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# GLYCOSYL-PYRROLO[2,1-*c*][1,4]BENZODIAZEPINE-5,11-DIONES. SYNTHESIS, TENSIOACTIVITY AND ANTIBACTERIAL ACTIVITY

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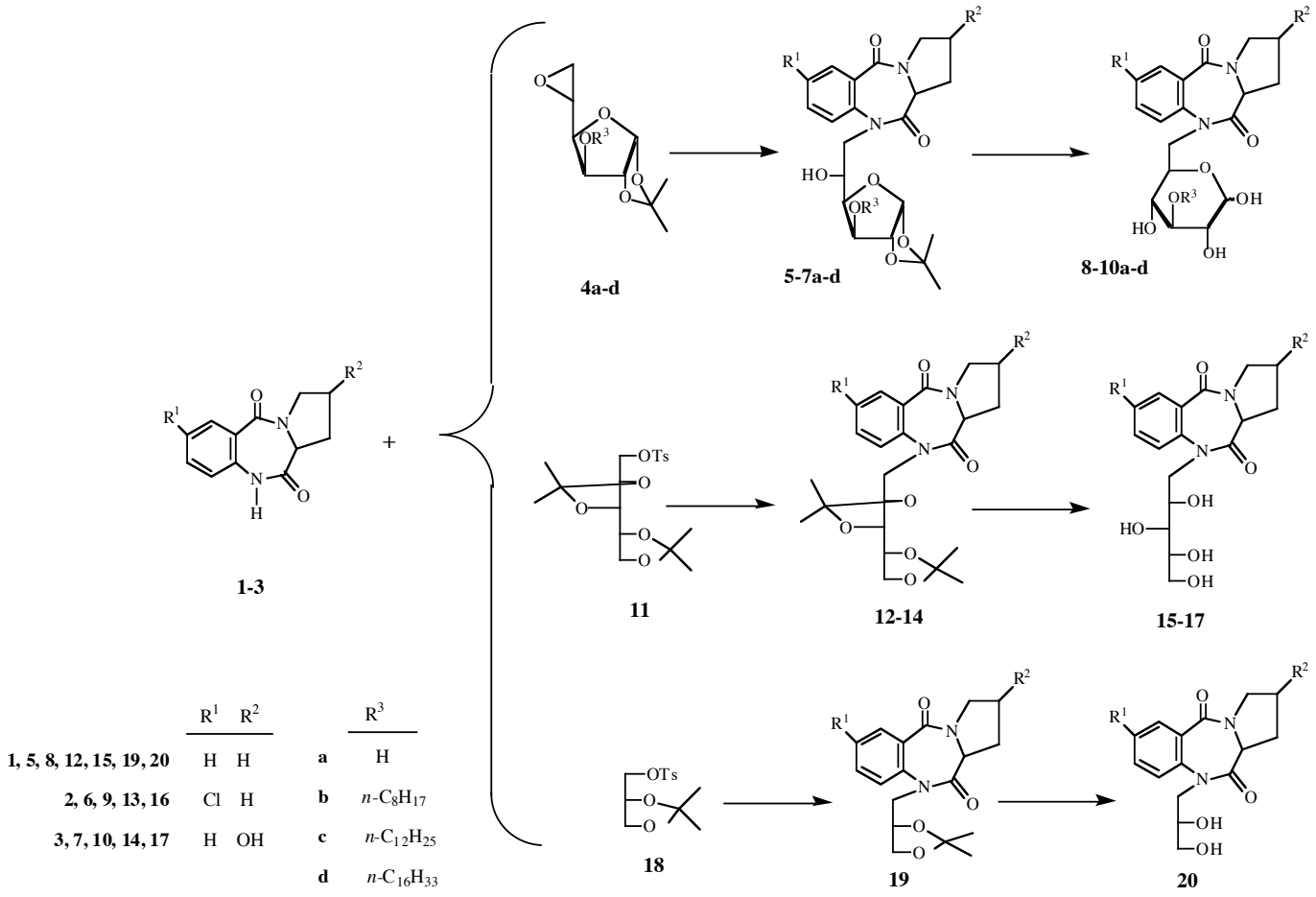
**Abstract-**Glycosyl-pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones have been obtained by condensing, at the N-10, different polyhydroxylated groups Su (Su = 6-deoxy-D-glucopyranos-6-yl, 6-deoxy-3-*O*-R-D-glucopyranos-6-yl (R = *n*-$C_nH_{2n+1}$; n = 8, 12 and 16), 1-deoxy-D,L-xylit-1-yl and 1-deoxy-D,L-glycer-1-yl). The structural variations of Su allowed us to compare amphiphilic data like water solubility (Sw), critical micelle concentration (CMC) and corresponding surface tension (γ) values. Results of a preliminary antibacterial study are also reported.

