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C-Glucopyranosyl-1,2,4-triazol-5-ones: synthesis and inhibition of glycogen phosphorylase

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ABSTRACT

Various *C*-glucopyranosyl-1,2,4-triazolones were designed as potential inhibitors of glycogen phosphorylase. Syntheses of these compounds were performed with *O*-perbenzoylated glucose derivatives as precursors. High temperature ring closure of N^1-carbamoyl-*C*-β-D-glucopyranosyl formamidrazone gave 3-β-D-glucopyranosyl-1,2,4-triazol-5-one. Reaction of N^1-tosyl-*C*-β-D-glucopyranosyl formamidrazone with ClCOOEt furnished 3-β-D-glucopyranosyl-1-tosyl-1,2,4-triazol-5-one. In situ prepared β-D-glucopyranosylcarbonyl isocyanate was transformed by PhNHNHBoc into 3-β-D-glucopyranosyl-1-phenyl-1,2,4-triazol-5-one, while the analogous 1-(2-naphthyl) derivative was obtained from the unsubstituted triazolone by naphthalene-2-boronic acid in a Cu(II) catalyzed *N*-arylation. Test compounds were prepared by Zemplén deacylation. The new glucose derivatives had weak or no inhibition of rabbit muscle glycogen phosphorylase b: the best inhibitor was 3-β-D-glucopyranosyl-1-(2-naphthyl)-1,2,4-triazol-5-one (K_i = 80 μM).

1. Introduction

Glycogen phosphorylase (GP) inhibitors (GPIs) may find applications in antidiabetic therapy especially in type 2 diabetes mellitus,[1] but also in other diseases like cerebral[2,3] and cardiac[4] ischemias, other cardiovascular impairments,[4,5] and tumours.[6,7] A very broad range of compounds with a number of scaffolds was shown to have inhibitory effect against GP[8] through binding to one (or sometimes more) of the binding sites discovered so far.[9] The catalytic site of GP can be targeted by glucose derivatives which are competitive inhibitors of the enzyme.[10,11] Several glucose based GPIs show submicromolar efficiency: the best known inhibitors can be found among glucopyranosylidene-spiro-heterocycles, *N*-acyl-*N*′-β-D-glucopyranosyl ureas, and *C*-β-D-glucopyranosyl heterocycles. In the latter class of compounds structure–activity relationships have been established for 5-membered heterorings and some of their benzologs (Chart 1). Thus, 2-β-D-glucopyranosyl benzothiazole **1** proved to be a weaker inhibitor in comparison to benzimidazole **2**.[12] This observation could be rationalized by X-ray crystallography of the enzyme-inhibitor complexes showing an H-bond between the imidazole NH and the main chain carbonyl of His377 in the vicinity of the active site of GP.[13] Extension of **2** by a further aromatic ring as in **3** resulted in an even stronger inhibitor indicating that a large hydrophobic moiety properly protruding into the β-channel[a] of the enzyme can be beneficial for the binding.[14] Studies with each possible *C*-glucosyl oxadiazole isomer revealed that the constitution of the heterocycles was also an important factor and 5-β-D-glucopyranosyl-3-substituted-1,2,4-oxadiazoles **4** and **7** proved to be the best inhibitors of these series.[15,16] Changing the oxadiazole to 1,2,4-triazole furnished inhibitors **5** and **8** exhibiting stronger binding most probably due to the H-bonding capacity of the triazoles,[17,18] and imidazoles **6** and **9** were shown to be even better inhibitors.[19] Although no structural data have yet been available to rationalize this finding, one may speculate that the stronger inhibition of imidazoles can be a result of the smaller number of ring tautomers in comparison to the case of triazoles. Tautomeric forms have recently been shown to have a very important contribution to the determination of the binding strength of GP inhibitors.[20] The observation that the naphthyl substituted compounds **7-9** bind stronger to the enzyme than the phenyl substituted **4-6** corroborates the role of the large hydrophobic group. Based on the above considerations, we have designed 3-*C*-glucopyranosyl-1-substituted-1,2,4-triazol-5-ones as further candidates of potential GPIs in which the presence of the carbonyl group might result in decreasing the number of tautomers due to the stability of the NHCO moiety.

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[a] The β-channel is an empty space next to the catalytic site of GP in the direction of the β-anomeric substituent of bound D-glucose surrounded by both polar and apolar amino acid side chains.

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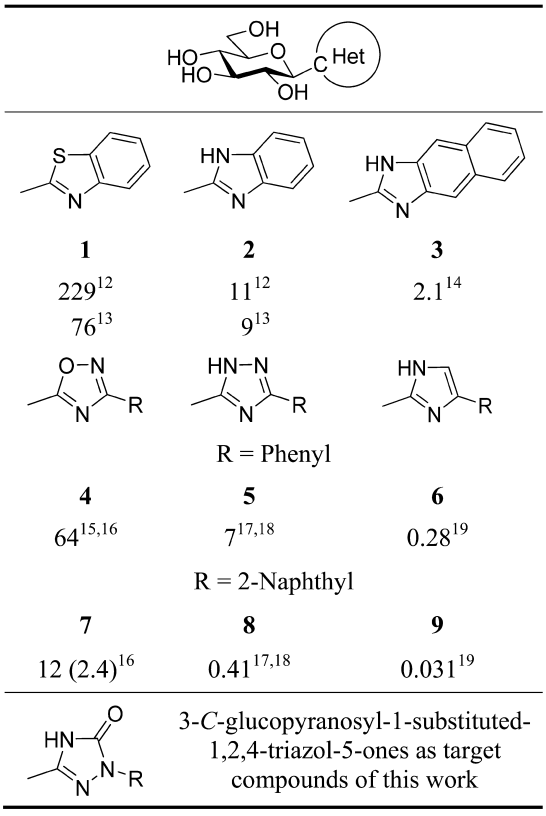
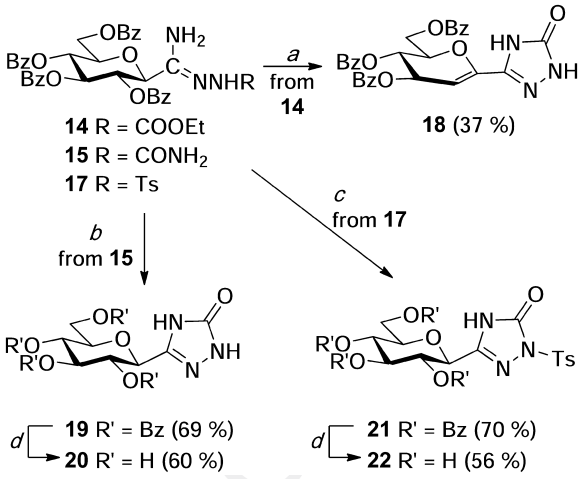


Chart 1. Inhibitory potency (K_i [μM]) of selected *C*-β-D-glucopyranosyl heterocycles against rabbit muscle glycogen phosphorylase *b* (RMGP*b*).

