C-(β-D-Glucopyranosyl) heterocycles as potential glycogen phosphorylase inhibitors

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Dedicated to Professor Sándor Antus on the occasion of his 60th birthday

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Abstract

Per-*O*-acetylated and -benzoylated β-D-glucopyranosyl cyanides were transformed into the corresponding 5-(β-D-Glucopyranosyl)tetrazoles, 2-(β-D-glucopyranosyl)benzothiazoles, and, via the benzoylated *C*-(β-D-glucopyranosyl) ethyl thioformimidate, 2-(β-D-glucopyranosyl)-benzimidazoles. Acylation of the tetrazoles, either by acetic or trifluoroacetic anhydride, gave 5-(β-D-glucopyranosyl)-2-methyl- and -2-trifluoromethyl-1,3,4-oxadiazoles, respectively. Removal of the protecting groups furnished new inhibitors of glycogen phosphorylase exhibiting inhibitor constants in the micromolar range.

Keywords: *C*-(β-D-Glucopyranosyl) heterocycles, tetrazole, benzothiazole, benzimidazole, 1,3,4-oxadiazole, inhibitors, glycogen phosphorylase

Introduction

Diabetes mellitus is a serious metabolic disease afflicting ~6 % of the population in Western societies. Its prevalence is dramatically increasing worldwide and the estimated number of diabetic patients is 220 million for the year 2010, indicating a 46 % enhancement in the world population during a decade.[1] This disease, characterized by chronically elevated blood glucose levels, is becoming one of the largest contributors to mortality especially due to its long term complications like retinopathy, neuropathy, and nephropathy, but first of all cardiovascular diseases.[2]

Diabetes is divided into two main forms: type 1 (or insulin dependent diabetes mellitus), that is characterized by total insulin deficiency; and type 2, representing more than 90 % of all diagnosed cases,[1,3] that exhibits impaired insulin secretion and/or insulin resistance. While type 1 diabetics can be treated by the administration of exogeneous insulin, for type 2 patients generally

diet, exercise, and oral hypoglycemic agents are prescribed,[2] however, the latter are inadequate for 30-40 % of the patients.[4] Therefore, several new approaches have been investigated intensively in an attempt to find more appropriate treatments for type 2 diabetes.[5] One of the emerging targets is the inhibition of glycogen phosphorylase (GP), the main regulatory enzyme in the liver, responsible for the control of blood sugar levels.[3,6]

Among small molecule inhibitors of these enzymes a large number of glucose derivatives have been investigated.[7] The tested glucose analog inhibitors comprise glucosides, *N*-acyl- β-D-glucopyranosylamines, thioglucosides, a 1-deoxy-D-*gluco*-heptulopyranose 2-phosphate, nojiritetrazole, 2,6-anhydro-heptonamides, and glucopyranosylidene-spiro-heterocycles.[8] The strongest inhibition (K_i values determined with rabbit muscle GP*b* enzyme) was achieved by a glucopyranosylidene-spiro-hydantoin[9,10] (Table 1, Entry 1: K_i = 3-4 μM) and its thio analog[11,10] (Table 1, Entry 2: K_i = 5 μM). *In vivo* hypoglycemic efficiency of the thiohydantoin derivative was also demonstrated.[12] The recently synthesized *N*-2-naphthoyl-*N*'- β-D-glucopyranosyl urea (Table 1, Entry 3: K_i = 0.4 μM) proved to be the best glucose derived inhibitor of GP known to date.[8] Most of these inhibitors target the so-called β-channel of the enzyme which is an empty pocket next to the highly glucose specific catalytic center surrounded by amino acid side chains of mixed character.[13] Since no *C*-(β-D-glucopyranosyl) heterocycles have yet been investigated as GP inhibitors, we have decided to prepare such derivatives exhibiting acidic, basic, and neutral properties in the heterocyclic moieties, in the hope that favorable interactions may arise with the β-channel of the enzyme.

