Non-natural nucleosides based on 1,2,4-triazolo[5,1-c][1,2,4]triazin-4(6H)-ones

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Dedicated to Prof. Henk van der Plas on the occasion of his 80th birthday

Abstract
Two regioselective methods for the synthesis of nucleosides in the series of 3-phenyl- and 3-ethoxycarbonyl-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones were developed. The first route involves a Vorbrüggen glycosylation reaction. The second one is based on condensation of 1,2,4-triazolo[5,1-c][1,2,4]triazin-4-one sodium salts with protected 1-bromo-sugar derivatives.

Keywords: 1,2,4-Triazolo[5,1-c][1,2,4]triazin-4-ones, glycosylation, NMR spectra, β-configuration, X-ray

Introduction
The synthesis of analogs of natural nucleosides based on modification of purines and pyrimidines is one of the most useful tools for development of antiviral compounds. In most cases, the structural transformations of nucleobases can be achieved by introduction or removal of different substituents. This methodology was successfully used for drug design of active antiviral agents: Brivudine [(E)-5-(2-bromovinyl)-2'-deoxyuridine], Idoxuridine (2'-deoxy-5-iodouridine), Famciclovir (2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediol diacetate).1-3

Another strategy for synthesis of antiviral compounds is based on isosteres of natural nucleobases or heterocycles containing fragments of purines or pyrimidines.
This way have been applied for the synthesis of Marbavir (1-(β-L-ribofuranosyl)-2-isopropylamino-5,6-dichlorobenzimidazole), Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) and of its analogs.  

Herein, we report the synthesis of abnormal nucleosides in the series of 1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones, considered as fused analogues of aza-isocytosines and exhibiting antiviral activity.

**Results and Discussion**

The Vorbrüggen reaction is one of the widely used routes for the synthesis of nucleosides. This method of glycosylation involves interaction of protected sugar derivatives with appropriately silylated NH-heterocycles in the presence of a Lewis acid.

We found that the conditions of the Vorbrüggen one-step method were useful for glycosylation of 1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones. Treatment on the NH-heterocycles with N,O-bis-(trimethylsilyl)acetamide (BSA) and trimethylsilyl triflate (TMSOTf) followed by addition of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose at room temperature gave compounds (Scheme 1). Although there are three possible positions for N-glycosylation (N1, N6 or N8), only products of N-1 glycosylation were observed. The sugar fragments in 2a-e had exclusively the β-configuration.

Removing the protecting acetyl of the compounds 2a-e in sodium methoxide solution gave nucleosides 3a-c. Meanwhile the deacetylation of 2d,e was carried out in acidic medium by mixture ethanol with acetyl chloride. Attempts to remove the acetyl-protecting groups in
compound 2d,e by reaction with sodium ethoxide gave products of decomposition or incomplete deacetylation — for example, the monoacetyl derivative 4 was obtained from 2e.

The reaction of 1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones 1a-c with β-D-glucose penta-acetate were carried out under the same conditions (BSA and TMSOTf) to give protected nucleoside 5a-c in 40-50% yield (Scheme 2).

Following removal of the protection groups the nucleosides 6a-c were produced. The best conditions for deacetylation were found to be heating of 5a-c under reflux in MeONa/MeOH solution.

Reactions of purines and pyrimidine sodium salts with halogen derivatives of sugars provide an alternative nucleoside-forming methodology.13-16 Previously reported conditions for alkylation of azolo[5,1-c][1,2,4]triazin-4-ones sodium salts17 with halo-alkanes proved to be successful for the synthesis of nucleosides, too. Compounds 5a-c were obtained by the reaction of tetra-acetyl-α-D-bromoglucose and the sodium salt of 1,2,4-triazolo[5,1-c][1,2,4]triazinones 7a-c, prepared from the heterocycles 1a-c in the presence of Na2CO3 (Scheme 3).

The signals in both the 1H- and 13C- NMR spectra of compounds 2a-e and 5a-c were assigned using 2D- 1H, 1H COSY, 1H, 13C gHSQC and gHMBC experiments.
The position of the tri-O-acetyl-β-D-ribofuranosyl and tetra-O-acetyl-β-D-glucopyranosyl fragments at the N-1 atom of the 1,2,4-triazine part in compounds 2a-e and 5a-c are evident from the observed cross-peaks between H-1' and C-8α in the HMBC spectra. NOESY spectra of 2a-e showed the β-configuration of the furanoses due to the presence of correlation of peaks H-1' with H-4'. The structure of the acetylated nucleoside 2d was confirmed by X-ray diffraction (Fig. 1). It was found that the ribofuranosyl fragment of 2d has a 3'-exo twist conformation.