2. Results and discussion

Several methods were reported for the syntheses of various 1,2,4-triazol-5-ones,[21] e.g. starting with nitriles,[22,23] imidates,[24] N^1-acyl-semicarbazides,[25] N^1-tosyl-amidrazones,[26] or aldehyde-semicarbazones.[27] *C*-Glycosyl-1,2,4-triazol-5-ones could not be located in the literature. The only related work found was that of Poonian and Nowoswiat[28] reporting the transformation of β-D-ribofuranosyl formimidate by (thio)semicarbazide to the corresponding *C*-β-D-ribofuranosyl-N^1-(thio)carbamoyl formamidrazones. While the ring closure of the thiocarbamoyl derivative to a 1,2,4-triazol-5-thione could be achieved at elevated temperature, similar attempts to get the corresponding 1,2,4-triazol-5-one failed.[28]

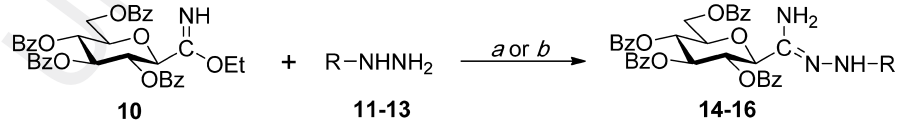


Scheme 1. Reagents and conditions: *a*) dry *m*-xylene, reflux; *b*) dry DMF, reflux; *c*) ClCOOEt, dry $CHCl_3$, dry pyridine, 0 °C to rt; *d*) cat. NaOMe in dry MeOH, rt.

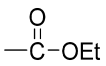
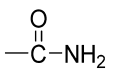
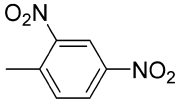
Since from earlier work we had in hand the *O*-perbenzoylated β-D-glucopyranosyl formimidate[14] (**10**, Table 1), this compound was used as the starting material for the preparation of some new amidrazones suitable for ring closure towards the expected 1,2,4-triazol-5-ones. Reactions of **10** with ethyl carbazate (**11**), semicarbazide (**12**) or 2,4-dinitrophenylhydrazine (**13**) smoothly gave the corresponding *C*-glucosyl formamidrazones **14-16**, respectively.

Boiling a solution of **14** in *m*-xylene brought about the expected ring closure; however, the reaction was accompanied by a 1,2-elimination of benzoic acid resulting in glucal **18** in low yield (Scheme 1). Cyclization of N^1-carbamoyl-amidrazone **15** in boiling DMF took place without concomitant elimination producing the expected triazolone **19** in good yield. Subsequent *O*-debenzoylation under Zemplén conditions gave test compound **20**. Attempted cyclization of **16** with ClCOOEt in $CHCl_3$ in the presence of 2 equiv. of pyridine or DIPEA at r. t. or with boiling failed; actually, no reaction could be observed. Reaction[26] of tosyl-amidrazone **17**[17,29] with ClCOOEt produced the tosylated triazolone **21** which was deprotected according to the Zemplén protocol to give the test compound **22**.

Table 1
Synthesis of *O*-perbenzoylated N^1-substituted *C*-β-D-glucopyranosyl formamidrazones



a) dry EtOH, reflux; b) dry pyridine, rt.

Reagent	R	Product	Conditions	Yield (%)
11		**14**	*a*	55
12		**15**	*b*	80
13		**16**	*a*	83

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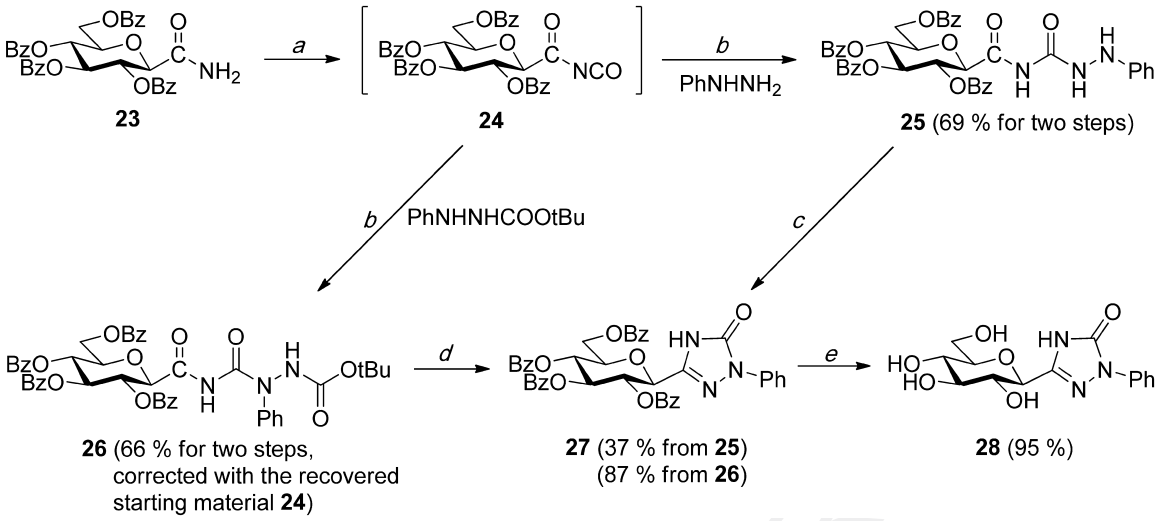


Scheme 2. Reagents and conditions: *a*) $(COCl)_2$, dry 1,2-dichloroethane, reflux; *b*) dry THF, 0 °C to rt; *c*) dry *m*-xylene, reflux; *d*) CF_3COOH, dry CH_2Cl_2, rt; *e*) cat. NaOMe in dry MeOH, rt.

