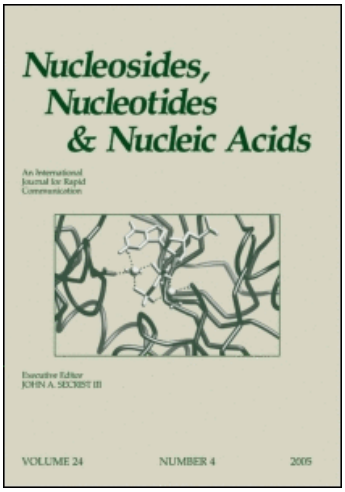

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SYNTHESIS OF 3-ALKYL PIPERAZIN-2-ONE NUCLEOSIDES WITH POTENTIAL ANTIRETROVIRAL ACTIVITY

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SYNTHESIS OF 3-ALKYL PIPERAZIN-2-ONE NUCLEOSIDES WITH POTENTIAL ANTIRETROVIRAL ACTIVITY

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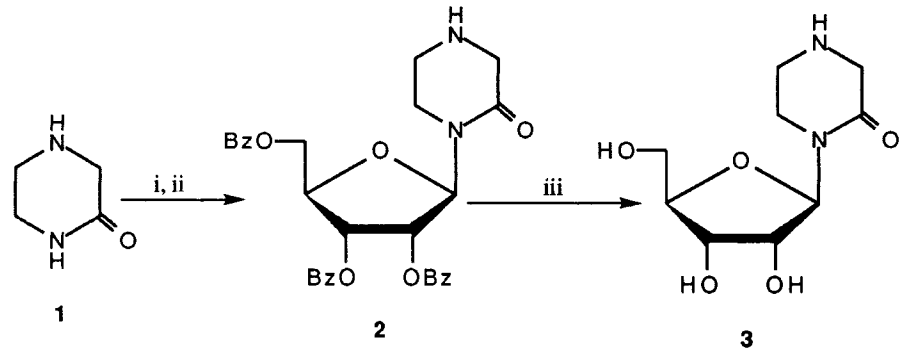
Abstract : Piperazinone nucleosides can be formed by N-glycosylation with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose of either piperazin-2-ones or pyrazin-2-ones followed by reduction of the heterocycle with rhodium on alumina. All the prepared compounds were tested for their activity against the Visna virus, but did not show significant antiviral activity.

Piperazine derivatives have earlier proven to have an antibacterial[1] and antiviral[2,3] activity. We have been interested in preparing the corresponding 1-β-D-ribofuranosyl piperazinone derivatives **3** and **7b,c** as potential antiviral compounds. Antiviral activity of these compounds have been evaluated against Visna virus which is the prototype of the lentivirus subgroup of retroviruses and is related to the human immunodeficiency virus (HIV)[4].

The rapidly growing literature dealing with the nucleoside analogs contains a remarkably small number of publications concerning the condensation of nonaromatic heterocycles with ribose derivatives.[5-7] However, these condensations were successfully catalyzed by $SnCl_4$ or TMSOTf under Vorbrüggen's conditions developed for the condensation of aromatic bases with sugar derivatives.[8] Our trial to condense *per*sylilated piperazin-2-one with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose by this procedure failed when $SnCl_4$ was used as a catalyst, and gave poor yield (15%) when the condensation was catalyzed by TMSOTf (Scheme 1). This failure could be explained by the only formation of *N,N*-bis(trimethylsilyl) piperazine which would be an unreactive intermediate. Indeed, it is well known that cyclic amides are essentially *N*-silylated unless the *O*-silyl form is sufficiently stabilized by heteroaromaticity or by the development of



i) BSTFA, CH_3CN. ii) 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, TMSOTf, dichloroethane. iii) NH_3/MeOH.

SCHEME 1

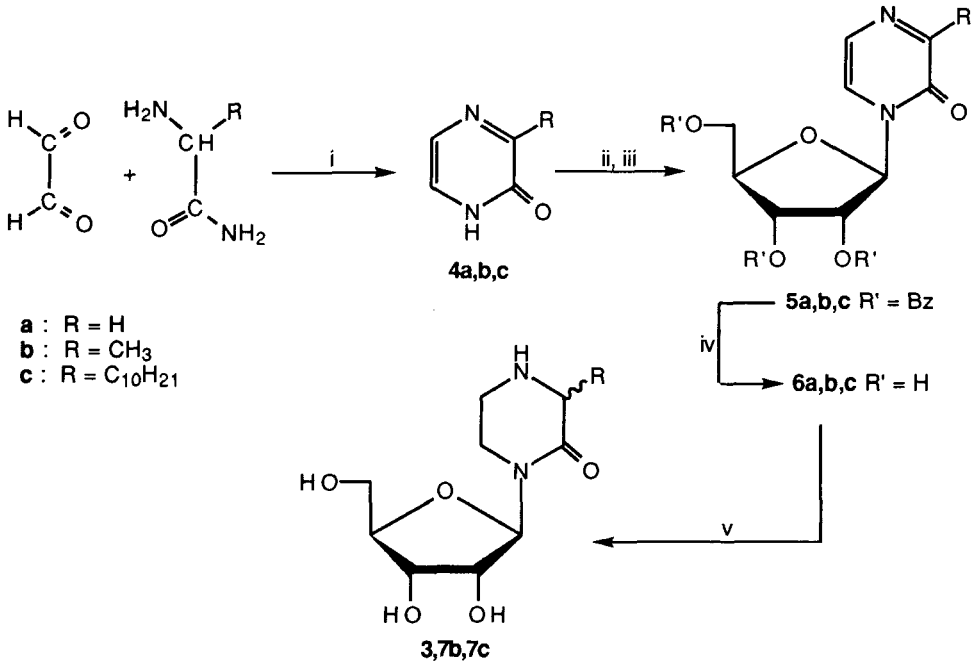
extended conjugation,[9] so do lactams, such as caprolactam, which undergoes *N*-silylation.[10,11]

Because of the low yield of the reported coupling procedure (15%) an alternative route for the preparation of 3-alkyl piperazin-2-one nucleosides was considered, starting from the readily available 3-alkyl pyrazin-2-ones, which were prepared by a modification of Jones's synthesis.[12] Glycosylation was performed according to the method of Vorbrüggen, followed by a reduction of the heterocyclic base (scheme 2).