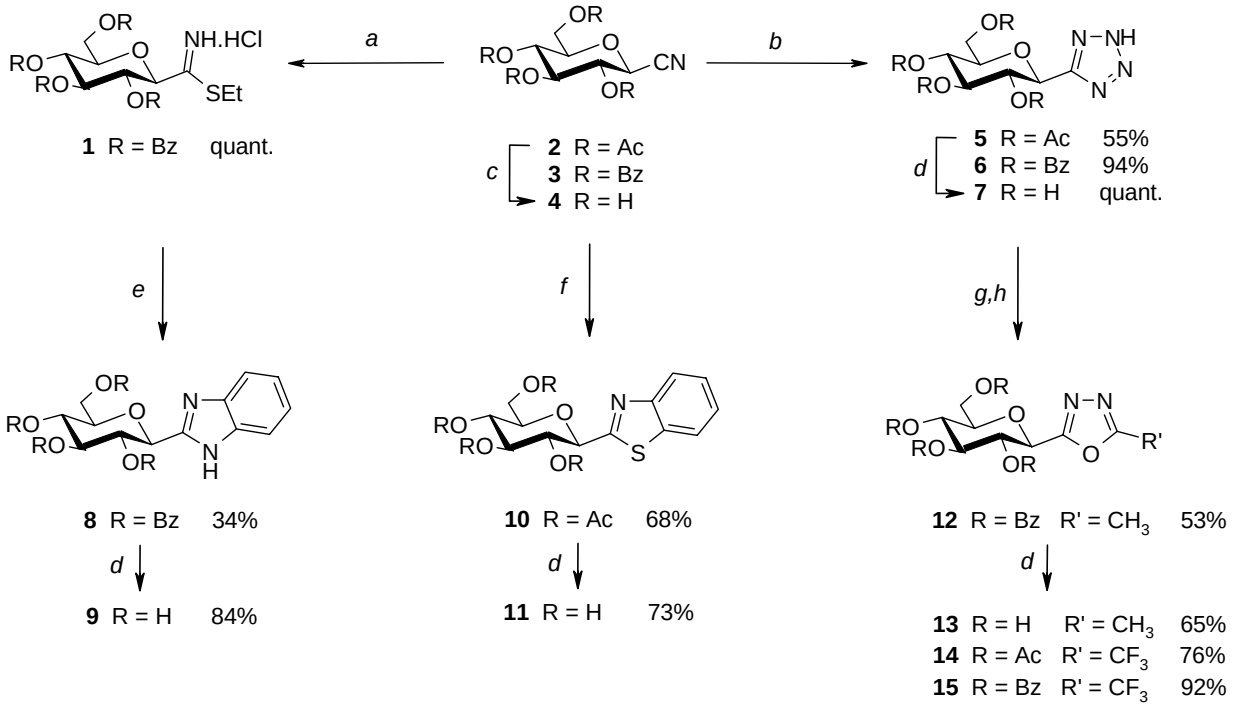
Results and Discussion

As starting materials the known 2,6-anhydro-aldononitriles (glucopyranosyl cyanides) **2**[14] and **3**[15] were selected. The nitrile group offers several possibilities for heterocyclization as has been demonstrated with 2,6-anhydro-aldononitriles of D-*galacto*, D-*xylo*, and D-*arabino* configuration.[16,17]

Reaction of both **2** and **3** with ammonium azide gave the expected per-*O*-acylated 5-(β-D-glucopyranosyl)tetrazoles **5** and **6**, respectively. Tetrazole **6** could be converted to the per-*O*-benzoylated 2-methyl- (**12**) and 2-trifluoromethyl-5-(β-D-glucopyranosyl)-1,3,4-oxadiazoles (**15**) by acetic anhydride and trifluoroacetic anhydride, respectively, in a Huisgen reaction. In a similar manner, tetrazole **5** gave the corresponding oxadiazole **14**. With 2-aminothiophenol, nitrile **2** produced the per-*O*-acetylated 2-(β-D-glucopyranosyl)benzothiazole **10** as expected. Neither **2** nor **3** reacted with 1,2-diaminobenzene in the presence of cHCl to yield benzimidazole **8**. Attempted cyclization of the corresponding 2,6-anhydroaldonic acid (**3**: COOH instead of CN), under similar conditions brought about no reaction even at elevated temperatures. Therefore, by adapting a literature procedure,[18] the hydrochloride **1** of the more reactive thioimidate was prepared from **3** by an acid catalyzed addition of ethanethiol to the nitrile group.

Salt **1** was used without purification for the next reaction with 1,2-diaminobenzene to give per-*O*-benzoylated 2-(β-D-glucopyranosyl)benzimidazole **8**.