Next we wished to prepare isomers of *N*-phenyl substituted triazolones. To obtain 5-β-D-glucopyranosyl-1-phenyl-1,2,4-triazol-3-one, compound **25** was prepared as the starting material (Scheme 2). *C*-Glucosyl formamide **23**[30,31] was converted by oxalyl chloride[32] into the acyl isocyanate **24** which was used without purification for the next reaction with $PhNHNH_2$ to give **25** in very good yield. Towards 3-β-D-glucopyranosyl-1-phenyl-1,2,4-triazol-5-one, intermediate **24** was reacted with Boc-protected $PhNHNH_2$ to give **26**. Treatment of **26** by CF_3COOH, in analogy with a reported procedure,[33] cleaved the protecting group and spontaneous ring closure gave the expected triazolone **27**. To our surprise, this compound proved identical with that obtained by heating **25** in *m*-xylene; however, this unexpected outcome had a precedent in the literature.[34] Besides the chemical evidence of the route **26**→**27**, spectroscopic verification for the structure of **27** was also sought for. To this end, a 2D ^1H-^1H ROESY spectrum was recorded which showed the vicinity of the triazolone NH to H1 and H2 of the sugar moiety, thereby indicating the position of the aromatic residue (Fig. 1; for the spectra see Supporting information). Deprotection of **27** under Zemplén conditions furnished test compound **28** in excellent yield.

In order to have a triazolone with a larger aromatic substituent, synthesis of the 2-naphthyl derivative was envisaged. Although a synthetic sequence analogous to **23**→**24**→**26**→**27** seemed straightforward, the unavailability of the necessary 2-naphthyl-hydrazine prevented the application of this route. Therefore, a copper catalyzed cross-coupling protocol for the *N*-arylation of amides was adapted.[35] The reaction of triazolone **19** with naphthalene-2-boronic acid in the presence of $Cu(OAc)_2$ and Et_3N gave low yield of **29** (Scheme 3). The structure of this product was considered to be analogous to that of **27** based on the coincidences of the chemical shifts both in the ^1H and ^{13}C NMR spectra of **27** and **29**. In addition, the structure was also corroborated by a 2D ^1H-^1H ROESY experiment (Fig. 1; for the spectra, see Supporting information). Zemplén deprotection of **29** produced test compound **30** in good yield.

The new compounds were assayed against rabbit muscle glycogen phosphorylase b (RMGPb) as described previously[36] (Table 2). The unsubstituted triazolone **20** and its 1-tosylated derivative **22** had no significant effect. In the case of **20**, the inefficiency may be explained by the relatively small size of the aglycon which cannot interact in the β-channel of the enzyme. This resembles the case of the similarly non inhibitory 5-β-D-glucopyranosyl tetrazole.[12] For **22**, where the tosyl substituent can occupy the β-channel, the lack of efficiency may be attributed to the presence of the SO_2 moiety. Such a tetrahedral linking element in the aglycon was shown to be detrimental to the binding in some types of glucose derived compounds.[8,11,38–40] The 1-aryl-substituted triazolones **28** and **30** had weak inhibitory effects whereby the 2-naphthyl derivative **30** showed stronger binding than the phenyl compound **28**. This reflects the general trend regarding the size and orientation of aryl substituents that were observed in many cases (cf examples **4-6** *vs* **7-9** in Chart 1). On the other hand, the triazolone ring between the sugar

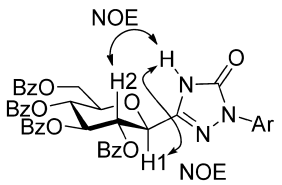
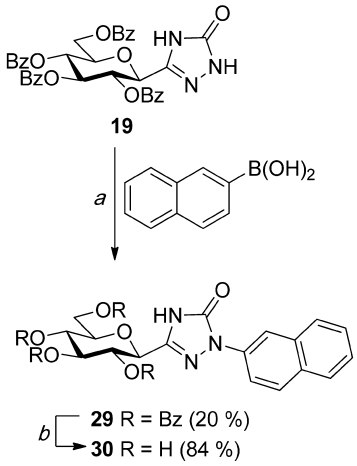


Fig. 1. Nuclear Overhauser effects in 1-aryl-3-β-D-glucopyranosyl-1,2,4-triazol-5-ones **27** (Ar = Ph) and **29** (Ar = 2-naphthyl).



Scheme 3. Reagents and conditions: *a*) $Cu(OAc)_2$, Et_3N, CH_2Cl_2, rt; *b*) cat. NaOMe in dry MeOH, rt.

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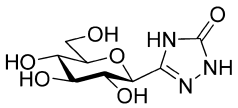
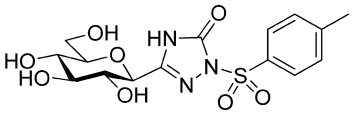
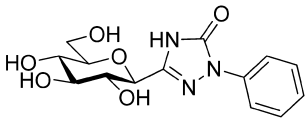
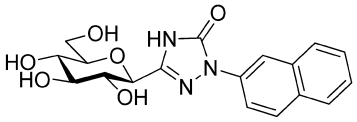
Table 2
Inhibition of RMGPb by *C*-glucopyranosyl-1,2,4-triazol-5-ones

Compound	Inhibition [μM]
 **20**	No inhibition at 625 μM
 **22**	No inhibition at 625 μM
 **28**	IC_{50} 350 K_i 191[a]
 **30**	K_i 80

[a] Calculated from the IC_{50} by a web-based tool.[37]

and the aromatic part must have insufficient interactions with the amino acid side chains of RMGPb, resulting in weaker inhibition than many of other 5-membered *C*-glucosyl heterocycles studied so far.

