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Note

Synthesis and amphiphilic properties of glycosyl-1,4-benzodiazepin-2,5-diones

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Abstract

Glycosyl-1,4-benzodiazepin-2,5-diones were prepared by coupling polyhydroxylated groups at N-1 of the corresponding benzodiazepine. The groups include 1-deoxy-D,L-xylit-1-yl, 6-deoxy-D-glucopyranos-6-yl, and 6-deoxy-3-*O*-R-D-glucopyranos-6-yl (R = *n*-C_nH_{2n+1}; $n = 8$, 12, and 16). The structural variations of the sugar group allowed comparison of such amphiphilic data as water solubility (Sw), critical micelle concentration (CMC), and corresponding surface tension (γ) values. At 25 °C, unsubstituted benzodiazepines have Sw values from 0.9 to 4.2 10^{-3} mol L^{-1}, whereas xylit-1-yl and 6-deoxy-D-glucopyranos-6-yl derivatives are, respectively, 7.4–25 and 58–204 times more soluble. Also, compounds with R = *n*-C_8H_{17} are more soluble than corresponding benzodiazepines (1.4–5.8 times) and give micelles with CMC from 2.7 to 5.6 10^{-3} mol L^{-1} and corresponding γ from 29 to 37 mN m^{-1}. In contrast, compounds with R = *n*-$C_{12}H_{25}$ and *n*-$C_{16}H_{33}$ are not soluble enough to reach the critical micelle concentration.

Keywords: Glycosyl-1,4-benzodiazepin-2,5-diones; Water solubility; Tensioactivity; Critical micelle concentration

1. Introduction

Benzodiazepine derivatives of types -2-one [1–7], -2,4-dione [8] and -2,5-dione [9,10] show biological properties as anxiolytics, anticonvulsivants, myorelaxants and hypnotics [1–4], as well as cholecytokinin antagonists [5,8], α-thrombin inhibitors [6], anti-HIV [7], or CpIIbIIIa antagonists [9,10]. These compounds have a low water solubility. To increase this factor, polyhydroxylated groups (Su), as polar heads, may be linked to the hydrophobic benzodiazepine moiety; these molecules may then have surfactant behaviour, characterized by a decrease in surface tension (γ) and by micelle formation.

In this work, we describe the synthesis of compounds in which Su groups were grafted regiospecifically at N-1 of 1,4-benzodiazepin-2,5-diones. The chosen Su groups are 1-deoxy-D,L-xylit-1-yl, 6-deoxy-D-glucopyranos-6-yl, and 6-deoxy-3-*O*-R-D-glucopyranos-6-yl (R = *n*-C_nH_{2n+1}; $n = 8$, 12, and 16). The structural variations of Su allowed us to compare such amphiphilic data as water solubility (Sw), critical micelle concentration (CMC), and corre-

