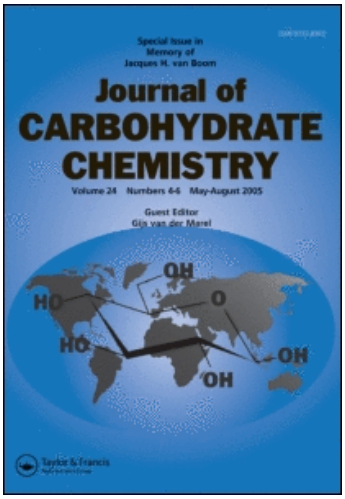

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis and Amphiphilic Behavior of *N,N*-Bis-glucosyl-1,5-benzodiazepin-2,4-dione

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Online publication date: 16 November 2004

To cite this Article Lakhrissi, Brahim , Essassi, El Mokhtar , Massoui, Mohamed , Goethals, Gérard , Lequart, Vincent , Monflier, Eric , Cecchelli, Roméo and Martin, Patrick(2004) 'Synthesis and Amphiphilic Behavior of *N,N*-Bis-glucosyl-1,5-benzodiazepin-2,4-dione', Journal of Carbohydrate Chemistry, 23: 6, 389 — 401

To link to this Article: DOI: 10.1081/CAR-200039373

URL: http://dx.doi.org/10.1081/CAR-200039373

JOURNAL OF CARBOHYDRATE CHEMISTRY
Vol. 23, No. 6&7, pp. 389–401, 2004

Synthesis and Amphiphilic Behavior of *N*,*N*-Bis-glucosyl-1,5-benzodiazepin-2,4-dione

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CONTENTS

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DOI: 10.1081/CAR-200039373
0732-8303 (Print); 1532-2327 (Online)

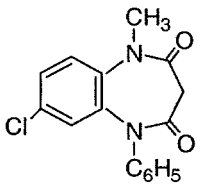
ABSTRACT

Glucosyl-1,5-benzodiazepin-2,4-diones were synthesized in order to study the influence of the glucidic moiety on the amphiphilic behaviour. The glucosyl groups include 6-deoxy-D-glucopyranos-6-yl and 6-deoxy-3-*O*-R-D-glucopyranos-6-yl ($R = n - C_nH_{2n+1}$; $n = 1$, 8, 10 and 12). Variation in the length of the hydrocarbon chain allowed comparison of such amphiphilic data as water solubility (Sw) and surface tension (γ) values. At 25°C, the glucopyranosyl benzodiazepines with R = H and CH_3 show a higher water solubility than the starting 1,5-benzodiazepin-2,4-diones. Some other glucidic benzodiazepine derivatives with an appropriate alkyl chain at C-3 carbon of the D-glucopyranose present a variable hydrosolubility and surface tension γ values close to 43 to 46 $mN \cdot m^{-1}$ at the corresponding saturation. Moreover, according to preliminary tests, these compounds seem to show a better affinity for the blood brain barrier.

Key Words: Glucosyl-1,5-benzodiazepin-2,4-diones; Water solubility; Surface tension.

INTRODUCTION

1,5-Benzodiazepin-2,4-diones and 1,4-benzodiazepin-1,5-diones constitute a class of heterocyclic compounds presenting interesting pharmacological properties.[1–8] They have found widespread therapeutic use across a range of disease states. They have a large application field by their five actions: anxiolytic, anticonvulsivant, myorelaxant, sedative, and hypnotic.



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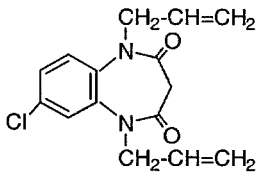

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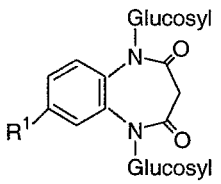
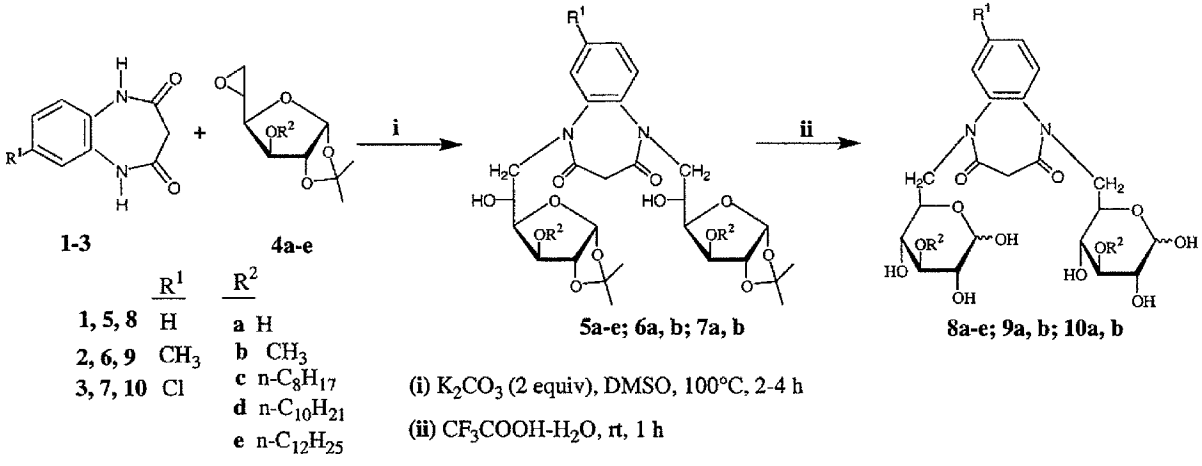