In conclusion, synthetic methods have been elaborated to obtain hitherto unknown 3-β-D-glucopyranosyl-1-(un)substituted-1,2,4-triazol-5-ones. Enzyme kinetic tests with rabbit muscle glycogen phosphorylase b revealed 1-aryl-triazolones to be weak inhibitors, thereby contributing to structure–activity relationships of *C*-glucosyl heterocycles.

3. Experimental

3.1. General methods

Melting points were measured on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at rt. NMR spectra were recorded with Bruker 360 (360/90 MHz for $^1H/^{13}C$) or Bruker 400 (400/100 MHz for $^1H/^{13}C$) spectrometers. 2D ^1H-^1H ROESY (400 MHz) spectra were acquired with 150 ms spinlock for mixing in overnight experiments. Chemical shifts are referenced to Me_4Si (^1H), or to the residual solvent signals (^{13}C). Mass spectra were obtained by Thermo Scientific LTQ XL or MicroTOF-Q type Qq-TOF MS (Bruker Daltonik, Bremen, Germany) instruments. TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck) plates, visualized under UV light and by gentle heating. For column chromatography, Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Toluene, *m*-xylene, CH_2Cl_2, $CHCl_3$ were distilled from P_4O_{10} and stored over 4 Å molecular sieves or sodium wires. MeOH was purified by distillation after refluxing for a couple of hours with magnesium turnings and iodine. THF was distilled from sodium benzophenone ketyl and stored over sodium wires. Anhydrous solvents: EtOH (Sigma-Aldrich), DMF (Sigma-Aldrich), 1,2-dichloroethane (Sigma-Aldrich) and pyridine (VWR) were purchased from the indicated companies. Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formimidate[14] (**10**), *N*^{1}-tosyl-*C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidrazone[17] (**17**), *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formamide[30] (**23**) and PhNHNHBoc[41] were synthesized according to published procedures.

3.2. General procedure for removal of benzoyl protecting groups by the Zemplén protocol

To a solution of an *O*-perbenzoylated compound in anhydrous MeOH (5 mL/100 mg, a few drops of anhydrous $CHCl_3$ were added in case of incomplete dissolution), a catalytic amount of a NaOMe solution (1 M in MeOH) was added and the mixture was left at rt. After completion of the reaction monitored by TLC (1:1 EtOAc-hexane and 7:3 $CHCl_3$-MeOH), the mixture was neutralized with a cation exchange resin Amberlyst 15 (H^+ form), then the resin was filtered off and the solvent was removed. The crude product was purified by column chromatography.

3.3. N^1-*Ethoxycarbonyl*-C-*(2,3,4,6-tetra*-O-*benzoyl-β-D-glucopyranosyl)formamidrazone (14)*

Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formimidate[14] (**10**, 1.00 g, 1.53 mmol) and ethyl carbazate (**11**, 0.16 g 1.53 mmol) were stirred in anhydrous EtOH (20 mL) at reflux temperature, and the reaction was monitored by TLC (1:1 EtOAc-hexane). After completion of the reaction (5 h), the mixture was evaporated under diminished pressure, and the crude product was purified by column chromatography (1:1 EtOAc-hexane) to yield 0.60 g (55%) white solid. Mp: 104–106 °C; $[\alpha]_D = -21$ (c 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 8.61 (1H, br s, NH), 8.04–7.82 (8H, m, Ar), 7.57–7.25 (12H, m, Ar), 5.99, 5.74, 5.63 (3 × 1H, 3 pseudo t, $J = 9.6$, 9.6 Hz in each, H-2, H-3, H-4), 5.15 (2H, br s, NH_2), 4.63 (1H, dd, $J = 12.3$, < 1 Hz, H-6a), 4.52 (1H, dd, $J = 12.3$, 5.3 Hz, H-6b), 4.46 (1H, d, $J = 9.6$ Hz, H-1), 4.25 (1H, ddd, $J = 9.6$, 5.3, < 1 Hz, H-5) 3.94 (2H, q, $J = 7.0$ Hz, CH_2), 1.00 (3H, t, $J = 7.0$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.0, 165.5 (2), 165.1 (C = O), 155.5 (COOEt), 146.9 (C = N), 133.3–128.1 (Ar), 77.4, 76.0, 73.6, 70.4, 69.2 (C-1 – C-5), 63.0, 61.4 (C-6, CH_2), 14.1 (CH_3). MS-ESI (*m/z*): Calcd. for $C_{38}H_{35}N_3NaO_{11}^+$ $[M + Na]^+$: 732.216. Found: 732.216.

3.4. N^1-*Carbamoyl*-C-*(2,3,4,6-tetra*-O-*benzoyl-β-D-glucopyranosyl)formamidrazone (15)*

Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formimidate[14] (**10**, 0.10 g, 0.15 mmol) and semicarbazide hydrochloride (**12**, 0.03 g, 0.31 mmol) were stirred in anhydrous pyridine (3 mL) at rt. After disappearance of the imidate (3 h) monitored by TLC (EtOAc), the pyridine was removed under diminished pressure and the residue was purified by column chromatography (EtOAc) to give 0.08 g (80%) white solid. Mp: 131–133 °C; $[\alpha]_D = +36$ (c 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.57 (1H, s, NH), 8.02–7.82 (4 × 2H, 4 d, $J = 7.3$ Hz, Ar), 7.55–7.24 (12H, m, Ar), 5.94, 5.83, 5.68 (3 × 1H, 3 pseudo t, $J = 9.2$, 9.2 Hz in each, H-2, H-3, H-4), 5.25 (2H, s, NH_2), 4.63 (1H, dd, $J = 12.6$, 2.6 Hz, H-6a), 4.46 (1H, dd, $J = 12.6$, 5.3 Hz, H-6b), 4.29 (1H, d, $J = 9.2$ Hz, H-1), 4.19 (1H, ddd, $J = 9.2$, 5.3, 2.6 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.1, 165.8, 165.5, 165.1 (C = O), 159.0 ($C = ONH_2$), 141.5 (C = N), 133.4–133.1, 129.7–128.2 (Ar), 77.2, 76.1, 74.0, 69.7, 69.2 (C-1 – C-5), 63.0 (C-6). MS-ESI (*m/z*): Calcd. for $C_{36}H_{33}N_4O_{10}^+$ $[M + H]^+$: 681.2. Found: 681.7.