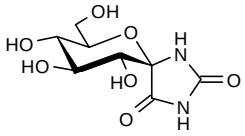
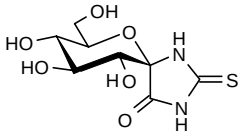
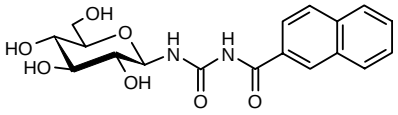
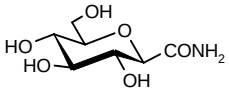
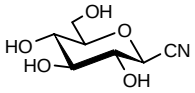
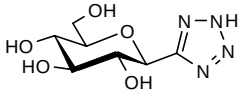
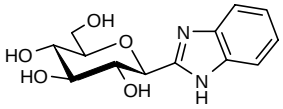
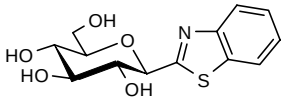
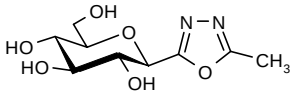
Deacylation of **5**, **8**, **10**, and **12** under Zemplén conditions was straightforward to yield the deprotected derivatives **7**, **9**, **11**, and **13**, respectively. Deacetylation of **2** had to be carried out using a short reaction time with cooling,[19] otherwise an unseparable mixture of several unidentified products was obtained. Trifluoromethyloxadiazoles **14** and **15** did not give isolable deprotected compounds under several deacylation conditions (a similar anomaly was observed with other sugar trifluoromethyloxadiazoles[20]).



Scheme 1. *a*: C_2H_5SH, Et_2O/HCl, 0 ºC, 4 h; *b*: NaN_3, NH_4Cl, abs. DMF, 80 ºC, 3 h; *c*: NaOMe/MeOH, 0 ºC; *d*: NaOMe/MeOH, r. t.; *e*: 1,2-diaminobenzene, abs. Py., r. t., 24 h; *f*: 2-aminothiophenol, abs. EtOH, Ar, reflux, 6 h; *g*: $(CH_3CO)_2O$, 60 ºC, 7 d; *h*: $(CF_3CO)_2O$, abs. $CHCl_3$, 60 ºC, 1 h.

The structure of the new compounds was established by NMR spectroscopy. The presence of a β-D-configured glucopyranosyl moiety in the $^4C_1$ conformation followed from the vicinal proton-proton coupling constants for each derivative. The presence of the nitrile in **4** was shown by a carbon resonance at 117.8 ppm, tetrazole was indicated by carbon resonances at 154-158 ppm for **5**-**7**; characteristic resonances appeared for C-2 of benzimidazoles **8** (148.5) and **9** (153.1), for C-2 of benzothiazoles **10** (166.4) and **11** (170.3), for C-2 and C-5 of methyl-oxadiazoles **12** and **13** at 164-165 and 161-164 ppm, and for trifluoromethyloxadiazoles **14** and **15** at ~163 and ~156 ppm, respectively.

Table 1. Preliminary kinetic data[a] on the inhibition of rabbit muscle glycogen phosphorylase *b* by the new compounds **4**, **7**, **9**, **11**, and **13**

Entry	Compound	K_i [μM]	Ref.
1.		3.1 4.2	9 10
2.		5.1	10
3.		0.4	8
4.		370	21
5.	 4	130	This work
6.	 7	No inhibiton	This work
7.	 9	11	This work
8.	 11	229	This work
9.	 13	212	This work

[a] Kinetic measurements were carried out as described before.[10]

Preliminary kinetic measurements with rabbit muscle glycogen phosphorylase *b* enzyme were performed as described before,[10] and the data are collected in Table 1. The new compounds have inhibitor constants in the micromolar range or are not inhibitory at all (Entries 5-9). The presence of the CN group in **4** instead of $CONH_2$ (Entries 4 and 5) makes the inhibition stronger.

The tetrazole ring of slightly acidic character (Entry 6) is clearly unfavorable for the binding of **7** to the enzyme. The neutral aglycons in **11** and **13** result in moderate inhibitors (Entries 8 and 9). The most efficient inhibitor of this series was benzimidazole **9** (Entry 7), however, even this compound is less effective than the best glucose analog (Entry 3). Its stronger effect in comparison with **11** must be due to the amphoteric character of the heterocycle (compare Entries 7 and 8), however, the present data do not allow more precise conclusions to be drawn for the nature of its binding. Detailed kinetic studies and X-ray crystallographic evaluation of the binding modes of these compounds to GP enzymes are in progress and will be published elsewhere.