The derivatives of glucopyranose, 5a-c, have a β-configuration, and this was also confirmed by 2D- gNOESY experiments showing cross-peaks H-1' with H-3' and H-5', and vicinal coupling constant of H-1'– H-2' (\( \tilde{J} \) 9.0-9.5 Hz) in the \(^1\)H NMR.\(^{18}\) A single-crystal X-ray diffraction analysis was carried out in order to confirm the molecular structure of 5a-c. The molecular structure of 5c (Fig. 2) demonstrated that the glucopyranosyl fragment is attached at the azine part, and the sugar has the β-configuration.

The position of the protecting group in compound 4 has been determined by the 2D- HMBC spectrum, where the signal for the carbon of the acetyl group gave cross peaks with H-5'α and H-5'β. The structures of the nucleosides 3a-e and 6a-c were confirmed by \(^1\)H NMR and mass spectra.

In conclusion, we have reported selective methods for synthesis of non-natural nucleosides based on 3-phenyl- and 3-ethoxycarbonyl-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones.
Experimental Section

General Procedures. IR spectra were recorded in KBr on a Perkin Elmer Spectrum One B FT-IR instrument. The $^1$H- and $^{13}$C- NMR spectra were measured on Bruker WM-250, Bruker DRX-400, and Bruker DRX-500 instruments. The $^{13}$C- and $^1$H- 2D NMR spectra were recorded on the Bruker DRX-500 spectrometer in DMSO-$d_6$. The mass spectra were obtained using a quadrupole Shimadzu LCMS-2010 system with a Supelco LC-18 column (4.6 × 250 mm), where a temperature of 60 °C was maintained. The mobile phase was acetonitrile (100 %). Positive chemical APCI ionization in the selective ion-monitoring (SIM) mode was used. The capillary voltage was set at 1.5 kV and cone voltage at 15.0 V. Microanalyses were performed on a Perkin Elmer PE 2400 series II CHNS/O analyzer. TLC was carried out on Silufol UV-254 plates using ethyl acetate as the eluent; spots were visualized by exposure to UV radiation. Column chromatography was performed on Merck Kieselgel-60. 1-Bromo-2,3,5-tri-$O$-acetyl-$\alpha$-D-glucose, 1,2,3,5-tetra-$O$-acetyl-$\beta$-D-ribofuranose, $\beta$-D-glucose penta-acetate, $N,O$-bis-(trimethylsilyl)acetamide and trimethylsilyl triflate were purchased from Aldrich. RT denotes room temperature.

1,2,4-Triazolo[5,1-c][1,2,4]triazin-4(6H)-ones (1a-e) was prepared according to the procedure described earlier.$^{19,20}$
1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones (2a-e).

N,O-Bis-(trimethylsilyl)acetamide (0.328 mL, 1.34 mmol), trimethylsilyl triflate (TMSOTf) (0.32 mL, 1.8 mmol) and 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (0.28 g, 0.90 mmol) were added to a solution of compound (1a-e) (0.94 mmol) in 5 ml acetonitrile. The reaction mixture was left at RT for 2.5 h, diluted with 10 ml acetonitrile with a few drops of water and neutralized with NaHCO₃. The resulting suspension was filtered. The filtrate was concentrated in vacuo. The product was isolated by column chromatography using ethyl acetate: hexane (4:1) as the eluent.

**Compound 2a.** Yield 0.20 g (45 %); mp 73 °C; [α]²⁰D -56.5º (c 1.0, EtOAc); MS (APCI, m/z (rel. %)) 472 (100%) [M+H]⁺; IR: CO 1721, 1745; ¹H NMR (DMSO-d₆): δ 1.78 (s, 3H, Me of 5'-Ac), 2.09 (s, 3H, Me of 3'-Ac), 2.11 (s, 3H, Me of 2'-Ac), 4.16 (d,d, 1H, H-5'b, J=5.0 Hz, J=12.5 Hz) 4.37 (d,d, 1H, H-5'a, J=3.2 Hz, J=12.3 Hz), 4.46 (m, H-4'), 5.67 (t, 1H, H-3', J=5.5 Hz), 5.91 (d,m, 1H, H-2', J=5.3 Hz), 6.49 (d, 1H, H-1', J=3.0 Hz), 7.54 (m, 3H, m-Ph), 8.06 (m, 2H, o-Ph). ¹³C NMR (DMSO-d₆): δ 19.93 (Me of 5'-Ac), 20.08 (Me of 2'-Ac + Me of 3'-Ac), 62.30 (C-5'), 69.73 (C-3'), 72.41 (C-2'), 79.06 (C-4'), 91.38 (C-1'), 128.13 (C-m), 128.55 (C-o), 130.70 (C-p), 140.58 (C-3'), 148.65 (C-4'), 150.61 (C-8a), 169.03 (CO of 2'-Ac), 169.27 (CO of 3'-Ac), 169.72 (CO of 5'-Ac). Calc. for C₂₁H₂₁N₅O₈: C, 53.50; H, 4.49; N, 14.86. Found: C, 54.02; H, 4.51; N, 14.20%.

