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### Structural Assignments of 1-( $\beta$ -d-Glucopyranosyl)-1,2,3-triazoles by $^1\text{H}$ - and $^{13}\text{C}$ -NMR Study

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## Structural Assignments of 1-( $\beta$ -D-Glucopyranosyl)-1,2,3-triazoles by $^1\text{H}$ - and $^{13}\text{C}$ -NMR Study

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### ABSTRACT

The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra of 1- $\beta$ -D-glucopyranosyl-1,2,3-triazole-4,5-dimethyl carboxylate, 1- $\beta$ -D-glucopyranosyl-1,2,3-triazole-4,5-dicarboxamide, -dialkylcarboxamide-*N*-nucleosides **4–18**, and 6-amino-4*H*-1-(1- $\beta$ -D-glucopyranosyl)-8-hydroxy-1,2,3-triazolo[4,5-*e*][1,3]-diazepin-4-one **19** had been studied. Resonance signals and anomeric configurations were assigned by homo- and heteronuclear two dimensional methods (DQF-COSY, HSQC, HMBC, HMQC, ROESY).

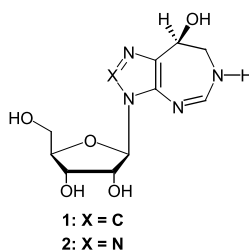
**Key Words:** Nucleosides; 1,2,3-Triazole;  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR studies.

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## INTRODUCTION

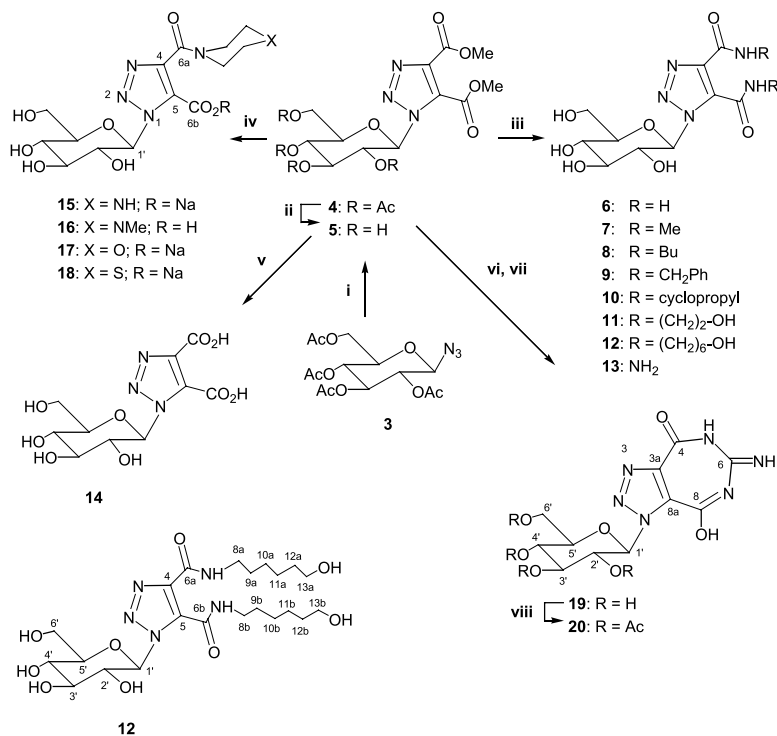
Various triazoles are known for their biological activities, e.g. as anticancer,<sup>[1–5]</sup> and antiviral agents,<sup>[6,7]</sup> or as deaminase inhibitors.<sup>[8]</sup> 1-[ $\beta$ -D-Glycopyranosyl-(halomethyl)]-1,2,3-triazoles, 1-( $\beta$ -D-glycopyranosyl)-1,2,3-triazole-4,5-dicarboxamide and 8-azainosine(3- $\beta$ -D-ribofuranosyl- $\nu$ -1,2,3-triazolo[4,5- $d$ ]pyrimid-7-one are examples showing cytotoxic activities in vitro against several tumor cell lines [human B-lymphoblast (WI-L2), ID<sub>50</sub> = 41  $\mu$ M; human myeloid leukemia (K562), ID<sub>50</sub> = 26  $\mu$ M; and HL-60, ID<sub>50</sub> = 32  $\mu$ M]. However, two analogues of the nucleoside antibiotic conformycines, **1** and (8*R*)-7,8-dihydro-3- $\beta$ -D-ribofuranosyl-6*H*- $\nu$ -triazolo[4,5- $d$ ][1,3] diazepin-8-ol (**2**, 2-aza-conformycine),<sup>[8]</sup> bearing imidazole and 1,2,3-triazole residues, respectively fused to expanded ring diazepine have been reported as inhibitors of the enzyme adenosine deaminase. These findings prompted several laboratories to synthesize numerous analogues of such compounds by different methods.<sup>[9,10]</sup> A combination of <sup>1</sup>H-<sup>1</sup>H DQF-COSY, <sup>1</sup>H-<sup>13</sup>C-HSQC, ROESY, HMQC and HMBC spectra enabled us to deduce the structures of the potentially antitumor agents 1- $\beta$ -D-glycosyl(carboxamide)-1,2,3-triazole nucleosides<sup>[9]</sup> and to assign completely their <sup>1</sup>H and <sup>13</sup>C NMR spectra.