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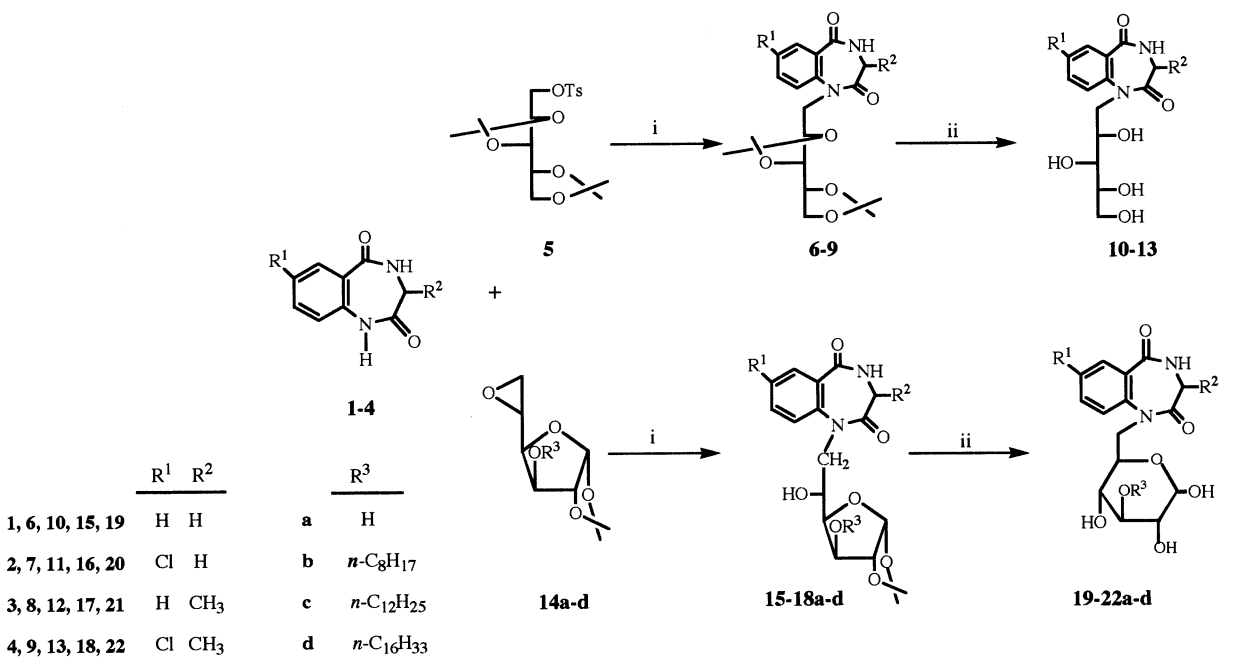
sponding surface tension (γ) values, which may influence the biodisponibility of this range of compounds.

2. Results and discussion

Synthesis.—The benzodiazepin-2,5-diones (**1**–**4**) have been described in the literature [11–15]. The corresponding polyhydroxylated derivatives were synthezised following Scheme 1.

The xylityl derivatives **10**–**13** were obtained by condensation of the racemic tosylate diacetal **5** [16] with benzodiazepines **1**–**4** [step (i)], followed by total deacetalation [step (ii)]. Initially, benzodiazepine **1** and tosylate **5** were stirred in DMF at 100 °C in the presence of K_2CO_3 (0.5 equivalents) during 12 h causing total disappearance of **5**, whereas the benzodiazepine had not reacted. The conditions were then modified by adding 0.1 equivalents of tetrabutylammonium bromide. After 12 h, some of the benzodiazepine had reacted and all the tosylate had disappeared. Extraction and subsequent silica gel chromatography led to pure product **6** in 52% yield. In this reaction, Bu_4NBr did not act as classical phase-transfer catalyst since the solution was homogeneous. The tetrabutylammonium cation presumably operated as an electrophilic catalyst, which promoted polarisation of the C–OTs bond to facilitate nucleophilic attack by N-1. Similar conditions applied to benzodiazepines **2**–**4** gave xylityl diacetal derivatives **7**–**9** in 47–55% yield (Table 1). Complete deacetalation (step (ii)) performed in 9:1 CF_3COOH–water at room temperature gave compounds **10**–**13** in 79–85% yield (Table 1).

Glucopyranosyl derivatives **19**–**22** were prepared from the corresponding anhydro substrates **14a**–**d** [17] using the same conditions as for the xylityl analogues. For step (i), no reaction was observed during 120 h in the absence of Bu_4NBr, whereas the addition of 0.1 equivalents gave the expected compounds **15**–**18** in 60–76% yield. The reaction times depended on the R^3 alkyl chain length (12–120 h, Table 1). Electrophilic catalysis by a tetrabutylammonium cation would likewise promote the C-6–O bond polarisation of the 5,6-anhydro group to facilitate nucleophilic attack of N-1 at the less-hindered C-6 site. Complete deacetalation at room temperature gave pure compounds **19**–**22** in 86–98% yield (Table 1). All protected and deprotected compounds were characterized (Tables 2–7). It is important to note that during step (i), we did not observe the corresponding N-4 condensation products nor those corresponding to N-1,



	R^1	R^2		R^3
1, 6, 10, 15, 19	H	H	**a**	H
2, 7, 11, 16, 20	Cl	H	**b**	*n*-C_8H_{17}
3, 8, 12, 17, 21	H	CH_3	**c**	*n*-$C_{12}H_{25}$
4, 9, 13, 18, 22	Cl	CH_3	**d**	*n*-$C_{16}H_{33}$

Scheme 1. Synthesis of glycosyl benzodiazepines.