III

Clobazam (1-methyl-5-phenyl-7-chloro-1,5-benzodiazepin-2,4-dione) **I**[9,10] is an example of this important family of therapeutic agents. Recent works showed that 7-chloro-1,5-diallyl-1,5-benzodiazepin-2,4-diones **II** induce a sedative effect on the central nervous system[11] comparable with that of Clobazam.

Because of the important lipophilic character of benzodiazepines, their passage in the central nervous system is fast.[11,12] Their action is then limited by a very low solubility in water and biological fluids. Polyhydroxylated compounds may be linked to the hydrophobic benzodiazepine moiety to increase the hydrophilic character of the latter. Therefore, the synthesis of modified benzodiazepines has been the subject of intense research.[13–16] In recent work,[17] we attached a glycopyranosyl group to N–1 of benzodiazepin-2, 5-dione and benzodiazepin-5,11-dione derivatives to increase the water solubility and to confer amphiphilic properties.



Scheme 1. Synthesis of the *N,N*-bis-(6-deoxyglucos-6-yl)-1.5-benzodiazepin-2,4-diones.

Here we describe the synthesis of a set of typical compounds **III** (Sch. 1) with $R^1 = H$, CH_3, and Cl, in which two 6-deoxy-D-glucopyranos-6-yl or 6-deoxy-3-*O*-R^2-D-glucopyranos-6-yl ($R^2 = n - C_nH_{2n+1}$; $n = 1$, 8, 10, and 12), were grafted regiospecifically at N–1 and N–5 of 1,5-benzodiazepin-2,4-diones. The variation of the alkyl chain length on the sugar unit allowed comparison amphiphilic data such as water solubility (Sw) and the corresponding surface tension (γ) values, which may influence the biological effect of this new range of benzodiazepine derivatives. Moreover, the presence of an alkyl chain ($R^2 = n - C_nH_{2n+1}$; $n = 8$, 10, and 12) can also improve the transmembrane anchoring of these compounds.[18] The goal of this work was to study the amphiphilic properties of these new compounds to be able to select and test some of them for their capacity to cross over the blood brain barrier.

RESULTS AND DISCUSSION

The benzodiazepin-2,4-diones (**1–3**) were prepared following methods described in the literature.[19,20] The corresponding glucopyranose derivatives were synthesized following Sch. 1. The glucopyranosyl derivatives **8–10** were obtained by regiospecific condensation (step i) of the benzodiazepines **1–3** on the anhydro glucosyl substrates **4a–e**[21] in DMSO, followed by total deacetalation (step ii).[22]

We carried out the grafting of the glucofuranose groups at site N–1 and N–5 of the 1,5-benzodiazepin-2,4-diones while reacting benzodiazepine **1–3** on the 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose **4a** in DMSO. With the aim of modulating hydrophilic-lipophilic balance, we replaced **4a** by homologuous 5,6-anhydro-3-*O*-alkyl-1,2-*O*-isopropylidene-α-D-glucofuranose **4b-e** ($R^2 = n - C_nH_{2n+1}$; $n = 1$, 8, 10 and 12). Acidic hydrolysis of the condensation products **5–7** at rt gave pure **8–10**, respectively, in 70–96% yield.

The ^{13}C NMR spectra always show a pyranose form for the glucose moiety (α–C1 and β–C1 close to 92 and 96 ppm, respectively). Moreover, all the glucosyl derivatives displayed slow conformer interconversion (Fig. 1) on the NMR time scale in $CDCl_3$ or

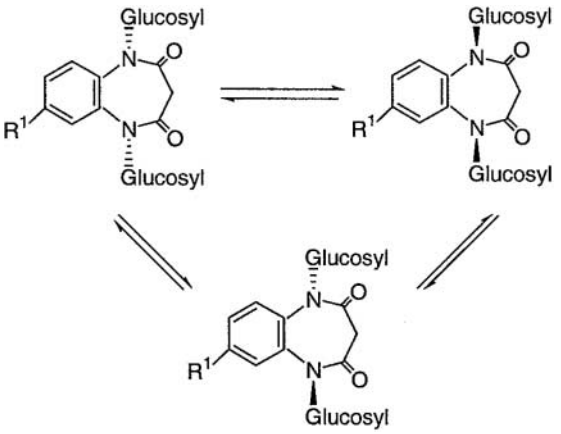


Figure 1. Possible isomerization in benzodiazepine derivatives.

Me_2SO-d_6 (double signals) at rt. Similar effect was observed in our recent study[17] with 1,4-benzodiazepin-2,5-dione analogues. All the benzodiazepines undergo N–1 and N–5 double condensation which was proved by NMR: the amide protons on N–1 and N–5 were absent in the spectra of the products.