Results and discussion

The synthesis of 2-piperazinone **1** starting from ethyl 2-chloroacetate has been described in our earlier work.[13] When the silylated piperazinone, prepared by using bis(trimethylsilyl)trifluoroacetamide (BSTFA) and freshly distilled acetonitrile, was reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of TMSOTf **2** was isolated with a 15% yield (scheme 1).

After purification, the protecting groups of **2** were removed by treatment with methanolic ammonia to give nucleoside **3**. The coupling constant value ($J_{1',2'}$ = 6.2 Hz) is in agreement with the β configuration of the ribose moiety. In contrast with TMSOTf, $SnCl_4$ did not give any result under the above reaction conditions. This could be attributed to the formation of a strong and non-dissociable complex with the *N,N*-bis(trimethylsilyl)-piperazine which was unable to react. The formation of σ-complexes between $SnCl_4$ and silylated uracils has been reported previously.[8a]



i) NaOH, MeOH. ii) HMDS, TMSCl. iii) 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, $SnCl_4$, dichloroethane. iv) MeONa/MeOH. v) H_2, Rh/Al_2O_3, THF.

SCHEME 2

Pyrazin-2-ones **4a,b** were prepared following the published procedure.[12] By analogy, condensation of 2-aminododecanamide[14] in methanol with commercially available glyoxal gave 3-decyl pyrazin-2-one **4c** in good yield (86%). The required 3-alkyl pyrazin-2-one nucleosides were prepared *via* the usual series of reactions,[8b] including silylation of the base, condensation with protected sugar and removal of the blocking groups under basic conditions (scheme 2).

Trimethylsilyloxy pyrazines were used without purification for condensation with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in dichloroethane at room temperature with $SnCl_4$ as a catalyst. This glycosylation gave protected nucleosides **5a** (70%), **5b** (65%), **5c** (63%). Treatment of **5a,b,c** with 1 M sodium methoxide in methanol led to **6a** (91%), **6b** (85%) and **6c** (92%). In that case NMR studies show also a β configuration for compounds **6a,b,c**.

Catalytic hydrogenation (rhodium on alumina under 30 psi in THF)[15] of **6a,b,c** gave, in good yields, 3-alkyl-2-piperazinone nucleosides **3** and **7b,c** (scheme 2). The epimers of

7c (*3R* and *3S*) were separated by preparative HPLC. In contrast with **7c**, attempts to separate **7b** epimers, by various chromatographic means remained unsuccessful. Epimers **7b***(3R)* and **7b***(3S)* were obtained in a 7/3 ratio based on ^{13}C NMR.

The differentiation between *(3R)* and *(3S)*-3-methyl-1-(β-D-ribofuranosyl)-piperazin-2-one **7b** was accomplished by using NMR. A 400 MHz NOESY spectrum revealed two important features : spatial proximity of H-3 and axial H-5 in the two epimers indicated that the base had the same conformation with the methyl in the equatorial position (Fig. 1). Secondly, the proximity of the equatorial proton H-6 of the base and the H-2' proton of the ribose moiety suggested that the base is in the *anti* orientation[16] for both epimers.

The equatorial position taken by the ribose moiety was assumed on the basis of the results given by Allinger *et al.*[17,18] These authors demonstrated that the conformational equilibrium of saturated heterocycles, as piperidine and piperazine, contains more than 90% of the chair conformation which places the N-alkyl substituent in the equatorial position by rapid inversion of nitrogen. These assumptions can be justified by approximations of free energy differences among the possible conformers. If we examine the coupling constants $J_{1',2'}$ of the two epimers the difference of 0.6 Hz, which is significant suggests a different North(N) $\rightleftharpoons$ South(S) pseudorotational equilibrium of the ribofuranose ring.[19] The percentage of the S form is given by : $\%S = 100 \times \frac{J_{1',2'}}{J_{1',2'} + J_{3',4'}}$.

According to Chattopadhyaya *et al.*,[20-22] the N $\rightleftharpoons$ S equilibrium in nucleosides is governed by the different gauche, steric and anomeric effects. It appears that the two epimers differ only by the orientation of the lone pair of the N atom linked to the ribose moiety. As the gauche, steric and endoanomeric effects are the same in the two epimers, the difference lies only on the exoanomeric effect.[23,24] The *(3R)* epimer in which an exoanomeric effect can be exerted (the nitrogen lone pair is antiperiplanar to the C(1')-O(4') bond) is likely to exhibit a more important percentage of pseudoaxial form (North) ($J_{1',2'}$ = 5.9 Hz and $J_{3',4'}$ = 4.4 Hz, 53% of the S form). Whereas, in the *(3S)* epimer no exoanomeric effect exists, the South form is favored ($J_{1',2'}$ = 6.5 Hz and $J_{3',4'}$ = 4.4 Hz, 60% of the S form).

