each, H-1, H-2, H-3, H-4), 4.36 (1H, dd, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.11 (1H, dd, H-6b), 3.89 (1H, ddd, $J_{5,6a} = 4.1$ Hz, $J_{5,6b} = 1.9$ Hz, $J_{4,5} = 10.1$ Hz, H-5), 2.39, 2.08, 2.05, 2.04, 2.02 (16H, 5 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.7, 170.5, 170.0, 169.5 (CO), 155.7 (NHCONH), 142.6 (CH=N), 140.3, 130.8, 129.5, 127.0 (Ar), 79.4, 73.2, 72.9, 70.3, 68.2 (C-1 to C-5), 61.7 (C-6), 21.5, 20.7 (CH₃). Anal. Calcd for C₂₃H₂₉N₃O₁₀ (507.49): C, 54.43; H, 5.76; N, 8.28. Found: C, 54.32; H, 5.64; N, 8.38.

4.9. 4-Nitrobenzaldehyde 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazone (5)

From isocyanate **1** (0.40 g, 1.07 mmol) and 4-nitrobenzaldehyde hydrazone (0.37 g, 2.14 mmol) according to General procedure I (Section 4.2). Purified by column chromatography (1:1 EtOAc/hexane) to yield 380 mg (66%) of **5** as an orange amorphous product. $[\alpha]_D^{25}$ -71 (c 0.35, CHCl₃); R_f: 0.18 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 10.10 (1H, br s, NH), 8.29 (2H, d, $J = 8.8$ Hz, Ar), 7.87 (2H, d, $J = 8.8$ Hz, Ar), 7.86 (1H, s, CH=N), 7.25 (1H, d, $J_{1,NH} = 9.2$ Hz, NH), 5.41, 5.24, 5.14, 5.12 (4H, 4 pt, $J = 9.3$, 9.8 Hz in each, H-1, H-2, H-3, H-4), 4.38 (1H, dd, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.13 (1H, dd, H-6b), 3.91 (1H, $J_{5,6a} = 4.1$ Hz, $J_{5,6b} = 2.1$ Hz, $J_{4,5} = 9.9$ Hz, m, H-5), 2.09, 2.06, 2.04 (12H, 3 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.7, 170.5, 169.9, 169.4 (CO), 155.7 (NHCONH), 148.2 (C-NO₂), 139.8 (CH=N), 139.6, 127.5, 124.0 (Ar), 79.3, 73.2, 72.5, 70.4, 68.1 (C-1 to C-5), 61.6 (C-6), 20.5

(CH₃). Anal. Calcd for C₂₂H₂₆N₄O₁₂ (538.46): C, 49.07; H, 4.87; N, 10.40. Found: C, 48.98; H, 4.80; N, 10.52.

4.10. 4-Fluorobenzaldehyde 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazone (6)

From isocyanate **1** (0.25 g, 0.67 mmol) and 4-fluorobenzaldehyde hydrazone (0.19 g, 1.23 mmol) according to General procedure I (Section 4.2). Purified by column chromatography (1:1 EtOAc/hexane) to yield 260 mg (76%) of **6** as a white amorphous product. $[\alpha]_D^{25}$ -54 (c 0.27, CHCl₃); R_f: 0.22 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 10.09 (1H, br s, NH), 7.78 (1H, s, CH=N), 7.68 (2H, dd, $J = 5.6$ Hz, $J = 7.9$ Hz, Ar), 7.21–7.07 (3H, m, Ar, NH), 5.41, 5.29, 5.15, 5.12 (4H, 4 pt, $J = 9.3$, 9.9 Hz in each, H-1, H-2, H-3, H-4), 4.38 (1H, dd, $J_{5,6a} = 3.7$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.12 (1H, dd, $J_{5,6b} < 1$ Hz, H-6b), 3.97–3.89 (1H, m, H-5), 2.05 (12H, s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.6, 170.5, 169.9, 169.4 (CO), 163.7 (d, $J = 250.0$ Hz, Ar), 155.8 (NHCONH), 141.4 (CH=N), 129.9 (Ar), 128.9 (d, $J = 7.3$ Hz, Ar), 115.8 (d, $J = 22.0$ Hz, Ar), 79.3, 73.1, 72.7, 70.3, 68.1 (C-1 to C-5), 61.6 (C-6), 20.5 (CH₃). Anal. Calcd for C₂₂H₂₆FN₃O₁₀ (511.45): C, 51.66; H, 5.12; N, 8.22. Found: C, 51.54; H, 5.23; N, 8.33.

4.11. 3-Chlorobenzaldehyde 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazone (7)

From isocyanate **1** (0.22 g, 0.59 mmol) and 3-chlorobenzaldehyde hydrazone (0.18 g, 1.18 mmol) according to General procedure I (Section 4.2). Purified by column chromatography (1:1 EtOAc/hexane) to yield 222 mg (71%) of **7** as a white amorphous product. $[\alpha]_D^{25}$ -65 (c 1.06, CHCl₃); R_f: 0.61 (5:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 9.60 (1H, br s, NH), 7.64–7.46 (3H, m, Ar, CH=N), 7.31–7.27 (2H, m, Ar), 7.12 (1H, d, $J_{1,NH} = 9.2$ Hz, NH), 5.31, 5.16, 5.07, 5.05 (4H, 4 pt, $J = 9.2$, 9.7 Hz in each, H-1, H-2, H-3, H-4), 4.29 (1H, dd, $J_{5,6a} = 3.9$ Hz, $J_{6a,6b} = 12.4$ Hz, H-6a), 4.06 (1H, dd, $J_{5,6b} = 1.0$ Hz, H-6b), 3.87–3.80 (1H, m, H-5), 2.02, 1.97 (12H, 2 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.7, 170.5, 170.0, 169.5 (CO), 155.7 (NHCONH), 141.0 (CH=N), 135.4, 134.9, 130.0, 126.9, 125.3 (Ar), 79.5, 73.3, 72.7, 70.4, 68.3 (C-1 to C-5), 61.7 (C-6), 20.7, 20.6 (CH₃). Anal. Calcd for C₂₂H₂₆ClN₃O₁₀ (527.91): C, 50.05; H, 4.96; N, 7.96. Found: C, 50.16; H, 4.84; N, 7.85.