It is to be noted that the derivative **5a** was also obtained by using 4 : 1 toluene-DMSO as the solvent instead of DMSO alone. Moreover under comparable conditions, substitution of the methylated glucosyl unit (**4b**) also occurred on each nitrogen atom, after 2 hours, but gave exclusively the unexpected product **11** (Sch. 2, 51% yield) which was identified [1-*N*-(6-deoxy-5-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranos-6-yl)-3-*N*-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranos-6-yl]-1,3-benzimidazol-2-one (**11**) by NMR spectroscopy.

Thus, in addition to *N,N'*-bis-substitution, a rearrangement also occurred resulting in ring contraction from a 1,5-diazepin-2,4-dione to 1,3-imidazol-2-one system along with simultaneous acetylation on C_5–OH of one of the glucose units. This unexpected structure was confirmed by analysis of the ^{13}C NMR spectra. The carbonyl of acetyl and imide groups appeared at 170.1 and 156.9 ppm, respectively. Subsequent deprotection of **11** was run in CF_3COOH–H_2O to give benzimidazolone derivative **12** in 81% overall yield.

As anticipated, the presence of a long alkyl chain (compounds **8c–e**) prevented any increase in water solubility. We did not consider it useful to graft alkylated derivatives **4c–e** on compounds **2** and **3**.

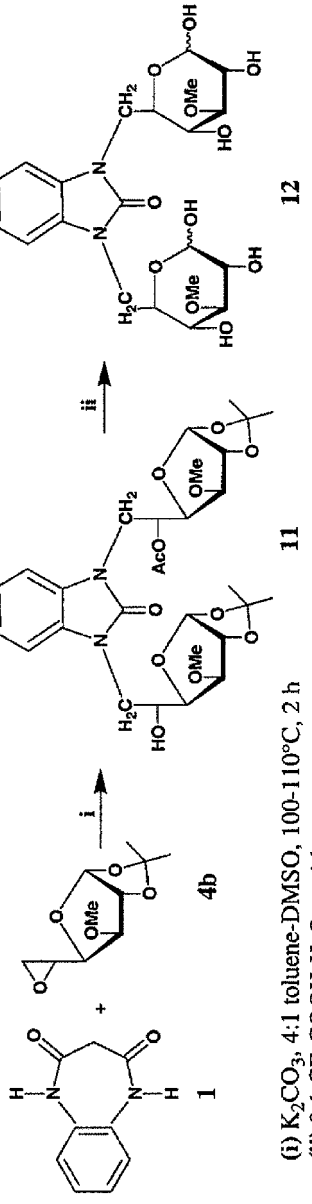
Data provided in Table 1 show that the benzodiazepines **1–3** have water solubility lower than $10^{-4}\,mol \cdot L^{-1}$, whereas the graft of two 6-deoxy-D-glucopyranos-6-yl **8a–10a** or two 6-deoxy-3-*O*-methyl-D-glucopyranos-6-yl **8b–10b** increases this factor more than 2000 times. In contrast, the ability of analogues **8c–e** bearing a long alkyl chain (C_8H_{17} to $C_{12}H_{25}$) is close to that of the benzodiazepines **1–3**. When measuring the surface tension γ at different concentrations, all studied compounds show a slope change, which characterizes the micelle formation (no CMC), as previously observed for 1-*N*-(6-deoxy-3-*O*-octyl-D-glucopyranos-6-yl)-1,4-benzodiazepin-2,5-dione.[17]

This new family of compounds does not show any thermotropic or lyotropic liquid crystalline properties. Thus, it is believed that 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.

In summary, this work provides a stereocontrolled synthesis of benzodiazepine analogues. Some of them showed an important hydrosolubility, and tests are ongoing in our laboratories in order to quantify the cross rate of these compounds through the blood brain barrier. Biological evaluation is run on the model worked out by Cecchelli and coll.[23] Preliminary results carried out with these new families of glucosylated benzodiazepine indicate that they have a better affinity for the blood brain barrier than the native compounds (**1–3**). Other thorough tests are currently in progress and will be reported in due course. The presence of a lipophilic chain seems to increase affinity even more.

EXPERIMENTAL

General methods. Melting points were determined on an automatic electrothermal apparatus, and are uncorrected. Optical rotations, for solutions in $CHCl_3$ or MeOH, were measured with a digital polarimeter JASCO model DIP-370, using a sodium lamp



Scheme 2. Rearrangement obtained using toluene-DMSO as solvent.

Table 1. Sw (10^{-3} mol · L^{-1}) and γ (mN · m^{-1}) of benzodiazepine derivatives at 25°C.

Product	1	8a	8b	8c	8d	8e	2	9a	9b	3	10a	10b
Sw	<0.1	>200	>200	0.07	0.06	0.05	<0.1	>200	>200	<0.1	>200	>200
γ	—	41[a]	52[a]	45[b]	46[b]	43[b]	—	47[a]	46[a]	—	56[a]	42[a]

[a]1 g · L^{-1} solution.
[b]at Sw value.