Table 1
Reaction times (h) and yields (%) on both condensation and deprotection reactions

Condensation step (i)				Deprotection step (ii)				
Substrate	Time	Product	Yield	Substrate	Time	Product	α:β	Yield
5	12	**6**	52	**6**	1	**10**		82
5	12	**7**	47	**7**	1	**11**		85
5	12	**8**	48	**8**	1	**12**		81
5	12	**9**	55	**9**	1	**13**		79
14a	12	**15a**	67	**15a**	1	**19a**	7:9	89
14b	72	**15b**	66	**15b**	1.5	**19b**	3:2	92
14c	96	**15c**	63	**15c**	1.5	**19c**	7:3	96
14d	120	**15d**	60	**15d**	1.5	**19d**	7:5	94
14a	12	**16a**	70	**16a**	1	**20a**	7:9	93
14b	72	**16b**	70	**16b**	1.5	**20b**	7:5	96
14c	96	**16c**	73	**16c**	1.5	**20c**	7:5	90
14d	120	**16d**	68	**16d**	1.5	**20d**	7:6	90
14a	12	**17a**	76	**17a**	1	**21a**	1:1	91
14b	72	**17b**	60	**17b**	1.5	**21b**	10:6	90
14c	96	**17c**	62	**17c**	1.5	**21c**	3:1	96
14d	120	**17d**	62	**17d**	1.5	**21d**	5:2	85
14a	12	**18a**	72	**18a**	1	**22a**	1:1	89
14b	72	**18b**	68	**18b**	1.5	**22b**	10:7	94
14c	96	**18c**	72	**18c**	1.5	**22c**	6:2	98
14d	120	**18d**	73	**18d**	1.5	**22d**	9:3	86

Table 2
Physicochemical and microanalytical data of protected benzodiazepine derivatives

Compound	$[\alpha]_D^{25}$ $CHCl_3$	Mp (°C)	Formula	Calcd			Found		
				C	H	N	C	H	N
6		156	$C_{20}H_{26}N_2O_6$	61.52	6.71	7.17	61.37	6.89	7.32
7		151	$C_{20}H_{25}ClN_2O_6$	56.54	5.93	6.59	56.71	6.09	6.27
8		oil	$C_{21}H_{28}N_2O_6$	62.36	6.97	6.92	62.19	7.03	6.82
9		oil	$C_{21}H_{27}ClN_2O_6$	57.46	6.20	6.38	57.31	6.12	6.53
15a	−25.6 (*c* 0.9)	oil	$C_{21}H_{26}N_2O_7$	60.28	6.26	6.69	60.17	6.32	6.48
15b	−12.5 (*c* 1.5)	57	$C_{29}H_{42}N_2O_7$	65.64	7.97	5.28	65.78	8.10	5.43
15c	−9.3 (*c* 1.2)	63	$C_{33}H_{50}N_2O_7$	67.55	8.59	4.77	67.73	8.71	4.61
15d	−9.4 (*c* 0.9)	60	$C_{37}H_{58}N_2O_7$	69.12	9.09	4.36	69.27	8.95	4.22
16a	−30.2 (*c* 1.3)	oil	$C_{21}H_{25}ClN_2O_7$	55.69	5.56	6.18	55.78	5.51	6.02
16b	−7.6 (*c* 0.6)	66	$C_{29}H_{41}ClN_2O_7$	76.87	9.12	6.18	76.95	9.19	6.11
16c	−10.7 (*c* 0.7)	60	$C_{33}H_{49}ClN_2O_7$	63.80	7.95	4.51	63.87	8.02	4.65
16d	−5.1 (*c* 1.3)	oil	$C_{37}H_{57}ClN_2O_7$	65.61	8.48	4.13	65.52	8.52	4.29
17a	−45.3 (*c* 1.2)	oil	$C_{22}H_{28}N_2O_7$	61.10	6.52	6.47	61.21	6.48	6.33
17b	−52.3 (*c* 1.0)	55	$C_{30}H_{44}N_2O_7$	66.15	8.14	5.14	66.08	8.17	5.21
17c	−55.4 (*c* 1.2)	48	$C_{34}H_{52}N_2O_7$	67.97	8.72	4.66	68.11	8.69	4.51
17d	−64.6 (*c* 1.0)	oil	$C_{38}H_{60}N_2O_7$	69.48	9.20	4.26	69.55	9.17	4.34
18a	−76.2 (*c* 0.6)	oil	$C_{22}H_{27}ClN_2O_7$	56.59	5.83	5.99	56.64	5.87	6.09
18b	−82.8 (*c* 1.1)	40	$C_{30}H_{43}ClN_2O_7$	62.22	7.48	4.83	62.14	7.39	4.75
18c	−121.6 (*c* 1.0)	62	$C_{34}H_{51}ClN_2O_7$	64.28	8.09	4.41	64.39	7.95	4.22
18d	−73.6 (*c* 1.1)	oil	$C_{38}H_{59}ClN_2O_7$	66.02	8.60	4.05	65.91	8.68	3.88