By analogy, the structure of the **7c***(3R)* is differentiated from that of **7c***(3S)* on the basis of their respective coupling constants $J_{1',2'}$ = 5.9 Hz and $J_{3',4'}$ = 4.8 Hz (55% of the S form), and $J_{1',2'}$ = 6.6 Hz and $J_{3',4'}$ = 4.5 Hz (60% of the S form).

Biological tests

Compounds **3**, **6a-c**, **7b** and **7c** were evaluated for their antiviral activities against a mammalian retrovirus, the Visna virus, strain K796, in sheep choroïd plexus cells (SCP cells).[25] 3'-Azido-3'-deoxythymidine, the most potent inhibitor of this virus was also

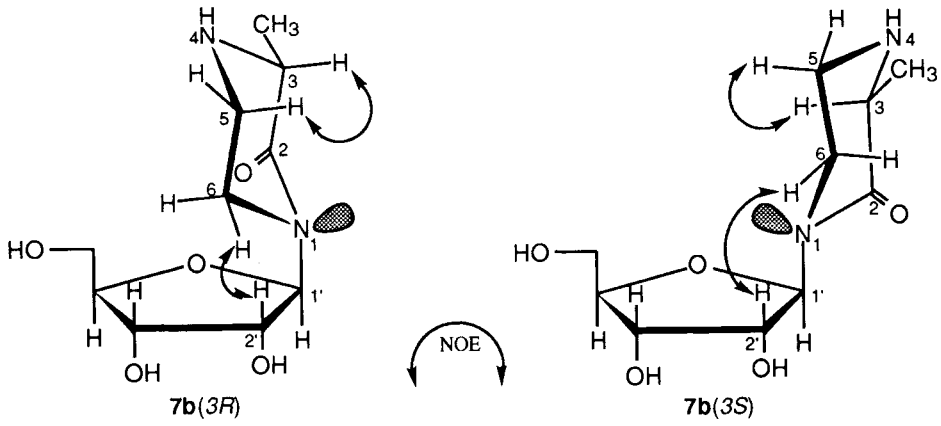


FIG. 1

tested in order to compare the effectiveness of the newly synthesized compounds. Antiviral activities were measured by a modified 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide method applied to adherent cells.[26] SCP cells were infected with Visna virus at a multiplicity of infection of 0.5 and incubated in the presence of test compounds. After 5 days incubation, the number of viable cells was determined. Among the compounds tested (Table 1), nucleosides **3**, **6a-c** and **7b** showed no antiretroviral activities. Compared to AZT only piperazinone nucleosides **7c***(3R)* and **7c***(3S)* with an aliphatic long chain exhibit moderate activity against Visna virus.

EXPERIMENTAL SECTION

General methods

Infrared spectra were measured in cm^{-1} on a Perkin Elmer 1310. UV-visible spectra were recorded on a Hewlett Packard 8452A Spectrophotometer using 1 cm quartz cells in the indicated solvent, wavelengths were measured in nm and extinction coefficient in $cm^{-1}.mol^{-1}.l$. The rotatory dispersion was measured at 22°C in the indicated solvent with a JASCO (DIP-370) polarimeter. Melting points were determined by capillary tube apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 or on Bruker DRX 400 with tetramethylsilane as internal standard. The chemical shift values are given in ppm and coupling constants in Hz in the indicated solvent. Electronic impact mass spectra (EI) were recorded on a SHIMADZU QP 1000 apparatus by the "Laboratoire Départemental d'Analyse", Limoges. Chemical ionization mass spectra (CI) were recorded

TABLE 1

Compounds	EC50 (μM)[a]	CC50 (μM)[b]
3	---	>330
6a	---	>330
6b	---	>330
6c	---	>50
7b	---	>330
7c*(3R)*	170	>400
7c*(3S)*	160	>400
AZT	5	>500

[a]EC50: 50% antiviral effective concentration.
[b]CC50: 50% cytotoxic concentration.

on a R3010 Nermag. FAB mass spectra were performed on a ZAB 2-SEC using triglycerol as matrix at the "Service Central d'Analyse", CNRS Solaize. Microanalyses were carried out by the "Service Régional de Microanalyse", Université Pierre et Marie Curie, Paris.

Chemicals

All solvents and reagents were purchased from Aldrich, Prolabo or Janssen. Acetonitrile and dichloroethane were distilled on CaH_2 and P_2O_5 before their use.

Chromatography

Analytical thin-layer chromatography (TLC) was performed on silica gel (Merck, 60 F_{254}). Column chromatography was carried out on silica gel 60 ACC (15-40 μm. Merck), preparative HPLC on reverse phase (Lichroprep RP18: 15-40 μm. Merck). The following solvent systems were used as eluents (v/v): A: chloroform-ethanol (50:50), B: chloroform-ethanol (70:30), C: chloroform-ethanol (80:20), D: chloroform-ethanol (90:10), E: chloroform-ethanol (95:5), F: chloroform-ethanol (98:2), G: chloroform-ethanol (99:9), H: methanol-water (98/2).