## EXPERIMENTAL

The NMR spectra were recorded using Bruker spectrometer DRX 600 (<sup>1</sup>H: 600.13 MHz; <sup>13</sup>C: 150.91 MHz) and WM-250 (<sup>1</sup>H: 250 MHz). Internal reference TMS;  $\delta$ -scale. Assignments of protons resonances were confirmed by homo decoupling and by COSY spectra. <sup>1</sup>H-<sup>13</sup>C COSY, DFQ-COSY, HSQC, HMQC and HMBC spectra were used for assignments of the <sup>13</sup>C resonances. The 2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucosyl azide (**3**)<sup>[12]</sup> was prepared from  $\beta$ -D-glucose azide.<sup>[11]</sup> Dimethyl-1-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -





**Scheme 1.** Reagents: (i) MeO<sub>2</sub>C—C≡C—CO<sub>2</sub>Me/toluene/80°C; (ii) NaOMe/MeOH; (iii) RNH<sub>2</sub>, 23°C, 16–18 h; (iv) R<sub>2</sub>NH/NaOMe; (v) 2.5 M NaOH/80°C/4 h; (vi) guanidine.HCl/NaOMe, 23°C, 48 h; (vii) Ac<sub>2</sub>O/pyridine, 23°C, 48 h; (viii) NaOMe/MeOH, 23°C, 24 h.

D-glucopyranosyl)-1,2,3-triazole-4,5-dicarboxylate (**4**), the free nucleoside analogue **5**, the corresponding amides **6–12**, the hydrazide **13**, the dicarboxylic acid **14**, the piperazines, and the thiomorpholine carbonyl compounds **15–18**, the 1,2,3-triazolo[4,5-*e*]-diazepines **19**, **20**, were prepared by a reported method.<sup>[9]</sup>

## RESULTS AND DISCUSSION

1,3-Dipolar cycloaddition<sup>[10]</sup> of dimethyl acetylenedicarboxylate (DMAD) to the acetylated  $\beta$ -D-glucopyranosyl azide **3**<sup>[11,12]</sup> in boiling toluene afforded the nucleoside **4**, which was deacetylated with NaOMe/



**Table 1.**  $^1\text{H}$ -NMR chemical shifts [ppm] and coupling constants<sup>1)</sup> for the 1,2,3-triazole *N*-nucleosides **4–20** (300 K, 600 MHz,  $\text{C}_5\text{D}_5\text{N}$ ).

	H-1'	H-2'	H-3'	H-4'	H-5'	H-6'a	H-6'b	OH	NH/NH <sub>2</sub>	CH <sub>2</sub> <sup>2)</sup> /OMe
<b>4</b> <sup>a,3)</sup>	6.12	5.94	5.41	5.24	4.00	4.29	4.14	–	–	3.98
<b>5</b>	5.69	4.10	←3.45	–	2.89→	3.82	3.68	5.56, 5.31, 5.19, 4.62	–	3.99
<b>6</b>	6.45	4.03	←3.31	–	3.21→	3.64	3.43	5.44, 5.30, 5.16, 4.15	(10.21, 8.56), 8.19 <sup>5)</sup>	
<b>7</b>	6.47	4.01	←3.34	–	3.17→	3.67	3.44	5.39, 5.5.19, 5.13, 4.61	10.74, 9.18 <sup>6)</sup>	
<b>8</b>	6.46	4.01	←3.34	–	3.20→	3.66	3.44	5.49, 5.26, 5.14, 4.61	10.83, 9.23 <sup>7)</sup>	1.52–1.22
<b>9</b>	6.39	4.04	←3.36	–	3.23→	3.66	3.45	5.44, 5.28, 5.15, 4.61	11.09, 9.81 <sup>8)</sup>	4.64–4.41
<b>10</b>	6.36	4.00	3.33	3.16	3.25	3.66	3.44	5.37, 5.24, 5.12, 4.59	10.75, 9.20 <sup>9)</sup>	2.91–2.83, 0.77–0.52
<b>11</b>	6.46	4.03	3.32	3.24	3.33	3.67	3.33	5.35, 5.24, 5.12, 4.59	10.80, 8.96	3.52, 3.36
<b>12</b>	6.47	4.03	3.32	3.24	3.33	3.67	3.46	5.34, 5.21, 5.09, 4.55	10.80, 9.17 <sup>10)</sup>	3.37, 3.27, 1.53, 1.40, 1.30, 1.29
<b>12</b> <sup>b</sup>	7.75	5.24	4.49	4.42	4.39	4.56	4.37	5.24	11.59, 9.80	3.81(13a,b) <sup>11)</sup> 3.60 (8a) <sup>12)</sup> 3.43(b) <sup>12)</sup> 1.71(12a,b)