4.12. 4-(1-Naphthaldehyde) 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazone (8)

From isocyanate **1** (0.40 g, 1.07 mmol) and 1-naphthaldehyde hydrazone (0.37 g, 2.14 mmol) according to General procedure I (Section 4.2). Purified by column chromatography (1:1 EtOAc/hexane) to yield 520 mg (89%) of **8** as a yellow amorphous product. $[\alpha]_D^{25}$ -53 (c 0.96, CHCl₃); R_f: 0.63 (5:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 9.63 (1H, br s, NH), 8.52 (1H, d, $J = 8.5$ Hz, Ar), 8.44 (1H, s, CH=N), 7.93–7.90 (3H, m, Ar), 7.68 (1H, pt, $J = 8.1$, 8.3 Hz, Ar), 7.58–7.51 (2H, m, Ar), 7.17 (1H, d, $J_{1,NH} = 9.6$ Hz, NH), 5.42, 5.34, 5.17, 5.16 (4H, 4 pt, $J = 9.5$, 9.7 Hz in each, H-1, H-2, H-3, H-4), 4.37 (1H, dd, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.11 (1H, dd, H-6b), 3.94 (1H, ddd, $J_{5,6a} = 3.9$ Hz, $J_{5,6b} = 2.0$ Hz, $J_{4,5} = 10.2$ Hz, H-5), 2.07, 2.06, 2.05 (12H, 3 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.7, 170.6, 170.0, 169.5 (CO), 155.7 (NHCONH), 142.1 (CH=N), 133.8, 130.5, 130.7, 128.9, 128.8, 127.3, 126.2, 125.3, 123.7 (Ar), 79.4, 73.3, 72.9, 70.3, 68.2 (C-1 to C-5), 61.6 (C-6), 20.7, 20.6 (CH₃). Anal. Calcd for C₂₆H₂₉N₃O₁₀ (543.52): C, 57.45; H, 5.38; N, 7.73. Found: C, 57.56; H, 5.27; N, 7.85.

4.13. 4-(2-Naphthaldehyde) 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)semicarbazone (9)

From isocyanate **1** (0.27 g, 0.71 mmol) and 2-naphthaldehyde hydrazone (0.24 g, 1.42 mmol) according to General procedure I (Section 4.2). Purified by column chromatography (1:1 EtOAc/hexane) to yield 310 mg (80%) of **9** as a yellow amorphous product. $[\alpha]_D^{25} -73$ (c 0.93, CHCl₃); R_f : 0.64 (5:1 EtOAc/hexane); $^1\text{H NMR}$ (CDCl₃, 360 MHz) δ (ppm) 9.83 (1H, s, NH), 7.99–7.83 (6H, m, Ar, CH=N), 7.53–7.50 (2H, m, Ar), 7.26 (1H, d, $J_{1,\text{NH}} = 9.8$ Hz, NH), 5.42, 5.32, 5.17, (4H, 3 pt, $J = 9.3$, 9.6 Hz in each, H-1, H-2, H-3, H-4), 4.39 (1H, dd, $J_{5,6a} = 3.8$ Hz, $J_{6a,6b} = 12.5$ Hz, H-6a), 4.14 (1H, dd, $J_{5,6b} < 1.0$ Hz, H-6b), 3.97–3.94 (1H, m, H-5), 2.06 (12H, s, CH₃). $^{13}\text{C NMR}$ (CDCl₃, 360 MHz) δ (ppm) 170.7, 170.6, 170.0, 169.5 (CO), 155.7 (NHCONH), 142.1 (CH=N), 134.2, 133.1, 131.4, 128.7, 128.3, 127.9, 127.0, 126.6, 122.7 (Ar), 79.5, 73.3, 72.9, 70.4, 68.3 (C-1 to C-5), 61.7 (C-6), 20.6 (CH₃). Anal. Calcd for C₂₆H₂₉N₃O₁₀ (543.52): C, 57.45; H, 5.38; N, 7.73. Found: C, 57.57; H, 5.49; N, 7.63.

4.14. Benzaldehyde 4-(β -D-glucopyranosyl)semicarbazone (10)

From **3** (0.15 g, 0.30 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 98 mg (99%) of **10** as a white amorphous product. $[\alpha]_D^{25} +33$ (c 0.54, CH₃OH); R_f : 0.34 (4:1 CHCl₃/MeOH); $^1\text{H NMR}$ (D₂O, 360 MHz) δ (ppm) 7.82 (1H, s, CH=N), 7.72–7.68 (5H, m, Ar), 4.97 (1H, d, $J_{1,2} = 8.3$ Hz, H-1), 3.90 (1H, dd, $J_{5,6b} = 1.5$ Hz, $J_{6a,6b} = 11.7$ Hz, H-6b), 3.75 (1H, dd, $J_{5,6a} = 5.2$ Hz, H-6a), 3.62–3.48 (4H, m, H-2, H-3, H-4, H-5). $^{13}\text{C NMR}$ (D₂O+1 drop CH₃OH, 360 MHz) δ (ppm) 158.4 (NHCONH), 144.1 (CH=N), 135.7, 130.9, 129.7, 128.1 (Ar), 82.4, 79.4, 78.8, 73.9, 71.4 (C-1 to C-5), 62.7 (C-6). Anal. Calcd for C₁₄H₁₉N₃O₆ (325.32): C, 51.69; H, 5.89; N, 12.92. Found: C, 51.57; H, 5.99; N, 12.81.