1-(2',3',5'-tri-*O*-Benzoyl-β-D-ribofuranosyl)-piperazin-2-one (2). To a suspension of **1** (0.6 g, 6 mmol) stirred in dry acetonitrile at room temperature was added a six-fold excess (5 g, 36 mmol) of bis(trimethylsilyl) trifluoroacetamide (BSTFA). The mixture was stirred for 2 h at room temperature, and the excess of reagent and solvent were removed under vacuum to leave a clear oil. The persilylated piperazinone was dissolved in 40 mL of dichloroethane followed by the addition of 1.8 mL (9 mmol) of TMSOTf. After

10 minutes 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3 g, 6 mmol) was added and the mixture stirred at room temperature for 12 h. The crude reaction product was poured slowly with vigorous stirring into a saturated $NaHCO_3$ solution (60 mL). The organic layer was separated, washed with H_2O, and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on a silica gel column with eluent E. The product **2** was obtained as a syrup (0.49 g, 15%), TLC eluent D, R_f 0.54. MS *m/z* (CI) : 545 MH^+. $[\alpha]_D$ -17.9° (c 0.84, $CHCl_3$). IR (NaCl) 1650 (C=O amide), 1705 (C=O ester), 3445 (NH amine). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.74 (1H, s, NH), 2.98 (1H, ddd, *J* = 13.3-7.4-4.6 Hz, H-5_a), 3.07 (1H, dt, *J* = 13.3-4.6 Hz, H-5_b), 3.36 (1H, ddd, *J* = 11.3-7.5-4.6 Hz, H-6_a), 3.47 (1H, dt, *J* = 11.3-4.7 Hz, H-6_b), 3.55 (2H, s, H-3), 4.56 (1H, dd, *J* = 13.4-4.0 Hz, H-5'$_a$), 4.58 (1H, q, *J* = 4.0 Hz, H-4'), 4.80 (1H, dd, *J* = 13.4-4.5 Hz, H-5'$_b$), 5.77 (1H, t, *J* = 6.0 Hz, H-2'), 5.79 (1H, dd, *J* = 6.0-3.5 Hz, H-3'), 6.57 (1H, d, *J* = 6.0 Hz, H-1'), 7.35-8.13 (15H, m, H_{Bz}), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 42.1 (C-5), 42.9 (C-6), 50.5 (C-3), 64.0 (C-5'), 70.0 (C-3'), 71.6 (C-2'), 79.0 (C-4'), 84.8 (C-1'), 169.1 (C-2), *benzoyl groups* : 128.4, 128.5, 128.6 (C-3,5); 128.7, 128.9, 129.5 (C-1); 129.6, 129.8, 129.9 (C-2,6); 133.4, 133.6 (C-4); 165.4, 165.5, 166.1 (*C*=O). Anal. Calcd for $C_{30}H_{30}N_2O_8$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.82; H, 5.61; N, 5.27.

1-β-D-Ribofuranosyl piperazin-2-one (3).

Procedure a : A solution of **2** (0.3 g, 0.55 mmol) in methanolic ammonia (2 M, 3 mL) was stirred at room temperature, for one week. Evaporation of the solvent, and chromatography by silica gel PLC of the crude product using eluent A yielded **3** (0.11g, 84%) as a syrup.

Procedure b : Compound **6a** (0.18 g, 0.8 mmol) in THF (7 mL) was hydrogenated under 30 psi in the presence of 5% Rh/Al_2O_3 (50 mg) for 4 h. The catalyst was filtered off, and the solvent was evaporated. Purification of the crude product by silica gel PLC using eluent A yielded 0.18 g (95%) of **3**.

TLC eluent A, R_f 0.45. MS *m/z* (FAB) : 247 MH^+. R_f 0.45, $[\alpha]_D$ -52.0° (c 0.45, methanol). IR (NaCl) 3360 (OH), 1625 (C=O amide). ^1H NMR (D_2O, 200 MHz) δ 2.85 (1H, ddd, *J* = 13.9-8.1-4.6 Hz, H-5_a), 3.01 (1H, dt, 13.9-5.7 Hz, H-5_b), 3.23 (1H, ddd, *J* = 12.7-8.1-4.6 Hz, H-6_a), 3.36 (1H, dt, 12.7-4.7 Hz, H-6_b), 3.39 (2H, s, H-3), 3.56 (1H, dd, *J* = 12.5-5.1 Hz, H-5'$_a$), 3.64 (1H, dd, *J* = 12.5-3.6 Hz, H-5'$_b$), 3.88 (1H, br dt, *J* = 5.3-3.7 Hz, H-4'), 3.99 (1H, dd, *J* = 5.6-4.1 Hz, H-3'), 4.16 (1H, t, *J* = 5.8 Hz, H-2'), 5.87 (1H, d, *J* = 6.2 Hz, H-1'), ^{13}C NMR (D_2O, 50 MHz) δ 40.7 (C-5), 40.8 (C-6), 47.9 (C-3), 60.9 (C-5'), 69.6 (C-3'), 69.7 (C-2'), 82.9 (C-4'), 85.6 (C-1'), 171.6 (C-2). Anal. Calcd for $C_9H_{16}N_2O_5$: C, 46.55; H, 6.94; N, 12.06. Found: C, 46.32; H, 6.98; N, 12.14.