**Compound 2b.** Yield 0.22 g (48 %); mp 173 °C; [α]²⁰D -53.4º (c 1, EtOAc); MS (APCI, m/z (rel. %)) 486 (100%) [M+H]⁺; IR: CO 1770, 1721; ¹H NMR (DMSO-d₆): δ 1.78 (s, 3H, Me of 5'-Ac), 2.10 (s, 3H, Me of 3'-Ac), 2.12 (s, 3H, Me of 2'-Ac), 2.45 (s, 3H, Me), 4.16 (d,d, 1H, H-5'b, J=5.0 Hz, J=12.5 Hz) 4.36 (d,d, 1H, H-5'a, J=3.5 Hz, J=12.3 Hz), 4.46 (m, H-4'), 5.66 (t, 1H, H-3', J=5.5 Hz), 5.91 (d,m, 1H, H-2', J=5.3 Hz), 6.45 (d, 1H, H-1', J=2.5 Hz), 7.52 (m, 3H, m-H-, p-Ph), 8.06 (m, 2H, o-Ph); ¹³C NMR (DMSO-d₆): δ 14.02 (Me), 19.93 (Me of 5'-Ac), 20.09 (Me of 2'-Ac + Me of 3'-Ac), 62.31 (C-5'), 69.78 (C-3'), 72.41 (C-2'), 79.06 (C-4'), 91.15 (C-1'), 128.12 (C-m), 128.98 (C-o), 131.70 (C-p), 140.58 (C-3), 148.65 (C-4), 150.61 (C-8a), 152.86 (C-7), 169.03 (CO of 2'-Ac), 169.27 (CO of 3'-Ac), 169.72 (CO of 5'-Ac). Calc. for C₂₂H₂₃N₅O₈: C, 54.43; H, 4.78; N, 14.43. Found: C, 54.06; H, 4.80; N, 14.22%.

**Compound 2c.** Yield 0.24 g (50 %); mp 121 °C; [α]²⁰D -38.3º (c 1, EtOAc); MS (APCI, m/z (rel. %)) 518 (100%) [M+H]⁺, 519 (32.7%) [M+1+H]⁺, 520 (6.7%) [M+2+H]⁺; IR: CO 1711; ¹H NMR (DMSO-d₆): δ 1.78 (s, 3H, Me of 5'-Ac), 2.10 (s, 3H, Me of 3'-Ac), 2.12 (s, 3H, Me of 2'-Ac), 2.67 (s, 3H, SMe), 4.15 (d,d, 1H, H-5'b, J=5.0 Hz, J=12.5 Hz) 4.36 (d,d, 1H, H-5'a, J=3.0 Hz, J=12.3 Hz), 4.46 (m, H-4'), 5.67 (t, 1H, H-3', J=5.5 Hz), 5.91 (d,m, 1H, H-2', J=5.3 Hz), 6.45 (d, 1H, H-1', J=2.5 Hz), 7.52 (m, 3H, m-H-, p-Ph), 8.05 (m, 2H, o-Ph); ¹³C NMR (DMSO-d₆): δ 13.40 (SMe), 19.93 (Me of 5'-Ac), 20.09 (Me of 2'-Ac + Me of 3'-Ac), 62.31 (C-5'), 69.78 (C-3'), 72.34 (C-2'), 79.06 (C-4'), 91.15 (C-1'), 128.12 (C-m), 128.53 (C-o), 129.96 (C-p), 131.78 (C-i), 140.58 (C-3), 148.16 (C-4), 150.83 (C-8a), 162.51 (C-7), 169.06 (CO of 2'-Ac), 169.30 (CO of 3'-Ac), 169.73 (CO of 5'-Ac). Calc. for C₂₂H₂₃N₅O₈S: C, 53.50; H, 4.49; N, 14.86. Found: C, 54.02; H, 4.51; N, 14.20%.