Experimental Section

General Procedures. Melting points were measured 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 AM 360 (360/90 MHz for $^{1}H/^{13}C$) or Bruker AM 400 (400/100 MHz for $^{1}H/^{13}C$) or Avance DRX 500 (500/125 MHz for $^{1}H/^{13}C$) spectrometers. Chemical shifts are referenced to Me_4Si (^{1}H), or to the residual solvent signals (^{13}C). TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck), and the plates were visualized by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063-0.200 mm) was used. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated in vacuo at 40-50°C (water bath).

β-D-Glucopyranosyl cyanide (4). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl cyanide[14] **2** (400 mg, 1.12 mmol) was dissolved in abs. methanol, cooled to 0 °C, and 1 drop of a cold 0.1 M methanolic sodium methoxide solution was added. The reaction mixture was kept at 0 °C for 10-15 min (longer reaction times resulted in inseparable mixtures) and then neutralized with a cation exchange resin Amberlyst 15 (H^+ form). After filtration and removal of the solvent the crude product was purified by column chromatography (chloroform–methanol 25:1) to give **4** (59 mg, 28 %) as a colorless syrup; $[\alpha]_D$ +24 (*c* 0.97, MeOH); δ_H (D_2O): 4.39 (1H, d, $J_{1',2'}$ 10.0 Hz, H-1), 3.92-3.65, 3.54-3.37 (6H, m, H-2, H-3, H-4, H-5, H6, H-6'); δ_C (D_2O): 117.8 (CN), 81.2, 76.9, 71.8, 69.5, 69.1 (C-1,2,3,4,5), 61.2 (C-6); Analysis: Calcd for $C_7H_{11}NO_5$ (189.18): C, 44.44; H, 5.87; N, 7.40. Found: C, 44.39; H, 5.95; N, 7.32.

5-(2′,3′,4′,6′-Tetra-*O*-acetyl- β-D-glucopyranosyl)tetrazole (5). To a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl cyanide[14] **2** (1 g, 2.80 mmol) in abs. DMF (4 ml), ammonium chloride (275 mg, 5.14 mmol) and sodium azide (334 mg, 5.14 mmol) were added. The reaction mixture was refluxed for 3.5 hours, then cooled to room temperature, filtered, the residue washed with acetone, and the solvent evaporated in vacuo. The obtained syrup was placed into an ice bath and pyridine (0.12 ml) and acetic anhydride (0.24 ml) were added. The mixture was allowed to stand at room temperature for 16 hours, then it was diluted with chloroform and water. The

aqueous phase was extracted with chloroform again, and the combined organic phases were succesively washed with saturated aqueous sodium hydrogen carbonate solution, 2 M hydrochloric acid, and water. The organic phase was dried over magnesium sulfate and concentrated in vacuo. Crystallisation from water gave **4** (615 mg, 55 %) as white crystals; mp 90-92 °C; $[\alpha]_D$ +0.8 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$): 5.39 (1H, t, $J_{3',4'}$ 9.5 Hz, H-3′), 5.29 (1H, t, $J_{2',3'}$ 9.5 Hz, H-2′), 5.19 (1H, t, $J_{4',5'}$ 9.5 Hz, H-4′), 5.01 (1H, d, $J_{1',2'}$ 10.0 Hz, H-1′), 4.34 (1H, dd, $J_{6'a,6'b}$ 12.6 Hz, H-6′a), 4.17 (1H, dd, $J_{5',6'b}$ 2.1 Hz, H-6′b), 3.94 (1H, ddd, $J_{5',6'a}$ 5.3 Hz, H-5′), 2.07, 2.06, 2.01, 1.97 (12H, 4s, 4 × OAc); δ_C ($CDCl_3$): 171.1, 170.2, 169.7, 169.6 (C=O), 154.2 (C-5), 76.5 (C-1′), 73.2, 71.2, 70.2, 68.0 (C-2′,3′,4′,5′), 62.1 (C-6′), 20.6, 20.5, 20.3 (CH_3). Analysis: Calcd for $C_{15}H_{20}N_4O_9$ (400.4): C, 45.00; H, 5.04; N, 13.99. Found: C, 45.26; H, 5.02; N, 14.03.