[illegible]

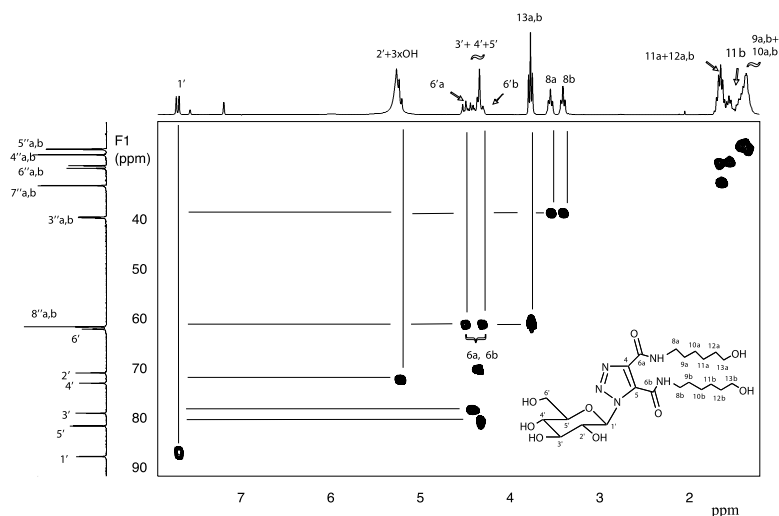
All spectra were measured in DMSO- $d_6$ , except: <sup>a)</sup> in  $\text{CDCl}_3$ , <sup>b)</sup> in  $\text{C}_5\text{D}_5\text{N}$ , <sup>c)</sup> in  $\text{DMSO}-d_6/\text{D}_2\text{O}$  <sup>1)</sup> ring couplings:  $J_{1,2} = 9.0-9.5$  Hz (d);  $J_{5,6\text{a}} = 4.2-6.1$  Hz (dd) or (m);  $J_{6\text{a},6\text{b}} = -10.5 - -12.6$  Hz (dd);  $J_{2,\text{OH}} = 5.4-5.8$  Hz (d), (br s) or (m);  $J_3/\text{OH} = 3.6-5.2$  Hz (d), (br s) or (m);  $J_{6\text{a},6\text{b},\text{OH}} = 5.0-5.8$  (t), (br s) or (m). <sup>2)</sup>  $\text{CH}_2$ : (m); <sup>3,4)</sup>  $J_{2,3} = J_{3,4} = J_{4,5} \sim 9.4$  Hz (t);  $J_{\text{NH},\text{NH}} =$  <sup>5)</sup> 9.0 Hz (d); <sup>6)</sup> 4.7 Hz (d); <sup>7)</sup> 5.2 Hz (t); <sup>8)</sup> 6.0 Hz (pt); <sup>9)</sup> 4.5 Hz (d); <sup>10)</sup> 5.7 Hz (pt); <sup>11)</sup> J = 6.5 Hz (t); <sup>12)</sup> J = 7.0 Hz (t). (br s): broad singlet; (d): doublet; (t): triplet; (pt): *pseudo*-triplet; (dd): doublet of doublets, (m): multiplet.

MeOH to give **5**. Treatment of **4** with primary amines such as  $\text{NH}_3/\text{MeOH}$ ,  $\text{MeNH}_2$ , *n*-butylamine, benzylamine, cyclopropylamine, ethanolamine, 1-amino-6-hexanol, and hydrazine furnished the carboxamides **6–13**. The dicarboxylic acid **14** was obtained by hydrolysis of the ester **4** with aqueous base. Treatment of compound **4** with the secondary amines piperazine, morpholine and thiomorpholine in the presence of base afforded the monocarboxamides **15**, **17**, **18**, respectively. The sodium salt obtained from **4** with *N*-methylpiperazine was neutralized with hydrochloric acid to give the acid **16**. With guanidine, compound **4** reacted to yield the triazolo-diazepine **19**, acetylation of which resulted in the formation of **20** (Scheme 1).