**Compound 2d.** Yield 0.20 g (46 %); mp 127 °C; [α]²⁰D -75.9º (c 1, EtOAc); MS (APCI, m/z (rel. %)) 468 (100%) [M+H]⁺; IR: CO 1759, 1744; ¹H NMR (CDCl₃): δ 1.41 (t, 3H, Me of OEt),...
2.03 (s, 3H, Me of 5'-Ac), 2.11 (s, 6H, Me of 3'-Ac + Me of 2'-Ac), 4.26 (d,d, 2H, H-5b', J=6.0 Hz, J=12.0 Hz), 4.39 (d,d, 2H, H-5a', J=3.5 Hz, J=12.2 Hz), 4.36-4.48 (m, 3H, CH₂ of OEt + H-4'), 5.63 (t, 1H, H-3', J=5.5 Hz), 5.83 (m, 1H, H-2'), 6.54 (d, 1H, H-1', J=3.0 Hz), 8.17 (s, 1H H-7). ¹³C NMR (CDCl₃): δ 13.99 (Me of OEt); 20.34 (Me of 5'-Ac), 20.39 (Me of 2'-Ac), 20.54 (Me of 3'-Ac), 63.02 (OCH₂ + C-5'), 70.60 (C-3'), 73.07 (C-2'), 80.92 (C-4'), 93.26 (C-1'), 133.19 (C-3), 145.61 (C-4), 150.27 (C-8a), 153.36 (C-7), 159.52 (CO), 169.56 (CO of 2'-Ac + CO of 3'-Ac), 170.35 (CO of 5'-Ac). Calc. for C₁₈H₂₁N₅O₁₀: C, 46.26; H, 4.53; N, 14.98. Found: C, 46.13; H, 4.54; N, 14.78%.

Compound 2e. Yield 0.19 g, (42 %); mp 153 °C; [α]²⁰D -60.3º (c 1, EtOAc); MS (APCI, m/z (rel. %)) 482 (100%) [M+H]+; IR: CO 1751, 1758; ¹H NMR (CDCl₃): δ 1.20 (t, 3H, Me of OEt), 2.04 (s, 3H, Me of 5'-Ac), 2.12 (s, 6H, Me of 3'-Ac + 2'-Ac), 2.55 (s, 3H, Me), 4.26 (d,d, 2H, H-5b', J=6.0 Hz, J=12.3 Hz), 4.39 (d,d, 2H, H-5a', J=3.5 Hz, J=12.3 Hz), 4.41-4.49 (m, 3H, CH₂ of OEt + H-4'), 5.65 (t, 1H, H-3', J=5.0 Hz), 5.87 (m, 1H, H-2'), 6.52 (d, 1H, H-1', J=3.0 Hz); ¹³C NMR (CDCl₃): δ 13.99 (Me of OEt), 14.61 (Me), 20.36 (Me of 5'-Ac), 20.40 (Me of 2'-Ac) 20.54 (Me of 3'-Ac), 62.98 (OCH₂ + C-5'), 70.62 (C-3'), 72.93 (C-2'), 81.43 (C-4'), 92.93 (C-1'), 133.20 (C-3), 145.37 (C-4), 159.65 (CO), 164.37 (C-7), 169.37 (CO of 2'-Ac + CO of 3'-Ac), 170.34 (CO of 5'-Ac). Calc. for C₁₉H₂₃N₅O₁₀: C, 47.40; H, 4.82; N, 14.55. Found: C, 47.06; H, 4.92; N, 14.31%.

1-(β-D-Ribofuranosyl)-3-phenyl-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones (3a-c). Compound (2a-c) (0.4 mmol) was added to a sodium methoxide solution, which was prepared from sodium (0.03 g, 1.30 mmol) and methanol (4 ml). The reaction mixture was refluxed for 0.5 h, cooled, neutralized acetic acid and concentrated in vacuo. The product was isolated by column chromatography using ethyl acetate as the eluent.

Compound 3a. Yield 0.082 g, (57%); mp 216 °C; [α]²⁰D -55.1º (c 0.3, MeCN); MS (APCI, m/z (rel. %)) 346 (100%) [M+H]+; IR: CO 1717; ¹H NMR (DMSO-d₆): δ 3.26-3.53 (m, 1H, H-5b'), 3.61-3.66 (m, 1H, H-5a'), 3.97 (q, 1H, H-4', J=5.5 Hz), 4.36 (q, 1H, H-3', J=6.0 Hz), 4.65 (m, 1H, OH), 4.67 (m, 1H, H-2'), 5.21 (d, 1H, OH, J=6.0 Hz), 5.55 (d, 1H, OH, J=4.8 Hz), 6.25 (d, 1H, H-1', J=2.8 Hz), 7.53 (m, 3H, m-, p-Ph), 8.00 (m, 2H, o-Ph), 8.46 (s, 1H, H-7). Calc. for C₁₅H₁₅N₅O₅·H₂O: C, 49.59; H, 4.72; N, 19.28. Found: C, 49.31; H, 4.73; N, 19.62%.