3-Decyl pyrazin-2-one (4c). A cooled to -25°C solution of 21.4 g (0.10 mol) of 2-aminododecane amide in 50 mL of methanol, was added to a solution of 18 g (0.10 mol) of

commercial 40% glyoxal in 25 mL of methanol also precooled to -25°C. After 10 minutes, 10 mL (0.125 mol) of aqueous 12.5 N sodium hydroxide solution was added dropwise while the temperature was maintained below -10°C. The mixture was allowed to stand at -5°C for 2 h, then left overnight at room temperature. 35 mL of 3% hydrochloric acid were added, the precipitate was collected and recrystallized from ethanol to afford 20.3 g (86 %) of **4c** as a white crystals: mp 86-88°C. TLC eluent E, R_f 0.53. MS *m/z* (EI) : 236 M^+, 95 $[M-C_{10}H_{21}]^+$. UV λ(EtOH) 228 (ε 6238), 310 (ε 5254). IR (KBr) 2920 (CH_2), 1640 (C=O). ^1H NMR ($CDCl_3$, 200 MHz) δ 7.13 (1 H, d, *J* = 4.1 Hz, H-5), 7.40 (1 H, d, *J* = 4.1 Hz, H-6), 13.09 (1 H, br s, H-1), *decyl groups* 0.87 (3 H, t, *J* = 6.4, CH_3), 1.26 (14 H, s, $(CH_2)_7$), 1.72 (2 H, quintet, *J* = 7.5 Hz, $^2CH_2$), 2.81 (2 H, t, *J* = 7.5 Hz, $^1CH_2$), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 123.4 (C-5), 124.3 (C-6), 158.0 (C-3), 161.3 (C-2), *decyl groups*: 14.1, 22.7, 26.5, 29.3, 29.5 (3C), 29.6, 31.9, 33.1. Anal. Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.23; N, 11.95. Found: C, 71.18; H, 10.14; N, 12.04.

1-(2',3',5'-tri-*O*-Benzoyl-β-D-ribofuranosyl) pyrazin-2-one (5a). Compound **4a** (0.67 g, 7 mmol) was heated under reflux in a mixture of 7 mL of hexamethyldisilazane (HMDS) and 3.5 mL of trimethylsilyl chloride (TMSCl). After 10 minutes the reaction mixture gave a yellow clear solution and heating was continued for two hours. Excess HMDS and TMSCl were then removed under vacuum at room temperature leaving crude 2-trimethylsilyloxy pyrazine, which was directly dissolved in dry dichloroethane (60 mL). 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose 3.5 g (7 mmol) and $SnCl_4$ 1.23 mL (10.5 mmol) were added to this solution, and the reaction mixture was stirred under an argon atmosphere at room temperature. After 2 h the mixture was poured slowly with vigorous stirring into a saturated $NaHCO_3$ solution (35 mL). The organic layer was separated, washed with H_2O, and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on a silica gel column using F as eluent. The solid obtained was recrystallized from CCl_4 to give 2.60 g (70%) of **5a** as an amorphous powder mp 90-92°C. TLC eluent E, R_f 0.42. MS *m/z* (CI) : 541 MH^+. $[\alpha]_D$ + 65.7° (c 0.95, $CHCl_3$). IR (KBr) 1655 (C=O amide), 1715 (C=O ester). UV λ(chloroform) 248 (ε 8220), 318 (ε 6621). ^1H NMR ($CDCl_3$, 200 MHz) δ 4.70 (1H, dd, *J* = 11.9-2.7 Hz, H-5'$_a$), 4.81 (1H, ddd, *J* = 5.6-3.5-2.7 Hz, H-4'), 4.89 (1H, dd, *J* = 11.9-3.5 Hz, H-5'$_b$), 5.81 (1H, dd, *J* = 5.6-4.4 Hz, H-2'), 5.91 (1H, t, *J* = 5.6 Hz, H-3'), 6.48 (1H, d, *J* = 4.4 Hz, H-1'), 7.22 (1H, d, *J* = 4.6 Hz, H-5), 7.96 (2H, s, H-3), 7.35-8.13 (16H, m, H-6 and H_{Bz}), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 63.4 (C-5'), 70.8 (C-3'), 74.7 (C-2'), 80.8 (C-4'), 88.1 (C-1'), 122.8 (C-5), 124.0 (C-6), 150.0 (C-3), 155.2 (C-2), *benzoyl groups* 128.5, 128.7 (C-3,5); 129.3 (C-1); 129.7, 129.8, 129.9 (C-2,6); 133.6, 133.7 (C-4); 165.1, 165.2, 166.1 (*C*=O). Anal. Calcd for $C_{30}H_{24}N_2O_8$: C, 66.66; H, 4.47; N, 5.18. Found: C, 66.41; H, 4.48; N, 5.21.

3-Methyl-1-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl) pyrazin-2-one (5b). Compound **5b** was prepared following the procedure described for **5a**. Starting from 3-methyl pyrazin-2-one (0.33 g, 3 mmol), we obtained after 6 h and chromatographic purification (eluent F) 1.1 g (65%) of a foamy solid mp 86-88°C (acetone). TLC eluent E, R_f 0.49. MS *m/z* (CI) : 555 MH^+. $[\alpha]_D$ + 56.8° (c 1.02, $CHCl_3$). IR (KBr) 1645 (C=O amide), 1720 (C=O ester). UV λ(chloroform) 248 (ε 6911), 312 (ε 6175). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.45 (3H, s, CH_3), 4.70 (1H, dd, *J* = 12.0-2.7 Hz, H-5'$_a$), 4.80 (1H, ddd, *J* = 5.8-3.7-2.7 Hz, H-4'), 4.89 (1H, dd, *J* = 12.0-3.7 Hz, H-5'$_b$), 5.84 (1H, dd, *J* = 5.8-3.9 Hz, H-2'), 5.92 (1H, t, *J* = 5.8 Hz, H-3'), 6.42 (1H, d, *J* = 3.9 Hz, H-1'), 7.10 (1H, d, *J* = 4.7 Hz, H-5), 7.29 (1H, d, *J* = 4.7 Hz, H-6), 7.35-8.13 (15H, m, H_{Bz}), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.7 (CH_3), 63.3 (C-5'), 70.7 (C-3'), 74.6 (C-2'), 80.4 (C-4'), 88.9 (C-1'), 121.4 (C-5), 122.8 (C-6), 158.9 (C-2), 155.4 (C-3), *benzoyl groups* 128.5, 128.7 (C-3,5); 129.3 (C-1); 129.7, 129.8, 129.9 (C-2,6); 133.6, 133.7 (C-4); 165.1, 165.2, 166.1 (*C*=O). Anal. Calcd for $C_{31}H_{26}N_2O_8$: C, 67.14; H, 4.72; N, 5.05. Found: C, 67.21; H, 4.81; N, 5.11.

