



# Novel stereoselective synthesis of 1-( $\beta$ -D- and $\alpha$ -L-glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles

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**Abstract**—1-( $\beta$ -D- and  $\alpha$ -L-Glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles **7**, **13–15** were synthesized stereoselectively from the corresponding glycopyranosyl aminoguanidine nitrates **1–3** in boiling acetic anhydride or from *N*<sup>1</sup>-(acetylated  $\beta$ -D- or  $\alpha$ -L-glycopyranosylamino)-*N*<sup>2</sup>,*N*<sup>3</sup>-triacetylguanidines **8–10** using catalytic amounts of NaOMe. Structures were confirmed by elemental analyses, IR, NMR and MS and possible mechanisms are discussed. In vitro antitumor and immuno activities are presented.

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## 1. Introduction

1- $\beta$ -D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide (Virazole, Ribavirin<sup>®</sup>), a broad spectrum antiviral agent, also inhibits replication of HIV in human T lymphocytes and displays some antitumor activity in mice.<sup>1–8</sup> Thus synthetic approaches to this molecule and its derivatives have attracted considerable attention.<sup>9–16</sup> Herein we report facile, novel procedures for the stereoselective synthesis of 1-( $\beta$ -D- and  $\alpha$ -L-glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles, which are closely related to 1- $\beta$ -D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and presented preliminary in vitro antitumor and immuno activities.

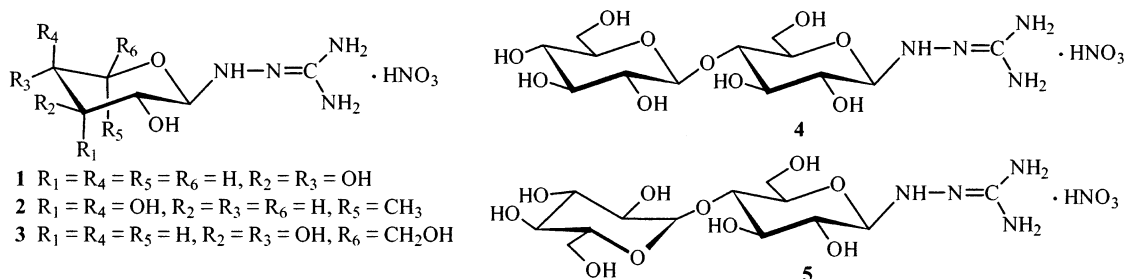
## 2. Results and discussion

We are seeking efficient, stereospecific strategies for successful construction of bioactive heterocycles linked

to carbohydrates.<sup>17–19</sup> In previous studies, methods for the synthesis of 1- $\beta$ -D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and its derivatives required preparation of activated glycosylating agents and 1,2,4-triazole derivatives, which were difficult and time-consuming. We noted that aromatic carboximide-amide-hydrazones treated with hot acetic anhydride or benzoyl chloride would afford 1,4-diacyl-3-acylamino-5-aryl-4,5-dihydro-1*H*-1,2,4-triazoles.<sup>20–22</sup> By analysis of the reaction characteristics and comparison of the structures of aromatic carboximide-amide-hydrazones with  $\beta$ -D-glucopyranosyl aminoguanidines,<sup>23</sup> we propose a novel procedure from  $\beta$ -D- and  $\alpha$ -L-glycopyranosyl aminoguanidines and have successfully obtained a series of 1-( $\beta$ -D- and  $\alpha$ -L-glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles.

The condensation products of saccharine with amino compounds are generally discussed in terms of acyclic and cyclic forms, which are often present as equilibrium mixtures in solution and, due to the presence of basic nitrogen atom(s), a strong influence of pH on this equilibrium would be anticipated. Feather and Szilagyi et al.<sup>23,24</sup> demonstrated that the structures of the condensation products from D-glucose, L-arabinose, D-galactose and D-mannose with aminoguanidine are pH-dependent. At pH 6, the condensation products existed exclusively in the  $\beta$ -D- or  $\alpha$ -L-glycopyranosyl

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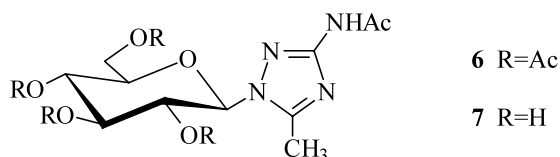


Scheme 1.

aminoguanidine forms, and at pH >12 only the acyclic *E*-carboximidamidehydrazone forms were present. Based on their results, we prepared and obtained, in good yields, glycopyranosyl aminoguanidine nitrates **1–5** (Scheme 1) by reaction of aminoguanidine nitrate with D-xylose, L-rhamnose, D-glucose, D-cellobiose and D-lactose in water solution (pH 6) at room temperature (Scheme 1).

For structural analyses of the condensation products of saccharides with amino compounds such as aldose oximes, hydrazones and carboximidamidehydrazones, a series of reports<sup>25–36</sup> confirmed that the <sup>1</sup>H and <sup>13</sup>C NMR data reflects the structures. Thus, for aldose oximes and hydrazones and substituted hydrazones, the <sup>1</sup>H NMR signal of the azomethine (C<sub>1</sub>H=N) proton is at ~7.4 ppm in the *E*-isomers and at 6.7–6.9 ppm in the *Z*-forms; The <sup>13</sup>C NMR signal of the *sp*<sup>2</sup>-hybridised C-1' of aldose oximes occurs at 151–153 ppm for *E*-isomers and at 153–155 ppm for *Z*-isomers, and the *J*<sub>C-1',H-1'</sub> values of ~163 and ~175 Hz for the *E*- and *Z*-oximes, respectively. The signals for C-1' of aldose hydrazones and substituted hydrazones are in the range 140–150 ppm with insignificant differences between *E*- and *Z*-isomers. The cyclic pyranose ring forms are readily identified by the signals at 3.5–5.0 ppm for H-1' and characteristic resonances in the range 80–95 ppm for anomeric carbons as well as the *J*<sub>C-1',H-1'</sub> values of 155–158 Hz. The <sup>1</sup>H and <sup>13</sup>C NMR data clearly indicate the exclusive presence of **1** and **3–5** are in the β-D-pyranose ring forms, and **2** is in the α-L-pyranose ring form. Elemental analyses and the IR, FABMS and ESIMS data of **1–5** produced additional evidence for the structures shown in Scheme 1. From the chemical shifts of the signals for H-1' and the *J*<sub>1',2'</sub> (*J* = ~8 Hz) and *J*<sub>2',3'</sub> (*J* = 5–9 Hz) values, we could also determine that the pyranose ring forms of **1–5** are all in a <sup>4</sup>C<sub>1</sub> configuration.