Compound 3b. Yield 0.101 g, (65%); mp 210 °C; [α]²⁰D -52.9º (c 0.2, EtOAc); MS (APCI, m/z (rel. %)) 360 (100%) [M+H]+; ¹H NMR (DMSO-d₆): δ 2.48 (s, 3H, Me), 3.48-3.55 (m, 1H, H-5b'), 3.61-3.66 (m, 1H, H-5'a), 3.95 (q, 1H, H-4', J=5.5 Hz), 4.36 (q, 1H, H-3', J=6.0 Hz), 4.65 (m, 1H, OH), 4.67 (m, 1H, H-2'), 5.21 (d, 1H, OH, J=6.0 Hz), 5.55 (d, 1H, OH, J=4.8 Hz), 6.25 (d, 1H, H-1', J=2.8 Hz), 7.53 (m, 3H, m-, p-Ph), 8.00 (m, 2H, o-Ph), 8.46 (s, 1H, H-7). Calc. for C₁₆H₁₇N₅O₅·H₂O: C, 50.93; H, 4.72; N, 19.28. Found: C, 51.30; H, 4.77; N, 19.62%.

Compound 3c. Yield 0.099 g (61%); mp 167 °C; [α]²⁰D -61.4º (c 0.5, MeCN); MS (APCI, m/z (rel. %)) 392 (100%) [M+H]+, 393 (19.5%) [M+1+H]+, 394 (9.0%) [M+2+H]+. IR: CO, 1727cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.66 (s, 3H, SMe), 3.47-3.52 (m, 1H, H-5'b'), 3.61-3.65 (m, 1H, H-5'a), 3.96 (q, 1H, H-4', J=4.5 Hz), 4.34 (q, 1H, H-3', J=5.0 Hz), 4.50-4.56 (m, 2H, OH + H-2'), 4.99 (d, 1H, OH, J=6.0 Hz), 5.30 (d, 1H, OH, J=5.0 Hz), 6.19 (d, 1H, H-1', J=3.5 Hz), 7.48 (m, 3H,
m-, p-Ph), 8.03 (m, 2H, o-Ph); Calc. for C_{16}H_{17}N_{5}O_{5}S·H_{2}O: C, 46.94; H, 4.68; N, 17.11. Found: C, 46.50; H, 4.49; N, 17.19%.

1-(β-D-Ribofuranosyl)-3-ethoxycarbonyl-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones (3d,e). Compound 2d or 2e (0.4 mmol) was added to a solution of HCl prepared from anhydrous ethanol (10 mL) and acetyl chloride (2 mL). The resulting solution was kept at r.t. for 48 h, then neutralized with AcONa and evaporated in vacuo. The product was isolated by column chromatography using ethyl acetate: hexane (3:1) as the eluent.

**Compound 3d.** Yield 0.02 g, (15%); mp 183 °C; [α]_{D}^{20} = -64.2º (c 0.3, MeCN); MS (APCI, m/z (rel. %)) 342 (100%) \[M+H\]^{+}; IR: CO 1742, 1710; 1H NMR (DMSO-d_{6}): δ 1.40 (t, 3H, Me of OEt), 3.50-3.55 (m, 1H, H-5'b), 3.57-3.64 (m, 1H, H-5'a), 4.02 (q, 1H, H-4', J=4.2 Hz), 4.22 (q, 1H, H-3', J=4.2 Hz), 4.37-4.50 (m, 4H, OCH_{2} of OEt + H-2' + OH), 4.93 (d, 1H, OH, J=6.0 Hz), 5.28 (d, 1H, OH, J=5.0 Hz), 6.19 (d, 1H, H-1', J=3.5 Hz), 8.17(s, 1H, H-7). Calc. for C_{12}H_{15}N_{5}O_{7}: C, 42.23; H, 4.43; N, 20.52. Found: C, 42.17; H, 5.00; N, 19.98%.

**Compound 3e.** Yield 0.017 g, (12%); mp 108 °C; [α]_{D}^{20} = -42.9º (c 0.3, MeCN); MS (APCI, m/z (rel. %)) 356 (100%) \[M+H\]^{+}; IR: CO 1741, 1707; 1H NMR (DMSO-d_{6}): δ 1.40 (t, 3H, Me of OEt), 2.49 (s, 3H, Me), 3.51-3.55 (m, 1H, H-5'b), 3.60-3.64 (m, 1H, H-5'a), 4.02 (q, 1H, H-4', J=3.7 Hz), 4.25-4.32 (m, 1H, H-3'), 4.37-4.50 (m, 4H, OCH_{2} of OEt + H-2' + OH), 4.93 (d, 1H, OH, J=3.7 Hz), 5.27 (d, 1H, OH, J=5.0 Hz), 6.14 (d, 1H, H-1', J=3.3 Hz). Calc. for C_{13}H_{17}N_{5}O_{7}: C, 43.95; H, 4.82; N, 19.71. Found: C, 43.80; H, 5.01; N, 19.98%.