## INTRODUCTION

The benzodiazepine derivatives are mainly known as anxiolitic, anticonvulsivant, myorelaxant or hypnotic drugs.[1-5] Moreover, in this large compound range, both pyrrolo[2,1-*c*][1,4]benzodiazepine-11-one and pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione derivatives showed antitumoral and antibiotic activities.[6-15] The very low water solubility of these compounds can restrict their potential applications ; to increase this factor, polar head like polyhydroxylated groups, here called Su, may be linked to the benzodiazepine moiety. We herein describe the synthesis of new glycosyl-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones in which Su (Su = 6-deoxy-D-glucopyranos-6-yl, 6-deoxy-3-*O*-R-D-glucopyranos-6-yl (R = *n*-$C_nH_{2n+1}$; n = 8, 12 and 16), 1-deoxy-D,L-xylit-1-yl and 1-deoxy-D,L-glycer-1-yl) is linked to the benzodiazepines (**1**-**3**) at the N-10. We examined the structural influence of Su on the amphiphilic properties (water solubility, critical micelle concentration and corresponding surface tension). Results of a preliminary antibacterial study are also reported.

## RESULTS AND DISCUSSION

***Synthesis***.—The pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (**1-3**) were described in literature.[13,16] The corresponding glycosyl derivatives were obtained according to Scheme 1.




| | $R^1$ | $R^2$ | | $R^3$ |
|---|---|---|---|---|
| **1, 5, 8, 12, 15, 19, 20** | H | H | **a** | H |
| **2, 6, 9, 13, 16** | Cl | H | **b** | *n*-$C_8H_{17}$ |
| **3, 7, 10, 14, 17** | H | OH | **c** | *n*-$C_{12}H_{25}$ |
| | | | **d** | *n*-$C_{16}H_{33}$ |

Scheme 1. Synthesis of glycosyl- pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones

The condensation of benzodiazepines with protected derivatives of D-glucose (**4a-d**),[17] xylitol (**11**)[18] and glycerol (**18**)[19] was performed in DMF at 130°C, in the presence of $K_2CO_3$ and $Bu_4NBr$ (70-90% yield, Table 1). The catalytic effects of these salts were discussed in a previous work.[20] Subsequent deacetalation was achieved in 9 :1 $CF_3COOH$-water at 25°C for glucose derivatives and in 4 :1 dioxane-water, 2M $H_2SO_4$ at 50°C for xylitol and glycerol derivatives (80-92% yield, Table I). All protected and deprotected compounds were characterized (Tables II-VI).

In contrast to benzodiazepines (**1-3**) we observed that the $^{13}C$ NMR spectra of all the corresponding glycosyl derivatives show split signals. Similar phenomenon for N-grafted benzodiazepine analogues was reported by Keating,[21] who proposed a slow conformer interconversion on the NMR time scale in $CDCl_3$ and in $Me_2SO$-$d_6$, at room temperature. This interconversion would be too fast with the corresponding benzodiazepines (**1-3**) to observe separate conformer resonance.

***Water solubility (SW), surface tension (g) and critical micelle concentration (CMC).***—Table VII reports experimental Sw, CMC and g values at 25 °C. Sw values for benzodiazepines (1-3) go from 0.02 to $4.31x10^{-3}$ mol·$L^{-1}$ at 25°C ; this variation can be attributed on one hand to the chlorine atom ($R^1$) which

decreases Sw and on the other hand to the hydroxyl group ($R^2$) which increases it (see **1,2** pairs and **1,3** pairs).