Treatment of **3** with boiling acetic anhydride yielded 1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-acetamido-5-methyl-1*H*-1,2,4-triazole **6** and action of catalytic amounts of NaOMe gave 1-(β-D-glucopyranosyl)-3-acetamido-5-methyl-1*H*-1,2,4-triazole **7** (Scheme 2). Structures were confirmed by elemental analyses, IR, MS and <sup>1</sup>H, <sup>13</sup>C NMR spectral data. The 3-acetamido group remained even after the action of NaOMe, probably due to the conjugation of acetyl group with 1,2,4-triazole ring. The yield of **7** was only 20%,



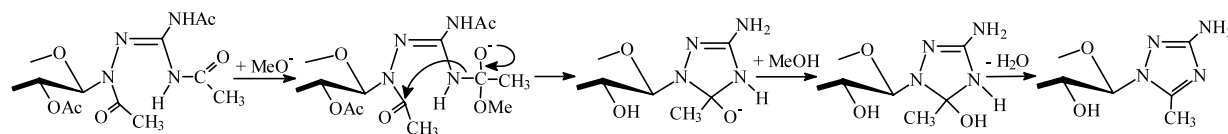
Scheme 2.

prompting us to think of alternative synthetic procedures to obtain higher yields of 1-(β-D- or α-L-glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles.

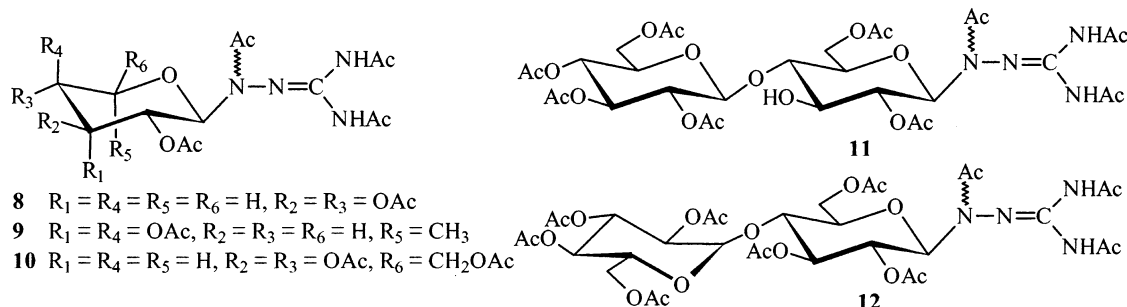
By comparing and analysing the structures of **6** with *N*<sup>1</sup>-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosylamino)-*N*<sup>1</sup>,*N*<sup>2</sup>,*N*<sup>3</sup>-triacetylguanidine **10**,<sup>23</sup> we deduced that the formation of 5-methyl-1*H*-1,2,4-triazole might be possible from **10** basing action of the strong base NaOMe through the following mechanism (Scheme 3).

We also considered the synthesis of *N*<sup>1</sup>-(acetylated β-D- or α-L-glycopyranosylamino)-*N*<sup>1</sup>,*N*<sup>2</sup>,*N*<sup>3</sup>-triacetylguanidines. Feather et al.<sup>23</sup> acetylated **3** in the usual way with 1:1 pyridine–Ac<sub>2</sub>O at room temperature affording crystalline heptaacetate **10** in 43% yield. Acetylation of **1–3** in cold pyridine and triethylamine with acetic anhydride<sup>19</sup> gave acetylated derivatives **8–10** (Scheme 4) in higher yields (60–80%), which were homogeneous by TLC and had sharp melting points. However, the <sup>1</sup>H, <sup>13</sup>C NMR spectra (CDCl<sub>3</sub>, ~25°C) of **8–10** indicated the presence of two different forms in solution in a ratio of ca. 1:0.6–0.7 (by integration of the <sup>1</sup>H NMR signals). This is due to the increasing steric hindrance of glycopyranosyl and guanyl groups after acetylation restricting the spin of C<sub>1</sub>–N<sub>1</sub> bonds and resulting in the two forms differing mainly in the orientations of the acetylated guanyl groups relative to the pyranose rings. When the <sup>1</sup>H NMR spectra were re-run at the higher temperature of 60°C, the effect disappeared, providing a single set of <sup>1</sup>H NMR signals, which represented the average of the two sets of signals observed in the 25°C spectra. These results are consistent with those of Feather et al.<sup>23</sup>

Acetylation of **4** and **5** through the usual way with 1:1 pyridine–Ac<sub>2</sub>O or cold pyridine–triethylamine–acetic anhydride system failed to provide the desired derivatives **11** and **12**. The elemental analyses, IR, ESIMS and <sup>1</sup>H and <sup>13</sup>C NMR spectral data of the derivatives of **4** and **5** after acetylation are all in good agreement



Scheme 3.