3.5. N^1-*(2,4-Dinitrophenyl)*-C-*(2,3,4,6-tetra*-O-*benzoyl-β-D-glucopyranosyl)formamidrazone (16)*

Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formimidate[14] (**10**, 0.10 g, 0.15 mmol) and 2,4-dinitrophenylhydrazine (**13**, 61 mg, 0.31 mmol) were refluxed in anhydrous EtOH (3 mL), and the reaction was monitored by TLC (2:3 EtOAc-hexane). After total consumption of the imidate (1 d), the solvent was removed and the

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residue was purified by column chromatography (3:7 EtOAc-hexane) to give 0.10 g (83%) red syrup. R_f: 0.50 (2:3 EtOAc-hexane); $[\alpha]_D$ = –66 (c 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 10.16 (1H, s, NH), 8.89 (1H, d, *J* = 2.6 Hz, Ar), 8.04–7.84 (4 × 2H, 4 dd, *J* = 7.3, 1.0 Hz in each, Ar), 7.62 (1H, dd, *J* = 9.6, 2.6 Hz, Ar), 7.54–7.24 (12H, m, Ar), 7.05 (1H, d, *J* = 9.6 Hz, Ar), 6.11, 5.82, 5.77 (3 × 1H, 3 pseudo t, *J* = 9.6, 9.6 Hz in each, H-2, H-3, H-4), 5.31 (2H, br s, NH_2), 4.75 (1H, dd, *J* = 12.6, 2.6 Hz, H-6a), 4.58 (1H, dd, *J* = 12.6, 5.3 Hz, H-6b), 4.54 (1H, d, *J* = 9.6 Hz, H-1), 4.36 (1H, ddd, *J* = 9.6, 5.3, 2.6 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.3, 165.8, 165.3 (2) (C = O), 150.1, 145.3 (C = N, DNP-C-1), 137.0 (DNP-C-4), 133.7–133.4, 129.9–128.4 (Ar), 123.2, 116.0 (DNP-C-3, DNP-C-6) 77.0, 76.6, 73.4, 70.5, 69.1 (C-1 – C-5), 63.0 (C-6). MS-ESI (*m/z*): Calcd. for $C_{41}H_{34}N_5O_{13}^+$ $[M+H]^+$: 804.2. Found: 804.5.

3.6. 3-(3′,4′,6′-Tri-O-benzoyl-2′-deoxy-D-arabino-hex-1′-enopyranosyl)-1H-1,2,4-triazol-5(4H)-one (18)

The solution of amidrazone **14** (0.40 g, 0.56 mmol) in anhydrous *m*-xylene (8 mL) was heated at 140 °C, and the reaction was monitored by TLC (4:1 EtOAc-hexane). After total consumption of the starting material (2 h) the solvent was removed, and the residue was purified by column chromatography (7:2 EtOAc-hexane) to yield 0.11 g (37%) pale yellow solid. Mp: 205–207 °C; $[\alpha]_D$ = +13 (c 0.51, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 11.92, 11.83 (2 × 1H, 2 s, NH), 7.97–7.93 (6H, m, Ar), 7.67–7.64 (3H, m, Ar), 7.54–7.48 (6H, m, Ar), 5.91 (1H, dd, *J* = 5.5, 3.7 Hz, H-3′), 5.83 (1H, d, *J* = 3.7 Hz, H-2′), 5.80 (1H, dd, *J* = 6.8, 5.5 Hz, H-4′), 5.06 (1H, ddd, *J* = 6.8, 5.5, 3.1 Hz, H-5′), 4.77 (1H, dd, *J* = 12.3, 5.5 Hz, H-6′a), 4.66 (1H, dd, *J* = 12.3, 3.1 Hz, H-6′b); ^{13}C NMR (DMSO-d_6) δ (ppm): 165.3, 165.0, 164.5 (C = O), 155.5 (triazolone C = O), 143.1, 140.4 (C-1′, triazolone C-3), 133.8, 133.7, 133.5, 129.4–128.7 (Ar), 98.1 (C-2′), 74.1, 67.8, 67.0 (C-3′ – C-5′), 61.4 (C-6′). MS-ESI (*m/z*): Calcd. for $C_{29}H_{24}N_3O_8^+$ $[M+H]^+$: 542.2. Found: 542.3.

3.7. 3-(2′,3′,4′,6′-Tetra-O-benzoyl-β-D-glucopyranosyl)-1H-1,2,4-triazol-5(4H)-one (19)

The amidrazone **15** (2.0 g, 2.94 mmol) was refluxed in anhydrous DMF (50 mL), and the reaction was monitored by TLC (EtOAc). After disappearance of the starting material (2 h), the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc) to yield 1.35 g (69%) white solid. Mp: 281–283 °C; $[\alpha]_D$ = –13 (c 0.47, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 11.91, 11.46 (2 × 1H, 2 s, NH), 8.04–7.36 (20H, m, Ar), 6.15, 5.82, 5.69 (3 × 1H, 3 pseudo t, *J* = 9.2, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.10 (1H, d, *J* = 9.2 Hz, H-1′), 4.67 (1H, ddd, *J* = 9.2, 5.3, < 1 Hz, H-5′), 4.53 (2H, s, H-6′a, H-6′b); ^{13}C NMR (DMSO-d_6) δ (ppm): 165.3, 165.1, 164.7, 164.3 (C = O), 155.8 (triazolone C = O), 143.3 (triazolone C-3), 133.8–133.4, 129.4–128.3 (Ar), 74.5, 73.8, 71.6, 70.1, 68.6 (C-1′ – C-5′), 62.3 (C-6′). MS-ESI (*m/z*): Calcd. for $C_{36}H_{30}N_3O_{10}^+$ $[M+H]^+$: 664.2. Found: 664.3.