**Table I** : Reaction times (h) and yields (%) on both condensation and deprotection reactions.

| condensation step | | | | deprotection step | | | |
|---|---|---|---|---|---|---|---|
| Substrate | Time | Product | Yield | Substrate | Product | α/β | Yield |
| **4a** | 12 | **5a** | 70 | **5a**[a] | **8a** | 5 : 6 | 88 |
| **4b** | 72 | **5b** | 70 | **5b**[a] | **8b** | 7 : 5 | 86 |
| **4c** | 96 | **5c** | 89 | **5c**[a] | **8c** | 7 : 6 | 90 |
| **4d** | 120 | **5d** | 80 | **5d**[a] | **8d** | 3 : 1 | 92 |
| **4a** | 12 | **6a** | 85 | **6a**[a] | **9a** | 1 : 2 | 82 |
| **4b** | 72 | **6b** | 70 | **6b**[a] | **9b** | 3 : 2 | 89 |
| **4c** | 96 | **6c** | 89 | **6c**[a] | **9c** | 4 : 3 | 87 |
| **4d** | 120 | **6d** | 75 | **6d**[a] | **9d** | 3 : 2 | 86 |
| **4a** | 12 | **7a** | 70 | **7a**[a] | **10a** | 1 : 1 | 89 |
| **4b** | 72 | **7b** | 70 | **7b**[a] | **10b** | 7 : 5 | 89 |
| **4c** | 96 | **7c** | 90 | **7c**[a] | **10c** | 7 : 5 | 87 |
| **4d** | 120 | **7d** | 80 | **7d**[a] | **10d** | 7 : 5 | 92 |
| **11** | 12 | **12** | 71 | **12**[b] | **15** | | 86 |
| **11** | 12 | **13** | 76 | **13**[b] | **16** | | 80 |
| **11** | 12 | **14** | 74 | **14**[b] | **17** | | 83 |
| **18** | 12 | **19** | 80 | **19**[b] | **20** | | 88 |

[a] 9 : 1 $CF_3COOH$-water at 25°C, 1 h. [b] 2M $H_2SO_4$ in 4 :1 dioxane-water at 50°C, 30 min.

**Table II** : Physicochemical and microanalytical data of protected benzodiazepine derivatives.

| Compound | $[\alpha]_D^{25}$ $CHCl_3$ | Formula | Calcd | | | Found | | |
|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | C | H | N |
| **5a** | -39° (*c* 0.8) | $C_{21}H_{26}N_2O_7$ | 60.28 | 6.26 | 6.69 | 60.42 | 6.18 | 6.49 |
| **5b** | -23° (*c* 1.7) | $C_{29}H_{42}N_2O_7$ | 65.64 | 7.98 | 5.28 | 65.81 | 8.05 | 4.99 |
| **5c** | -93° (*c* 1.3) | $C_{33}H_{50}N_2O_7$ | 67.55 | 8.59 | 4.77 | 67.39 | 8.42 | 4.91 |
| **5d** | -69° (*c* 0.8) | $C_{37}H_{58}N_2O_7$ | 69.13 | 9.09 | 4.36 | 68.98 | 8.97 | 4.49 |
| **6a** | -60° (*c* 0.9) | $C_{21}H_{25}N_2O_7Cl$ | 55.69 | 5.56 | 6.19 | 55.80 | 5.41 | 6.32 |
| **6b** | -86° (*c* 0.7) | $C_{29}H_{41}N_2O_7Cl$ | 61.64 | 7.31 | 4.96 | 61.51 | 7.38 | 5.10 |
| **6c** | -25° (*c* 1.1) | $C_{33}H_{49}N_2O_7Cl$ | 63.80 | 7.95 | 4.51 | 63.69 | 8.06 | 4.68 |
| **6d** | -50° (*c* 1.0) | $C_{37}H_{57}N_2O_7Cl$ | 65.61 | 8.48 | 4.14 | 65.49 | 8.39 | 4.27 |
| **7a** | 35° (*c* 0.7) | $C_{21}H_{26}N_2O_8$ | 58.06 | 6.03 | 6.45 | 58.18 | 6.11 | 6.29 |
| **7b** | 49° (*c* 0.8) | $C_{29}H_{42}N_2O_8$ | 63.72 | 7.74 | 5.12 | 63.83 | 7.82 | 5.30 |
| **7c** | 71° (*c* 0.9) | $C_{33}H_{50}N_2O_8$ | 65.76 | 8.36 | 4.65 | 65.60 | 8.40 | 4.50 |
| **7d** | 42° (*c* 1.0) | $C_{37}H_{58}N_2O_8$ | 67.45 | 8.87 | 4.25 | 67.51 | 8.91 | 4.38 |
| **12** | | $C_{23}H_{30}N_2O_6$ | 64.17 | 7.02 | 6.51 | 64.28 | 6.94 | 6.39 |
| **13** | | $C_{23}H_{29}N_2O_6Cl$ | 59.42 | 6.29 | 6.03 | 59.53 | 6.33 | 5.91 |
| **14** | | $C_{23}H_{30}N_2O_7$ | 61.87 | 6.77 | 6.27 | 61.72 | 6.71 | 6.38 |
| **19** | | $C_{18}H_{22}N_2O_4$ | 65.44 | 6.71 | 8.48 | 65.51 | 6.79 | 8.39 |