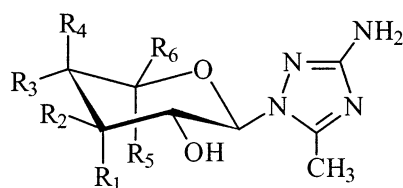
Scheme 4.

with the structures of 4-*O*-(2',3',4',6'-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl)-1,2,3,6-tetra-*O*-acetyl- $\alpha,\beta$ -D-glucopyranose (acetylated D-cellobiose) and 4-*O*-(2',3',4',6'-tetra-*O*-acetyl- $\beta$ -D-galacopyranosyl)-1,2,3,6-tetra-*O*-acetyl- $\alpha,\beta$ -D-glucopyranose (acetylated D-lactose), indicating that **4** and **5** lose the aminoguanidine groups in the presence of acetic anhydride and pyridine and/or triethylamine. We believe this phenomenon has not been reported previously.

Treatment of **8–10** with catalytic amounts of NaOMe yielded 1-( $\beta$ -D- or  $\alpha$ -L-glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles **13–15** as expected in good yields (60–

75%). The structures were characterized by elemental analyses, IR, MS and  $^1H$ ,  $^{13}C$  NMR spectral data. Thus, we successfully obtained 1-( $\beta$ -D- or  $\alpha$ -L-glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles **13–15** (Scheme 5) from glycopyranosyl aminoguanidine nitrates **1–3** through their acetylated derivatives **7–9** in two steps, but with higher overall yields.

The in vitro antitumor and immuno activities of the resulting 1-( $\beta$ -D- or  $\alpha$ -L-glycopyranosyl)-5-methyl-1*H*-1,2,4-triazoles **7**, **13–15** against HL-60, BGC-823, Bel-7402, 293, KB, Hela and T-, B-lymphocytes were evaluated. The results are listed in Table 1.



**13**  $R_1 = R_4 = R_5 = R_6 = H, R_2 = R_3 = OH$

**14**  $R_1 = R_4 = OH, R_2 = R_3 = R_6 = H, R_5 = CH_3$

**15**  $R_1 = R_4 = R_5 = H, R_2 = R_3 = OH, R_6 = CH_2OH$

Scheme 5.

Table 1. Inhibition ratio (%) of **7**, **13–15** on tumor cells and B-, T-lymphocytes

Compd	<b>7</b>			<b>13</b>			<b>14</b>			<b>15</b>		
	0.1	1	10	0.1	1	10	0.1	1	10	0.1	1	10
<b>A</b> <sup>a</sup>	20.02	25.86	1.28	10.33	23.47	15.94	5.51	1.81	−2.09	1.05	4.25	6.41
<b>B</b> <sup>b</sup>	−48.98	−20.68	10.11	−35.85	−10.26	14.91	19.62	−4.83	11.92	−5.36	15.62	10.72
<b>C</b> <sup>b</sup>	20.92	12.33	9.10	17.60	9.51	5.93	25.93	16.16	14.78	27.37	20.77	13.25
<b>D</b> <sup>b</sup>	22.63	31.97	30.82	30.32	26.08	23.35	−25.96	3.94	−4.69	−18.93	18.56	6.94
<b>E</b> <sup>b</sup>	0.28	2.29	0.49	−1.06	2.75	0.56	−0.67	1.94	1.48	−0.60	1.34	0.78
<b>F</b> <sup>b</sup>	−31.66	−22.04	−5.86	38.01	40.67	17.68	35.98	42.28	45.09	7.53	−30.26	−8.51
<b>G</b> <sup>a</sup>	−18.84	−18.72	3.64	−25.15	−24.75	−4.77	−13.57	0.38	6.26	−14.82	−4.90	1.63
<b>H</b> <sup>a</sup>	−14.11	−9.38	−16.15	−32.55	−9.61	−11.27	−10.95	4.49	−20.41	−9.46	−7.17	−31.21

**A:** HL-60, **B:** BGC-823, **C:** Bel-7402, **D:** 293, **E:** KB, **F:** Hela, **G:** B-, **H:** T-.

<sup>a</sup> Detected by the standard MTT method.

<sup>b</sup> Detected by the standard SRB method.

### 3. Experimental

#### 3.1. General methods

Melting points were determined using an X<sub>4</sub> micromelting apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer model 241MC polarimeter. Mass spectra were obtained on either ZAB-HS or HP 1100-MSD mass spectrometers. IR spectra were recorded with a Biorad FT-40 spectrophotometer, using KBr pellets for the crystalline samples and films for the syrup samples. All NMR spectra were recorded on a Varian Unity Plus 300 spectrometer (299.95 MHz for <sup>1</sup>H, 75.43 MHz for <sup>13</sup>C), from DMSO-*d*<sub>6</sub> solution with the solvent multiplet as an internal standard related to Me<sub>4</sub>Si with  $\delta$  2.49 ppm (<sup>1</sup>H) and  $\delta$  39.5 ppm (<sup>13</sup>C). Column chromatography was performed on silica gel (200–300 mesh) and silica gel GF<sub>254</sub> (the Qingdao Chemical Company (China)) was used for TLC and detection was effected by spraying the plates with 5% ethanolic H<sub>2</sub>SO<sub>4</sub> (followed by heating at 110°C for 10 min) or by direct UV irradiation of the plate.

#### 3.2. Glycopyranosyl aminoguanidine nitrates 1–5

A solution of D-xylose, L-rhamnose, D-glucose, D-maltose, D-cellobiose or D-lactose (20 mmol) with aminoguanidine nitrate (20 mmol) in distilled water (pH 6) was stirred at room temperature until TLC (solvent: pyridine–AcOH–H<sub>2</sub>O 9:1:0.75) showed that the reaction was complete. The water was mostly evaporated off and the solution titrated with 95% EtOH to turbidity and cooled to obtain the pure crystalline glycopyranosyl aminoguanidine nitrates 1–5.