3.8. 3-(β-D-Glucopyranosyl)-1H-1,2,4-triazol-5(4H)-one (20)

Prepared from compound **19** (0.27 g, 0.41 mmol) according to the general procedure (Section 3.2.). Reaction time: 1 d. Purified by column chromatography (5:4 $CHCl_3$-MeOH) to yield 60 mg (60%) colourless syrup. R_f = 0.32 (1:1 $CHCl_3$-MeOH), $[\alpha]_D$ = +9 (c 0.10, MeOH); ^{1}H NMR (DMSO-d_6 + 1 drop D_2O) δ (ppm): 4.70 (1H, d, *J* = 9.9 Hz, H-1′), 4.46 (1H, dd, *J* = 11.9, 2.6 Hz, H-6′a), 4.25–4.18 (2H, m, H-2′ or H-3′ or H-4′, H-6′b), 4.06–4.00 (2H, m, H-2′ or H-3′ or H-4′, H-5′), 3.93 (1H, pseudo t, *J* = 9.9, 9.2 Hz, H-2′ or H-3′ or H-4′); ^{13}C NMR (DMSO-d_6) δ (ppm): 156.1 (triazolone C = O), 145.7 (triazolone C-3), 81.3, 77.7, 74.7, 71.0, 69.8 (C-1′ – C-5′), 61.1 (C-6′). MS-ESI (*m/z*): Calcd. for $C_8H_{14}N_3O_6^+$ $[M+H]^+$: 248.1; $C_8H_{13}N_3NaO_6^+$ $[M+Na]^+$: 270.1. Found: $[M+H]^+$: 248.2; $[M+Na]^+$: 270.5. Anal: Calcd for $C_8H_{13}N_3O_6$ (M 247.205): C, 38.87; H, 5.30; N, 17.00. Found: C, 39.09; H, 5.43; N,16.89.

3.9. 3-(2′,3′,4′,6′-Tetra-O-benzoyl-β-D-glucopyranosyl)-1-tosyl-1H-1,2,4-triazol-5(4H)-one (21)

To a solution of amidrazone[17] **17** (0.20 g, 0.25 mmol) in anhydrous $CHCl_3$ (3 mL) anhydrous pyridine (37 μL, 0.45 mmol, 1.8 equiv.) was added. The mixture was then cooled in an ice bath, and a solution of ethyl chloroformate (36 μl, 0.38 mmol, 1.5 ekv.) in anhydrous $CHCl_3$ (3 mL) was added dropwise over 15 minutes. The mixture was then stirred at rt, and the reaction was monitored by TLC (2:3 EtOAc-hexane). After 1 week, the mixture was concentrated under diminished pressure, and the crude product was purified by column chromatography (1:2 EtOAc-hexane) to give 0.14 g (70%) white solid. Mp: 105–107 °C; $[\alpha]_D$ = +6 (c 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 10.89 (1H, br s, NH), 8.06–7.16 (22H, m, Ar), 7.02 (2H, d, *J* = 7.4 Hz, Ar), 6.01 (1H, pseudo t, *J* = 9.2, 9.2 Hz, H-2′ or H-3′ or H-4′), 5.84–5.78 (2H, m, H-2′ and/or H-3′ and/or H-4′), 4.86 (1H, d, *J* = 9.2 Hz, H-1′), 4.63 (1H, dd, *J* = 12.3, < 1 Hz, H-6′a), 4.50 (1H, dd, *J* = 12.3, 4.9 Hz, H-6′b), 4.32 (1H, ddd, *J* = 9.2, 4.9, < 1 Hz, H-5′), 2.26 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.2, 165.6, 165.1, 164.8 (C = O), 151.9 (triazolone C = O), 145.6, 145.0 (triazolone C-3, Ts-C-1 or Ts-C-4), 133.7 (Ts-C-1 or Ts-C-4), 133.4–133.1, 130.0–127.9 (Ar), 76.6, 73.5, 72.6, 69.8, 69.0 (C-1′ – C-5′), 63.0 (C-6′), 21.5 (CH_3). MS-ESI (*m/z*): Calcd. for $C_{43}H_{36}N_3O_{12}S^+$ $[M+H]^+$: 818.2. Found: 818.5.

3.10. 3-(β-D-Glucopyranosyl)-1-tosyl-1H-1,2,4-triazol-5(4H)-one (22)

Prepared from compound **21** (0.20 g, 0.24 mmol) according to the general procedure (Section 3.2). Reaction time: 7 h. Purified by column chromatography (9:1 $CHCl_3$-MeOH) to yield 55 mg (56%) colourless syrup. R_f = 0.54 (7:3 $CHCl_3$-MeOH), $[\alpha]_D$ = –7 (c 0.31, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 12.34 (1H, br s, NH), 7.84, 7.48 (2 × 2H, 2 d, *J* = 7.9 Hz in each, Ar), 5.24, 5.14, 5.02, 4.46 (4 × 1H, OH), 3.89 (1H, d, *J* = 9.2 Hz, H-1′), 3.64 (1H, dd, *J* = 11.9, 2.6 Hz, H-6′a), 3.22–3.07 (5H, m, H-2′, H-3′, H-4′, H-5′, H-6′b), 2.41 (3H, s, CH_3); ^{13}C NMR (CD_3OD) δ (ppm): 154.4, 150.6, 147.7 (triazolone C = O, triazolone C-3, Ts-C-1 or Ts-C-4), 135.7, 131.2 (2), 129.1 (2) (Ar), 82.2, 78.9, 76.0, 73.0, 70.9 (C-1′ – C-5′), 62.4 (C-6′), 21.7 (CH_3). MS-ESI (*m/z*): Calcd. for $C_{15}H_{20}N_3O_8S^+$ $[M+H]^+$: 402.1. Found: 402.3. Anal: Calcd for $C_{15}H_{19}N_3O_8S$ (M 401.39): C, 44.88; H, 4.77; N, 10.47. Found: C, 45.16; H, 4.85; N, 10.42.