The  $^1\text{H}$  NMR spectra of **4** and **5** showed signals located at 3.98 ppm and 3.99 ppm, respectively, which are characteristic of the OMe groups. The large coupling magnitudes between the diaxial protons H-2'–H-5' indicated a pyranosidic ring form with equatorial substituents, and indicative of the  $^4\text{C}_1$ -conformation of the sugar moiety. The  $^1\text{H}$  NMR data of compounds **4–20** as obtained from the phase-sensitive double quantum filtered (DFQ-COSY) spectra,<sup>[13]</sup> are listed in Table 1. When the six-membered ring of a sugar moiety is in a chair conformation, the geminal coupling constants are ca 12.0 Hz. Axial-axial vicinal protons generally have coupling constants of 8.0–12.0 Hz, while axial-equatorial vicinal protons and equatorial-equatorial vicinal protons have *J* values of 0–5.0 Hz.<sup>[14]</sup> Therefore, the large coupling constants (9.0–9.5 Hz) of the anomeric protons of **4–20** are typical for  $\beta$ -configured glucopyranose. In this case, phase-sensitive DQF-COSY spectra provide not only connectivity information but also the ability to measure coupling constants for the off-diagonal responses. Additional proofs for  $\beta$ -configurations came from rotating frame nuclear Overhauser enhancement spectroscopy (ROESY)<sup>[15–17]</sup> suggesting small distances between H-1' and H-5'. In agreement with  $^4\text{C}_1$ -conformations of the pyranose rings are, for instance, the observed large couplings between the protons H-4' and H-5' (approximately 9.4 Hz), as well as the cross signals in the ROESY spectra between the signals of H-1', H-2' and H-5' (e.g: compound **12**; 7.75, 5.24, and 4.39 ppm, respectively) (Figure 3).

Heteronuclear multiple quantum coherence spectra (HMQC),<sup>[18]</sup> heteronuclear multiple bond correlation (HMBC),<sup>[19]</sup> and gradient selected heteronuclear single quantum coherence (HSQC)<sup>[20,21]</sup> spectra made possible the assignments of the carbon resonances (Table 2). Compound **12** is selected for this study as a typical example since it bears the long chain methylene groups (C-8a,b–C-13a,b). The gradient selected  $^1\text{H}$ ,  $^{13}\text{C}$ -HSQC spectrum in  $\text{D}_5$ -pyridine of **12** is shown in Figure 1 and Figure 2. The doublet for H-1' (7.75 ppm,  $J_{1',2'} = 9.1$  Hz) is coupled to C-1' (88.0 ppm). The multiplet resonance of H-2' at about 5.24 ppm, superposed by signals of the hydroxyl groups, is coupled to C-2' at 70.0 ppm, while the triplet at 4.49 ppm ( $J = 9.0$





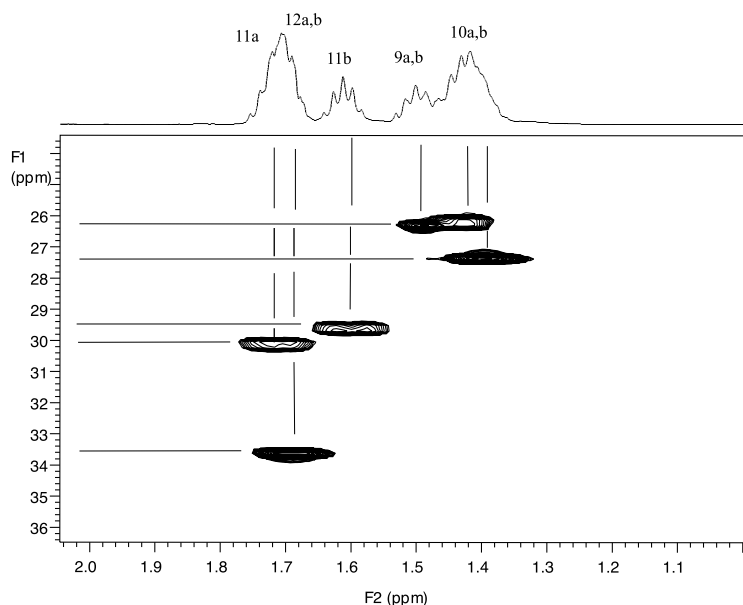
**Figure 1.** 2D Gradient selected HSQC spectrum of **12** in  $C_5D_6N$  (600 MHz, 300 K) showing proton/carbon correlation.

Hz) for H-3' is coupled to C-3' at 76.8 ppm. Correspondingly, the resonances for H-4' as doublet of doublets at 4.42 ppm ( $J_{4',5'} = 9.5$  Hz), is cross linked to C-4' at 72.0 ppm, and the doublet of triplets of H-5' at 4.39 ppm, is coupled to C-5' at 80.0 ppm. The two doublet of doublets at 4.56 ppm and 4.37 are assigned to H-6a' ( $J_{6a',5a'} = 4.5$  Hz), and H-6b' ( $J_{6a',6b'} = -13.0$  Hz), respectively, are coupled to C-6' at 61.0 ppm. The triplets at 3.81 ppm ( $J = 6.5$  Hz), 3.60 ppm ( $J = 7.0$  Hz), and 3.43 ppm ( $J = 7.0$  Hz) were assigned to the protons 13a,b and 8a,b, cross linked to C-13a,b (62.0 ppm) and C-8a,b (38.2 ppm). For the groups  $CH_2$ -12a,b,  $CH_2$ -11a,  $CH_2$ -11b,  $CH_2$ -9a,  $CH_2$ -9b, and  $CH_2$ -10a,b signals were found at  $\delta_H/\delta_C$  1.71/33.4, 1.69/30.1, 1.67/29.4, 1.49/26.2, 1.43/26.2, 1.40/27.3. In  $DMSO-d_6$  slightly different chemical shifts were observed (Tables 1, 2).