5-(2′,3′,4′,6′-Tetra-*O*-benzoyl-β-D-glucopyranosyl)tetrazole (6). To a solution of 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl cyanide[15] **3** (1 g, 1.65 mmol) in abs. DMF (2.3 ml) ammonium chloride (163 mg, 3.05 mmol) and sodium azide (198 mg, 3.05 mmol) were added. The reaction mixture was refluxed for 3.5 hours. It was then cooled to room temperature, filtered, and the residue was washed with acetone. The filtrate was concentrated in vacuo. The obtained syrup was dissolved in ethyl acetate and was extracted with 2 M hydrochloric acid. The combined aqueous phases were reextracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent evaporated in vacuo. The residual syrup was purified by silica gel column chromatography with chloroform-methanol 7:3 eluent to give **5** as a colorless syrup (1.08 g, quant. yield); $[\alpha]_D$ +6 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$): 7.96-7.08 (20H, m, Ar), 6.58 (1H, br s, NH), 6.16 (1H, t, $J_{4',5'}$ 9.5 Hz, H-4′), 6.05 (1H, t, $J_{2',3'}$ 9.7 Hz, H-2′), 5.96 (1H, t, $J_{3',4'}$ 9.5 Hz, H-3′), 5.46 (1H, d, $J_{1',2'}$ 9.9 Hz, H-1′), 4.68 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, H-6′a), 4.64 (1H, dd, $J_{5',6'b}$ 2.9 Hz, H-6′b), 4.45 (1H, ddd, $J_{5',6'a}$ 5.3 Hz, H-5′); δ_C ($CDCl_3$): 167.2, 166.2, 165.8, 165.6 (C=O), 155.8 (C-5), 77.5 (C-1′), 74.2, 72.6, 71.8, 70.0 (C-2′,3′,4′,5′), 63.9 (C-6′). Analysis: Calcd for $C_{35}H_{28}N_4O_9$ (648.6): C, 64.81; H, 4.35; N, 8.64. Found: C, 64.85; H, 4.33; N, 8.62.

2-(2′,3′,4′,6′-Tetra-*O*-benzoyl-β-D-glucopyranosyl)benzimidazole (8). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl cyanide[14] **2** (100 mg, 0.17 mmol) was dissolved in diethyl ether (15 ml) and ethanethiol (25 µl, 0.33 mmol) was added to the solution. The mixture was cooled down in an ice bath, and hydrogen chloride gas was introduced for 5 hours. The solvent was then evaporated, the residue (550 mg) dissolved in abs. pyridine (15 ml), and 1,2-benzenediamine (92.9 mg, 0.86 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours. The solvent was then evaporated in vacuo and the obtained syrup was purified by column chromatography (eluent: hexane-ethyl acetate 3:2) to give **7** as white crystals (183 mg, 34 %); mp 120-123 °C; $[\alpha]_D$ –59 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$): 8.07-7.21 (20H, m, Ar), 6.16, 5.89, 5.88 (3 × 1H, 3 × pseudo t, *J* ~9.5 Hz in each, H-2′, H-3′, H-4′), 5.27 (1H, d, $J_{1',2'}$ 9.5 Hz, H-1′), 4.75 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, H-6′a), 4.60 (1H, dd, $J_{5',6'b}$ 5.14 Hz, H-6′b), 4.45 (1H, m, $J_{5',6'a}$ 2.4 Hz, H-5′); δ_C ($CDCl_3$): 166.3, 165.8, 165.2 (C=O), 148.5 (C-2), 142.8 (C-3a, C-7a), 123.3, 122.1, 119.7, 111.3 (C-4,5,6,7), 76.9, 75.3, 74.0, 71.5, 69.5 (C-1′,2′,3′,4′,5′), 63.4 (C-6′). Analysis: Calcd for $C_{41}H_{32}N_2O_9$ (696.7): C, 70.68; H, 4.63; N, 4.02. Found: C, 70.71; H, 4.62; N, 4.01.