3.11. N[1]-Phenyl-N[4]-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosylcarbonyl)semicarbazide (25)

To a solution of *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl) formamide[30] (**23**, 2.5 g, 4.0 mmol) in anhydrous 1,2-dichloroethane (50 mL) oxalyl chloride (0.68 mL, 8.0 mmol) was added, and the mixture was refluxed for 1 d. The reaction mixture was then concentrated under diminished pressure, and traces of oxalyl chloride was removed by repeated co-evaporations with toluene. The remaining syrup was dissolved in anhydrous THF (50 mL), the solution was cooled to 0 °C and phenylhydrazine (0.6 mL, 6.0 mmol) was added. Subsequently the reaction mixture was allowed to warm to rt and stirred for 1 d. The solvent was then removed under reduced pressure, and the residue was crystallized from diethyl ether to give 2.1 g (69% for two steps) pale yellow solid. Mp: 219–221; $[\alpha]_D$ = –17 (c 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.53, 9.47 (2 × 1H, 2 s, NH), 8.03–6.86 (25H, m, Ar), 6.21 (1H, s, NH), 5.89 (1H, pseudo t, *J* = 9.0, 8.5 Hz, H-2′ or H-3′ or H-4′), 5.75–5.64 (2H, m, H-2′ and/or H-3′ and/or H-4′), 4.64 (1H, dd, *J* = 11.5, < 1 Hz, H-6′a), 4.42 (1H, dd, *J* = 11.5, 3.4 Hz, H-6′b), 4.15 (1H, d, *J* = 9.3 Hz, H-1′), 4.09 (1H, m, H-5′); ^{13}C

NMR ($CDCl_3$) δ (ppm): 168.0, 166.4, 165.7, 165.1 (2), 154.1 (C = O), 147.6, 133.6–133.2, 129.8–128.3, 121.0, 113.1 (Ar), 76.4, 76.2, 73.2, 69.4, 69.0 (C-1′ – C-5′), 63.0 (C-6′). MS-ESI (*m/z*): Calcd. for $C_{42}H_{36}N_3O_{11}^+$ $[M+H]^+$: 758.2. Found: 758.5.

3.12. N[1]-(tert-Butoxycarbonyl)-N[2]-phenyl-N[4]-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosylcarbonyl)semicarbazide (26)

To a solution of *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl) formamide[30] (**23**, 0.5 g, 0.80 mmol) in anhydrous 1,2-dichloroethane (12 mL) oxalyl chloride (136 μL, 0.16 mmol) was added, and the mixture was heated at reflux temperature for 1 d. The reaction mixture was then concentrated under diminished pressure, and traces of oxalyl chloride was removed by repeated co-evaporations with toluene. The remaining syrup was dissolved in anhydrous THF (10 mL), the solution was cooled to 0 °C and PhNHNHBoc (0.25 g, 1.2 mmol) was added. Subsequently, the reaction mixture was allowed to warm to rt and stirred for 3 h. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography (1:2 EtOAc-hexane) to obtain the title compound **26** (0.35 g) as the first than amide **23** (0.12 g) as the second fraction. Yield of the title compound for two steps: 66% (corrected with the recovered starting material **23**). Mp: 192–194 °C (white solid); $[\alpha]_D = -7$ (c 0.21, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ (ppm): 10.03, 9.86 (2 × 1H, 2 br s, NH), 7.98–7.17 (25H, m, Ar), 6.03, 5.80, 5.68 (3 × 1H, 3 pseudo t, J = 9.4, 9.4 Hz in each, H-2′, H-3′, H-4′), 4.91 (1H, d, J = 9.4 Hz, H-1′), 4.57–4.41 (3H, m, H-5′, H-6′a, H-6′b), 1.34 (9H, s, C(CH_3)$_3$; ^{13}C NMR (DMSO-d_6) δ (ppm): 165.3 (2), 165.1, 164.6, 164.4, 154.5, 150.3 (C = O), 141.0, 133.7–133.4, 129.2–128.4, 124.0 (Ar), 80.6 (*C*(CH_3)$_3$), 75.5, 74.6, 74.0, 69.4, 68.6 (C-1′ – C-5′), 62.8 (C-6′), 27.7 (C(*C*H_3)$_3$). MS-ESI (*m/z*): Calcd. for $C_{47}H_{44}N_3O_{13}^+$ $[M+H]^+$: 858.3. Found: 858.1.

3.13. 1-Phenyl-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1H-1,2,4-triazol-5(4H)-one (27)

A: The solution of compound **25** (1.0 g, 1.32 mmol) in anhydrous *m*-xylene (40 mL) was heated at boiling temperature, and the reaction was monitored by TLC (1:1 EtOAc-hexane). After total consumption of the starting material (1 d), the solvent was removed, and the residue was purified by column chromatography (1:2 EtOAc-hexane) to give 0.36 g (37%) colourless syrup. **B**: To a solution of compound **26** (0.23 g, 0.27 mmol) in anhydrous CH_2Cl_2 (10 mL) trifluoroacetic acid (124 μL, 1.61 mmol) was added and the mixture was stirred at rt. After disappearance of the starting material (4 d) monitored by TLC (2:3 EtOAc-hexane), the solvent was removed under diminished pressure, and the residue was purified by column chromatography (1:2 EtOAc-hexane) to yield 0.17 g (87%) colourless syrup. R_f: 0.54 (1:1 EtOAc-hexane); $[\alpha]_D = +16$ (c 0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 11.58 (1H, br s, NH), 8.00–7.83 (4 × 2H, 4 d, J = 7.0 Hz in each, Ar), 7.67 (2H, d, J = 7.8 Hz, Ar), 7.52–7.10 (15H, m, Ar), 6.06, 5.91, 5.80 (3 × 1H, 3 pseudo t, J = 9.4, 9.4 Hz in each, H-2′, H-3′, H-4′), 4.90 (1H, d, J = 9.4 Hz, H-1′), 4.69 (1H, dd, J = 12.5, 3.1 Hz, H-6′a), 4.57 (1H, dd, J = 12.5, 5.5 Hz, H-6′b), 4.35 (1H, ddd, J = 9.4, 5.5, 3.1 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.2, 165.8, 165.1, 165.0 (C = O), 153.4 (triazolone C = O), 142.6 (triazolone C-3), 137.3, 133.5–133.1, 129.9–128.3, 125.5, 118.7 (Ar), 76.8, 73.5, 72.7, 70.2, 69.2 (C-1′ – C-5′), 63.1 (C-6′). ESI-MS positive mode (m/z): calcd for $C_{42}H_{34}N_3O_{10}^+$ $[M+H]^+$: 740.2. Found: 740.4.