More arguments might arise concerning the configuration assignment of compound **12** from the HSQC spectrum, measured at room temperature, in comparison to those of some  $\beta$ -D-glycosylpyranosylumazine and isopterine-*N*-nucleosides,<sup>[21]</sup> which revealed a mixture of *syn*- and *anti*-rotamers, showing especially the H-1' signals as two doublets ( $J_{1',2'} = 9.5$ –10.4 Hz) in the region of 6.13–6.72 ppm. The appearance of the anomeric protons of **8**–**12** and **15**–**18** in the HSQC spectra as single doublets, indicative for the existence of these compounds in the more stable configuration (*anti*) where the sugar moiety is located stereochemically in the less hindered position to





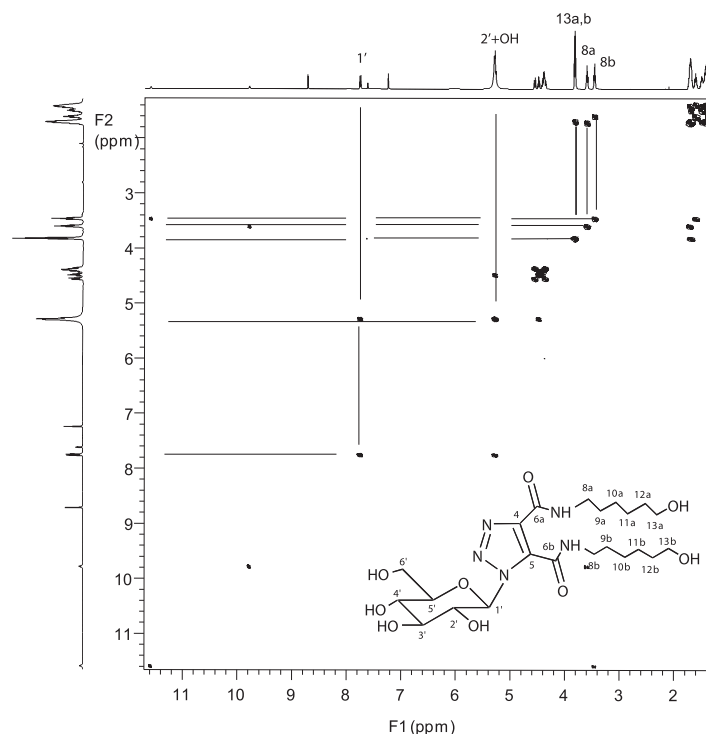


**Figure 2.** Enlarged portion of the gradient selected HSQC spectrum of **12** between 1.0–2.0 ppm.

the mono- and disubstituted triazole groups, and excluded the presence of two rotamers.

Furthermore, all the methylenes of the carboxamide groups at **8–12** as well as those of the piperazine, morpholine, and thiomorpholine residues at **15–18** were inferred from the COSY, HMQC, and HMBC spectra, via the  $^3J_{\text{CO,CH}_2}$  couplings. Carbons **4** and **5** of the triazole ring were elucidated from the HMBC spectra, as shown in Table 2, which is located between 137.7–144.8 ppm and 132.0–140.0 ppm, respectively. Also, this technique allowed also a clear interpretation for the monosubstitution of the ester group of compound **4** by *sec*-amine at C-4 and not C-5 of the triazole ring. The monosubstitution was visible in the HMBC spectra of **15–18**, when carbonyl groups at C-4 resonated at highest fields (142.1, 144.3, 142.7, 144.8 ppm, respectively) in comparison to those of the disubstituted carboximides **6–13** (between 137.7–138.9 ppm).

The ROESY spectrum of **12** shows cross signals between the resonances of the anomeric proton and of both H-2' and H-3'. Similarly, cross signals were observed for the signals of H-8a,b and the other CH<sub>2</sub> groups (Figure 3). The gradient selected heteronuclear single quantum coherence spectrum of **12**