Table 3
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
10			72	$C_{14}H_{18}N_2O_6$	54.19	5.85	9.03	54.35	5.97	8.79
11			oil	$C_{14}H_{17}ClN_2O_6$	48.77	4.97	8.13	48.56	5.09	7.86
12			71	$C_{15}H_{20}N_2O_6$	55.55	6.22	8.64	55.76	6.31	8.93
13			oil	$C_{15}H_{19}ClN_2O_6$	50.22	5.34	7.81	50.48	5.29	8.02
19a	7:9	−50.3; 19.9 (*c* 1.0) [a]	97	$C_{15}H_{18}N_2O_7$	53.25	5.36	8.28	53.48	5.42	8.57
19b	3:2	−40.2 (*c* 1.1)	79	$C_{23}H_{34}N_2O_7$	61.31	7.60	6.21	60.93	7.49	5.93
19c	7:3	−29.8 (*c* 1.1)	70	$C_{27}H_{42}N_2O_7$	64.00	8.35	5.53	63.85	8.53	5.19
19d	7:5	−28.9 (*c* 1.0)	75	$C_{31}H_{50}N_2O_7$	66.16	8.95	4.98	66.37	9.17	5.31
20a	7:9	40.8; 18.8 (*c* 0.7) [a]	86	$C_{15}H_{17}ClN_2O_7$	48.33	4.60	7.51	48.09	4.48	7.27
20b	7:5	−44.1 (*c* 1.0)	82	$C_{23}H_{33}ClN_2O_7$	56.96	6.86	5.77	56.71	6.69	5.50
20c	7:5	−35.4 (*c* 1.0)	86	$C_{27}H_{41}ClN_2O_7$	59.93	7.64	5.17	60.15	7.78	4.93
20d	7:6	−35.0 (*c* 0.7)	80	$C_{31}H_{49}ClN_2O_7$	62.35	8.27	4.69	62.63	8.45	4.33
21a	1:1	58.4; 14.7 (*c* 0.7) [a]	81	$C_{16}H_{20}N_2O_7$	54.54	5.72	7.95	54.35	5.86	7.78
21b	10:6	−38.6 (*c* 1.0)	90	$C_{24}H_{36}N_2O_7$	62.05	7.81	6.03	62.41	7.59	6.30
21c	3:1	−13.1 (*c* 1.1)	90	$C_{28}H_{44}N_2O_7$	64.61	8.52	5.38	64.68	8.41	5.77
21d	5:2	−24.7 (*c* 1.0)	82	$C_{32}H_{52}N_2O_7$	66.64	9.09	4.86	66.49	8.96	5.18
22a	1:1	79.7; 22.2 (*c* 0.6) [a]	86	$C_{16}H_{19}ClN_2O_7$	49.68	4.95	7.24	49.87	5.11	6.98
22b	10:7	−35.1 (*c* 1.1)	108	$C_{24}H_{35}ClN_2O_7$	57.77	7.07	5.61	57.59	7.05	5.27
22c	6:2	−65.3 (*c* 1.0)	75	$C_{28}H_{43}ClN_2O_7$	60.58	7.81	5.04	60.49	7.73	5.38
22d	9:3	−29.6 (*c* 1.0)	88	$C_{32}H_{51}ClN_2O_7$	62.88	8.41	4.58	63.12	8.39	4.27