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 IUT de Béthune, Département Chimie (Béthune, France). Reactions were monitored by either HPLC (Waters 721), using the reverse phase columns RP-18 (Merck) or PN 27-196 (Waters), or by GC (Girdel) with OV 17 or SE 30 columns. Analytical TLC were 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). The measurement of water solubility, Sw, was performed for each sample 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 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 the thermostated cell (25°C).

General procedure for condensation (step i). To a solution of benzodiazepine, K_2CO_3 (2.0 equiv) in DMSO or 4 : 1 toluene-DMSO (33 g · L^{-1}) at 100°C, was added activated carbohydrate derivative (2 equiv). When no more starting material was detected by TLC or HPLC, the mixture was concentrated under diminished pressure. The residue was extracted with toluene-water and the organic phase was separated, washed with an aqueous solution saturated in NaCl, dried (Na_2SO_4), and concentrated under diminished pressure. The crude product was chromatographed on silica gel with pressure (hexane-acetone, gradient).

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 reduced pressure. The crude product was chromatographed on silica gel with pressure (hexane-acetone, gradient).

1,5-Bis-(6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (5a). white solid. 73% yield. mp 153–155°C; $[\alpha]_D^{27}$ −11.5° (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ **glucose** 5.90, 5.82 (2d, 2H, $J_{1,2} = 3.6$ Hz, H-1), 4.44 (2d, 2H, $J_{2,3} = 0.0$ Hz, H-2), 4.30, 4.20 (2d, 2H, $J_{3,4} = 2.2$ Hz, H-3), 4.13 (m, 2H, H-5), 4.05 (2dd, 2H, $J_{4,5} = 8.3$ Hz, H-4), 3.90-3.61 (m, 4H, $J_{6a,6b} = 12.4$ Hz, H-6), 1.30–1.15 (4s, 12H, CH_{3iso}), **benzodiazepine** 7.18–7.00 (m, 4H, H_{arom}), 3.30–3.20 (m, 2H, H_{Bzd}); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 111.6, 111.4 (C_{iso}), 105.0 (C-1), 84.9 (C-2), 81.5, 81.2 (C-4), 74.5, 74.2 (C-3), 67.2, 66.6 (C-5), 52.9, 50.1 (C-6), 26.8–26.1 (CH_{3iso}), **benzodiazepine** 167.2, 166.4 (C-2, C-4), 137.7, 133.9 (C-10, C-11), 127.3, 127.0 (C-7, C-8), 124.2, 123.8 (C-6, C-9), 44.6 (C-3).

Anal. Calcd for $C_{27}H_{36}N_2O_{11}$ (564): C, 57.44; H, 6.42; N, 4.96. Found: C, 57.25; H, 6.39; N, 4.64.

1,5-Bis-(6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (5b). white solid. 78% yield. mp 143–145°C; $[\alpha]_D^{27}$ −30.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ **glucose** 5.90, 5.70 (2d, 2H, $J_{1,2} = 3.6$ Hz, H-1), 4.45 (2d, 2H, $J_{2,3} = 0.0$ Hz, H-2), 4.20 (m, 2H, $J_{5,6a} = 2.3$ Hz, $J_{5,6b} = 6.1$ Hz, H-5), 4.05 (dd, 2H, $J_{4,5} = 7.7$ Hz, H-4), 3.90 (2d, 2H, $J_{3,4} = 2.6$ Hz, H-3), 3.85 (dd, 2H, $J_{6a,6b} = 14.7$ Hz, H-6b), 3.75 (dd, 2H, H-6a), 3.22, 3.18 (2s, 6H, O-CH_3), 1.30–1.10 (m, 12H, CH_{3iso}), **benzodiazepine** 7.30–7.00 (m, 4H, H_{arom}), 3.35–3.23 (m, 2H, H_{Bzd}); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 111.5, 111.3 (C_{iso}), 105.1, 105.0 (C-1), 83.8, 83.7 (C-3), 81.4, 81.3 (C-2), 81.0 (C-4), 66.8 (C-5), 57.9 (O-CH_3), 53.3, 49.6 (C-6), 26.6–26.0 (CH_{3iso}), **benzodiazepine** 166.9, 166.0 (C-2, C-4), 138.0, 134.0 (C-10, C-11), 126.9, 126.5 (C-7, C-8), 124.2, 123.5 (C-6, C-9), 44.4 (C-3).

Anal. Calcd for $C_{28}H_{38}N_2O_{11}$ (578): C, 58.12; H, 6.62; N, 4.84. Found: C, 57.97; H, 6.58; N, 4.87.