**3.2.1.  $\beta$ -D-Xylopyranosyl aminoguanidine nitrate 1.** Yield 90%, mp 78–79°C,  $[\alpha]_D^{22} = -8$  (*c* 1.1, H<sub>2</sub>O),  $\nu_{\max}$ : 3489.0 (s, OH), 3222.7 (s, NH), 1697.3, 1670.1 (s, C=N), 908.8 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 8.82 (1H, s, NH-2), 7.44, 6.84 (2H, br, NH<sub>2</sub>-4), 5.91 (1H, d, *J* = 8.4 Hz, NH-1), 3.72 (1H, d, *J*<sub>1',2'</sub> = 7.8 Hz, H-1'), 2.96 (1H, dd, *J*<sub>2',3'</sub> = 8.7 Hz, H-2'), 3.15 (1H, ddd, *J*<sub>3',4'</sub> = 8.4 Hz, H-3'), 3.01 (1H, dd, *J*<sub>4',5a'</sub> = 6.9 Hz, *J*<sub>4',5b'</sub> = 3.3 Hz, H-4'), 3.67 (1H, dd, *J*<sub>5a',5b'</sub> = 6.4 Hz, H-5a'), 3.32 (1H, dd, H-5b'), 4.93 (3H, d, <sup>3</sup>*J* = 1.5 Hz, HO-2',3',4') ppm;  $\delta_C$ : 158.58 (Guanyl C), 91.22 (C-1', *J* = 156.1 Hz), 70.92 (C-2'), 76.97 (C-3'), 69.44 (C-4'), 66.84 (C-5') ppm; FABMS (%): *m/z* 207 [M+1] (62), 189 (58), 149 (10), 93 (100), 75 (36), 57 (26), 43 (22). Anal. calcd for C<sub>6</sub>H<sub>15</sub>N<sub>5</sub>O<sub>7</sub> (%): C, 26.77, H, 5.62, N, 26.01; Found: C, 26.81, H, 5.73, N, 25.96.

**3.2.2.  $\alpha$ -L-Rhamnopyranosyl aminoguanidine nitrate 2.** Yield 94%, mp 72–73°C,  $[\alpha]_D^{22} = +6$  (*c* 1.1, H<sub>2</sub>O),  $\nu_{\max}$ : 3477.4 (s, OH), 3252.9 (s, NH), 1681.5 (s, C=N), 910.3 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 8.53 (1H, s, NH-2), 6.97 (2H, br, NH<sub>2</sub>-4), 6.07 (1H, d, *J* = 3.9 Hz, NH-1), 3.62 (1H, d, *J*<sub>1',2'</sub> = 9.3 Hz, H-1'), 3.14 (1H, dd, *J*<sub>2',3'</sub> = 9.0 Hz, H-2'), 3.50 (1H, d, *J*<sub>3',4'</sub> = 9.3 Hz, H-3'), 3.45 (1H, dd, *J*<sub>4',5'</sub> = 1.9 Hz, H-4'), 3.59 (1H, dd, *J*<sub>5',6'</sub> = 2.7 Hz, H-5'), 1.10 (3H, d, *J*<sub>6a',6b'</sub> = 6.3 Hz, H-6'), 4.56 (1H, d,

<sup>3</sup>*J* = 5.4 Hz, HO-2'), 4.80 (1H, d, <sup>3</sup>*J* = 6.0 Hz, HO-3'), 4.33 (1H, d, <sup>3</sup>*J* = 3.1 Hz, HO-4') ppm;  $\delta_C$ : 158.79 (Guanyl C), 94.00 (C-1', *J* = 155.8 Hz), 70.46 (C-2'), 71.55 (C-3'), 72.45 (C-4'), 67.69 (C-5'), 18.02 (C-6') ppm; FABMS (%): *m/z* 221 [M+1] (15), 154 (80), 149 (100), 138 (22), 137 (50), 136 (70), 107 (30), 89 (41), 75 (98), 57 (78). Anal. calcd for C<sub>7</sub>H<sub>17</sub>N<sub>5</sub>O<sub>7</sub> (%): C, 29.67, H, 6.05, N, 24.73; Found: C, 29.78, H, 6.02, N, 24.86.

**3.2.3.  $\beta$ -D-Glucopyranosyl aminoguanidine nitrate 3.** Yield 88%, mp 136–137°C,  $[\alpha]_D^{22} = -13$  (*c* 1.1, H<sub>2</sub>O),  $\nu_{\max}$ : 3446.5 (s, OH), 3243.6 (s, NH), 1670.8 (s, C=N), 912.2 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 8.72 (1H, s, NH-2), 7.45, 6.86 (2H, br, NH<sub>2</sub>-4), 5.94 (1H, d, *J* = 8.9 Hz, NH-1), 3.81 (1H, d, *J*<sub>1',2'</sub> = 8.8 Hz, H-1'), 3.17 (1H, dd, *J*<sub>2',3'</sub> = 8.6 Hz, H-2'), 3.38 (1H, dd, *J*<sub>3',4'</sub> = 8.7 Hz, H-3'), 3.22 (1H, m, H-4'), 3.31 (1H, dd, *J*<sub>5',6a'</sub> = 9.0 Hz, *J*<sub>5',6b'</sub> = 2.4 Hz, H-5'), 3.74 (1H, dd, *J*<sub>6a',6b'</sub> = 6.0 Hz, H-6a'), 3.53 (1H, dd, H-6b'), 4.77 (1H, d, <sup>3</sup>*J* = 3.6 Hz, HO-2'), 4.97 (1H, d, <sup>3</sup>*J* = 5.0 Hz, HO-3'), 4.40 (1H, d, <sup>3</sup>*J* = 4.8 Hz, HO-4'), 4.27 (1H, d, <sup>3</sup>*J* = 5.1 Hz, HO-6') ppm;  $\delta_C$ : 158.54 (Guanyl C), 90.97 (C-1', *J* = 155.2 Hz), 69.00 (C-2'), 73.71 (C-3'), 68.80 (C-4'), 76.27 (C-5'), 60.65 (C-6') ppm; FABMS (%): *m/z* 237 [M+1] (54), 185 (86), 149 (10), 93 (100), 75 (61), 57 (48). Anal. calcd for C<sub>7</sub>H<sub>17</sub>N<sub>5</sub>O<sub>8</sub> (%): C, 28.09, H, 5.73, N, 23.40; Found: C, 28.16, H, 5.82, N, 23.33.