[a] Measured in MeOH with fresh solution and after 3 days.

N-4 double condensation. Exclusive condensation of all polyhydroxylated Su groups at N-1 was proven by the NMR spectra: the H-4 proton was present, while the H-1 signal disappeared. We also observed that all compounds having a Su group displayed slow interconversion of conformers (Fig. 1) on the NMR time-scale in $CDCl_3$ and Me_2SO-d_6 at room temperature (Tables 4–7). This interconversion is not very fast, since the ^{13}C NMR signals are split. The separation of signals is larger for the glucopyranosyl derivatives than for the xylityl ones, while the corresponding benzodiazepines show coalescence into a single resonance. Similar effects were observed with 1,4-benzodiazepin-2,5-dione analogues by exploring a temperature range from 37 to 100 °C [13].

Water solubility (Sw), surface tension (γ) *and critical micelle concentration (CMC).*—Table 8 reports experimental Sw, CMC and γ values at 25 °C.

Benzodiazepines **1**–**4** have Sw values from 0.9 to 4.2 10^{-3} mol L^{-1}, this variation can be attributed to the chlorine atom (R^1), which decreases Sw and to the methyl group (R^2), which increases it (see 1,2 pairs, 1,3 pairs, and 2,4 pairs). Xylityl derivatives **10**–**13** have Sw values 7.4–25 times higher than the corresponding benzodiazepines **1**–**4**; these values are still higher for glucopyranosyl derivatives **19a**–**22a** (from 58 to 204 times higher than those of compounds **1**–**4**). The difference in the polyhydroxylated group effect is evidently a consequence of the acyclic xylityl structure, which allows conformations having two or four neighbouring OH groups in cis disposition, allowing intramolecular hydrogen-bonding that decreases the hydrophilic character; in contrast the cyclic glucopyranosyl structure allows intramolecular hydrogen bondings only between the C-1–OH and C-2–OH groups in the α configuration.

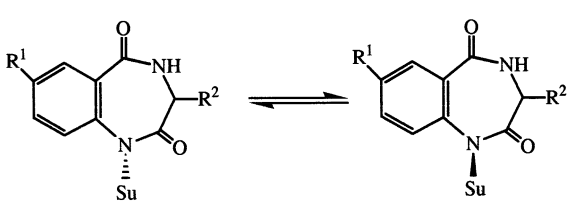


Fig. 1. Conformational isomerism in benzodiazepine derivatives.

Table 4
^{13}C NMR data of **1** and corresponding glycosyl compounds **6**, **10**, **15a**,**b**, and **19a**,**b**