1,5-Bis-(6-deoxy-1,2-*O*-isopropylidene-3-*O*-octyl-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (5c). white solid. 67% yield. mp 43–45°C; $[\alpha]_D^{27}$ −23.3° (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ **glucose** 5.95, 5.80 (2d, 2H, $J_{1,2} = 3.8$ Hz, H-1), 4.50 (2d, 2H, H-2), 4.20 (m, 2H, $J_{5,6a} = 2.4$ Hz, Hz, H-5), 4.05 (dd, 2H, $J_{4,5} = 7.2$ Hz, H-4), 3.90 (2d, 2H, $J_{3,4} = 3.3$ Hz, H-3), 3.85 (m, 2H, $J_{6a,6b} = 15.1$ Hz, H-6b), 3.75 (dd, 2H, H-6a), 3.54, 3.42 (2dt, 4H, 2O-CH_2^{α}), 1.45 (quint, 4H, $2CH_2^{\beta}$), 1.25 (m, 4H, $2CH_2^{\gamma}$), 1.21–1.18 (m, 16H, $8CH_2$), 0.90 (t, 6H, $2CH_3^{\omega}$), 1.40–1.10 (m, 12H, CH_{3iso}), **benzodiazepine** 7.30–7.02 (m, 4H, H_{arom}), 3.34–3.23 (m, 2H, H_{Bzd}); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 112.2, 111.9 (C_{iso}), 105.6 (C-1), 83.1 (C-3), 82.7, 82.6 (C-2), 81.6, 81.4 (C-4), 71.4, 71.3 (2O-CH_2^{α}), 68.2, 67.3 (C-5), 54.5, 50.5 (C-6), 30.0, 29.8 ($2CH_2^{\beta}$), 32.2, 30.0, 29.6 ($6CH_2$), 27.2–26.6 (CH_{3iso}), 26.4, 26.3 ($2CH_2^{\gamma}$), 23.0 ($2CH_3^{\omega-1}$), 14.5 ($2CH_3^{\omega}$), **benzodiazepine** 167.5, 166.6 (C-2, C-4), 138.6, 134.8 (C-10, C-11), 127.5, 127.1 (C-7, C-8), 124.7, 124.1 (C-6, C-9), 44.9 (C-3).

Anal. Calcd for $C_{35}H_{52}N_2O_{11}$ (676): C, 62.12; H, 7.74; N, 4.14. Found: C, 62.05; H, 7.69; N, 4.18.

1,5-Bis-(6-deoxy-3-*O*-decyl-1,2-*O*-isopropylidene-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (5d). white solid. 65% yield. mp 39–41°C; $[\alpha]_D^{27}$ −20.9° (*c* 1.0, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 112.0, 111.8 (C_{iso}), 105.5 (C-1), 83.1 (C-3), 82.7, 82.6 (C-2), 81.6, 81.5 (C-4), 71.4, 71.1 (2O-CH_2^{α}), 68.2, 67.3 (C-5), 54.5, 50.5 (C-6), 30.0–22.5 (CH_2), 27.2–26.6 (CH_{3iso}), 14.5 ($2CH_3^{\omega}$), **benzodiazepine** 167.4, 166.9 (C-2, C-4), 138.6, 136.5 (C-10, C-11), 127.5, 127.1 (C-7, C-8), 124.7, 124.1 (C-6, C-9), 44.9 (C-3).

Anal. Calcd for $C_{37}H_{56}N_2O_{11}$ (704): C, 63.05; H, 8.01; N, 3.97. Found: C, 63.00; H, 7.95; N, 4.02.

1,5-Bis-(6-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (5e). white solid. 66% yield. mp 36–38°C; $[\alpha]_D^{27}$ −20.2° (*c* 0.9, $CHCl_3$); δ **glucose** 112.3, 111.9 (C_{iso}), 105.8 (C-1), 83.0 (C-3), 82.5 (C-2), 81.6, 81.1 (C-4), 71.4, 71.3 (2O-CH_2^{α}), 68.2, 67.8 (C-5), 54.5, 50.7 (C-6), 30.0–21.8 (CH_2), 27.2–26.8 (CH_{3iso}), 14.6 ($2CH_3^{\omega}$), **benzodiazepine** 167.3, 167.0 (C-2, C-4), 138.4, 136.8 (C-10, C-11), 127.5, 127.3 (C-7, C-8), 124.6, 124.5 (C-6, C-9), 45.2 (C-3).

Anal. Calcd for $C_{39}H_{60}N_2O_{11}$ (732): C, 63.91; H, 8.25; N, 3.82. Found: C, 63.85; H, 8.18; N, 3.85.

7-Methyl-1,5-bis-(6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (6a). white solid. 75% yield. mp 141–143°C; $[\alpha]_D^{27}$ −7.0° (*c* 0.6, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 111.7, 111.5 (C_{iso}), 105.2, 105.0 (C-1), 85.0 (C-2), 81.5, 81.1 (C-4), 74.7, 74.4 (C-3), 67.7, 67.4 (C-5), 52.2, 50.6 (C-6), 26.8–26.1 (CH_{3iso}), **benzodiazepine** 167.4, 166.5 (C-2, C-4), 137.7, 137.4, 133.9 (C-10, C-11), 128.4, 128.0 (C-7, C-8), 124.3, 123.8, 123.5 (C-6, C-9), 44.6 (C-3). 21.0 (CH_3).

Anal. Calcd for $C_{28}H_{38}N_2O_{11}$ (578): C, 58.12; H, 6.62; N, 4.84. Found: C, 58.06; H, 6.55; N, 4.89.