**Figure 3.** 2D ROESY spectrum of **12** in  $C_5D_5N$  (300 K, 600 MHz).

allowed for assignments of the resonances of the substituent at C-5 via  $^3J_{C,H}$  couplings (Figure 4). The carbonyl carbon atoms C-6a, C-6b at  $\delta_C$  162.0 and 158.0 ppm show  $^3J_{C,H}$  correlations to  $CH_2$ -8a ( $\delta_H$  3.60) and  $CH_2$ -8b ( $\delta_H$  3.43). C-5 ( $\delta_C$  132.0) of the triazole ring was identified by its  $^3J_{C,H}$  coupling to the anomeric proton H-1'. For C-12a,b and C-11a,b  $^2J_{C,H}$  and  $^3J_{C,H}$  couplings to the protons H-13 were observed. Similarly,  $^3J_{C,H}$  couplings of the anomeric protons H-1' to the carbon atoms 5 of compounds **15–17** provided evidence for assignments of these atoms. Since the chemical shifts of carbon atoms substituted with a carboxyl group are upfield from the shifts of similar carbon atom substituted with a carboxamide group, the observed  $^3J_{C,H}$  couplings of the anomeric protons H-1' to carbon atoms 5 of compounds **15–17** indicated that these carbon atoms (C-5: 133.3–135.5 ppm) are substituted with a carboxyl group (C-6a: 160.2–163.6 ppm), while carbon atoms C-4 (142.1–144.3 ppm) are connected to a carboxamide group (C-6b: 159.4–176.7 ppm).



**Table 2.**  $^{13}\text{C}$ -NMR chemical shifts [ppm] (300 K, 150.91 MHz) of compounds **4–20**. \*

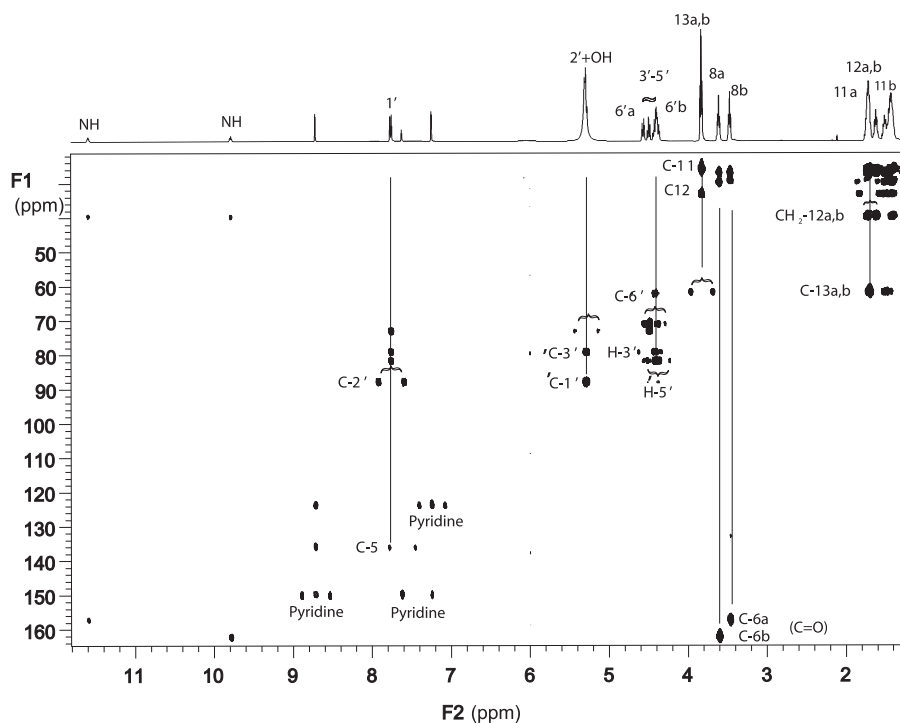
	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-4	C-5	C-6a, C-6b	CH <sub>2</sub> a/CH <sub>2</sub> b	Others
<b>4</b>	85.2	69.7	73.2	67.4	75.2	61.4	140.1	130.8	159.9, 158.5		53.6, 52.8 (OMe)
<b>5</b>	88.9	72.9	77.2	70.1	81.0	61.5	139.1	132.9	161.0, 159.8		55.0, 53.8 (OMe)
<b>6</b>	86.2	71.8	77.5	69.7	80.4	60.7	138.9	132.2	163.1, 158.0		
<b>7</b>	86.4	71.8	77.4	69.6	80.4	61.5	138.5	133.0	161.2, 156.9		26.2, 25.8 (NMe)
<b>8</b>	86.4	71.7	77.3	69.6	80.3	60.6	138.7	132.0	160.7, 156.2	38.7/38.6, 30.8/30.6, 19.5/19.4	13.6, 13.5 (Me) <i>a,b</i> -Bu
<b>9</b>	86.5	71.7	77.3	69.5	80.3	60.8	138.7	132.3	160.7, 156.5	25.6, 25.9 (CH <sub>2</sub> -Ph)	
<b>10</b>	86.8	72.1	77.7	70.0	80.7	61.0	139.9	132.4	162.4, 157.9	23.4/23.0, 6.3, 6.1, 6.0	
<b>11</b>	86.2	72.6	77.1	69.4	80.1	60.4	138.7	132.1	160.8, 156.4	59.1(CH <sub>2</sub> OH) 41.7(NCH <sub>2</sub> )	
<b>12</b>	86.0	71.4	77.0	69.2	80.0	60.3	138.7	132.0	160.7, 156.1	60.3(C-13a,b) 38.6(C-8a,b) 32.1(C-12a,b) 28.4(C-11a,b) 25.9(C-9a,b) 24.9(C-10a,b)	