4.15. 4-Methylbenzaldehyde 4-(β -D-glucopyranosyl)semicarbazone (11)

From **4** (0.09 g, 0.18 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 60 mg (98%) of **11** as a white amorphous product. $[\alpha]_D^{25} +30$ (c 0.48, CH₃OH); R_f : 0.48 (3:1 CHCl₃/MeOH); $^1\text{H NMR}$ (CD₃OD, 360 MHz) δ (ppm) 7.85 (1H, s, CH=N), 7.59 (2H, d, $J = 8.5$ Hz, Ar), 7.20 (2H, d, $J = 8.5$ Hz, Ar), 4.97 (1H, d, $J_{1,2} = 8.4$ Hz, H-1), 3.89 (1H, dd, $J_{5,6b} < 1.0$ Hz, $J_{6a,6b} = 11.7$ Hz, H-6b), 3.73 (1H, dd, $J_{5,6a} = 3.8$ Hz, H-6a), 3.48–3.35 (4H, m, H-2, H-3, H-4, H-5), 2.35 (3H, s, CH₃). $^{13}\text{C NMR}$ (CD₃OD, 360 MHz) δ (ppm) 158.4 (NHCONH), 144.1 (CH=N), 141.3, 133.0, 130.4, 128.1 (Ar), 82.4, 79.5, 78.9, 74.0, 71.4 (C-1 to C-5), 62.7 (C-6), 21.5 (CH₃). Anal. Calcd for C₁₅H₂₁N₃O₆ (339.34): C, 53.09; H, 6.24; N, 12.38. Found: C, 52.98; H, 6.35; N, 12.26.

4.16. 4-Nitrobenzaldehyde 4-(β -D-glucopyranosyl)semicarbazone (12)

From **5** (0.15 g, 0.28 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (1:1 CHCl₃/MeOH) to yield 107 mg (93%) of **12** as an orange amorphous product. $[\alpha]_D^{25} +30$ (c 0.29, DMSO); R_f : 0.70 (2:3 CHCl₃/MeOH); $^1\text{H NMR}$ (CD₃OD, 400 MHz) δ (ppm) 8.28 (2H, d, $J = 8.7$ Hz, Ar), 8.00 (2H, d, $J = 9.0$ Hz, Ar), 7.98 (1H, s, CH=N), 4.94 (1H, d, $J_{1,2} = 8.5$ Hz, H-1), 3.84 (1H, dd, $J_{5,6b} = 1.0$ Hz, $J_{6a,6b} = 12.3$ Hz, H-6b), 3.70 (1H, dd, $J_{5,6a} = 4.5$ Hz, $J_{6a,6b} = 11.9$ Hz, H-6a), 3.51–3.43 (2H, m, H-2 or H-3 or H-4, H-5), 3.40–3.36 (2H, m, H-2 and/or H-3, and/or H-4). $^{13}\text{C NMR}$ (DMSO-*d*₆, 360 MHz) δ (ppm) 155.0 (NHCONH), 147.3 (C-NO₂), 138.0 (CH=N), 141.0, 127.8, 129.8 (Ar), 80.9, 78.4, 77.4, 71.9, 69.9 (C-1 to C-5), 61.0 (C-6). Anal. Calcd for C₁₄H₁₈N₄O₈

(370.31): C, 45.41; H, 4.90; N, 15.13. Found: C, 45.54; H, 4.79; N, 15.24.

4.17. 4-Fluorobenzaldehyde 4-(β -D-glucopyranosyl)semicarbazone (13)

From **6** (0.12 g, 0.24 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 80 mg (98%) of **13** as a brown amorphous product. $[\alpha]_D^{25} +42$ (c 0.28, DMSO); R_f : 0.20 (4:1 CHCl₃/MeOH); $^1\text{H NMR}$ (CD₃OD, 400 MHz) δ (ppm) 7.89 (1H, s, CH=N), 7.78 (2H, dd, $J = 5.6$ Hz, $J = 8.5$ Hz, Ar), 7.15 (2H, pt, $J = 8.7$ Hz, Ar), 4.95 (1H, d, $J_{1,2} = 8.4$ Hz, H-1), 3.86 (1H, dd, $J_{5,6b} < 1.0$ Hz, $J_{6a,6b} = 11.7$ Hz, H-6b), 3.70 (1H, dd, $J_{5,6a} = 4.0$ Hz, H-6a), 3.48–3.29 (4H, m, H-2, H-3, H-4, H-5). $^{13}\text{C NMR}$ (DMSO-*d*₆, 360 MHz) δ (ppm) 162.8 (d, $J = 246.4$ Hz, Ar), 155.4 (NHCONH), 138.0 (CH=N), 131.2, 129.2 (d, $J = 6.4$ Hz, Ar), 115.8 (d, $J = 21.6$ Hz, Ar), 80.9, 78.4, 77.5, 72.1, 70.1 (C-1 to C-5), 61.1 (C-6). Anal. Calcd for C₁₄H₁₈FN₃O₆ (343.31): C, 48.98; H, 5.28; N, 12.24. Found: C, 49.10; H, 5.41; N, 12.13.