2-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)benzothiazole (10). To a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl cyanide[14] **2** (400 mg, 1.12 mmol) in abs. ethanol (3 ml) 2-aminothiophenol (0.32 ml, 2.99 mmol) was added. The reaction mixture was refluxed for 6 hours under Ar then it was allowed to stand at -4 °C overnight. During this time the product crystallized from the solution. Recrystallization from ethanol gave **9** (353 mg, 68 %); mp 128-129 °C; $[\alpha]_D$ –22 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$): 7.98-7.41 (4H, m, Ar), 5.42, 5.33, 5.26 (3 × 1H, 3 × pseudo t, *J* ~9.5 Hz in each, H-2′, H-3′, H-4′), 4.92 (1H, d, $J_{1',2'}$ 9.5 Hz, H-1′), 4.32 (1H, dd, $J_{5',6'a}$ 4.7 Hz, H-6′a), 4.26 (1H, dd, $J_{6'a,6'b}$ 12.6 Hz, H-6′b), 3.95 (1H, ddd, $J_{5',6'b}$ 2.1 Hz, H-5′), 2.12, 2.08, 2.03, 1.97 (12H, 4s, 4 × OAc); δ_C ($CDCl_3$): 170.6, 170.1, 169.4, 169.2 (C=O), 166.4 (C-2), 152.5 (C-3a), 134.8 (C-7a), 126.1, 125.5, 123.2, 121.8 (C-4,5,6,7), 77.4, 76.3, 73.5, 71.3, 68.2 (C-1′,2′,3′,4′,5′), 61.9 (C-6′), 20.7, 20.5, 20.4 (CH_3). Analysis: Calcd for $C_{21}H_{23}NO_9S$ (465.5): C, 54.19; H, 4.98; N, 3.01. Found: C, 67.12; H, 4.55; N, 4.22.

5-Methyl-2-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole (12). A solution of tetrazole **5** (502 mg, 0.77 mmol) in acetic anhydride (2 ml) was heated at 70 °C for 48 hours. The mixture was then concentrated and co-evaporated with 5 ml methanol in vacuo. The obtained syrup was dissolved in chloroform and washed with saturated aqueous sodium hydrogen carbonate solution and water. The organic phase was dried over magnesium sulfate, concentrated in vacuo and purified by column chromatography (eluent: hexane-ethyl acetate 2:1) to give **11** as a syrup (272 mg, 53 %); $[\alpha]_D$ –5 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$): 8.06-7.31 (20H, m, Ar), 6.07, 5.87, 5.83 (3 × 1H, 3 × pseudo t, *J* ~9.5 Hz in each, H-2′, H-3′, H-4′), 5.17 (1H, d, $J_{1',2'}$ 9.7 Hz, H-1′), 4.68 (1H, dd, $J_{5',6'a}$ 2.4 Hz, H-6′a), 4.54 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, H-6′b), 4.35 (1H, ddd, $J_{5',6'b}$ 5.3 Hz, H-5′); δ_C ($CDCl_3$): 166.5, 166.1, 165.7, 165.6, 165.3 (C=O + C-2), 161.7 (C-5), 77.5 (C-1′), 74.0, 72.3, 70.8, 69.4 (C-2′,3′,4′,5′), 63.4 (C-6′). Analysis: Calcd for $C_{37}H_{30}N_2O_{10}$ (662.7): C, 67.07; H, 4.56; N, 4.23. Found:

2-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-trifluoromethyl-1,3,4-oxadiazole (14). To a solution of tetrazole **4** (500 mg, 1.25 mmol) in abs. chloroform (3 ml) trifluoroacetic anhydride (0.5 ml, 3.54 mmol) was added accompanied by a vigorous gas evolution. The reaction mixture was stirred at 60 °C for 30 minutes. Then, it was concentrated and co-evaporated with methanol (3 × 3 ml). The obtained syrup was dissolved in chloroform, washed with saturated aqueous sodium hydrogen carbonate solution and water. The organic phase was dried over magnesium sulfate, concentrated in vacuo, and the residual syrup was purified by column chromatography (eluent: hexane-ethyl acetate 3:1) and then crystallized from ethanol to give **13** as white needles (444 mg, 76 %); mp 137-139 °C; $[\alpha]_D$ –5 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$): 5.40, 5.31, 5.21 (3 × 1H, 3 × pseudo t, *J* ~9.6 Hz in each, H-2′, H-3′, H-4′), 4.88 (1H, d, $J_{1',2'}$ 9.6 Hz, H-1′), 4.29 (1H, dd, $J_{5',6'a}$ 5.1 Hz, H-6′a), 4.19 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, H-6′b), 3.91 (1H, ddd, $J_{5',6'b}$ 2.2 Hz, H-5′), 2.11, 2.07, 2.04, 1.95 (12H, 4s, 4 × OAc); δ_C ($CDCl_3$): 170.4, 169.9, 169.2, 169.2 (C=O), 163.2 (C-2), 156.2 (q, $^2J_{C,F}$ 44 Hz, C-5), 116.0 (q, $^1J_{C,F}$ 272 Hz, CF_3), 76.9 (C-1′), 72.7, 71.2, 69.6, 67.7 (C-2′,3′,4′,5′), 61.7 (C-6′), 20.6, 20.5, 20.2 (CH_3). Analysis: Calcd for $C_{17}H_{19}F_3N_2O_{10}$ (468.3): C, 43.60; H, 4.09; N, 5.98. Found: C, 43.50; H, 4.08; N, 5.97.