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<b>12<sup>a</sup></b>	88.0	70.0	76.8	72.0	80.0	61.0	138.4	132.0	162.0, 158.0	62.0(C-13a,b) 38.2(C-8a,b) 33.4(C-12a,b) 30.1(C-11a) 29.4(C-11b) 27.3(C-10a,b) 26.2(C-9a,b)
<b>13</b>	86.3	71.7	77.4	69.6	80.4	60.6	137.7	130.7	159.0, 155.1	
<b>14</b>	87.9	73.0	70.6	70.6	80.5	62.1	143.1	140.0	180.0(CO <sub>2</sub> H)	
<b>15</b>	86.2	72.3	77.4	69.8	80.6	61.1	142.1	133.3	163.6, 159.6	56.4/49.0, 45.4/43.0
<b>16</b>	85.2	72.2	76.9	69.7	80.3	61.1	144.3	135.3	163.5, 176.7	54.5, 53.9, 45.8, 45.7
<b>17</b>	86.6	70.0	77.2	69.9	80.5	61.2	142.7	134.7	160.2, 159.4	66.9, 66.7, 47.1, 46.7
<b>18</b>	86.5	70.0	77.3	69.9	80.5	61.1	144.8	135.5	163.4, 159.9	49.7, 49.1, 26.7, 26.5
<b>19</b>	85.6	72.2	77.9	70.2	80.6	61.2	143.3 (C-3a)	135.2 (C-8a)	164.3 (C-6), 163.1 (C-4), 160.6 (C-8)	

<sup>a</sup>Compounds **4** was measured in CDCl<sub>3</sub> as solvent, and compounds **12** in C<sub>3</sub>D<sub>5</sub>N. The other compounds were measured in DMSO-*d*<sub>6</sub>.



**Figure 4.** Gradient selected HMBC spectrum of **12** in  $C_5D_5N$  (600 MHz, 300 K). One-bond couplings are highlighted by brackets. Both pairs of methylene groups were assigned via their heteronuclear  $^3J$  couplings.

Although several tautomeric structures are possible for compounds **19** and **20**, the NMR spectra showed the presence of only the one tautomer shown in Scheme 1.

## CONCLUSION

Solution structures of **4–20** were determined through a variety of two dimensional NMR techniques. DFQ-COSY was applied to obtain proton connectivities and their stereochemical configurations. The ROESY technique was the key to the assignment of the  $\beta$ -anomeric configurations with large coupling constants of the sugar moiety ( $J_{1',2'} \sim 9.0\text{--}9.5$  Hz), as well as the identification of  $CH_2\text{-}8a\text{-}b\text{-}CH_2\text{-}13a,b$  of compound **12**. The

ROESY technique also provided conformation for the proton and carbon assignments and as their stereochemical configurations e.g.: the  $^4C_1$  conformation of the sugar moiety, as have been shown from the large coupling constants ( $J_{H,H} \sim 9.0-12.6$  Hz). In this study, the HSQC technique clearly showed the direct heteronuclear correlations, and proved the existence of compound **12** as a single, stable rotamer (*anti*). In addition, the HMBC technique assigned, via  $^2J_{C,H}$  and  $^3J_{C,H}$  couplings, the C/H correlation of CH<sub>2</sub>-8a,b-CH<sub>2</sub>-13a,b of compound **12** and other methylene groups. The mono substitution of the C-4 ester group at compound **4** by the *sec*-amines was explained in term of the highest field resonance at  $^{13}C$  NMR spectra, in comparison to those of the disubstituted carboxamide nucleosides.

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### REFERENCES

1. De las Heras, F.G.; Alonso, R.; Alonso, G. Alkylating nucleosides 1. Synthesis and cytostatic activity of *N*-glycosyl(halomethyl)-1,2,3-triazoles. A new type of alkylating agents. *J. Med. Chem.* **1979**, *22*, 496–501, and references therein.
2. Lalezari, I.; Gomez, L.A.; Khorshidi, M. Synthesis of 1-aryl-1,2,3-triazole-4,5-dimethanol-4,5-bis-(isopropylcarbamates) as potential anti-neoplastic agents. *J. Heterocycl. Chem.* **1990**, *27*, 687–689.
3. De la Heras, F.G.; Camarasa, M.-J. Synthesis of alkylating 1-glycosyl-5-substituted 1,2,4-triazoles. *Nucleosides Nucleotides* **1982**, *1*, 45–56.
4. Sanghvi, Y.S.; Bhattacharya, B.K.; Kini, G.D.; Matsumoto, S.S.; Larson, S.B.; Jolley, W.B.; Robins, R.K.; Revankar, G.R. Growth inhibition and induction of cellular differentiation of human mycloid leukemia cells in culture by carbamoyl congeners of ribavirin. *J. Med. Chem.* **1990**, *33*, 336–344.
5. Hutzenlaub, W.; Tolman, R.L.; Robins, R.K. Azapurine nucleosides. I. Synthesis and antitumor activity of certain 3- $\beta$ -D-ribofuranosyl- and 2'-deoxy-D-ribofuranosyl-v-triazolo[4,5-*d*]pyrimidines. *J. Med. Chem.* **1972**, *15*, 879–883.