**3.2.4.  $\beta$ -D-Cellobiosyl aminoguanidine nitrate 4.** Yield 83%, mp 147–148°C,  $[\alpha]_D^{22} = -24$  (*c* 1.1, H<sub>2</sub>O),  $\nu_{\max}$ : 3427.2 (s, OH), 3365.5 (s, NH), 1679.9 (m, C=N), 908.5 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 8.59 (1H, s, NH-2), 7.28, 6.77 (2H, br, NH<sub>2</sub>-4), 6.70 (1H, d, *J* = 6.0 Hz, NH-1), 4.33 (1H, d, *J*<sub>1',2'</sub> = 7.5 Hz, H-1'), 2.96 (1H, dd, *J*<sub>2',3'</sub> = 5.5 Hz, H-2'), 3.72–3.15 (5H, m, H-3',4',5',6'), 4.25 (1H, d, *J*<sub>1'',2''</sub> = 8.0 Hz, H-1''), 3.72–3.15 (5H, m, H-3'',4'',5'',6''), 5.26–4.60 (7H, m, HO-2',3',6',2'',3'',4'',6'') ppm;  $\delta_C$ : 158.82 (Guanyl C), 96.68 (C-1', *J* = 156.5 Hz), 73.37 (C-2'), 74.78 (C-3'), 76.52 (C-4'), 80.79 (C-5'), 61.08 (C-6'), 103.22 (C-1''), 70.09 (C-2''), 74.54 (C-3''), 75.10 (C-4''), 76.82 (C-5''), 60.58 (C-6'') ppm; ESIMS (%): *m/z* 421 [M+Na] (42), 399 [M+1] (44), 381 (14), 345 (18), 305 (25), 237 (22), 219 (13), 97 (17), 75 (70), 57 (100). Anal. calcd for C<sub>13</sub>H<sub>27</sub>N<sub>5</sub>O<sub>13</sub> (%): C, 33.83, H, 5.90, N, 15.18; Found: C, 33.80, H, 5.83, N, 15.16.

**3.2.5.  $\beta$ -D-Lactosyl aminoguanidine nitrate 5.** Yield 91%, mp 139–140°C,  $[\alpha]_D^{22} = -19$  (*c* 1.1, H<sub>2</sub>O),  $\nu_{\max}$ : 3336.2 (s, OH), 3272.9 (s, NH), 1680.6 (s, C=N), 911.6 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 8.60 (1H, s, NH-2), 7.28, 6.77 (2H, br, NH<sub>2</sub>-4), 6.36 (1H, d, *J* = 4.5 Hz, NH-1), 4.91 (1H, d, *J*<sub>1',2'</sub> = 7.8 Hz, H-1'), 3.14 (1H, dd, *J*<sub>2',3'</sub> = 6.5 Hz, H-2'), 3.74–2.94 (5H, m, H-3',4',5',6'), 4.17 (1H, d, *J*<sub>1'',2''</sub> = 4.5 Hz, H-1''), 3.74–2.94 (5H, m, H-3'',4'',5'',6''), 5.13–4.50 (7H, m, HO-2',3',6',2'',3'',4'',6'') ppm;  $\delta_C$ : 158.80 (Guanyl C), 92.07 (C-1', *J* = 156.7 Hz), 69.82 (C-2'), 71.38 (C-3'), 73.24 (C-4'), 81.34 (C-5'), 60.58 (C-6'), 103.88 (C-1''), 68.18 (C-2''), 70.64 (C-3''), 72.17 (C-4''), 75.51 (C-5''), 60.43 (C-6'') ppm; ESIMS (%): *m/z* 421 [M+Na] (52), 399 [M+1] (48),

381 (16), 345 (10), 305 (35), 237 (12), 219 (19), 97 (27), 75 (76), 57 (100). Anal. calcd for  $C_{13}H_{27}N_5O_{13}$  (%): C, 33.83, H, 5.90, N, 15.18; Found: C, 33.86, H, 5.93, N, 15.22.

### 3.3. 1-(2',3',4',6'-Tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl)-3-acetamido-5-methyl-1*H*-1,2,4-triazole **6**

A mixture of  $\beta$ -D-glucopyranosyl aminoguanidine nitrate **3** (3.0 g, 10 mmol) and anhydrous NaOAc (2.8 g) in distilled  $Ac_2O$  (15 mL) was refluxed for ~20 min. The reaction mixture was cooled, poured onto ice-water, extracted with  $CH_2Cl_2$  (3×40 mL), washed with cold saturated aqueous  $NaHCO_3$  and water, dried ( $Na_2SO_4$ ), and evaporated under reduced pressure. The residue was crystallized from EtOH– $H_2O$  to give 1-(2',3',4',6'-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl)-3-acetamido-5-methyl-1*H*-1,2,4-triazole **6** (0.97 g, 20%), mp 93–94°C,  $[\alpha]_D^{25} = -13$  (c 1.0,  $CH_2Cl_2$ ),  $\nu_{max}$ : 3325.6 (m, NH), 1750.2 (vs, C=O), 1699.4, 1675.2, 1640.8 (s, C=N), 916.3 (m,  $C_1$ -H)  $cm^{-1}$ ;  $\delta_H$ : 10.25 (1H, br, NH-3), 6.07 (1H, d,  $J_{1,2'} = 9.1$  Hz, H-1'), 5.49 (1H, dd,  $J_{2,3'} = 9.5$  Hz, H-2'), 5.43 (1H, dd,  $J_{3,4'} = 9.5$  Hz, H-3'), 5.08 (1H, dd,  $J_{4,5'} = 9.4$  Hz, H-4'), 4.31 (1H, m, H-5'), 4.20 (1H, dd,  $J_{5,6a'} = 1.9$  Hz,  $J_{6a',6b'} = 12.0$  Hz, H-6a'), 4.08 (1H, dd,  $J_{5,6b'} = 4.7$  Hz, H-6b'), 2.44 (3H, s,  $CH_3$ -5), 2.03, 2.01, 2.00, 1.97, 1.91 (15H, 5s, 5× $CH_3CO$ ) ppm;  $\delta_C$ : 171.26, 170.79, 170.56, 169.97, 168.78 (5× $CH_3CO$ ), 155.56 (C-3), 153.84 (C-5), 81.68 (C-1'), 72.68 (C-2'), 69.55 (C-3'), 67.91 (C-4'), 73.14 (C-5'), 61.58 (C-6'), 23.20, 20.54, 20.28, 20.23, 20.18 (5× $CH_3CO$ ), 11.48 ( $CH_3$ -5) ppm; FABMS (%):  $m/z$  453 [M+1] (45), 475 [M+Na] (85), 491 [M+K] (78), 331 (100). Anal. calcd for  $C_{19}H_{24}N_4O_9$  (%): C, 50.44, H, 5.31, N, 12.39; Found: C, 50.53, H, 5.38, N, 12.33.