7-Methyl-1,5-bis-(6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranos-6-yl-benzodiazepin-2,4-dione (6b). white solid. 73% yield. mp 142–144°C; $[\alpha]_D^{27}$ −37.4° (*c* 1.0, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 111.7, 111.4 (C_{iso}), 105.2, 105.1 (C-1), 84.0, 83.9 (C-3), 81.5, 81.4 (C-2), 81.1, 81.0 (C-4), 67.0, 66.6 (C-5), 44.5 (C-6), 58.0 (O-CH_3), 26.7–26.1 (CH_{3iso}), **benzodiazepine** 167.2, 167.1, 166.3, 166.1 (C-2, C-4), 137.6, 137.2 (C-10, C-11), 135.6–127.5 (C-7, C-8), 124.5–123.2 (C-6, C-9), 44.5 (C-3). 21.4, 21.3 (CH_3).

Anal. Calcd for $C_{29}H_{40}N_2O_{11}$ (592): C, 58.77; H, 6.80; N, 4.72. Found: C, 58.71; H, 6.75; N, 4.76.

7-Chloro-1,5-bis-(6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (7a). white solid. 79% yield. mp 144–146°C; $[\alpha]_D^{27}$ −15.6° (*c* 0.6, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 111.8, 111.5 (C_{iso}), 105.1 (C-1), 84.9 (C-2), 81.0, 80.8 (C-4), 74.5 (C-3), 67.1 (C-5), 53.2, 50.4 (C-6), 58.0, 26.8–26.1 (CH_{3iso}), **benzodiazepine** 166.9, 166.8, 166.0 (C-2, C-4), 132.6, 132.3 (C-10, C-11), 127.7, 127.3 (C-7, C-8), 125.4–123.9 (C-6, C-9), 44.4 (C-3).

Anal. Calcd for $C_{27}H_{35}ClN_2O_{11}$ (599): C, 54.13; H, 5.48; N, 4.68; Cl, 5.93. Found: C, 54.08; H, 5.78; N, 4.71; Cl, 5.89.

7-Chloro-1,5-bis-(6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (7b). white solid. 72% yield. mp 139–141°C; $[\alpha]_D^{27}$ −33.7° (*c* 1.0, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 111.7, 111.4 (C_{iso}), 105.2, 105.1 (C-1), 84.1, 83.7 (C-3), 81.5, 81.1 (C-2), 81.5, 80.9 (C-4), 66.9, 66.1 (C-5), 44.4, 44.1 (C-6), 58.0, 57.9 (O-CH_3), 26.4–26.1 (CH_{3iso}), **benzodiazepine** 166.7, 165.7, 165.6 (C-2, C-4), 139.0, 135.2 (C-10, C-11), 132.7–127.3 (C-7, C-8), 124.8–123.6 (C-6, C-9), 44.4 (C-3).

Anal. Calcd for $C_{28}H_{37}ClN_2O_{11}$ (613): C, 54.84; H, 6.08; N, 4.57; Cl, 5.78. Found: C, 54.78; H, 6.04; N, 4.61; Cl, 5.74.

1,5-Bis-(6-deoxy-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (8a). white solid. 96% yield (α/β, 5 : 4). mp 94–96°C; $[\alpha]_D^{27}$ + 37.7–42.9° (*c* 1.0, MeOH (3 days)); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ **glucose** 96.7 (C-1β), 92.1 (C-1α), 76.1–67.7 (C-2, C-3, C-4, C-5), 52.3, 49.6 (C-6), **benzodiazepine** 164.9, 164.6 (C-2, C-4), 136.9, 136.6 (C-10, C-11), 126.2 (C-8), 125.2 (C-7), 124.9, 124.4 (C-6, C-9), 44.0 (C-3).

Anal. Calcd for $C_{21}H_{28}N_2O_{11}$ (484): C, 52.06; H, 5.83; N, 5.78. Found: C, 51.94; H, 5.79; N, 5.87.

1,5-Bis-(6-deoxy-3-*O*-methyl-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (8b). white solid. 89% yield (α/β, 1 : 1). mp 109–111°C; $[\alpha]_D^{27}$ + 36.7–34.5° (*c* 1.0, MeOH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ **glucose** 96.7 (C-1β), 92.0 (C-1α), 85.9, 82.8 (C-3), 74.6–66.9 (C-2, C-4, C-5), 59.8, 59.7 (O-CH_3), 52.0, 48.8 (C-6), **benzodiazepine** 165.0–164.6 (C-2, C-4), 136.8, 136.6 (C-10, C-11), 126.2 (C-8), 125.2 (C-7), 125.0, 124.4 (C-6, C-9), 44.6 (C-3).

Anal. Calcd for $C_{22}H_{30}N_2O_{11}$ (498): C, 53.01; H, 6.07; N, 5.62. Found: C, 52.96; H, 6.04; N, 5.66.