3-Decyl-1-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl) pyrazin-2-one (5c). Compound **5c** was prepared following the procedure described for **5a**. Starting from 3-decyl pyrazin-2-one (1.48 g, 6.25 mmol), we obtained after 12 h and chromatographic purification (eluent G) 2.18 g (63%) of **5c** as a clear syrup. TLC eluent F, R_f 0.55. MS *m/z* (CI) : 681 MH^+. $[\alpha]_D$ + 42.6° (c 1.5, $CHCl_3$). IR (KBr) 1650 cm^{-1} (C=O amide), 1718 cm^{-1} (C=O ester), 2920 (CH_2). UV λ(chloroform) 248 (ε 11089), 314 (ε 7453). ^1H NMR ($CDCl_3$, 200 MHz) δ 4.70 (1H, dd, *J* = 12.0-3.6 Hz, H-5'$_a$), 4.80 (1H, ddd, *J* = 5.7-3.6-2.7 Hz, H-4'), 4.90 (1H, dd, *J* = 12.0-2.7 Hz, H-5'$_b$), 5.83 (1H, dd, *J* = 5.7-4.0 Hz, H-2'), 5.93 (1H, t, *J* = 5.7 Hz, H-3'), 6.46 (1H, d, *J* = 4.0 Hz, H-1'), 7.14 (1H, d, *J* = 4.7 Hz, H-5), 7.29 (1H, d, *J* = 4.7 Hz, H-6), 7.35-8.13 (15H, m, H_{Bz}), *decyl groups* 0.88 (3H, t, *J* = 6.7 Hz, CH_3), 1.29 (14H, s, $(CH_2)_7$), 1.67 (2H, quintet, *J* = 7.5 Hz, $^2(CH_2)$), 2.80 (2H, dd, *J* = 7.5 Hz, $^1(CH_2)$), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 63.3 (C-5'), 70.7 (C-3'), 74.9 (C-2'), 80.4 (C-4'), 88.6 (C-1'), 120.9 (C-5), 122.9 (C-6), 155.8 (C-2), 161.9 (C-3), *decyl groups* 14.1, 22.7, 26.7, 29.3, 29.5 (4C), 31.9, 33.4, *benzoyl groups* 128.5, 128.7 (C-3,5); 129.3 (C-1); 129.7, 129.8, 129.9 (C-2,6); 133.6, 133.7 (C-4); 165.1, 165.2, 166.1 (*C*=O). Anal. Calcd for $C_{40}H_{44}N_2O_8$: C, 70.57; H, 6.51; N, 4.11. Found: C, 70.65; H, 6.54; N, 4.13.

1-β-D-Ribofuranosyl pyrazin-2-one (6a). A 1 M $NaOCH_3$ solution (7.5 mL, 2.5 mmol), was added to **5a** (1.35 g, 2.5 mmol) in dry methanol (30 mL). After 2 h at 22°C, neutralization with Amberlyst (15 mesh) ion exchange resin and washing with 15 mL of CH_3OH-H_2O (2/1 : v/v), the filtrate was concentrated in *vacuo*, and the residue was purified by flash chromatography (eluent C). The solid obtained was recrystallized from

ethanol to give 1.04 g (91%) of **6a** as white needles mp 142°C. TLC eluent B, R_f 0.52. MS *m/z* (FAB) : 229 MH^+. $[\alpha]_D$ -24.7° (c 0.95, methanol). IR (KBr) 3370 (OH), 1655 (C=O amide). UV λ(methanol) 320 (ε 5076). ^1H NMR (CD_3OD, 200 MHz) δ 3.78 (1H, dd, *J* = 12.4-2.7 Hz, H-5'$_a$), 3.96 (1H, dd, *J* = 12.4-2.3 Hz, H-5'$_b$), 4.11 (1H, m, H-4'), 4.13 (1H, m, H-3'), 4.15 (1H, m, H-2'), 6.00 (1H, d, *J* = 2.4 Hz, H-1'), 7.41 (1H, d, *J* = 4.6 Hz, H-6), 8.00 (1H, d, *J* = 1.2 Hz, H-3), 8.10 (1H, dd, *J* = 4.6-1.2 Hz, H-5), ^{13}C NMR (CD_3OD, 50 MHz) δ 61.4 (C-5'), 70.3 (C-3'), 76.8 (C-2'), 86.2 (C-4'), 91.6 (C-1'), 125.2 (C-5), 126.1 (C-6), 149.0 (C-3), 157.7 (C-2). Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.27. Found: C, 47.28; H, 5.41; N, 12.21.