### 3.4. 1-( $\beta$ -D-Glucopyranosyl)-3-acetamido-5-methyl-1*H*-1,2,4-triazole **7**

A mixture of 1-(2',3',4',6'-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl)-3-acetamido-5-methyl-1*H*-1,2,4-triazole **6** (0.5 g, 1.11 mmol) in NaOMe (0.5 M)–MeOH (10 mL) was stirred from 0°C to room temperature until TLC (solvent: toluene– $AcOEt$  3:2) showed that the compound **7** disappeared, neutralized with AcOH, purified through a short silica gel column to give syrupy 1-( $\beta$ -D-glucopyranosyl)-3-acetamido-5-methyl-1*H*-1,2,4-triazole **7** (0.27 g, 80%),  $[\alpha]_D^{25} = -10$  (c 1.0,  $H_2O$ ),  $\nu_{max}$ : 3467.6 (s, OH), 3344.8 (s, NH), 1745.9 (vs, C=O), 1633.5, 1556.2 (C=N), 912.7 (m,  $C_1$ -H)  $cm^{-1}$ ;  $\delta_H$ : 10.20 (1H, br, NH-3), 5.22, 4.64 (4H, 2s, HO-2',3',4',6'), 5.19 (1H, d,  $J_{1,2'} = 8.9$  Hz, H-1'), 3.75 (1H, dd,  $J_{2,3'} = 9.0$  Hz, H-2'), 3.40 (1H, dd,  $J_{3,4'} = 9.0$  Hz, H-3'), 3.17 (1H, dd,  $J_{4,5'} = 9.1$  Hz, H-4'), 3.43 (1H, m, H-5'), 3.68 (1H, dd,  $J_{5,6a'} = 2.2$  Hz,  $J_{6a',6b'} = 11.2$  Hz, H-6a'), 3.44 (1H, dd,  $J_{5,6b'} = 5.1$  Hz, H-6b'), 2.39 (3H, s,  $CH_3$ -5), 2.03 (3H, s,  $CH_3CO$ ) ppm;  $\delta_C$ : 168.95 ( $CH_3CO$ ), 155.01 (C-3), 153.46 (C-5), 85.10 (C-1'), 71.63 (C-2'), 77.66 (C-3'), 70.03 (C-4'), 80.12 (C-5'), 61.08 (C-6'), 23.23 ( $CH_3CO$ ), 11.53 ( $CH_3$ -5) ppm; ESIMS (%):  $m/z$  303 [M+1] (30), 325 [M+Na] (100), 341 [M+K] (26). Anal. calcd for  $C_{11}H_{18}N_4O_6$  (%): C, 43.71, H, 5.96, N, 18.54; Found: C, 43.82, H, 5.87, N, 18.43.

### 3.5. $N^1$ -(Acetylated $\beta$ -D- or $\alpha$ -L-glycopyranosylamino)- $N^1,N^2,N^3$ -triacylguanidines **8–10**

A mixture of  $\beta$ -D- or  $\alpha$ -L-glycopyranosyl aminoguanidine nitrates **1–3** (10 mmol) in anhydrous pyridine (60 mL) and  $Et_3N$  (2.5 mL) was stirred in an ice–water bath, while distilled  $Ac_2O$  (40 mL) was added dropwise. The reaction mixture continued stirring from 0°C slowly up to room temperature until TLC (solvent: pyridine– $AcOH$ – $H_2O$  9:1:0.75) showed that the compounds **1–3** disappeared, then poured into ice–water, extracted with  $CH_2Cl_2$  (3×40 mL), washed with water, dried ( $Na_2SO_4$ ), evaporated under reduced pressure. The residue was crystallized from EtOH–petroleum ether (60–90°) or by chromatography to give  $N^1$ -(acetylated  $\beta$ -D- or  $\alpha$ -L-glycopyranosylamino)- $N^1,N^2,N^3$ -triacylguanidines **8–10**.