**Table III** : Physicochemical and microanalytical data of deprotected benzodiazepine derivatives.

| Compound | α/β | $[\alpha]_D^{25}$ $CHCl_3$ | Mp (°C) | Formula | Calcd | | | Found | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | C | H | N |
| **8a** | 5 : 6 | 15° (*c* 1.0)* | 72.2 | $C_{20}H_{28}N_2O_6$ | 61.21 | 7.19 | 7.14 | 61.33 | 7.12 | 7.22 |
| **8b** | 7 : 5 | 86° (*c* 1.1) | 77.3 | $C_{28}H_{44}N_2O_6$ | 66.64 | 8.79 | 5.55 | 66.58 | 8.82 | 5.49 |
| **8c** | 7 : 6 | 42° (*c* 1.1) | 69.0 | $C_{32}H_{52}N_2O_6$ | 68.54 | 9.35 | 5.00 | 68.65 | 9.28 | 4.89 |
| **8d** | 3 : 1 | 36° (*c* 1.0) | 68.7 | $C_{36}H_{60}N_2O_6$ | 70.09 | 9.80 | 4.54 | 69.98 | 9.73 | 4.68 |
| **9a** | 1 : 2 | 17° (*c* 0.7)* | 109.0 | $C_{18}H_{21}N_2O_7Cl$ | 52.37 | 5.13 | 6.79 | 52.45 | 5.06 | 6.86 |
| **9b** | 3 : 2 | 19° (*c* 1.0) | 70.8 | $C_{26}H_{37}N_2O_7Cl$ | 59.48 | 7.10 | 5.34 | 59.39 | 7.15 | 5.28 |
| **9c** | 4 : 3 | 22° (*c* 1.0) | 73.5 | $C_{30}H_{45}N_2O_7Cl$ | 62.00 | 7.80 | 4.82 | 62.10 | 7.85 | 4.73 |
| **9d** | 3 : 2 | 42° (*c* 0.7) | 75.0 | $C_{34}H_{53}N_2O_7Cl$ | 64.08 | 8.38 | 4.40 | 64.15 | 8.42 | 4.35 |
| **10a** | 1 : 1 | 136°(*c* 0.7)* | 109.0 | $C_{18}H_{22}N_2O_8$ | 54.82 | 5.62 | 7.10 | 54.75 | 5.69 | 7.21 |
| **10b** | 7 : 5 | 96° (*c* 1.0) | 75.6 | $C_{26}H_{38}N_2O_8$ | 61.64 | 7.56 | 5.53 | 61.58 | 7.61 | 5.48 |
| **10c** | 7 : 5 | 71° (*c* 1.1) | 61.2 | $C_{30}H_{46}N_2O_8$ | 64.03 | 8.24 | 4.98 | 63.95 | 8.18 | 5.09 |
| **10d** | 7 : 5 | 76° (*c* 1.0) | 71.0 | $C_{34}H_{54}N_2O_8$ | 65.99 | 8.80 | 4.53 | 65.87 | 8.78 | 4.64 |
| **15** | | | oil | $C_{17}H_{22}N_2O_6$ | 58.28 | 6.33 | 8.00 | 58.32 | 6.36 | 8.11 |
| **16** | | | oil | $C_{17}H_{21}N_2O_6Cl$ | 53.06 | 5.50 | 7.28 | 53.17 | 5.45 | 7.37 |
| **17** | | | oil | $C_{17}H_{22}N_2O_7$ | 55.73 | 6.05 | 7.65 | 55.81 | 6.10 | 7.71 |
| **20** | | | oil | $C_{15}H_{18}N_2O_4$ | 62.06 | 6.25 | 9.65 | 61.95 | 6.31 | 9.57 |

[a] measured in MeOH after 3 days.