2-(2′,3′,4′,6′-Tetra-O-benzoyl-β-D-glucopyranosyl)-5-trifluoromethyl-1,3,4-oxadiazole (15). To a solution of tetrazole **5** (1.0 g, 1.54 mmol) in abs. chloroform (2 ml), trifluoroacetic anhydride (0.5 ml, 3.54 mmol) was added accompanied by vigorous gas evolution. The reaction mixture was kept in a water bath for 1.5 hours. Then, it was concentrated and co-evaporated with methanol (3 × 5 ml). The obtained syrup was dissolved in chloroform, washed with saturated aqueous sodium hydrogen carbonate solution and water. The organic phase was dried over magnesium sulfate, concentrated in vacuo, and the obtained syrup was purified by column chromatography (eluent: hexane-ethyl acetate 1:1) to give **14** as white crystals (739 mg, 67 %); mp 139-141 °C; $[\alpha]_D$ –1 (*c* 0.2, $CHCl_3$); δ_H ($CDCl_3$): 8.04-7.26 (20H, Ar), 6.11, 5.83, 5.77 (3 × 1H, 3 × t, *J* ~9.6 Hz in each, H-2′, H-3′, H-4′), 5.24 (1H, d, $J_{1',2'}$ 9.6 Hz, H-1′), 4.68 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, H-6′a), 4.53 (1H, dd, $J_{5,6'b}$ 5.2 Hz, H-6′b), 4.37 (1H, ddd, $J_{5',6'a}$ 2.9 Hz, H-5′); δ_C ($CDCl_3$): 166.1, 165.6, 165,1 (C=O), 163.3 (C-2), 156.3 (q, $^2J_{C,F}$ 44 Hz, C-5), 116.0 (q, $^1J_{C,F}$ 272 Hz, CF_3), 77.3 (C-1′), 73.0, 71.7, 70.7, 68.8 (C-2′,3′,4′,5′), 62.8 (C-6′). Analysis: Calcd for $C_{37}H_{27}F_3N_2O_{10}$ (716.63): C, 62.01; H, 3.80; N, 3.91. Found: C, 61.93; H, 3.81; N, 3.90.

General procedure for the Zemplén deacylation

The acetylated and benzolated compounds were dissolved in abs. methanol and 1 M methanolic sodium methoxide solution was added to the solutions in catalytic amount. The reaction mixture was kept at room temperature for a given time and then neutralized with a cation exchange resin Amberlyst 15 (H^+ form). Filtration and removal of the solvent resulted in the corresponding deacylated sugar derivatives.

5-(β-D-Glucopyranosyl)tetrazole (7). Prepared by the general procedure from **5**. Yield: quant. (syrup); $[\alpha]_D$ 14 (*c* 0.3, MeOH); δ_H (D_2O): 4.70 (1H, d, $J_{1',2'}$ 9.5 Hz, H-1′), 3.82 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, $J_{5',6'a}$ 1.8 Hz, H-6′), 3.67 (1H, m, H-5′), 3.67 (1H, t, *J* 9.4 Hz, *J* 9.3 Hz, H-2′ or H-3′ or H-4′), 3.57 (1H, t, *J* 8.8 Hz, *J* 9.1 Hz, H-2′ or H-3′ or H-4′), 3.53 (1H, dd, *J* 1.8 Hz, *J* 5.2 Hz, H-6′b)**?**; δ_C (D_2O): 158.7 (C-5), 80.8 (C-1′), 77.6, 73.5, 73.4, 70.1 (C-2′,3′,4′,5′), 61.5 (C-6′); Analysis: Calcd for $C_7H_{12}N_4O_5$ (232.20): C, 36.21; H, 5.21; N, 24.13. Found: C, 36.18; H, 5.20; N, 24.04.