4.18. 3-Chlorobenzaldehyde 4-(β -D-glucopyranosyl)semicarbazone (14)

From **7** (0.15 g, 0.28 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 96 mg (94%) of **14** as a yellow amorphous product. $[\alpha]_D^{25} +30$ (c 0.54, CH₃OH); R_f : 0.40 (4:1 CHCl₃/MeOH); $^1\text{H NMR}$ (CD₃OD, 360 MHz) δ (ppm) 7.83–7.32 (5H, m, Ar, CH=N), 4.97 (1H, d, $J_{1,2} = 8.3$ Hz, H-1), 3.85 (1H, dd, $J_{5,6b} < 1.0$ Hz, $J_{6a,6b} = 11.8$ Hz, H-6b), 3.71–3.67 (1H, m, H-6a), 3.52–3.39 (4H, m, H-2, H-3, H-4, H-5). $^{13}\text{C NMR}$ (CD₃OD, 360 MHz) δ (ppm) 158.2 (NHCONH), 142.4 (CH=N), 137.8, 135.8, 131.2, 130.6, 127.3, 126.9 (Ar), 82.4, 79.4, 78.8, 73.8, 71.3 (C-1 to C-5), 62.6 (C-6). Anal. Calcd for C₁₄H₁₈ClN₃O₆ (359.76): C, 46.74; H, 5.04; N, 11.68. Found: C, 46.62; H, 5.13; N, 11.80.

4.19. 1-Naphthaldehyde 4-(β -D-glucopyranosyl)semicarbazone (15)

From **8** (0.17 g, 0.18 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 93 mg (80%) of **15** as a brown amorphous product. $[\alpha]_D^{25} +32$ (c 0.48, CH₃OH); R_f : 0.41 (4:1 CHCl₃/MeOH); $^1\text{H NMR}$ (CD₃OD, 360 MHz) δ (ppm) 8.66 (1H, s, CH=N), 8.41–7.48 (7H, m, Ar), 4.98 (1H, d, $J_{1,2} = 8.7$ Hz, H-1), 3.87 (1H, dd, $J_{5,6b} = 1.5$ Hz, $J_{6a,6b} = 12.0$ Hz, H-6b), 3.71 (1H, dd, $J_{5,6a} = 4.6$ Hz, H-6a), 3.52–3.38 (4H, m, H-2, H-3, H-4, H-5). $^{13}\text{C NMR}$ (CD₃OD, 360 MHz) δ (ppm) 158.3 (NHCONH), 142.3 (CH=N), 135.3–124.1 (Ar), 82.4, 79.5, 79.0, 74.1, 71.4 (C-1 to C-5), 62.7 (C-6). Anal. Calcd for C₁₈H₂₁N₃O₆ (375.38): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.70; H, 5.52; N, 11.29.

4.20. 2-Naphthaldehyde 4-(β -D-glucopyranosyl)semicarbazone (16)

From **9** (0.14 g, 0.26 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 96 mg (98%) of **16** as a white amorphous product. $[\alpha]_D^{25} +39$ (c 0.47, CH₃OH); R_f : 0.43 (4:1 CHCl₃/MeOH); $^1\text{H NMR}$ (CD₃OD, 360 MHz) δ (ppm) 8.08–7.46 (8H, m, Ar, CH=N), 4.97 (1H, d, $J_{1,2} = 8.6$ Hz, H-1), 3.87 (1H, dd, $J_{5,6b} < 1.0$ Hz, $J_{6a,6b} = 12.0$ Hz, H-6b), 3.71 (1H, dd, $J_{5,6a} = 4.3$ Hz, H-6a), 3.51–3.38 (4H, m, H-2, H-3, H-4, H-5). $^{13}\text{C NMR}$ (CD₃OD, 360 MHz) δ (ppm) 157.9 (NHCONH), 143.9 (CH=N), 135.6–123.9 (Ar), 82.4, 79.5, 78.9, 74.0, 71.4 (C-1 to C-5), 62.7 (C-6). Anal. Calcd for C₁₈H₂₁N₃O₆ (375.38): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.46; H, 5.75; N, 11.08.

4.21. 5-Phenyl-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)-1,3,4-oxadiazole (17)

(a) From **3** (0.11 g, 0.23 mmol) according to General procedure II (Section 4.3). Purified by column chromatography (1:1 EtOAc/hexane) to yield 50 mg (45%) of **17** as a white amorphous product.

(b) From **3** (0.25 g, 0.51 mmol) according to General procedure III (Section 4.4). Purified by column chromatography (1:1 EtOAc/hexane) to yield 212 mg (85%) of **17** as a white amorphous product. $[\alpha]_D^{20}$ (c 0.28, CHCl₃); R_f : 0.23 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 7.96–7.83 (2H, m, Ar), 7.54–7.42 (3H, m, Ar), 6.22 (1H, br s, NH), 5.39 (1H, pt, J = 9.4 Hz, H-2 or H-3 or H-4), 5.21 (1H, d, $J_{1,2}$ = 9.0 Hz, H-1), 5.14, 5.11 (2H, 2 pt, J = 9.4, 9.9 Hz in each, H-2 and/or H-3, and/or H-4), 4.33 (1H, dd, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.11 (1H, dd, $J_{5,6b}$ = 1.2 Hz, H-6b), 3.98–3.88 (1H, m, H-5), 2.09, 2.06, 2.05 (12H, 3 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.8, 170.5, 169.8, 169.5 (CO), 161.4, 160.0 (C-oxadiazole), 131.0, 128.9, 125.0, 123.8 (Ar), 82.7, 73.4, 72.6, 70.6, 68.1 (C-1 to C-5), 61.6 (C-6), 20.6, 20.5 (CH₃). Anal. Calcd for C₂₂H₂₅N₃O₁₀ (491.45): C, 53.77; H, 5.13; N, 8.55. Found: C, 53.89; H, 5.24; N, 8.64.