**Table IV** : $^{13}$C NMR data of **1** and corresponding glycosyl compounds.

| Product | Benzodiazepine moiety | | | | | | | | Sugar moiety | | | | | | | | $R^3$ Chain | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-1 | C-2 | C-3 | C-5 | C-5a | C-9a | C-11 | C-11a | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | $CMe_2$ | $CMe_2$ | C-1 | $CH_3$ |
| **1**[a] | 25.6 | 22.9 | 46.7 | 164.4 | 126.4 | 136.2 | 170.5 | 56.0 | | | | | | | | | | |
| **5a**[b] | 26.5 | 22.6 | 46.5 | 165.8 | 129.7 | 140.4 | 170.3 | 57.7 | 105.1 | 84.7 | 74.9 | 81.8 | 69.4 | 54.1 | 111.5 | 26.7 | | |
| | | | | | | 138.7 | 170.0 | 57.4 | | | 74.5 | | 66.2 | 51.3 | | 26.1 | | |
| **8a**[b] | 26.0 | 23.2 | 45.9 | 165.1 | 130.8 | 140.8 | 169.2 | 56.9 | 96.9 | 76.3 | 73.1 - 67.5 | | | 50.6, 59.4 | | | | |
| | 25.0 | | | 164.4 | 130.6 | 139.1 | 169.0 | | 92.2, 91.9 | 83.9, 83.7 | | | | 50.1, 49.7 | | | | |
| **5b**[b] | 25.9 | 23.7 | 46.4 | 165.0 | 130.0 | 140.0 | 171.4 | 57.2 | 105.1 | 82.8 | 82.3 | 81.8 | 69.8 | 54.7 | 111.6 | 26.7 | 70.8 | 14.0 |
| | | | | 164.9 | | 139.4 | 170.4 | | | | 82.2 | 80.9 | 67.6 | 53.3 | | 26.2 | 70.4 | |
| **8b**[a] | 26.3 | 23.4 | 46.4 | 165.6 | 129.2 | 140.9 | 170.2 | 58.0 | 96.8 | 83.9, 83.7 | 74.5 - 67.1 | | | 51.1, 51.0 | | | 72.9 | 14.0 |
| | 25.9 | | | 165.3 | 129.0 | 138.0 | 168.9 | 57.6 | 92.3, 91.7 | 82.1, 81.9 | | | | 48.8 | | | 72.8 | |
| **12**[b] | 22.6 | 23.7 | 46.8 | 165.0 | 130.1 | 140.0 | 169.7 | 57.0 | 52.8 | 75.4 | 79.2 | 74.9 | 66.9 | | 110.0 | 26.8 | | |
| | | | 46.5 | 164.9 | 130.0 | 139.7 | 169.3 | | 50.9 | | | | 65.6 | | 109.6 | 25.3 | | |
| **15**[a] | 26.1 | 23.2 | 46.7 | 164.1 | 129.1 | 140.5 | 169.2 | 56.6 | 51.6 | 72.3 - 67.6 | | | 62.4 | | | | | |
| | | | 46.0 | | | 139.8 | | | | | | | | | | | | |
| **19**[b] | 25.7 | 24.1 | 46.9 | 165.4 | 130.8 | 140.4 | 170.2 | 57.7 | 53.6 | 68.1 | | 74.3 | | | 110.0 | 26.6 | | |
| | | | | | 130.5 | 139.9 | 169.9 | | 51.2 | 67.8 | | 73.8 | | | 109.2 | 25.8 | | |
| **20**[b] | 27.0 | 24.2 | 46.9 | 165.0 | 130.7 | 140.9 | 140.1 | 57.6 | 52.6 | 64.9 | | 70.2 | | | | | | |
| | | | | | | 140.7 | | | 51.5 | 64.7 | | 68.9 | | | | | | |

[a] In $Me_2SO$-$d_6$. [b] In $CDCl_3$.

**Table V** : $^{13}$C NMR data of **2** and corresponding glycosyl compounds.

| Product | Benzodiazepine moiety | | | | | | | | Sugar moiety | | | | | | | | $R^3$ Chain | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-1 | C-2 | C-3 | C-5 | C-5a | C-9a | C-11 | C-11a | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | *C*Me$_2$ | C*Me*$_2$ | C-1 | CH$_3$ |
| **2**[a] | 25.6 | 22.9 | 46.8 | 163.9 | 127.7 | 131.8 | 170.3 | 56.0 | | | | | | | | | | |
| **6a**[b] | 26.5 | 22.6 | 46.5 | 164.3 | 129.4 | 138.9 | 169.8 | 57.4 | 105.1 | 84.8 | 74.7 | 81.7 | 69.0 | 53.8 | 111.6 | 26.7 | | |
| | | | | 164.2 | | 137.5 | 169.5 | 57.3 | | | 74.5 | | 66.1 | 51.8 | | 26.1 | | |
| **9a**[b] | 26.0 | 23.1 | 46.0 | 163.6 | 129.7 | 139.9 | 170.0 | 56.8 | 96.8 | 76.3 | 73.3 - 66.9 | | | 50.6, 59.0 | | | | |
| | 25.0 | | 45.9 | 163.1 | 129.2 | 138.1 | 168.8 | | 92.1, 92.0 | 74.6,74.5 | | | | 49.3 | | | | |
| **6b**[b] | 25.9 | 23.7 | 46.6 | 163.8 | 129.7 | 138.5 | 170.8 | 57.2 | 105.1 | 82.8 | 82.1 | 80.8 | 69.4 | 54.3 | 111.6 | 26.7 | 70.7 | 14.0 |
| | | | | 163.7 | | 138.0 | 169.8 | | | | 81.8 | 80.7 | 67.4 | 53.4 | | 26.2 | 70.4 | |
| **9b**[a] | 26.1 | 23.4 | 46.3 | 165.0 | 131.6 | 139.5 | 169.4 | 57.5 | 96.9 | 83.9 | 74.5 - 65.5 | | | 51.3, 51.0 | | | 72.7 | 14.0 |
| | 25.8 | | 46.2 | 164.7 | 131.9 | 138.8 | 168.5 | 57.4 | 92.3, 91.8 | 82.0, 81.8 | | | | 49.3, 49.0 | | | 72.3 | |
| **13**[b] | 26.5 | 23.8 | 46.7 | 164.5 | 130.6 | 138.5 | 171.0 | 57.1 | 53.4 | 75.4 | 79.2 | 74.7 | 69.8 | | 110.2 | 26.8 | | |
| | | | 46.4 | 163.8 | 129.8 | 138.2 | 168.3 | | 51.6 | 75.2 | 78.9 | 74.4 | 69.2 | | 109.8 | 25.3 | | |
| **16**[a] | 26.5 | 23.2 | 46.9 | 163.2 | 128.4 | 139.6 | 170.4 | 56.6 | 51.6 | 72.3 – 67.5 | | | 62.5 | | | | | |
| | 26.1 | 22.9 | 46.1 | 162.8 | 127.7 | 138.7 | 168.9 | 56.1 | | | | | 62.2 | | | | | |