3-Methyl-1-(β-D-ribofuranosyl) pyrazin-2-one (6b). Compound **5b** (1.1 g, 2 mmol) was deprotected according to the procedure described for **6a**. The crude product was purified by flash chromatography (eluent B) to give 0.41 g (85%) of **6b** as a slightly yellowish foam, which was homogenous on TLC (eluent B), R_f 0.54. MS *m/z* (FAB) : 243 MH^+. $[\alpha]_D$ +90.6° (c 0.81, methanol). IR (NaCl) 3350 (OH), 1640 (C=O amide). UV λ(methanol) 316 (ε 5038). ^1H NMR (CD_3OD, 200 MHz) δ 2.38 (3H, d, *J* = 0.5 Hz, C*H*$_3$), 3.78 (1H, dd, *J* = 12.5-2.9 Hz, H-5'$_a$), 3.95 (1H, dd, *J* = 12.5-2.2 Hz, H-5'$_b$), 4.09 (1H, m, H-4'), 4.11 (1H, m, H-3'), 4.13 (1H, m, H-2'), 6.01 (1H, d, *J* = 2.5 Hz, H-1'), 7.24 (1H, d, *J* = 4.7 Hz, H-6), 7.95 (1H, dq, *J* = 4.7-0.5 Hz, H-5), ^{13}C NMR (CD_3OD, 50 MHz) δ 20.3 (CH_3), 61.6 (C-5'), 70.4 (C-3'), 76.7 (C-2'), 86.1 (C-4'), 91.7 (C-1'), 123.5 (C-5), 124.3 (C-6), 157.4 (C-2), 158.2 (C-3). Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.49; H, 5.92; N, 11.49.

3-Decyl-1-(β-D-ribofuranosyl) pyrazin-2-one (6c). Compound **5c** (2.4 g, 3.5 mmol) was deprotected as above. The crude product was purified by flash chromatography (eluent D) to give 1.13 g (92%) of **6c** as white needles mp 116-118°C (ethanol). TLC eluent D, R_f 0.55. MS *m/z* (FAB) : 369 MH^+. $[\alpha]_D$ + 65.5° (c 0.78, methanol). IR (KBr) 3370 (OH), 1635 (C=O amide), 2910 (CH_2). UV λ(methanol) 316 (ε 5685). ^1H NMR (CD_3OD, 200 MHz) δ 3.78 (1H, dd, *J* = 12.5-2.9 Hz, H-5'$_b$), 3.94 (1H, dd, *J* = 12.5-2.3 Hz, H-5'$_a$), 4.09 (1H, m, H-4'), 4.11 (1H, m, H-3'), 4.13 (1H, m, H-2'), 6.02 (1H, d, *J* = 3.6 Hz, H-1'), 7.94 (1H, dq, *J* = 4.7-0.5 Hz, H-5), 7.28 (1H, d, *J* = 4.7 Hz, H-6), *decyl groups* 0,89 (3H, t, *J* = 6.7 Hz, C*H*$_3$), 1.28 (14H, s, (C*H*$_2$)$_7$), 1.67 (2H, quintet, *J* = 7.1 Hz, ^{2}(C*H*$_2$)), 2.75 (2H, dd, *J* = 8.3-6.8 Hz, ^{1}(C*H*$_2$)), ^{13}C NMR (CD_3OD, 50 MHz) δ 61.6 (C-5'), 76.8 (C-2'), 70.4 (C-3'), 86.1 (C-4'), 91.7 (C-1'), 123.6 (C-5), 124.0 (C-6), 157.1 (C-2), 161.2 (C-3), *decyl groups* 14.4, 23.7, 27.8, 30.4, 30.5 (3C), 30.7, 33.1, 34.1. Anal. Calcd for $C_{19}H_{32}N_2O_5$: C, 61.93; H, 8.75; N, 7.60. Found: C, 61.88; H, 8.79; N, 7.68.

3-Methyl-1-(β-D-ribofuranosyl) piperazin-2-one (7b). Compound **6b** (0.12 g, 0.5 mmol) in THF (7 mL) was converted to **7b** according to procedure b described for the

preparation of **3**. Purification on silica gel PLC (eluent A) gave 0.10 g (85%) of **7b** (*3R* and *3S*) as a syrup. TLC eluent A, R_f 0.48. MS *m/z* (FAB) : 261 MH^+. IR (NaCl) 3340 (OH), 1635 (C=O amide).

7b*(3R)* ^1H NMR (D_2O, 400 MHz) δ 1.22 (3H, d, *J* = 7.2 Hz, CH_3), 2.89 (1H, ddd, *J* = 13.9-7.5-4.6 Hz, H-5_a), 3.04 (1H, dt, *J* = 13.9-5.2 Hz, H-5_b), 3.30 (2H, m, H-6), 3.49 (1H, q, *J* = 7.0 Hz, H-3), 3.59 (1H, dd, *J* = 12.5-5.1 Hz, H-5'$_a$), 3.67 (1H, dd, *J* = 12.5-3.4 Hz, H-5'$_b$), 3.85 (1H, br dt, *J* = 5.3-3.9 Hz, H-4'), 3.98 (1H, dd, *J* = 5.5-4.4 Hz, H-3'), 4.14 (1H, t, *J* = 5.8 Hz, H-2'), 5.85 (1H, d, *J* = 5.9 Hz, H-1'), ^{13}C NMR (D_2O, 100 MHz) δ 16.4 (CH_3), 38.8 (C-5), 41.5 (C-6), 53.0 (C-3), 60.9 (C-5'), 69.7 (C-3'), 70.1 (C-2'), 82.8 (C-4'), 86.5 (C-1'), 174.6 (C-2).