4.22. 5-(4-Methylphenyl)-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)-1,3,4-oxadiazole (18)

From **4** (0.29 g, 0.57 mmol) according to General procedure III (Section 4.4). Purified by column chromatography (1:1 EtOAc/hexane) to yield 190 mg (66%) of **18** as a white amorphous product. $[\alpha]_D^{20}$ (c 0.27, CHCl₃); R_f : 0.31 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 7.78 (2H, d, J = 8.1 Hz, Ar), 7.24 (2H, d, J = 8.0 Hz, Ar), 6.40 (1H, br s, NH), 5.38 (1H, pt, J = 9.4 Hz, H-2 or H-3 or H-4), 5.21 (1H, d, $J_{1,2}$ = 9.3 Hz, H-1), 5.14, 5.12 (2H, 2 pt, J = 9.3, 9.7 Hz in each, H-2 and/or H-3, and/or H-4), 4.31 (1H, dd, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.09 (1H, dd, H-6b), 3.92 (1H, ddd, $J_{5,6a}$ = 4.2 Hz, $J_{5,6b}$ = 1.8 Hz, $J_{4,5}$ = 9.8 Hz, H-5), 2.39, 2.07, 2.04, 2.03 (16H, 4 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.6, 170.5, 169.8, 169.4 (CO), 161.2, 160.0 (C-oxadiazole), 141.3, 129.5, 125.9, 121.0 (Ar), 82.6, 73.2, 72.7, 70.5, 68.0 (C-1 to C-5), 61.6 (C-6), 21.4 (CH₃), 20.6, 20.5 (CH₃). Anal. Calcd for C₂₃H₂₇N₃O₁₀ (505.47): C, 54.65; H, 5.38; N, 8.31. Found: C, 54.78; H, 5.49; N, 8.42.

4.23. 5-(4-Nitrophenyl)-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)-1,3,4-oxadiazole (19)

(a) From **5** (0.19 g, 0.35 mmol) according to General procedure II (Section 4.3). Purified by column chromatography (1:1 EtOAc/hexane) to yield 80 mg (43%) of **19** as a white amorphous product.

(b) From **5** (0.25 g, 0.46 mmol) according to General procedure III (Section 4.4). Purified by column chromatography (1:1 EtOAc/hexane) to yield 130 mg (53%) of **19** as a white amorphous product. $[\alpha]_D^{20}$ (c 0.23, CHCl₃); R_f : 0.27 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 8.34 (2H, d, J = 8.6 Hz, Ar), 8.10 (2H, d, J = 8.6 Hz, Ar), 6.45 (1H, br s, NH), 5.41 (1H, pt, J = 9.4 Hz, H-2 or H-3 or H-4), 5.24 (1H, d, $J_{1,2}$ = 9.0 Hz, H-1), 5.16, 5.12 (2H, 2 pt, J = 9.7, 10.0 Hz in each, H-2 and/or H-3, and/or H-4), 4.34 (1H, dd, $J_{5,6a}$ = 4.3 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.14 (1H, dd, $J_{5,6b}$ < 1.0 Hz, H-6b), 4.00–3.91 (1H, m, H-5), 2.10, 2.07 (12H, 2 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.9, 170.5, 169.8, 169.5 (CO), 162.1, 158.2 (C-oxadiazole), 148.9 (C-NO₂), 129.3, 126.7, 124.3 (Ar), 82.6, 73.4, 72.5, 70.6, 68.0 (C-1 to C-5), 61.5 (C-6), 20.6, 20.5 (CH₃). Anal. Calcd for C₂₂H₂₄N₄O₁₂ (536.45): C, 49.26; H, 4.51; N, 10.44. Found: C, 49.37; H, 4.42; N, 10.33.

4.24. 5-(4-Fluorophenyl)-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)-1,3,4-oxadiazole (20)

(a) From **6** (0.20 g, 0.39 mmol) according to General procedure II (Section 4.3). Purified by column chromatography (1:1 EtOAc/hexane) to yield 48 mg (24%) of **20** as a white amorphous product.

(b) From **6** (0.1 g, 0.19 mmol) according to General procedure III (Section 4.4). Purified by column chromatography (1:1 EtOAc/hexane) to yield 85 mg (88%) of **20** as a white amorphous product. $[\alpha]_D^{20}$ (c 0.30, CHCl₃); R_f : 0.33 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 7.91 (2H, dd, J = 5.4 Hz, J = 8.2 Hz, Ar), 7.16 (2H, pt, J = 8.4 Hz, Ar), 6.27 (1H, br s, NH), 5.39 (1H, pt, J = 9.4 Hz, H-2 or H-3 or H-4), 5.21 (1H, d, $J_{1,2}$ = 9.2 Hz, H-1), 5.14, 5.10 (2H, 2 pt, J = 9.3, 9.8 Hz in each, H-2 and/or H-3, and/or H-4), 4.34 (1H, dd, $J_{5,6a}$ = 4.3 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.12 (1H, dd, $J_{5,6b}$ < 1.0 Hz, H-6b), 3.98–3.88 (1H, m, H-5), 2.09, 2.06, 2.05 (12H, 3 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.8, 170.5, 169.8, 169.5 (CO), 164.1 (d, J = 252.0 Hz, Ar), 161.4, 159.1 (C-oxadiazole), 128.2 (d, J = 8.0 Hz, Ar), 120.1, 116.2 (d, J = 22.3 Hz, Ar), 82.6, 73.3, 72.6, 70.5, 68.0 (C-1 to C-5), 61.5 (C-6), 20.6, 20.5 (CH₃). Anal. Calcd for C₂₂H₂₄FN₃O₁₀ (509.44): C, 51.87; H, 4.75; N, 8.25. Found: C, 51.76; H, 4.87; N, 8.38.