[a] In $Me_2SO$-$d_6$. [b] In $CDCl_3$.

**Table VI** : $^{13}$C NMR data of **3** and corresponding glycosyl compounds.

| Product | Benzodiazepine moiety | | | | | | | | Sugar moiety | | | | | | | | $R^3$ Chain | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-1 | C-2 | C-3 | C-5 | C-5a | C-9a | C-11 | C-11a | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | *C*Me$_2$ | C*Me*$_2$ | C-1 | CH$_3$ |
| **3**[a] | 34.2 | 67.3 | 53.9 | 165.0 | 125.8 | 136.1 | 170.2 | 55.1 | | | | | | | | | | |
| **7a**[b] | 34.9 | 69.1 | 56.7 | 165.0 | 130.1 | 140.9 | 171.0 | 57.7 | 105.2 | 82.1 | 85.1 | 75.0 | 70.2 | 54.3 | 112.0 | 27.1 | | |
| | | 68.3 | 56.4 | 164.9 | 129.8 | 140.0 | 170.8 | | | | | 74.6 | 69.1 | 52.2 | | 26.6 | | |
| **10a**[b] | 34.7 | 69.3 | 56.8 | 165.7 | 130.0 | 141.7 | 169.6 | 57.0 | 97.9 | 77.3 | 74.0 - 68.6 | | | 54.1, 51.6 | | | | |
| | | | 56.7 | | 129.7 | | | | 92.9 | 75.4 | | | | 50.8, 44.5 | | | | |
| **7b**[b] | 34.8 | 69.0 | 56.6 | 165.6 | 129.3 | 140.0 | 171.5 | 57.6 | 105.1 | 82.9 | 82.2 | 80.8 | 69.7 | 54.8 | 111.6 | 26.7 | 70.8 | 14.0 |
| | | | | 165.4 | | 139.2 | 170.8 | | | | 81.7 | | 67.2 | 53.8 | | 26.2 | 70.4 | |
| **10b**[a] | 34.8 | 68.8 | 56.5 | 167.0 | 129.4 | 140.9 | 171.4 | 58.3 | 96.7 | 83.9 | 74.6 - 66.8 | | | 53.3, 51.4 | | | 72.8 | 14.0 |
| | | | 56.2 | 166.9 | 129.2 | 137.8 | 168.6 | | 92.3, 91.7 | 82.2, 81.8 | | | | 51.0, 49.5 | | | 72.3 | |
| **14**[b] | 34.7 | 65.5 | 55.9 | 165.5 | 129.5 | 139.8 | 171.1 | 57.2 | 52.9 | 75.0 | 79.0 | 75.1 | 69.6 | | 109.9 | 26.7 | | |
| | 34.4 | | | 165.0 | | | 168.8 | | 51.2 | | 78.0 | | 68.6 | | 109.5 | 25.2 | | |
| **17**[a] | 34.7 | 65.5 | 55.9 | 165.5 | 129.5 | 139.8 | 171.1 | 57.2 | 51.5 | 72.3 - 67.6 | | | 62.4 | | | | | |
| | 34.4 | | | 165.0 | | | 168.8 | | | | | | 62.1 | | | | | |

[a] In $Me_2SO$-$d_6$. [b] In $CDCl_3$.