7b*(3S)* ^1H NMR (D_2O, 400 MHz) δ 1.22 (3H, d, *J* = 7.2 Hz, CH_3), 2.82 (1H, ddd, *J* = 13.9-9.2-5.2 Hz, H-5_a), 3.08 (1H, dt, *J* = 13.9-4.0 Hz, H-5_b), 3.26 (2H, m, H-6), 3.46 (1H, q, *J* = 7.0 Hz, H-3), 3.59 (1H, dd, *J* = 12.5-5.1 Hz, H-5'$_a$), 3.68 (1H, dt, *J* = 12.5-3.5 Hz, H-5'$_b$), 3.86 (1H, br dt, *J* = 5.3-3.9 Hz, H-4'), 3.98 (1H, dd, *J* = 5.5-4.4 Hz, H-3'), 4.15 (1H, t, *J* = 6.3 Hz, H-2'), 5.84 (1H, d, *J* = 6.5 Hz, H-1'), ^{13}C NMR (D_2O, 100 MHz) δ 16.7 (CH_3), 39.9 (C-5), 41.1 (C-6), 53.7 (C-3), 60.9 (C-5'), 69.5 (C-3'), 69.7 (C-2'), 82.9 (C-4'), 85.7 (C-1'), 174.3 (C-2). Anal. Calcd for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.37; N, 11.37. Found: C, 48.75; H, 7.43; N, 11.31.

3-Decyl-1-(β-D-ribofuranosyl) piperazin-2-one (7c). Compound **6c** (0.25 g, 0.7 mmol) in THF (8 mL) was hydrogenated according to the procedure b described for **3**. Crude **7c** was purified by silica gel PLC (eluent B) and the two diastereoisomers *3R* and *3S* were separated by HPLC on reverse phase using eluent H to give 0.12 g (50%) and 0.08 g (33%) of **7c**(*3R*) and **7c**(*3S*) respectively.

7c(*3R*) mp 56°C. TLC eluent B, R_f 0.44. MS *m/z* (FAB) : 373 MH^+. $[\alpha]_D$ -45° (c 0.24, methanol). IR (KBr) 3360 (OH), 1635 (C=O amide), 2900 (CH_2). ^1H NMR (CD_3OD, 400 MHz) δ 2.96 (1H, ddd, *J* = 12.6-8.2-4.2 Hz, H-5_a), 3.12 (1H, dt, *J* = 12.6-5.1 Hz, H-5_b), 3.29 (2H, dt, *J* = 12.4-4.6 Hz, H-6_a), 3.50 (1H, ddd, *J* = 12.4-8.2-4.4 Hz, H-6_b), 3.37 (1H, dd, *J* = 8.4-4.0 Hz, H-3), 3.65 (1H, dd, *J* = 12.0-4.4 Hz, H-5'$_a$), 3.75 (1H, dd, *J* = 12.0-3.6 Hz, H-5'$_b$), 3.86 (1H, q, *J* = 4.2 Hz, H-4'), 4.02 (1H, dd, *J* = 5.9-4.8 Hz, H-3'), 4.12 (1H, t, *J* = 5.9 Hz, H-2'), 5.95 (1H, d, *J* = 5.9 Hz, H-1'), *decyl groups* 0.89 (3H, t, *J* = 6.7 Hz, CH_3), 1,29 (16H, s, $(CH_2)_8$), 1.70 (2H, m, $^1(CH_2)$), ^{13}C NMR (CD_3OD, 100 MHz) δ 42.0 (C-5), 43.9 (C-6), 60.2 (C-3), 63.9 (C-5'), 72.0 (C-2'), 71.0 (C-3'), 84.2 (C-4'), 88.3 (C-1'), 174.2 (C-2), *decyl groups* 23.7, 26.6, 30.5, 30.7 (4C), 28.4, 33.9, 14.7. Anal. Calcd for $C_{19}H_{36}N_2O_5$: C, 61.26; H, 9.74; N, 7.52. Found: C, 61.28; H, 9.82; N, 7.46.

7c(*3S*) syrup. TLC eluent B, R_f 0.44. MS *m/z* (FAB) : 373 MH^+. $[\alpha]_D$ +34° (c 0.16, methanol). IR (KBr) 3360 (OH), 1635 (C=O amide), 2900 (CH_2). ^1H NMR (CD_3OD,

400 MHz) δ 2.92 (1H, ddd, J = 12.6-7.5-5.1 Hz, H-5_a), 3.16 (1H, dt, J = 12.6-4.6 Hz, H-5_b), 3.43 (2H, dt, J = 12.4-4.8 Hz, H-6_a), 3.47 (1H, ddd, J = 12.4-7.9-4.4 Hz, H-6_b), 3.39 (1H, dd, J = 8.4-4.0 Hz, H-3), 3,65 (1H, dd, J = 12.0-4.4 Hz, H-5'$_a$), 3.78 (1H, dd, J = 12.0-3.4 Hz, H-5'$_b$), 3.86 (1H, q, J = 4.2 Hz, H-4'), 4.04 (1H, dd, J = 6.3-4.5 Hz, H-3'), 4.15 (1H, t, J = 6.4 Hz, H-2'), 5.93 (1H, d, J = 6.6 Hz, H-1'), *decyl groups* 0.89 (3H, t, J = 6.7 Hz, CH_3), 1.29 (16H, s, $(CH_2)_8$), 1.70 (2H, m, $^1(CH_2)$), ^{13}C NMR (CD_3OD, 100 MHz) δ 42.9 (C-5), 43.7 (C-6), 60.6 (C-3), 63.7 (C-5'), 71.8 (C-2'), 70.7 (C-3'), 84.5 (C-4'), 88.6 (C-1'), 175.5 (C-2), *decyl groups* 23.8, 26.6, 30.5, 30.6 (4C), 28.5, 33.9, 14,7. Anal. Calcd for $C_{19}H_{36}N_2O_5$: C, 61.26; H, 9.74; N, 7.52. Found: C, 61.34; H, 9.79; N, 7.47.

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