Product	Benzodiazepine moiety									Sugar moiety								R^3 Chain	
	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-1	C-2	C-3	C-4	C-5	C-6	CMe_2	CMe_2	C-1	CH_3
1 [a]	171.0	44.3	167.9	130.6	123.7	132.1	120.8	137.0	125.4										
6 [a]	169.7	45.4	169.3	130.4	126.2	132.3	122.9	140.7	127.9	50.6	75.5	79.0	75.0	65.5		109.6	25.2		
						132.5	123.4			51.7		79.2	75.3			110.0	26.7		
10 [b]	170.2	45.0	168.4	129.4	125.7	131.6	123.0	140.1	129.2	51.2	67.9–72.4			62.1					
	171.3		168.9				123.5	140.5	129.4					62.3					
15a [a]	169.7	45.3	168.2	130.0	124.2	132.0	123.5	140.1	129.4	104.8	84.7	73.4	82.2	63.7	50.9	110.8	26.3		
					125.3	132.4		141.9	129.7				82.5	65.8	51.9		26.9		
19a [b]	169.3	45.0	168.4	129.0	125.6	131.8	123.5	139.7	129.2	92.0 (α)	74.7 (α)	67.7–73.4			48.8 (α)				
	169.4		168.6	129.4			123.7	141.6		96.9 (β)	76.2 (β)				49.5 (β)				
15b [a]	170.6	45.4	169.3	130.4	126.3	132.4	122.6	139.7	127.7	105.0	82.0	82.3	81.1	66.8	51.5	111.6	25.8	70.6	14.0
	171.4		169.5			132.6	123.2	141.1	128.9		82.1		81.3	69.1	54.3		26.6	70.9	
19b [a]	170.9	45.5	169.7	129.0	126.4	132.3	123.8	138.7	126.9	91.9, 92.3 (α)	81.5, 81.9 (α)	67.4–74.6			47.7, 48.2 (α)			73.0	14.0
	171.1		169.9	129.7	126.7	132.7		141.7	127.0	96.6, 96.9 (β)	83.8, 84.0 (β)				50.6 (β)			73.4	

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

Table 5
^{13}C NMR data of **2** and corresponding glycosyl compounds **7**, **11**, **16a**,**b**, and **20a**,**b**

Product	Benzodiazepine moiety									Sugar moiety								R^3 Chain	
	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-1	C-2	C-3	C-4	C-5	C-6	CMe_2	CMe_2	C-1	CH_3
2 [a]	171.0	44.2	167.0	130.0	136.0	132.0	122.9	127.8	127.0										
7 [a]	168.9	45.3	168.1	131.9	139.3	132.3	124.7	130.1	129.2	50.9	75.2	78.9	74.8	65.6		109.7			
						132.6	125.1			51.9			74.4			110.1	26.7		
11 [b]	169.0	44.9	168.4	130.9	138.7	131.4	126.0	129.1	128.5	51.3	67.8–72.5			62.2					
			168.6	131.0	139.7		126.4	129.3						62.4					
16a [a]	170.6	45.0	170.3	133.8	137.4	133.1	124.7	129.9	127.8	104.8	80.5	84.4	74.3	66.3	51.2	112.5	25.8		
					139.2	133.4	125.3		128.4					66.7	53.2		26.2		
20a [b]	169.0	44.8	166.9	130.7	138.7	131.6	125.7	129.5	128.4	92.0 (α)	74.5 (α)	67.7–73.7			48.8 (α)				
	169.2		167.0		138.8		125.9	129.7	128.7	96.9 (β)	76.1 (β)				49.8 (β)				
16b [a]	169.9	45.4	167.9	132.0	138.31	132.5	124.2	130.1	129.2	105.1	82.0	82.5	80.9	67.0	51.9	111.7	25.9	70.5	14.0
	170.8				39.5		124.9							68.9	54.0		26.7	70.8	
20b [a]	170.2	45.4	169.1	130.9	137.7	132.1	125.4	130.3	129.3	92.0, 92.3 (α)	81.5, 81.8 (α)	67.5–74.5			47.7, 48.1 (α)			73.1	14.0
	170.6		169.4	131.0	140.3	132.5			129.6	96.6, 96.8 (β)	83.8, 84.0 (β)				50.9 (β)			73.4	

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

Table 6
^{13}C NMR data of **3** and corresponding glycosyl compounds **8**, **12**, **17a**,**b**, and **21a**,**b**