4.25. 5-(3-Chlorophenyl)-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)-1,3,4-oxadiazole (21)

(a) From **7** (0.13 g, 0.24 mmol) according to General procedure II (Section 4.3). Purified by column chromatography (1:1 EtOAc/hexane) to yield 65 mg (52%) of **21** as a white amorphous product.

(b) From **7** (0.17 g, 0.33 mmol) according to General procedure III (Section 4.4). Purified by column chromatography (1:1 EtOAc/hexane) to yield 110 mg (64%) of **21** as a white amorphous product. $[\alpha]_D^{20}$ (c 0.32, CHCl₃); R_f : 0.29 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 7.89 (1H, br s, Ar), 7.80 (1H, d, J = 7.3 Hz, Ar), 7.51–7.36 (2H, m, Ar), 6.22 (1H, br s, NH), 5.39 (1H, pt, J = 9.4 Hz, H-2 or H-3 or H-4), 5.21 (1H, d, $J_{1,2}$ = 9.2 Hz, H-1), 5.14, 5.10 (2H, 2 pt, J = 9.4, 9.8 Hz in each, H-2 and/or H-3, and/or H-4), 4.33 (1H, dd, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.13 (1H, dd, $J_{5,6b}$ < 1.0 Hz, H-6b), 3.99–3.90 (1H, m, H-5), 2.09, 2.06, 2.05 (12H, 3 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.9, 170.5, 169.8, 169.5 (CO), 161.5, 158.8 (C-oxadiazole), 135.0, 131.0, 130.3, 125.9, 125.4, 124.1 (Ar), 82.6, 73.4, 72.6, 70.6, 68.1 (C-1 to C-5), 61.6 (C-6), 20.6, 20.5 (CH₃). Anal. Calcd for C₂₂H₂₄ClN₃O₁₀ (525.89): C, 50.25; H, 4.60; N, 7.99. Found: C, 50.38; H, 4.71; N, 7.89.

4.26. 5-(1-Naphthyl)-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)-1,3,4-oxadiazole (22)

From **8** (0.34 g, 0.63 mmol) according to General procedure III (Section 4.4). Purified by column chromatography (1:1 EtOAc/hexane) to yield 305 mg (89%) of **22** as a white amorphous product. $[\alpha]_D^{20}$ (c 0.29, CHCl₃); R_f : 0.32 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 360 MHz) δ (ppm) 9.01 (1H, d, J = 8.4 Hz, Ar), 7.86–7.69 (3H, m, Ar), 7.52–7.26 (3H, m, Ar), 6.94 (1H, br s, NH), 5.32 (1H, pt, J = 9.2 Hz, H-2 or H-3 or H-4), 5.19 (1H, d, $J_{1,2}$ = 9.0 Hz, H-1), 5.09, 5.06 (2H, 2 pt, J = 9.5, 9.8 Hz in each, H-2 and/or H-3, and/or H-4), 4.22 (1H, dd, $J_{5,6a}$ = 4.0 Hz, $J_{6a,6b}$ = 12.7 Hz, H-6a), 4.02 (1H, dd, $J_{5,6b}$ < 1.0 Hz, H-6b), 3.90–3.80 (1H, m, H-5), 1.98, 1.93, 1.90 (12H, 3 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 170.3, 170.2, 169.7, 169.3 (CO), 161.2, 159.5 (C-oxadiazole), 133.4–120.1 (Ar), 82.4, 73.1, 72.7, 70.4, 67.9 (C-1 to C-5), 61.5 (C-6), 20.3 (CH₃). Anal. Calcd for C₂₆H₂₇N₃O₁₀ (541.51): C, 57.67; H, 5.03; N, 7.76. Found: C, 57.55; H, 5.12; N, 7.63.

4.27. 5-(2-Naphthyl)-2-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosylamino)-1,3,4-oxadiazole (23)

From **9** (0.31 g, 0.57 mmol) according to General procedure II (Section 4.3). Purified by column chromatography (1:1 EtOAc/hexane) to yield 150 mg (49%) of **23** as a white amorphous product. $[\alpha]_D^{25} -19$ (c 0.28, CHCl₃); R_f: 0.20 (1:1 EtOAc/hexane); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.34 (1H, s, Ar), 8.10–7.69 (4H, m, Ar), 7.68–7.40 (2H, m, Ar), 6.09 (1H, br s, NH), 5.41 (1H, pt, J = 9.4 Hz, H-2 or H-3 or H-4), 5.25 (1H, d, J_{1,2} = 8.3 Hz, H-1), 5.15, 5.12 (2H, 2 pt, J = 9.2, 9.8 Hz in each, H-2 and/or H-3, and/or H-4), 4.35 (1H, dd, J_{5,6a} = 3.8 Hz, J_{6a,6b} = 12.2 Hz, H-6a), 4.13 (1H, dd, J_{5,6b} < 1.0 Hz, H-6b), 4.02–3.88 (1H, m, H-5), 2.10, 2.06 (12H, 2 s, CH₃). ¹³C NMR (CDCl₃, 360 MHz) δ (ppm) 171.0, 170.6, 169.9, 169.5 (CO), 161.4, 160.2 (C-oxadiazole), 134.3–121.1 (Ar), 82.7, 73.4, 72.6, 70.6, 68.1 (C-1 to C-5), 61.6 (C-6), 20.7, 20.5 (CH₃). Anal. Calcd for C₂₆H₂₇N₃O₁₀ (541.51): C, 57.67; H, 5.03; N, 7.76. Found: C, 57.79; H, 5.14; N, 7.87.