1,5-Bis-(6-deoxy-3-*O*-octyl-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (8c). white solid. 89% yield (α/β, 1 : 1). mp 109–111°C; $[\alpha]_D^{27} + 31.7°$ (*c* 1.0, MeOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 97.1 (C-1β), 92.4 (C-1α), 84.1, 81.1 (C-3), 74.9–66.9 (C-2, C-4, C-5), 71.0 (O-CH_2^{α}), 52.0, 48.5 (C-6), 32.3–23.1 (CH_2), 14.5 ($2CH_3^{\omega}$), **benzodiazepine** 167.3, 167.1 (C-2, C-4), 138.2–135.3 (C-10, C-11), 126.6 (C-7, C-8), 124.9, 124.8 (C-6, C-9), 44.9 (C-3).

Anal. Calcd for $C_{29}H_{44}N_2O_{11}$ (596): C, 58.37; H, 7.43; N, 4.69. Found: C, 58.34; H, 7.39; N, 4.74.

1,5-Bis-(6-deoxy-3-*O*-decyl-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (8d). white solid. 70% yield (α/β, 6 : 7). mp 80–82°C; $[\alpha]_D^{27} + 38.8°$ (*c*1.0, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 97.0 (C-1β), 92.5 (C-1α), 84.1, 81.5 (C-3), 74.8–66.9 (C-2, C-4, C-5), 71.3 (O-CH_2^{α}), 52.0, 48.5 (C-6), 32.3–23.2 (CH_2), 14.5 ($2CH_3^{\omega}$), **benzodiazepine** 167.3, 167.2 (C-2, C-4), 137.2, 135.5 (C-10, C-11), 126.5 (C-7, C-8), 124.9, 124.6 (C-6, C-9), 50.1 (C-3).

Anal. Calcd for $C_{31}H_{48}N_2O_{11}$ (624): C, 59.60; H, 7.74; N, 4.48. Found: C, 59.56; H, 7.71; N, 4.45.

1,5-Bis-(6-deoxy-3-*O*-dodecyl-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (8e). white solid. 70% yield (α/β, 2 : 1). mp 90–92°C; $[\alpha]_D^{27} + 33.2°$ (*c* 1.0, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 97.0 (C-1β), 92.3 (C-1α), 84.3, 81.2 (C-3), 75.0–67.2 (C-2, C-4, C-5), 71.2 (O-CH_2^{α}), 51.9, 48.3 (C-6), 32.5–22.5 (CH_2), 14.6 ($2CH_3^{\omega}$), **benzodiazepine** 167.3 (C-2, C-4), 137.0, 135.6 (C-10, C-11), 126.8 (C-7, C-8), 124.7 (C-6, C-9), 50.1 (C-3).

Anal. Calcd for $C_{33}H_{52}N_2O_{11}$ (652): C, 60.72; H, 8.03; N, 4.29. Found: C, 60.68; H, 7.98; N, 4.34.

7-Methyl-1,5-bis-(6-deoxy-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (9a). white solid. 89% yield (α/β, 9 : 7). mp 68–70°C; $[\alpha]_D^{27} + 32.1–33.4°$ (*c* 1.0, MeOH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ **glucose** 96.8 (C-1β), 92.0 (C-1α), 76.1–67.9 (C-2, C-3, C-4, C-5), 52.3, 48.5 (C-6), **benzodiazepine** 165.0, 164.8, 164.6 (C-2, C-4), 136.5, 135.5 (C-10, C-11), 134.3 (C-8), 127.0 (C-7), 125.0, 124.4 (C-6, C-9), 44.7 (C-3).

Anal. Calcd for $C_{22}H_{30}N_2O_{11}$ (498): C, 53.01; H, 6.07; N, 5.62. Found: C, 52.96; H, 6.06; N, 5.65.

7-Methyl-1,5-bis-(6-deoxy-3-*O*-methyl-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (9b). white solid. 87% yield (α/β, 2 : 1). mp 102–104°C; $[\alpha]_D^{27} + 28.4–29.2°$ (*c* 1.0, MeOH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ **glucose** 96.8 (C-1β), 92.0 (C-1α), 86.0, 82.8 (C-3), 74.4–66.9 (C-2, C-4, C-5), 59.8, 59.7 (O-CH_3), 51.6, 49.0 (C-6), **benzodiazepine** 164.8–164.5 (C-2, C-4), 136.4, 135.6 (C-10, C-11), 134.5, 134.3 (C-8), 127.0 (C-7), 124.9, 124.5 (C-6, C-9), 44.7 (C-3), 20.6, 20.4 (CH_3).

Anal. Calcd for $C_{23}H_{32}N_2O_{11}$ (512): C, 53.90; H, 6.29; N, 5.47. Found: C, 53.86; H, 6.24, N, 5.49.

7-Chloro-1,5-bis-(6-deoxy-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (10a). white solid. 80% yield (α/β, 1 : 1). mp 185–187°C; $[\alpha]_D^{27} + 31.6–28.3°$ (*c* 1.0, MeOH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ **glucose** 96.8 (C-1β), 92.2 (C-1α), 76.2–67.7 (C-2, C-3, C-4, C-5), 54.8, 48.4 (C-6), **benzodiazepine** 164.5, 164.3 (C-2, C-4), 138.1, 137.8, 135.6 (C-10, C-11), 136.0, 135.6 (C-8), 129.9, 126.1 (C-7), 124.8, 124.3 (C-6, C-9), 44.6 (C-3).