**3.5.1.  $N^1$ -(2',3',4'-Tri-*O*-acetyl- $\beta$ -D-xylopyranosylamino)- $N^1,N^2,N^3$ -triacylguanidine **8**.** Yields 60%, mp 105–106°C,  $[\alpha]_D^{25} = -9$  (c 1.0,  $CH_2Cl_2$ ),  $\nu_{max}$ : 3245.8 (m, NH), 1758.0 (vs, C=O), 1695.4, 1673.2, 1639.5 (s, C=N), 905.7 (w,  $C_1$ -H)  $cm^{-1}$ ;  $\delta_H$ : 12.95, 10.58 (2H, 2s, 2×NH-3), 5.29 (1H, d,  $J_{1,2'} = 6.9$  Hz, H-1'), 5.37 (1H, dd,  $J_{2,3'} = 7.8$  Hz, H-2'), 5.82 (1H, dd,  $J_{3,4'} = 8.0$  Hz, H-3'), 4.90 (1H, m, H-4'), 4.10 (1H, dd,  $J_{4,5b'} = 5.1$  Hz, H-5b'), 3.43 (1H, dd,  $J_{4',5a'} = 8.0$  Hz,  $J_{5a',5b'} = 10.8$  Hz, H-5a'), 2.30, 2.26, 2.14, 2.07, 2.03, 1.99 (18H, 6s, 6× $CH_3CO$ ) ppm;  $\delta_C$ : 173.42, 172.60, 170.96, 169.95, 169.62, 169.34 (6× $CH_3CO$ ), 155.57 (C-3), 80.33 (C-1'), 68.55 (C-2'), 73.58 (C-3'), 64.60 (C-4'), 60.21 (C-5'), 28.46, 24.82, 21.19, 20.88, 20.49, 20.29 (6× $CH_3CO$ ) ppm; FABMS (%):  $m/z$  459 [M+1] (60), 481 [M+Na] (38), 497 [M+K] (100), 259 (18). Anal. calcd for  $C_{18}H_{26}N_4O_{10}$  (%): C, 47.18, H, 5.72, N, 12.22; Found: C, 47.23, H, 5.68, N, 12.13.

**3.5.2.  $N^1$ -(2',3',4'-Tri-*O*-acetyl- $\alpha$ -L-rhamnopyranosylamino)- $N^1,N^2,N^3$ -triacylguanidine **9**.** Yield 66%, syrupy,  $[\alpha]_D^{25} = +19$  (c 1.0,  $CH_2Cl_2$ ),  $\nu_{max}$ : 3241.8 (m, NH), 1756.0 (vs, C=O), 1698.4, 1675.2, 1640.5 (s, C=N), 908.7 (w,  $C_1$ -H)  $cm^{-1}$ ;  $\delta_H$ : 12.88, 10.60 (2H, 2s, 2×NH-3), 5.36 (1H, d,  $J_{1,2'} = 7.4$  Hz, H-1'), 3.53 (1H, dd,  $J_{2,3'} = 7.6$  Hz, H-2'), 5.08 (1H, dd,  $J_{3,4'} = 8.0$  Hz, H-3'), 4.90 (1H, m, H-4'), 5.10 (1H, dd,  $J_{4,5'} = 1.8$  Hz, H-5'), 2.32, 2.28, 2.16, 2.05, 2.03, 2.01 (18H, 6s, 6× $CH_3CO$ ), 1.16 (3H, d,  $J_{5',6'} = 6.0$  Hz, H-6') ppm;  $\delta_C$ : 173.52, 172.66, 170.80, 169.94, 169.60, 169.22 (6× $CH_3CO$ ), 155.56 (C-3), 82.36 (C-1'), 69.75 (C-2'), 70.58 (C-3'), 71.77 (C-4'), 67.80 (C-5'), 18.14 (C-6'), 28.55, 24.77, 21.25, 20.86, 20.55, 20.33 (6× $CH_3CO$ ) ppm; FABMS (%):  $m/z$  473 [M+1] (80), 495 [M+Na] (45), 511 [M+K] (100). Anal. calcd for  $C_{19}H_{28}N_4O_{10}$  (%): C, 48.29, H, 5.98, N, 11.86; Found: C, 48.22, H, 5.88, N, 11.76.

**3.5.3.  $N^1$ -(2',3',4',6'-Tetra-*O*-acetyl- $\beta$ -D-glucopyranosylamino)- $N^1,N^2,N^3$ -triacylguanidine **10**.** Yield 80%, mp 171–172°C,  $[\alpha]_D^{25} = -2.0$  (c 1.0,  $CH_2Cl_2$ ),  $\nu_{max}$ : 3326.4 (m, NH), 1753.7 (vs, C=O), 1696.4, 1670.9, 1638.0 (s, C=N), 920.8 (m,  $C_1$ -H)  $cm^{-1}$ ;  $\delta_H$ : 12.93, 10.63 (2H, 2s, 2×NH-3), 5.93 (1H, d,  $J_{1,2'} = 8.7$  Hz, H-1'), 5.09 (1H, dd,  $J_{2,3'} = 8.5$  Hz, H-2'), 5.37 (1H, dd,  $J_{3,4'} = 8.7$  Hz, H-3'), 5.15 (1H, dd,  $J_{4,5'} = 8.8$  Hz, H-4'), 3.90 (1H, m,

H-5'), 4.14 (1H, dd,  $J_{5',6a'}=1.5$  Hz,  $J_{6a',6b'}=12.2$  Hz, H-6a'), 4.05 (1H, dd,  $J_{5',6b'}=5.7$  Hz, H-6b'), 2.27, 2.24, 2.10, 2.07, 2.03, 1.98, 1.93 (21H, 7s, 7×CH<sub>3</sub>CO) ppm;  $\delta_C$ : 173.63, 172.73, 172.11, 171.79, 170.18, 169.87, 169.60 (7×CH<sub>3</sub>CO), 155.57 (C-3), 80.13 (C-1'), 64.51 (C-2'), 72.33 (C-3'), 67.01 (C-4'), 70.36 (C-5'), 61.30 (C-6'), 28.50, 24.78, 21.36, 20.86, 20.50, 20.48, 20.39 (7×CH<sub>3</sub>CO) ppm; FABMS (%):  $m/z$  531 [M+1] (100), 553 [M+Na] (65), 569 [M+K] (100), 331 (78). Anal. calcd for C<sub>21</sub>H<sub>30</sub>N<sub>4</sub>O<sub>12</sub> (%): C, 47.55, H, 5.70, N, 10.56; Found: C, 47.46, H, 5.68, N, 10.63.