The condensation of polyhydroxylated groups strongly increases water solubility (for example, compounds (**8a**, **15** and **20**) are respectively 1028, 172 and 394 times more soluble than the corresponding benzodiazepine (**1**). However when comparing the data of the different glycosyl linked-benzodiazepines, it appears that Sw value do not rise in parallel to the OH group number of the polyhydroxylated moiety. For example, both the xylityl and the glucopyranosyl derivatives (**15**) and (**8a**) have four OH groups, but **15** is 6 times less soluble than **8a**. Moreover **15** is also 2.3 times less soluble than the corresponding glyceryl derivative (**20**) which has only two OH groups. The observed drop in the Sw values for the xylitol derivatives might be a consequence of the acyclic xylityl structure which allows privileged conformations with two or four neighbouring OH groups in *cis* disposotion, giving intramolecular hydrogen-bondings which decrease the hydrophilic character.

The $R^3$ alkyl chain in the glucopyranosyl moiety was introduced as a linear lipophilic tail in view to give an amphiphilic behavior which may favour nonspecific interactions and may add energetic barriers impairing the transference of drug from a self-aggregating structure to the binding site. This chain decreases water solubility as its length increases ; nevertheless all derivatives with $R^3 = n\text{-}C_8H_{17}$ (**8b-10b**) are significantly more soluble than corresponding benzodiazepines (respectively 10, 50 and 3 times more soluble), as well as some compounds with $R^3 = n\text{-}C_{12}H_{25}$ (**8c**, **9c**) or $R^3 = n\text{-}C_{16}H_{33}$ (**9d**). Moreover all the glucopyranosyl derivatives with $R^3 = n\text{-}C_8H_{17}$ (**8b-10b**) have a critical micelle concentration (CMC) which corresponds to the saturation of the liquid surface by monomers. In contrast CMC values were not observed either for glycosyl derivatives without alkyl chain or for those having $R^3 = n\text{-}C_{12}H_{25}$ or $n\text{-}C_{16}H_{33}$. The first series does not have appropriate lipophilic tail (like a linear alkyl chain) to form micelles from dilute solutions, so $\gamma$ decreases unceasing by adding compound until the saturated solution. The second series is not enough soluble to saturate the liquid surface by monomers.

***Antibacterial activity***.—In a preliminary study, we examined the antibacterial activities of benzodiazepines (**1-3**) and corresponding glucopyranosyl derivatives on six pathogen bacteria. Table VIII results show that all the tested bacteria are resistant or weakly sensitive to benzodiazepines (**1-3**). In contrast, sensitive antibacterial effects (+) are observed with their glucopyranosyl derivatives : **8a** on *Salmonella enteritis* and *Pseudomonas aeruginosa* ; **9a** on *Klebsiella pneumoniae* ; **9b** and **9c** on both *Escherichia coli* and *Streptococcus D*. However, these preliminary results do not allow to rationalize the influence of the $R^3$ alkyl chain since **9a** ($R^3$ = H) is more active than **9b** ($R^3 = n\text{-}C_8H_{17}$) and **9c** ($R^3 = n\text{-}C_{12}H_{25}$) on *Klebsiella pneumoniae* whereas **9b** and **9c** are active and **9a** inactive on both *Escherichia coli* and *Streptococcus D*.

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**EXPERIMENTAL**

***General methods***.—Melting points were determined on an electrothermal automatic apparatus, and are uncorrected. Optical rotations, for solutions in $CHCl_3$ or MeOH, were measured with a digital polarimeter

**Table VII** : Sw ($10^{-3}$ mol.$L^{-1}$), CMC ($10^{-3}$ mol.$L^{-1}$) and γ (mN.$m^{-1}$) of benzodiazepine derivatives, at 25 °C.

| Product | **1** | **8a** | **8b** | **8c** | **8d** | **15** | **20** | **2** | **9a** | **9b** | **9c** | **9d** | **16** | **3** | **10a** | **10b** | **10c** | **10d** | **17** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sw | 0.18 | 185 | 2.0 | 0.7 | 0.1 | 31 | 71 | 0.02 | 153 | 0.95 | 0.5 | 0.06 | 23 | 4.3 | 328 | 13.8 | 0.7 | 0.4 | 33 |
| CMC | | | 1.8 | | | | | | | 0.76 | | | | | | 4.6 | | | |
| γ | | 55* | 39 | 35* | 44* | 39 | 46 | | 42* | 45 | 44* | 51* | 58 | | 37* | 35 | 32* | 33* | 56 |

* At Sw value.