Anal. Calcd for $C_{21}H_{27}ClN_2O_{11}$ (518): C, 48.61; H, 5.24; N, 5.40; Cl, 6.83. Found: C, 48.56; H, 5.23; N, 5.43; Cl, 6.81.

7-Chloro-1,5-bis-(6-deoxy-3-*O*-methyl-D-glucofuranos-6-yl)-benzodiazepin-2,4-dione (10b). white solid. 83% yield (α/β, 7 : 5). mp 162–164°C; $[\alpha]_D^{27} + 26.1°$ (measured after 24 h, *c* 1.0, MeOH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ **glucose** 96.7 (C-1β), 92.0 (C-1α), 85.9, 82.8 (C-3), 74.7–67.9 (C-2, C-4, C-5), 59.8, 59.7 (O-*CH*$_3$), 51.9, 49.1 (C-6), **benzodiazepine** 164.6–164.4 (C-2, C-4), 138.0, 135.9, 135.6 (C-10, C-11), 129.9, 129.7 (C-8), 126.1 (C-7), 124.7, 124.3 (C-6, C-9), 44.5 (C-3).

Anal. Calcd for $C_{22}H_{29}ClN_2O_{11}$ (532): C, 49.58; H, 5.48; N, 5.26; Cl, 6.65. Found: C, 49.53; H, 5.42; N, 5.31; Cl, 6.63.

[1-*N*-(6-Deoxy-5-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranos-6-yl)-3-*N*-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranos-6-yl]-1,3-benzimidazol-2-one (11). white solid. 51% yield. mp 156–158°C; $[\alpha]_D^{27} -94.7°$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ **glucose** 5.95–5.90 (2d, 2H, $J_{1,2} = 3.6$ Hz, H-1), 5.25, 4.20 (2m, 2H, $J_{5,6a} = 3.1$ Hz, $J_{5,6b} = 5.6$ Hz, H-5), 4.51, 4.50 (2d, 2H, $J_{2,3} = 0.0$ Hz, H-2), 4.42 (m, 2H, H-6b), 4.40, 4.25 (2dd, 2H, $J_{6a,6b} = 12.0$ Hz, H-6a), 4.16, 3.91 (2dd, 2H, $J_{4,5} = 8.6$ Hz, H-4), 3.81, 3.65 (2d, 2H, $J_{3,4} = 3.0$ Hz, H-3), 3.45, 3.24 (2s, 6H, O-*CH*$_3$), 1.95 (s, 3H, CO*CH*$_3$), 1.45–1.15 (4s, 12H, *CH*$_{3iso}$), **benzimidazolone** 7.25–7.00 (m, 4H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ **glucose** 170.1 (*C*OCH_3), 111.9 (C_{iso}), 105.6, 105.4 (C-1), 82.1, 81.7 (C-2), 82.8 (C-3), 80.4, 78.7 (C-4), 69.2, 68.9 (C-5), 58.5, 58.3 (O-*CH*$_3$), 45.9, 42.0 (C-6), 26.9, 26.8, 26.7, 26.4 (*CH*$_{3iso}$), 21.0 (CO*CH*$_3$), **benzimidazolone** 156.9 (CO), 130.1, 130.0 (C-5, C-6), 129.8, 129.6 (C-8, C-9), 108.8 (C-4, C-7). EI $[M]^+$ m/z 608.

Anal. Calcd for $C_{29}H_{40}N_2O_{12}$ (608): C, 57.23; H, 6.57; N, 4.60. Found: C, 56.25; H, 6.55; N, 4.62.

1-*N*-*N*-Bis-(6-deoxy-3-*O*-methyl-D-glucopyranos-6-yl)-benzimidazolone (12). white solid. 81% yield. (α/β 4 : 3). mp 124–126°C; $[\alpha]_D^{27}$ 48.6–50.2° (*c* 0.6, MeOH); ^{13}C NMR (75 MHz, DMSO-d_6): δ **glucose** 96.6 (C-1β), 92.1 (C-1α), 85.8 (C-3β), 82.7 (C-3α), 74.1–69.5 (C-2, C-4, C-5), 59.9 (O-*CH*$_3$), 42.7 (C-6), **benzimidazolone** 153.8 (C-2), 129.6 (C-8, C-9), 120.7 (C-5, C-6), 108.7, 108.4 (C-4, C-7).

Anal. Calcd for $C_{20}H_{28}N_2O_{11}$ (472): C, 50.80; H, 5.97; N, 5.93. Found: C, 50.75; H, 5.92; N, 5.96.

ACKNOWLEDGMENTS

This work was carried out within the framework of the Pole de compétence Pharmacochimie. We thank the Ministère Délégué de la Recherche Scientifique du Maroc for financial support. We also are grateful to Pr. Herbaux for help in manuscript preparation.

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Received April 7, 2004
Accepted July 16, 2004