1-(5'-O-Acetyl-β-D-ribofuranosyl)-3-ethoxycarbonyl-1,2,4-triazolo-4(1H)-one (4). Compound (2e) (0.19 g, 0.4 mmol) was added to a sodium methoxide solution, which was prepared from sodium (0.005 g, 0.022 mmol) and anhydrous ethanol (15 mL). The reaction mixture was kept at r.t. for 0.25 h, cooled, neutralized with acetic acid and concentrated in vacuo. The product was isolated by column chromatography using ethyl acetate: hexane (7:1) as the eluent. Yield: 0.087 g, (55%); mp 92 °C; [α]_{D}^{20} = -31.3º (c 0.5, MeCN); MS (APCI, m/z (rel. %)) 398 (100%) \[M+H\]^{+}; IR: CO 1744, 1732, 1706; 1H NMR (CDCl_{3}): δ 1.41 (t, 3H, Me of OEt), 2.05 (s, 3H, Me of OAc), 2.53 (s, 3H, Me), 3.35 (br. s, 1H, OH), 4.03 (br. s, 1H, OH), 4.27 (d,d, 2H, H-5'b', J=6.5 Hz, J=11.7 Hz), 4.27 (d,d, 2H, H-5'a', J=6.5 Hz, J=11.0 Hz), 4.40-4.46 (m, 3H, CH_{2} of OEt + H-4'), 4.55 (t, 1H, H-3', J=5.0 Hz), 4.78 (d, 1H, H-2', J=4.0 Hz), 6.47 (d, 1H, H-1', J=2.0 Hz). 13C NMR (CDCl_{3}): δ 14.04 (CH_{3} of OEt), 14.53 (Me), 20.65 (Me of Ac), 63.01 (CH_{2} of OEt), 63.95 (C-5'), 71.31 (C-3'), 73.72 (C-2'), 82.84 (C-4'), 95.22 (C-1'), 132.55 (C-3), 145.67 (C-4), 150.90 (C-8a), 160.20 (CO), 164.61 (C-7), 171.10 (CO of Ac). Calc. for C_{13}H_{19}N_{3}O_{5}: C, 45.34; H, 4.82; N, 17.63. Found: C, 45.55; H, 5.03; N, 17.26%.

1-(2',3',4',5'-Tetra-O-acetyl-β-D-glucopyranosyl)-3-phenyl-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones (5a-c). Method A. N,O-Bis-(Trimethylsilyl)acetamide (0.328 ml, 1.34 mmol), trimethylsilyl triflate (TMSOTf) (0.32 ml, 1.8 mmol) and β-D-glucose penta-acetate (0.39 g, 1.00 mmol) were added to a solution of compound (1a-c) (0.94 mmol) in 7 mL acetonitrile. The reaction mixture was left at r.t. for 2.5 h, diluted with 10 mL acetonitrile with a few drops water, and neutralized (NaHCO_{3}). The resulting suspension was filtered, the filtrate concentrated in

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vacuo, and the product isolated by column chromatography using ethyl acetate: hexane (3:1) as the eluent.

**Method B.** Compound (1a-c) (0.94 mmol) was suspended in a 17% sodium carbonate solution (3 mL). The precipitate was filtered off and dried. The resulting solid was dissolved in DMF (5 mL), acetobromo-α-D-glucose (0.390 g, 0.95 mmol) was added, and the mixture was heated on a water bath for 3 h. Then the reaction mixture was concentrated in vacuo. The product was isolated by column chromatography using ethyl acetate: hexane (3:1) as eluent.

**Compound 5a.** Yield of (A) 0.23 g, (45%); of B 0.15g, (30%); mp 184 °C; [α]20D -37.4º (c 0.3, MeCN); MS (APCI, m/z (rel. %)) 544 (100%) [M+H]+; IR: CO 1749, 1724; 1H NMR (DMSO-d6): δ 1.97 (s, 3H, Me of 2'-Ac), 2.00 (s, 3H, Me of 6'-Ac), 2.01 (s, 3H, Me of 3'-Ac), 2.03 (s, 3H, Me of 4'-Ac), 4.04 (dd, 1H, H-6'b, J=2 Hz, J=12 Hz), 4.19 (dd, 1H, H-6'a, J=5.0 Hz, J=12.5 Hz), 4.47 (m, 1H, H-5'), 5.08 (t, 1H, H-3', J=10.0 Hz), 5.69 (t, 1H, H-3', J=9.5 Hz), 5.89 (t, 1H, H-2', J=9.5 Hz), 6.50 (d, 1H, H-1'), 7.53 (m, 3H, m-, p-Ph), 8.01 (m, 2H, o-Ph), 8.45 (s, 1H, H-7). 13C NMR (DMSO-d6): 20.08 (Me of Ac), 20.15 (Me of Ac + Me of Ac), 20.25 (Me of Ac), 61.43 (C-6'), 67.44 (C-2' + C-4'), 72.60 (C-3'), 72.94 (C-5'), 85.00 (C-1'), 128.00 (Cm), 128.80 (Co), 129.90 (Cp), 131.69 (Ci), 141.50 (C-3), 151.10 (C-8a), 152.85 (C-7), 168.64 (CO of 2'-Ac), 169.06 (CO of 4'-Ac), 169.34 (CO of 3'-Ac), 169.91 (CO of 6'-Ac). Calc. for C24H25N5O10·H2O: C, 52.84; H, 4.99; N, 12.84. Found: C, 52.41; H, 4.62; N, 11.99%.