Product	Benzodiazepine moiety										Sugar moiety								R^3 Chain	
	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	CH_3	C-1	C-2	C-3	C-4	C-5	C-6	CMe_2	CMe_2	C-1	CH_3
3 [a]	172.0	47.1	167.6	130.2	123.7	132.0	120.7	136.6	126.7	13.6										
8 [a]	170.7	48.0	168.7	129.9	125.9	132.1	123.0	140.2	128.6	14.0	51.2	75.3	78.9	74.9	65.5		109.5	25.1		
	170.9		168.9	130.0		132.4	123.4	140.4	129.4		52.2						109.9	26.8		
12 [b]	170.7	47.5	167.5	129.6	125.8	131.7	123.0	140.0	129.1	13.9	51.2	67.8–72.3			62.3					
	170.9		169.9				123.5	140.7	129.3						62.4					
17a [a]	171.6	48.3	169.6	129.5	126.2	132.5	123.3	141.3	129.0	13.7	105.0	84.8	74.2	81.6	67.8	50.8	111.5	26.0		
						132.8	123.7		129.5				74.5	82.0	69.8	53.5		26.6		
21a [b]	170.5	47.7	168.1	130.0	125.2	131.7	123.5	140.3	128.4	13.9	91.1, 91.9 (α)	74.5 (α)	66.2–73.4			49.1 (α)				
			168.9	130.2	125.4	131.9	123.8		129.0		96.7, 97.0 (β)	76.3, 76.6 (β)				50.5 (β)				
17b [a]	170.6	48.3	169.3	130.4	126.3	132.4	122.6	139.7	127.7	14.0	105.1	82.2	82.5	80.9	67.1	52.3	111.6	26.1	70.6	14.1
	171.4		169.5			132.6	123.2	141.1	128.9					81.3	69.8	54.9		26.7	70.9	
21b [a]	171.2	48.8	170.1	130.5	126.7	132.3	123.7	138.2	129.0	13.9	92.0, 92.3 (α)	81.9 (α)	66.5-74.4			47.9, 48.8 (α)			73.2	14.0
	171.3		170.3	130.7	127.1	132.8	123.9	141.5	129.5		96.7, 97.0 (β)	83.9, 84.0 (β)				51.0 (β)			73.7	

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

Table 7
^{13}C NMR data of **4** and corresponding glycosyl compounds **9**, **13**, **18a**,**b**, and **22a**,**b**

Product	Benzodiazepine moiety										Sugar moiety								R^3 chain	
	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	CH_3	C-1	C-2	C-3	C-4	C-5	C-6	CMe_2	CMe_2	C-1	CH_3
4 [a]	171.9	47.1	166.3	129.5	135.6	132.0	123.0	127.7	127.6	13.5										
9 [a]	170.4	48.0	167.5	131.5	138.8	132.0	124.7	129.	129.5	13.7	51.2	75.3	78.9	74.9	65.5		109.5	25.1		
	170.5		167.7		139.0	132.3	125.2	130.8	129.7		52.2						109.9	26.8		
13 [b]	170.4	47.9	168.9	131.3	138.8	131.8	125.9	128.3	127.8	13.8	51.6	67.5–72.3			62.2					
				131.7	139.7	132.0	126.3	129.0	127.9						62.5					
18a [a]	171.2	48.3	167.3	132.0	138.0	131.9	124.3	130.8	129.4	14.0	105.0	84.6	74.4	81.6	66.0	51.0	111.6	25.6		
	172.2		167.7		139.6	132.5	125.0								66.4	53.6		26.3		
22a [b]	170.2	47.6	166.7	129.2	139.8	131.3	125.7	127.9	126.7	13.8	92.0 (α)	74.5 (α)	69.3–73.6			48.6 (α)				
			167.3	129.4	140.1	131.7	126.0	128.1			97.0 (β)	76.3 (β)				50.1 (β)				
18b [a]	171.3	48.3	167.3	131.8	138.0	132.5	124.3	130.9	129.7	14.0	105.2	81.9	82.3	80.8	67.1	52.3	111.7	25.9	70.6	14.1
	172.3		167.6		139.2		125.1		129.8			82.1	82.5	81.2	69.5	54.4		26.7	70.8	
22b[a]	170.4	48.8	168.8	131.1	137.3	132.0	125.5	130.2	129.0	13.9	92.0, 92.3 (α)	81.7 (α)	66.3–74.6			48.0, 48.5 (α)			73.2	14.0
	170.8		169.1	131.6	140.0	132.5	126.0		129.3		96.7, 97.0 (β)	83.9 (β)				51.0, 51.4 (β)			73.5	