6. Hirota, K.; Hosono, H.; Kitade, Y.; Maki, Y.; Chu, C.K.; Schinazi, R.F.; Nakane, H.; Ono, K. Synthesis and anti-human immunodeficiency virus (HIV-1) activity of 3'-deoxy-3'-(triazol-1-yl)thymidines and 2',3'-dideoxy-3'-(triazol-1-yl)uridines, and inhibition of reverse transcriptase by their 5'-triphosphates. *Chem. Pharm. Bull.* **1990**, *38*, 2597–2601.
7. Chen, H.-M.; Sood, R.; Hosmane, R.S. An efficient, short synthesis and potent anti-hepatitis B viral activity of a novel ring-expanded purine nucleoside analogue containing a 5:7-fused, planar, aromatic, imidazo[4,5-*e*][1,3]diazepine ring system. *Nucleosides Nucleotides* **1999**, *18*, 331–335.
8. Acevedo, O.L.; Krawczyk, S.H.; Townsend, L.B. Total synthesis of (4*R*)- and (4*S*)-5,6-dihydro-1-β-D-ribofuranosyl-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol and (8*R*)- and (8*S*)-7,8-dihydro-3-β-D-ribofuranosyl-6*H*-triazolo[4,5-*d*][1,3]diazepin-8-ol: Two heterocyclic analogues of the nucleoside antibiotic conformycin. *J. Org. Chem.* **1986**, *51*, 1050–1058.
9. Al-Masoudi, N.A.; Al-Soud, Y.A. New glycosyl-(carboxamide)-1,2,3-triazole-*N*-nucleosides: synthesis and antitumor activity. *Nucleosides Nucleotides Nucleic Acids* **2002**, *21*, 361–375, and references therein.
10. Inguaggiato, G.; Jasamai, M.; Smith, J.E.; Simons, M.S.C. Novel triazole 2'-deoxy-4'-thionucleosides: stereoselective synthesis and biological evaluation. *Nucleosides Nucleotides* **1999**, *18*, 457–467.
11. Williams, J.M. Tautomerism of saccharide hydrazones in solution and their reaction with nitrous acid. *Carbohydr. Res.* **1983**, *117*, 89–94.
12. Györgydeák, Z.; Szilágyi, L. Einfache synthesen der anomerer, an C-6 modifizierten galacto- und glycopyranosylazide. *Liebigs Ann. Chem.* **1987**, 235–241.
13. Piantini, U.; Sørensen, O.W.; Ernst, R.R. Multiple quantum filters for elucidating NMR coupling networks. *J. Am. Chem. Soc.* **1982**, *104*, 6800–6801.
14. Lambert, L.B.; Shurvell, H.F.; Lightar, D.; Cooks, R.G. *Introduction to Organic Spectroscopy*; Macmillan. New York, 1987.
15. Bothner-By, A.A.; Stephens, R.L.; Lee, J.; Warren, C.D.; Jeanloz, R.W. Structure determination of a tetrasaccharide: Transient nuclear overhauser effects in the rotating frame. *J. Am. Chem. Soc.* **1984**, *106*, 811–813.
16. Bax, A.; Davis, D.G. Practical aspects of two-dimensional transverse NOE spectroscopy. *J. Magn. Reson.* **1985**, *63*, 207–213.
17. Müller, L. Sensitivity enhanced detection of weak nuclei using heteronuclear multiple quantum coherence. *J. Am. Chem. Soc.* **1979**, *101*, 4481–4484.
18. Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. Gradient



- selection in inverse heteronuclear correlation spectroscopy. *Magn. Reson. Chem.* **1993**, *31*, 287–292, references therein.
19. Summers, M.F.; Marzilli, L.G.; Bax, A. Complete  $^1\text{H}$  &  $^{13}\text{C}$  assignments of coenzyme  $\text{B}_{12}$  through the use of new two-dimensional NMR experiments. *J. Am. Chem. Soc.* **1986**, *108*, 4285–4294.
  20. Davis, A.L.; Keeler, J.; Laue, E.D.; Moskau, D. Experiments for recording pure-absorption heteronuclear correlation spectra using pulsed field gradients. *J. Magn. Reson.* **1992**, *98*, 207–216.
  21. Al-Masoudi, N.A.; Pfeleiderer, W. Synthesis and reactions of 1-(5-thio- $\beta$ -D-xylopyranosyl) lumazine and pyrimidine nucleosides. *Tetrahedron* **1993**, *49*, 7579–7592, references therein.

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