**Compound 5b.** Yield of (A) 0.25 g, (48%); of B 0.17 g, (33%). mp 243 °C; [α]20D -35.5º (c 0.3, MeCN); MS (APCI, m/z (rel. %)) 558 (100%) [M+H]+; IR: CO 1746, 1735; 1H NMR (DMSO-d6): δ 1.85 (s, 3H, Me of 2'-Ac), 1.95 (s, 3H, Me of 6'-Ac), 1.97 (s, 3H, Me of 3'-Ac), 2.02 (s, 3H, Me of 4'-Ac), 2.47 (s, 3H, Me), 4.02 (d,x m, 1H, H-6'b, J=12.0 Hz), 4.20 (d,d, 1H, H-6'a, J=4.5 Hz, J=12.7 Hz), 4.48 (m, 1H, H-5'), 5.07 (t, 1H, H-4', J=9.5 Hz), 5.68 (t, 1H, H-3', J=10.0 Hz), 5.87 (t, 1H, H-2', J=9.5 Hz), 6.53 (d, 1H, H-1', J=9.0 Hz), 7.53 (m, 3H, m-, p-Ph), 7.99 (m, 2H, o-Ph). 13C NMR (DMSO-d6): δ 14.18 (Me), 20.21 (Me of Ac), 20.30 (Me of Ac + Me of Ac), 20.39 (Me of Ac), 61.39 (C-6'), 67.39 (C-2' + C-4'), 72.61 (C-3'), 72.94 (C-5'), 84.72 (C-1'), 128.10 (Cm), 128.89 (Co), 139.98 (Cp), 131.88 (Ci), 148.70 (C-3), 148.24 (C-4), 151.28 (C-8a), 162.51 (C-7), 168.79 (CO of 2'-Ac), 169.19 (CO of 4'-Ac), 169.45 (CO of 3'-Ac), 169.88 (CO of 6'-Ac). Calc. for C25H27N5O10: C, 53.86; H, 4.88; N, 12.56. Found: C, 53.81; H, 4.50; N, 12.43%.

**Compound 5c.** Yield of (A) 0.28 g, (50%); of B 0.22 g, (40%); mp 224 °C; [α]20D -25.9º (c 0.5, MeCN); MS (APCI, m/z (rel. %)) 590 (100%) [M+H]+; IR: CO 1750, 1720; 1H NMR (DMSO-d6): δ 1.96 (s, 3H, Me of 2'-Ac), 1.97 (s, 3H, Me of 6'-Ac), 2.01 (s, 3H, Me of 3'-Ac), 2.02 (s, 3H, Me of 4'-Ac), 2.68 (s, 3H, SMe), 4.02 (d,x m, 1H, H-6'b, J=12 Hz), 4.16 (dd, 1H, H-6'a, J=4.5 Hz, J=12 Hz), 4.46 (m, 1H, H-5'), 5.07 (t, 1H, H-4', J=9.5 Hz), 5.67 (t, 1H, H-3', J=9.5 Hz), 5.85 (t, 1H, H-2', J=9.0 Hz), 6.50 (d, 1H, H-1', J=9.5 Hz), 7.52 (m, 3H, m-, p-Ph), 7.99 (m, 2H, o-Ph). 13C NMR (DMSO-d6): δ 13.51 (SMe), 20.21 (Me of Ac), 20.32 (Me of Ac + Me of Ac), 20.40 (Me of Ac), 61.48 (C-6'), 67.39 (C-2' + C-4'), 72.60 (C-3'), 72.96 (C-5'), 84.70 (C-1'), 128.14 (Cm), 128.80 (Co), 130.12 (Cp), 131.79 (Ci), 141.24 (C-3), 147.45 (C-4), 151.70 (C-8a), 165.35 (C-7), 168.84 (CO of 2'-Ac), 169.22
(CO of 4'-Ac), 169.50 (CO of 3'-Ac), 169.91 (CO of 6'-Ac). Calc. for C_{25}H_{27}N_{5}O_{10}S: C, 50.93; H, 4.62; N, 11.67%.

1-(β-D-Glucopyranosyl)-3-phenyl-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones (6a-c). Compound (5a-c) (0.4 mmol) was added to a sodium methoxide solution, prepared from sodium (0.03 g, 1.30 mmol) and methanol (5 ml). The reaction mixture was heated at reflux for 0.5 h, cooled, neutralized with acetic acid and concentrated in vacuo. The product was isolated by column chromatography using ethyl acetate as the eluent.