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

Table 8
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**	**10**	**19a**	**19b**	**19c**	**19d**	**2**	**11**	**20a**	**20b**	**20c**	**20d**
Sw	1.4	35	180	4.5	1.2	0.8	0.9	23	180	5.2	1.2	0.9
CMC				2.7						2.9		
γ		33 [a]	44 [a]	37	47 [a]	48 [a]		27 [a]	27 [a]	37	39 [a]	51 [a]
Product	**3**	**12**	**21a**	**21b**	**21c**	**21d**	**4**	**13**	**22a**	**22b**	**22c**	**22d**
Sw	4.2	31	240	6.4	0.8	0.3	2.2	20	200	3.0	1.3	0.7
CMC				5.6						2.2		
γ		44 [a]	41 [a]	29	32	33		29 [a]	36 [a]	41	42 [a]	50 [a]

[a] At Sw value.

The R^3 alkyl chain in the glucopyranosyl group decreases the water solubility as its length increases. Thus the compounds with $R^3 = n\text{-}C_8H_{17}$ (**19b**–**22b**) are more soluble than the benzodiazepines **1**–**4** (1.4–5.8 times higher), whereas compounds with $R^3 = n\text{-}C_{12}H_{25}$ and $n\text{-}C_{16}H_{33}$ (**19c**,**d**–**22c**,**d**) are less soluble. Moreover, compounds **19b**–**22b** give micelles with CMC from 2.7 to 5.6 10^{-3} mol L^{-1} and corresponding γ values from 29 to 37 mN m^{-1}. In contrast, CMC was not observed with either polyhydroxylated derivatives without an alkyl chain (**10**–**13** and **19a**–**22a**) nor with glucose derivatives having $R^3 = n\text{-}C_{12}H_{25}$ and $n\text{-}C_{16}H_{33}$ (**19c**,**d**–**22c**,**d**). The first series does not have the required 'linear' hydrophobic tail (such as an alkyl chain) to form micelles; the compounds of the second series are not soluble enough to allow liquid surface saturation, so the CMC is not reached.

The surface activity of the derivatives may favor nonspecific interactions and may add energetic barriers impairing transfer of the drug from a self-aggregating structure to the binding site.

3. 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 Jasco digital polarimeter 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 high-performance liquid chromatography (HPLC) (Waters 721), using either reversed-phase columns RP-18 (E. Merck) or PN 27-196 (Waters), or CPG (Girdel) with columns of either OV 17 or SE 30. Analytical thin-layer chromatography (TLC) was performed on E. Merck aluminium-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), *and critical micelle concentration (CMC).*—The water solubility (Sw) was performed for each sample at 25 °C. For the CMC study, an initial aq soln (C_0) of each compound was prepared at 25 °C. Several samples were obtained by diluting S_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 a thermostated cell (25 °C). The CMC was determined from a plot of $\gamma = f(\log C)$. The classical slope change coordinates gave CMC and corresponding γ values, respectively.

General procedure for condensation step (i).—To a solution of benzodiazepine, K_2CO_3 (0.5 equiv) and Bu_4NBr (0.1 equiv) in DMF (33 g L^{-1}) at 100 °C, was added activated carbohydrate derivative (1 equiv). When no more starting material was detected by TLC or HPLC, the mixture was concentrated under diminished pressure. The residue was extracted with Et_2O–water, 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 petroleum ether–acetone and the solid product was recrystallized from Et_2O (Tables 1–7).

General procedure for deprotection step (ii).—The protected derivative was added to a stirred solution of 9:1 CF_3COOH–water (100 g L^{-1}) at rt. When no more starting material was detected by TLC or HPLC, the solution was concentrated to dryness under diminished pressure. The crude product was purified by column chromatography using petroleum ether–acetone and the solid product was recrystallized from Et_2O (Tables 1–7).

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