### 3.6. 1-( $\beta$ -D- or $\alpha$ -L-Glycopyranosyl)-5-methyl-1H-1,2,4-triazoles 13–15

A mixture of *N*<sup>1</sup>-(acetylated  $\beta$ -D- or  $\alpha$ -L-glycopyranosylamino)-*N*<sup>1</sup>,*N*<sup>2</sup>,*N*<sup>3</sup>-triacylguanidines **8–10** (0.5 g, 1.11 mmol) in NaOMe (0.5 M)–MeOH (10 mL) was stirred from 0°C to room temperature until TLC (solvent: toluene–AcOEt 3:2) showed that the compounds **8–10** disappeared, neutralized with AcOH, purified through a short silica gel column to give syrupy 1-( $\beta$ -D- or  $\alpha$ -L-glycopyranosyl)-5-methyl-1H-1,2,4-triazoles **13–15**.

#### 3.6.1. 1-( $\beta$ -D-Xylopyranosyl)-5-methyl-1H-1,2,4-triazole

**13**. Yield 68%,  $[\alpha]_D^{25}=-8.0$  (*c* 1.0, H<sub>2</sub>O),  $\nu_{\max}$ : 3366.1 (s, OH), 3346.8 (m, NH), 1637.6, 1577.3 (C=N), 906.7 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 5.15–5.00 (5H, m, HO-2',3',4', NH-3), 4.92 (1H, d,  $J_{1',2'}=9.0$  Hz, H-1'), 3.74 (1H, dd,  $J_{2',3'}=9.2$  Hz, H-2'), 3.35 (1H, m, H-3'), 3.70 (1H, dd,  $J_{4',5'}=8.6$  Hz, H-4'), 4.12 (1H, dd,  $J_{4',5a'}=5.4$  Hz,  $J_{5a',5b'}=12.0$  Hz, H-5a'), 3.17 (1H, d,  $J_{4',5a'}=5.1$  Hz, H-5b'), 2.23 (3H, s, CH<sub>3</sub>-5) ppm;  $\delta_C$ : 162.27 (C-3), 152.24 (C-5), 84.99 (C-1'), 71.20 (C-2'), 77.33 (C-3'), 69.30 (C-4'), 67.79 (C-5'), 11.31 (CH<sub>3</sub>-5) ppm; ESIMS (%):  $m/z$  231 [M+1] (10), 253 [M+Na] (30). Anal. calcd for C<sub>8</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub> (%): C, 38.69, H, 6.50, N, 22.58; Found: C, 38.72, H, 6.57, N, 22.53.

#### 3.6.2. 1-( $\alpha$ -L-Rhamnopyranosyl)-5-methyl-1H-1,2,4-triazole

**14**. Yield 60%,  $[\alpha]_D^{25}=+9$  (*c* 1.0, H<sub>2</sub>O),  $\nu_{\max}$ : 3367.8 (s, OH), 3340.8 (s, NH), 1638.6, 1568.2 (C=N), 910.7 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 5.20–5.03 (5H, m, HO-2',3',4' and NH-3), 5.00 (1H, d,  $J_{1',2'}=8.9$  Hz, H-1'), 3.98 (1H, dd,  $J_{2',3'}=9.0$  Hz, H-2'), 3.68 (1H, dd,  $J_{3',4'}=9.0$  Hz, H-3'), 3.36 (1H, dd,  $J_{4',5'}=3.6$  Hz, H-4'), 3.92 (1H, m, H-5'), 1.16 (3H, d,  $J_{6a',6b'}=6.0$  Hz, H-6), 2.25 (3H, s, CH<sub>3</sub>-5) ppm;  $\delta_C$ : 162.15 (C-3), 152.20 (C-5), 85.13 (C-1'), 70.63 (C-2'), 71.66 (C-3'), 72.03 (C-4'), 68.71 (C-5'), 18.31 (C-6'), 11.40 (CH<sub>3</sub>-5) ppm; ESIMS (%):  $m/z$  245 [M+1] (30), 268 [M+Na] (80), 284 [M+K] (40). Anal. calcd for C<sub>9</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub> (%): C, 41.20, H, 6.92, N, 21.37; Found: C, 41.22, H, 6.95, N, 21.30.

#### 3.6.3. 1-( $\beta$ -D-Glucopyranosyl)-5-methyl-1H-1,2,4-triazole

**15**. Yield 78%,  $[\alpha]_D^{25}=-14$  (*c* 1.0, H<sub>2</sub>O),  $\nu_{\max}$ : 3469.6 (s, OH), 3346.8 (s, NH), 1636.5, 1558.2 (C=N), 912.8 (m, C<sub>1</sub>-H) cm<sup>-1</sup>;  $\delta_H$ : 5.03 (1H, br, NH-3), 4.84–4.36 (4H, m, HO-2',3',4',6'), 4.90 (1H, d,  $J_{1',2'}=9.2$  Hz, H-1'), 4.20 (1H, dd,  $J_{2',3'}=9.0$  Hz, H-2'), 3.80 (1H, m, H-3'), 3.46 (1H, ddd,  $J_{4',5'}=9.1$  Hz, H-4'), 3.54 (1H, m, H-5'), 4.00 (1H, dd,  $J_{5',6a'}=2.0$  Hz,  $J_{6a',6b'}=10.6$  Hz, H-6a'), 3.96

(1H, dd,  $J_{5',6b'}=5.4$  Hz, H-6b'), 2.23 (3H, s, CH<sub>3</sub>-5) ppm;  $\delta_C$ : 161.96 (C-3), 152.03 (C-5), 85.34 (C-1'), 68.44 (C-2'), 74.05 (C-3'), 68.44 (C-4'), 77.55 (C-5'), 60.63 (C-6'), 11.50 (CH<sub>3</sub>-5) ppm; ESIMS (%):  $m/z$  279 [M+1] (8), 301 [M+Na] (25). Anal. calcd for C<sub>9</sub>H<sub>18</sub>N<sub>4</sub>O<sub>6</sub> (%): C, 38.85, H, 6.52, N, 20.14; Found: C, 38.82, H, 6.49, N, 20.13.

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