2-(β-D-Glucopyranosyl)benzimidazole (9)

Prepared by the general procedure from **8**. Yield: 84 % (syrup); $[\alpha]_D$ 25 (*c* 0.2, MeOH); δ_H (CD_3OD): 7.59-7.57 (2H, m, H-4, H-7), 7.26-7.24 (2H, m, H-5, H-6), 4.53 (1H, d, $J_{1',2'}$ 9.7 Hz, H-1′), 3.93 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, $J_{5',6'a}$ 1.5 Hz, H-6′a), 3.78 (1H, dd, $J_{5',6'b}$ 4.6 Hz, H-6′b), 3.68 (1H, t, *J* 9.2 Hz, H-2′ or H-3′ or H-4′), 3.58 (1H, t, *J* 8.8 Hz, H-2′ or H-3′ or H-4′), 3.52 (1H, t, 9.2 Hz, H-2′ or H-3′ or H-4′), 3.55 (1H, m, H-5′); δ_C (CD_3OD): 153.1 (C-2), 138.4 (C-3a, C-7a), 122.9 (C-4, C-7), 115.3 (C-5, C-6), 81.5 (C-1′), 78.6, 76.6, 74.1, 70.5 (C-2′,3′,4′,5′), 62.0 (C-6′); Analysis: Calcd for $C_{13}H_{16}N_2O_5$ (280.28): C, 55.71; H, 5.75; N, 9.99. Found: C, 55.90; H, 5.76; N, 10.01.

2-(β-D-Glucopyranosyl)benzothiazole (11). Prepared by the general procedure from **10**. Yield: 73 % (white crystals); mp 87-89 °C; $[\alpha]_D$ 19 (*c* 0.2, MeOH); δ_H (D_2O): 7.95-8.05 (2H, 2d, H-4, H-7), 7.60-7.40 (2H, 2t, H-5, H-6), 3.89 (1H, d, $J_{1',2'}$ 12,3 Hz, H-1′), 3.76 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, $J_{5',6'a}$ 5.0 Hz, H-6′a), 3.68-3.52 (5H, m, H-2′,3′,4′,5′,6′b); δ_C (D_2O): 170.3 (C-2), 152.1 (C-3a), 135.0 (C-7a), 127.4, 126.7, 123.1, 123.0 (C-4,5,6,7), 81.0 (C-1′), 79.2, 77.5, 74.5, 70.1 (C-2′,3′,4′,5′), 61.5 (C-6′); Analysis: Calcd for $C_{13}H_{15}NO_5S$ (297.33): C, 52.52; H, 5.09; N, 4.71. Found: C, 52.63; H, 5.08; N, 4.72.

5-Methyl-2-(β-D-glucopyranosyl)-1,3,4-oxadiazole (13). Prepared by the general procedure from **12**. Yield: 65 % (white crystals); mp 214-216 °C; $[\alpha]_D$ 20 (*c* 0.2, MeOH); δ_H (D_2O): 4.66 (1H, d, $J_{1',2'}$ 9.9 Hz, H-1′), 3.86 (1H, dd, $J_{6'a,6'b}$ 12.5 Hz, H-6′a), 3.74 (1H, t, *J* 9.4 Hz, *J* 9.6 Hz, H-2′ or H-3′ or H-4′), 3.69 (1H, dd, $J_{5',6'b}$ 5.6 Hz, H-6′b), 3.59 (1H, t, *J* 9 Hz, *J* 9.1 Hz, H-2′ or H-3′ or H-4′), 3.57 (1H, m, H-5′), 3.48 (1H, t, *J* 9.3 Hz, *J* 9.4 Hz, H-2′ or H-3′ or H-4′), 2.53 (3H, s, CH_3); δ_C (D_2O): 164.1 (C-2), 163.8 (C-5), 81.7 (C-1′), 77.4, 72.6, 71.7, 69.9 (C-2′,3′,4′,5′), 61.0 (C-6′), 10.5 (CH_3); Analysis: Calcd for $C_9H_{14}N_2O_6$ (246.22): C, 43.90; H, 5.73; N, 11.38. Found: C, 44.06; H, 5.74; N, 11.41.

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