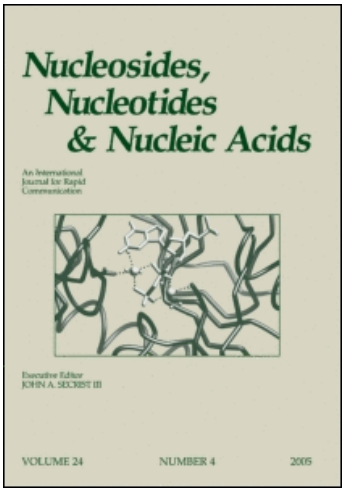

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Synthesis and Antiviral Evaluation of Pyrazinones Substituted with Acyclic Chains.

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SYNTHESIS AND ANTIVIRAL EVALUATION OF PYRAZINONES SUBSTITUTED WITH ACYCLIC CHAINS.

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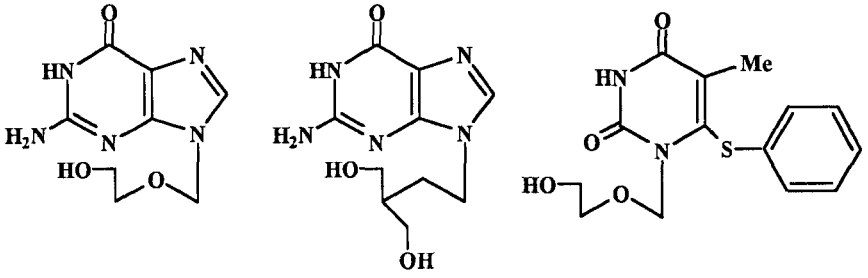
Abstract: The synthesis of a series of pyrazine analogues of the anti-herpes compound, acyclovir is described. These syntheses were accomplished by various methods: in the presence of a Lewis acid or NaH for hydroxyethoxymethyl and hydroxybutyl groups or by sequential oxidation/reduction of 1-(β-D-ribofuranosyl)-2-pyrazinones for 2',3'-acyclonucleosides. Antiviral (HSV-1, CMV, Cox B4, HIV-1) properties of these compounds were determined.

Since the discovery of 9-[2-(hydroxyethoxy)methyl]guanine (acyclovir)[1] [Fig. 1], a selective antiherpes virus agent, considerable interest has been focused on the synthesis of novel acyclic analogues of nucleosides.[2] As a result, a number of derivatives of guanine have been identified as potential antiviral drugs .

9-(4-Hydroxybutyl) guanine exhibits high anti-herpes activity *in vitro*[3] and 9-(4-hydroxy-3-hydroxymethylbutyl)guanine, DHBG [Fig. 1], has been extensively investigated as an antiviral agent both *in vitro* and *in vivo*.[4] Recently, certain 6-substituted acyclic pyrimidine nucleosides related to acyclovir, such as 1-[2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) [Fig. 1] have been shown to be selective inhibitors of human immunodeficiency virus in various human lymphocytes.[5]

Since acyclic nucleoside and nucleoside analogues are potential antiviral compounds and since acyclopyrazine analogues have not yet to our knowledge been investigated, we decided to synthesize a series of acyclic pyrazinone compounds. These compounds bear



acyclovir DHBG HEPT

FIG 1

substituents of various lipophilic character, such as hydrogen, methyl and n-decyl, which may increase their cellular permeability. The synthesis and biological evaluation of this series of alkyloxy or alkyl pyrazinones **3a,b,c**, **6a,b,c**, **8a,b,c** and **10a,b,c** will be described (scheme 1).

The antiviral activities (HSV-1, CMV, Cox B4, vaccinia, HIV-1) of these new compounds were determined in cell cultures.