**Table VIII** : Antibacterial activity of benzodiazepines (**1-3**) and corresponding glucopyranosyl derivatives.

| Bacteria | **1** | **8a** | **2** | **9a** | **9b** | **9c** | **3** | **10a** | **10b** | **10c** |
|---|---|---|---|---|---|---|---|---|---|---|
| *Escherichia coli* | - | +/- | - | - | + | + | +/- | - | - | +/- |
| *Salmonella enteritis* | - | + | - | +/- | - | - | - | +/- | - | - |
| *Klebsiella pneumoniae* | - | - | - | + | +/- | +/- | - | +/- | - | - |
| *Pseudomonas aeruginosa* | - | + | - | +/- | - | - | - | - | +/- | - |
| *Streptococcus D* | - | - | - | - | + | + | +/- | - | +/- | +/- |
| *Staphylococcus aureus* | +/- | - | +/- | - | +/- | +/- | - | - | - | +/- |

+ : sensitive  +/- : weakly sensitive  - : resistant

JASCO model DIP-370, using a sodium lamp at 25 °C. NMR spectra were recorded with a Bruker WB-300 instrument for solutions in $CDCl_3$ or $Me_2SO$-$d_6$ (internal $Me_4Si$). Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France). Reactions were monitored by either HPLC (Waters 721), using either the reverse phase columns RP-18 (Merck) or PN 27-196 (Waters), or CPG (Girdel) with either the columns OV 17 or SE 30. Analytical TLC was performed on Merck aluminum-backed silica gel (Silica Gel F254). Column chromatography was performed on silica gel (60 mesh, Matrex) by gradient elution with hexane-acetone (in each case the ratio of silica gel to product mixture to be purified, was 30:1).

***Water solubility (Sw), surface tension (γ), critical micelle concentration (CMC).***—Watersolubility, Sw, was performed at 25 °C. For CMC study, an initial aqueous solution ($C_0$) of each compound was prepared at 25 °C. Several samples were obtained by diluting $C_0$ in the concentration range $C_0$ : $C_0/2$, $C_0/4$, $C_0/8$, $C_0/16$, $C_0/32$, $C_0/64$, $C_0/128$ and $C_0/256$. The surface tension (γ) of each sample was measured by the Wilhelmy plate method (Prolabo TD 2000 tensiometer), after a period of more than 6 h in the thermostated cell (25 °C). The critical micelle concentration (CMC) was determined from a plot of γ = f(log *C*). The classical slope change coordinates gave, respectively, CMC and corresponding γ values.

***Antibacterial activity.***—Bacteria were obtained from infected patients in the Laboratoire d'Analyses Médicales of Kénitra (Morocco). For each bacterial strain, three colonies were seeded and cultured for 24h in a gelose/$Na_2HPO_4$ 0.1M, pH = 7.2 medium. The bacterial concentration was assessed by measurement of the optical density at 550 nm. Antibiograms were performed in Petri dishes containing Muller-Minton medium using diluted bacterial suspensions at a final concentration of $2\text{-}3x10^6$ $L^{-1}$. Dishes were dried at 37°C before adding a disk impregnated with the tested benzodiazepine derivative in aqueous solution (1 $mg.mL^{-1}$). The efficiency of the drugs was evaluated by measuring the diameter of the inhibition area after 18 h incubation at 37°C under humidified atmosphere.

***General procedure for condensation step***— To a solution of benzodiazepine (100 mmol), $K_2CO_3$ (6.9 g, 50 mmol) and $Bu_4NBr$ (3.2 g, 10 mmol) in DMF (200 mL), at 130 °C, was added activated carbohydrate derivative (100 mmol). When no more starting material was detected by TLC or HPLC, the mixture was concentrated under reduced pressure. The residue was extracted with $Et_2O$-$H_2O$, the organic phase was separated, washed with water (twice), dried ($Na_2SO_4$) and concentrated under diminished pressure. The crude product was purified by column chromatography using hexane-acetone (Tables I-VI). All protected products were isolated as an oil.

***General procedure for deprotection step***—Protected glucose derivatives (50 mmol) were added to a stirred solution of 9:1 $CF_3COOH$-$H_2O$ (200 mL) at 20 °C. After 1 h, the solution was concentrated to dryness under diminished pressure. The crude product was purified by column chromatography using petroleum ether-acetone gradient and solid product was recrystallized in $Et_2O$ (100 mL) (Tables 1-6). Protected xylitol and glycerol derivatives were added to a stirred solution of 2M $H_2SO_4$ in 4:1 dioxane-$H_2O$ (200 mL) at 50°C. After 30 min, the solution was neutralized and concentrated to dryness under diminished pressure. The crude product was purified by column chromatography using hexane-acetone gradient (Tables I-VI).

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