4.28. 2-(β -D-Glucopyranosylamino)-5-phenyl-1,3,4-oxadiazole (24)

From **17** (0.09 g, 0.18 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 41 mg (70%) of **24** as a white amorphous product. $[\alpha]_D^{25} +7$ (c 0.5, MeOH); R_f: 0.50 (3:1 CHCl₃/MeOH); ¹H NMR (CD₃OD, 360 MHz) δ (ppm) 7.94–7.84 (2H, m, Ar), 7.55–7.45 (3H, m, Ar), 4.80 (1H, d, J_{1,2} = 8.6 Hz, H-1), 3.87 (1H, dd, J_{5,6b} = 1.3 Hz, J_{6a,6b} = 11.8 Hz, H-6a), 3.68 (1H, dd, J_{5,6a} = 5.0 Hz, H-6b), 3.50–3.33 (4H, m, H-2, H-3, H-4, H-5). ¹³C NMR (CD₃OD, 360 MHz) δ (ppm) 164.8, 160.7 (C-oxadiazole), 132.3, 130.3, 126.9, 125.1 (Ar), 85.6, 79.5, 78.9, 74.2, 71.4 (C-1 to C-5), 62.7 (C-6). Anal. Calcd for C₁₄H₁₇N₃O₆ (323.30): C, 52.01; H, 5.30; N, 13.00. Found: C, 52.13; H, 5.19; N, 13.12.

4.29. 2-(β -D-Glucopyranosylamino)-5-(4-methylphenyl)-1,3,4-oxadiazole (25)

From **18** (0.14 g, 0.28 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (3:1 CHCl₃/MeOH) to yield 31 mg (33%) of **25** as a white amorphous product. $[\alpha]_D^{25} +2$ (c 0.18, DMSO); R_f: 0.40 (3:1 CHCl₃/MeOH); ¹H NMR (CD₃OD, 400 MHz) δ (ppm) 7.80 (2H, d, J = 8.2 Hz, Ar), 7.34 (2H, d, J = 8.0 Hz, Ar), 4.80 (1H, d, J_{1,2} = 8.7 Hz, H-1), 3.87 (1H, dd, J_{5,6b} = 1.8 Hz, J_{6a,6b} = 12.0 Hz, H-6b), 3.70 (1H, dd, J_{5,6a} = 5.1 Hz, H-6a), 3.50–3.35 (4H, m, H-2, H-3, H-4, H-5), 2.42 (3H, s, CH₃). ¹³C NMR (DMSO-d₆, 360 MHz) δ (ppm) 162.8, 157.9 (C-oxadiazole), 140.5, 129.7, 125.1, 121.3 (Ar), 84.4, 78.4, 77.4, 72.4, 69.8 (C-1 to C-5), 60.8 (C-6), 21.0 (CH₃). Anal. Calcd for C₁₅H₁₉N₃O₆ (337.33): C, 53.41; H, 5.68; N, 12.46. Found: C, 53.53; H, 5.59; N, 12.58.

4.30. 2-(β -D-Glucopyranosylamino)-5-(4-nitrophenyl)-1,3,4-oxadiazole (26)

From **19** (0.13 g, 0.24 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 70 mg (79%) of **26** as an orange amorphous product. $[\alpha]_D^{25} +6$ (c 0.15, DMSO); R_f: 0.19 (4:1 CHCl₃/MeOH); ¹H NMR (CD₃OD, 400 MHz) δ (ppm) 8.40 (2H, d, J = 8.4 Hz, Ar), 8.16 (2H, d, J = 8.4 Hz, Ar), 4.84 (1H, d, J_{1,2} = 8.7 Hz, H-1), 3.88 (1H, dd, J_{5,6b} = 1.0 Hz, J_{6a,6b} = 11.7 Hz, H-6b), 3.73–3.35 (5H, m, H-2, H-3, H-4, H-5, H-6a). ¹³C NMR (DMSO-d₆ + D₂O, 360 MHz) δ (ppm) 164.0, 157.2 (C-oxadiazole), 129.7, 126.8, 124.9 (Ar), 84.4, 78.6, 77.3, 72.5, 70.0 (C-1 to C-5), 61.0 (C-6). Anal. Calcd for C₁₄H₁₆N₄O₈ (368.10): C, 45.66; H, 4.38; N, 15.21. Found: C, 45.77; H, 4.49; N, 15.12.

4.31. 5-(4-Fluorophenyl)-2-(β -D-glucopyranosyl)-1,3,4-oxadiazole (27)

From **20** (0.09 g, 0.18 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 50 mg (83%) of **27** as a white amorphous product. $[\alpha]_D^{25} +4$ (c 0.20, DMSO); R_f: 0.20 (4:1 CHCl₃/MeOH); ¹H NMR (CD₃OD, 400 MHz) δ (ppm) 7.97 (2H, dd, J = 5.3 Hz, J = 8.6 Hz, Ar), 7.28 (2H, pt, J = 8.7 Hz, Ar), 4.80 (1H, d, J_{1,2} = 8.7 Hz, H-1), 3.88 (1H, dd, J_{5,6b} = 1.6 Hz, J_{6a,6b} = 12.0 Hz, H-6b), 3.70 (1H, dd, J_{5,6a} = 5.2 Hz, H-6a), 3.50–3.30 (4H, m, H-2, H-3, H-4, H-5). ¹³C NMR (DMSO-d₆ + D₂O, 360 MHz) δ (ppm) 163.3 (d, J = 249.0 Hz, Ar), 163.0, 157.3 (C-oxadiazole), 128.0 (d, J = 7.2 Hz, Ar), 120.7 (Ar), 116.6 (d, J = 22.4 Hz, Ar), 84.3, 78.4, 77.3, 72.4, 69.8 (C-1 to C-5), 60.8 (C-6). Anal. Calcd for C₁₄H₁₆FN₃O₆ (341.29): C, 49.27; H, 4.27; N, 12.31. Found: C, 49.15; H, 4.38; N, 12.42.