**Compound 6a.** Yield 0.076 g, (48%); mp 211 °C; [α]^{20}_D 2.9º (c 0.3, MeCN); MS (APCI, m/z (rel. %)) 376 (100%) [M+H]^+. IR: CO, 1717 cm\(^{-1}\). \(^1\)H NMR (DMSO-d\(_6\)): δ 3.25-3.34 (m, 1H, H-6'\(^b\)), 3.34-3.57 (m, 3H, H-6'\(^a\) + H-5' + H-4'), 3.69-3.76 (m, 1H, H-3'), 4.07 (m, 1H, H-2'), 4.39 (t, 1H, OH, J=5.7 Hz), 5.03 (d, 1H, OH, J=5.2 Hz), 5.15 (d, 1H, OH, J=4.7 Hz), 5.25 (d, 1H, OH, J=4.5 Hz), 5.70 (d, 1H, H-1', J=8.3 Hz), 7.50 (m, 3H, m-, p-Ph), 8.03 (m, 2H, o-Ph), 8.30 (s, 1H, H-7). Calc. for C\(_{16}\)H\(_{17}\)N\(_5\)O\(_6\)·H\(_2\)O: C, 48.86; H, 4.87; N, 17.80. Found: C, 48.24; H, 4.84; N, 17.28%.

**Compound 6b.** Yield 0.099 g, (64%); mp 237 °C; [α]^{20}_D 30.5º (c 0.5, DMSO); MS (APCI, m/z (rel. %)) 390 (100%) [M+H]^+. IR: CO 1717 cm\(^{-1}\). \(^1\)H NMR (DMSO-d\(_6\)): δ 2.48 (s, 3H, Me), 3.23-3.36 (m, 1H, H-6'\(^b\)), 3.40-3.54 (m, 3H, H-6'\(^a\) + H-5' + H-4'), 3.69-3.73 (m, 1H, H-3'), 4.05 (m, 1H, H-2'), 4.27 (t, 1H, OH, J=5.0 Hz), 4.92 (br. s, 1H, OH), 5.02 (br. s, 1H, OH), 5.18 (br. s, 1H, OH), 5.67 (d, 1H, H-1', J=8.7 Hz), 7.48 (m, 3H, m-, p-Ph), 8.04 (m, 2H, o-Ph). Calc. for C\(_{17}\)H\(_{19}\)N\(_5\)O\(_6\): C, 52.44; H, 4.92; N, 17.99. Found: C, 52.19; H, 4.91; N, 18.04%.

**Compound 6c.** Yield 0.053 g, (30%); mp 258 °C; [α]^{20}_D 3.5º (c 0.1, MeCN); MS (APCI, m/z (rel. %)) 422 (100%) [M+H]^+, 423 (26.6%) [M+1+H]^+, 424 (10.5%) [M+2+H]^+. IR: CO 1718; \(^1\)H NMR (DMSO-d\(_6\)): δ 2.68 (s, 3H, SMe), 3.22-3.34 (m, 1H, H-6'\(^b\)), 3.39-3.52 (m, 3H, H-6'\(^a\) + H-5' + H-4'), 3.69-3.73 (m, 1H, H-3'), 4.07 (m, 1H, H-2'), 4.25 (t, 1H, OH, J=5.2 Hz), 4.92 (d, 1H, OH, J=5.0 Hz), 5.02 (d, 1H, OH, J=5.2 Hz), 5.18 (d, 1H, OH, J=4.7 Hz), 5.70 (d, 1H, H-1', J=9.0 Hz), 7.50 (m, 3H, m-, p-Ph), 8.03 (m, 2H, o-Ph). Calc. for C\(_{17}\)H\(_{19}\)N\(_5\)O\(_6\)S·H\(_2\)O: C, 46.46; H, 4.82; N, 15.94. Found: C, 46.70; H, 4.79; N, 15.20%.

**X-Ray data collection and structure refinement.** Data collection for compound 2e (crystallized from 2-propanol) was carried out using a Bruker SMART 1000 CCD diffractometer using graphite- monochromated Mo-K\(\alpha\) (\(\lambda = 0.71073\) Å). X-ray data of blocked nucleoside 5c (crystallized from acetic acid) were collected on CAD4 Enraf-Nonius graphite-monochromated Mo-K\(\alpha\) (\(\lambda = 0.71073\) Å). All calculations were carried out using the SHELXTL program package. A summary of the fundamental crystal and refinement date is given in Table 1. Crystallographic data for 2e and 5b have been deposited at Cambridge Crystallographic Date Centre. The CCDC numbers are listed in Table 1. Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK: FAX: +44 (1223) 336033, e-mail: deposit@ccdc.cam.ac.uk.
Table 1. Crystal date and structure refinement for compounds 2e and 5c

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Acknowledgements

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References