3.14. 3-(β-D-Glucopyranosyl)-1-phenyl-1H-1,2,4-triazol-5(4H)-one (28)

Prepared from compound **27** (0.23 g, 0.31 mmol) according to the general procedure (Section 3.2). Reaction time: 6 h. Purified by column chromatography (85:15 $CHCl_3$-MeOH) to yield 94 mg (95%) white solid. Mp: 238–240 °C $[\alpha]_D = +30$ (c 0.40, MeOH); ^{1}H NMR (DMSO-d_6 + 1 drop D_2O) δ (ppm): 7.83 (2H, d, J = 7.8 Hz, Ar), 7.43 (2H, pseudo t, J = 7.8 Hz, Ar), 7.21 (1H, t, J = 7.8 Hz, Ar), 4.04 (1H, d, J = 9.4 Hz, H-1′), 3.69 (1H, dd, J = 11.7, 5.5 Hz, H-6′a), 3.46 (1H, pseudo t, J = 9.4, 9.4 Hz, H-2′ or H-3′ or H-4′), 3.44 (1H, dd, J = 11.7, 3.1 Hz, H-6′b), 3.30–3.25 (2H, m, H-2′ or H-3′ or H-4′, H-5′), 3.16 (1H, pseudo t, J = 9.4, 9.4 Hz, H-2′ or H-3′ or H-4′); ^{13}C NMR (DMSO-d_6) δ (ppm): 152.6 (triazolone C = O), 145.7 (triazolone C-3), 137.7, 129.0 (2), 124.7, 117.9, 117.7 (Ar), 81.4, 77.5, 74.5, 71.1, 69.8 (C-1′ – C-5′), 61.1 (C-6′). MS-ESI (*m/z*): Calcd. for $C_{14}H_{18}N_3O_6^+$ $[M+H]^+$: 324.1. Found: 324.2. Anal: Calcd for $C_{14}H_{17}N_3O_6$ (M 323.30): C, 52.01; H, 5.30; N, 13.00. Found: C, 52.09; H, 5.46; N,12.85.

3.15. 1-(2-Naphthyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1H-1,2,4-triazol-5(4H)-one (29)

To a solution of compound **19** (0.10 g, 0.15 mmol) in anhydrous CH_2Cl_2 (3 mL) 2-naphthylboronic acid (52 mg, 0.30 mmol), $Cu(OAc)_2$ (27 mg, 0.15 mmol) and Et_3N (42 μL, 0.30 mmol) were added, and the reaction mixture was stirred at rt. When the TLC (1:1 EtOAc-hexane) showed total consumption of **20** (1 d), the solvent was evaporated. The residue was purified by column chromatography (2:3 EtOAc-hexane) to give 24 mg (20%) pale yellow amorphous solid. R_f: 0.51 (1:1 EtOAc-hexane); $[\alpha]_D = +11$ (c 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 11.89 (1H, br s, NH), 8.12 (1H, s, Ar), 7.97–7.20 (26H, m, Ar), 6.10, 5.98, 5.84 (3 × 1H, 3 pseudo t, J = 9.2, 9.2 Hz in each, H-2′, H-3′, H-4′), 4.95 (1H, d, J = 9.2 Hz, H-1′), 4.72 (1H, dd, J = 11.9, 2.6 Hz, H-6′a), 4.61 (1H, dd, J = 11.9, 5.3 Hz, H-6′b), 4.37 (1H, ddd, J = 9.2, 5.3, 2.6 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.2, 165.8, 165.1 (2) (C = O), 153.7 (triazolone C = O), 142.9 (triazolone C-3), 134.8–125.4, 118.0, 116.2 (Ar), 76.7, 73.5, 72.6, 70.3, 69.3 (C-1′ – C-5′), 63.1 (C-6′). ESI-MS positive mode (m/z): calcd for $C_{46}H_{36}N_3O_{10}^+$ $[M+H]^+$: 790.2. Found: 790.4.

3.16. 3-(β-D-Glucopyranosyl)-1-(2-naphthyl)-1H-1,2,4-triazol-5(4H)-one (30)

Prepared from compound **29** (0.12 g, 0.15 mmol) according to the general procedure (Section 3.2). Reaction time: 4 h. Purified by column chromatography (85:15 $CHCl_3$-MeOH) to yield 48 mg (84%) colourless syrup. R_f = 0.43 (7:2 $CHCl_3$-MeOH), $[\alpha]_D = +33$ (c 0.13, MeOH); ^{1}H NMR (DMSO-d_6 + 1 drop D_2O) δ (ppm): 8.31 (1H, s, Ar), 8.04–7.88, 7.54–7.45 (6H, m, Ar), 4.10 (1H, d, J = 9.4 Hz, H-1′), 3.69 (1H, dd, J = 11.7, 2.3 Hz, H-6′a), 3.50 (1H, pseudo t, J = 9.4, 9.4 Hz, H-2′ or H-3′ or H-4′), 3.47 (1H, dd, J = 11.7, 5.5 Hz, H-6′b), 3.34–3.29 (2H, m, H-2′ or H-3′ or H-4′, H-5′), 3.21 (1H, pseudo t, J = 9.4, 9.4 Hz, H-2′ or H-3′ or H-4′); ^{13}C NMR (DMSO-d_6) δ (ppm): 152.7 (triazolone C = O), 145.9 (triazolone C-3), 135.3, 133.0, 130.3, 128.9, 127.8, 127.6, 127.5, 127.4, 117.6, 114.5 (Ar), 81.4, 77.4, 74.6, 71.1, 69.8 (C-1′ – C-5′), 61.0 (C-6′). MS-ESI (*m/z*): Calcd. for $C_{18}H_{20}N_3O_6^+$ $[M+H]^+$: 374.1. Found: 374.3. Anal: Calcd for $C_{18}H_{19}N_3O_6$ (M 373.36): C, 57.90; H, 5.13; N, 11.25. Found: C, 57.83; H, 5.31; N, 11.39.

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Supplementary material

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