4.32. 5-(3-Chlorophenyl)-2-(β -D-glucopyranosylamino)-1,3,4-oxadiazole (28)

From **21** (0.11 g, 0.21 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (4:1 CHCl₃/MeOH) to yield 55 mg (74%) of **28** as a white amorphous product. $[\alpha]_D^{25} +15$ (c 0.21, DMSO); R_f: 0.19 (4:1 CHCl₃/MeOH); ¹H NMR (CD₃OD, 400 MHz) δ (ppm) 7.90 (1H, br s, Ar), 7.84 (1H, d, J = 7.9 Hz, Ar), 7.56–7.48 (2H, m, Ar), 4.82 (1H, d, J_{1,2} = 8.7 Hz, H-1), 3.88 (1H, dd, J_{5,6b} = 1.4 Hz, J_{6a,6b} = 11.9 Hz, H-6b), 3.70 (1H, dd, J_{5,6a} = 5.1 Hz, J_{6a,6b} = 12.0 Hz, H-6a), 3.52–3.35 (4H, m, H-2, H-3, H-4, H-5). ¹³C NMR (DMSO-d₆ + D₂O, 360 MHz) δ (ppm) 163.6, 157.5 (C-oxadiazole), 134.4, 131.8, 131.1, 126.0, 125.2, 124.4 (Ar), 84.5, 78.6, 77.4, 72.7, 70.1 (C-1 to C-5), 61.2 (C-6). Anal. Calcd for C₁₄H₁₆ClN₃O₆ (357.75): C, 47.00; H, 4.51; N, 11.75. Found: C, 47.10; H, 4.62; Cl, 9.93; N, 11.87.

4.33. 2-(β -D-Glucopyranosylamino)-5-(1-naphthyl)-1,3,4-oxadiazole (29)

From **22** (0.09 g, 0.24 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (3:1 CHCl₃/MeOH) to yield 50 mg (84%) of **29** as a brown amorphous product. $[\alpha]_D^{25} +5$ (c 0.18, DMSO); R_f: 0.40 (3:1 CHCl₃/MeOH); ¹H NMR (CD₃OD, 360 MHz) δ (ppm) 9.00 (1H, d, J = 8.3 Hz, Ar), 8.06–7.88 (3H, m, Ar), 7.67–7.47 (3H, m, Ar), 4.90 (1H, d, J_{1,2} = 8.5 Hz, H-1), 3.93 (1H, dd, J_{5,6b} = 2.0 Hz, J_{6a,6b} = 12.0 Hz, H-6b), 3.93 (1H, dd, J_{5,6a} = 5.3 Hz, H-6a), 3.66–3.40 (4H, m, H-2, H-3, H-4, H-5). ¹³C NMR (CD₃OD, 360 MHz) δ (ppm) 164.6, 160.5 (C-oxadiazole), 135.3–121.7 (Ar), 85.7, 79.6, 74.2, 71.4 (C-1 to C-5), 62.7 (C-6). Anal. Calcd for C₁₈H₁₉N₃O₆ (373.36): C, 57.90; H, 5.13; N, 11.25. Found: C, 57.78; H, 5.24; N, 11.36.

4.34. 2-(β -D-Glucopyranosylamino)-5-(2-naphthyl)-1,3,4-oxadiazole (30)

From **23** (0.12 g, 0.22 mmol) according to General procedure IV (Section 4.5). Purified by column chromatography (5:1 CHCl₃/MeOH) to yield 70 mg (84%) of **30** as a white amorphous product. $[\alpha]_D^{25} +9$ (c 0.20, DMSO); R_f: 0.20 (5:1 CHCl₃/MeOH); ¹H NMR (DMSO-d₆ + D₂O, 360 MHz) δ (ppm) 9.03 (1H, d, J = 8.4 Hz, Ar), 8.10 (1H, d, J = 8.2 Hz, Ar), 8.03 (2H, t, J = 7.3 Hz, Ar), 7.74–7.57 (3H, m, Ar), 4.71 (1H, d, J_{1,2} = 8.1 Hz, H-1), 3.78–3.65 (1H, m, H-6b), 3.45 (1H, dd, J_{5,6a} = 5.6 Hz, J_{6a,6b} = 11.7 Hz, H-6a), 3.32–3.20 (3H, m, H-2, H-3, H-4), 3.17–3.10 (1H, m, H-5). ¹³C NMR (DMSO-d₆ + D₂O, 360 MHz) δ (ppm) 162.7, 157.7 (C-oxadiazole), 133.4–120.3 (Ar), 84.4, 78.5, 77.4, 72.5, 69.9 (C-1 to C-5), 61.2 (C-6). Anal. Calcd for C₁₈H₁₉N₃O₆ (373.36): C, 57.90; H, 5.13; N, 11.25. Found: C, 57.79; H, 5.22; N, 11.14.

Acknowledgements

This work was supported by the Hungarian Scientific Research Fund (OTKA CK77712, CNK80709), TÁMOP-4.2.2.-08/1/2008-0014, 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 János Research Fellowships of the Hungarian Academy of Sciences (to M.T. and T.D.).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.carres.2013.04.025>.

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