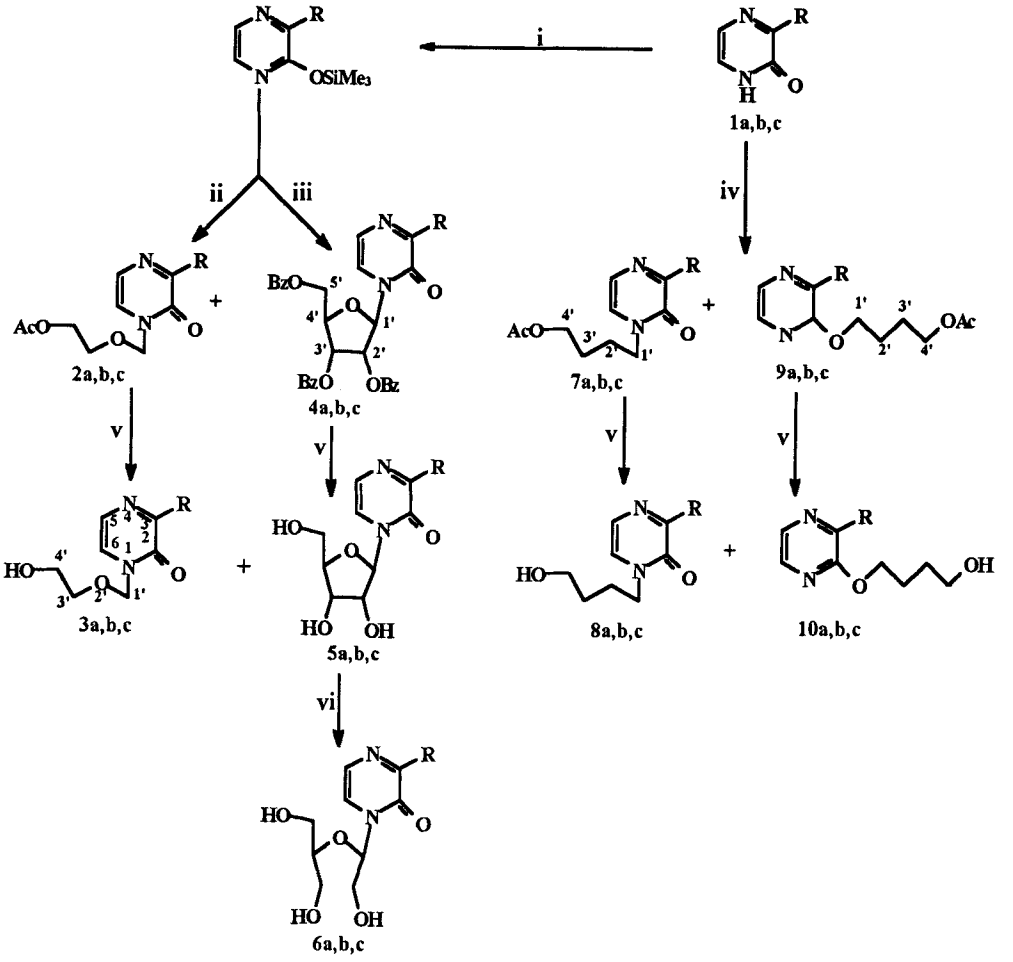
Results and Discussion

The 3-substituted pyrazinones **1a,b** were synthesized according to Jones procedure[6]. A stightly modified procedure was used for the synthesis of **1c**.[7]

Starting from **1**, the synthesis of compounds **3**, **6**, **8** and **10** is outlined in Scheme I.

Compounds **2a-c** were prepared by condensing (2-acetoxyethoxy)methylchloride with the silylated 3-substituted pyrazinones in the presence of $SnCl_4$ (20-52% conversion). The acyclic haloether side chain was synthesized with acetyl chloride in 1,3-dioxolane at reflux.[8] Attempts to synthesize **2a** making use of a weak base such as potassium carbonate[9], did not lead to the desired compound. Removal of the acetyl group of **2** with sodium methoxide gives the unprotected compounds **3.**

The 2',3'-seconucleosides, **6a-c,** retain the carbon framework of ribose nucleosides and chirality of the anomeric carbon, yet allow for greater flexibility than the furanose moiety. The synthetic route chosen for these analogues was periodate oxidation of



a R=H, b R=CH_3, c R=$C_{10}H_{21}$

i) HMDS, TMSCl,$C_2H_4Cl_2$. ii) $SnCl_4$, $ClCH_2O(CH_2)_2OAc$,CH_2Cl_2. iii) 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose, CH_2Cl_2, $SnCl_4$. iv) NaH, $Br(CH_2)_4OAc$, DMF. v) MeONa/MeOH. vi) periodate- and borohydride-bound resins.

SCHEME 1

ribopyrazinones and reduction of the obtained dialdehyde with borohydride. To synthesize the ribopyrazinones **4a,b,c**, the silylated pyrazinones were coupled with 1-O-acetyl, 2,3,5-tri-O-benzoyl-β-D-ribofuranose *via* the Vorbrüggen procedure[10] in presence of $SnCl_4$ in dichloroethane. Removal of the benzoyl protecting groups was performed with sodium methoxide in methanol. In the case of **5a** and **5b**, the resulting methyl benzoate was eliminated by extraction using ether/water; in the case of **5c**, purification using silica gel was necessary as the unprotected product was equally soluble in the organic phase. Oxidation/reduction was carried out using periodate- and borohydride bound resins[11,12] which gave better results than the solution phase chemistry [13]. The final products **6a,b,c** were easily recovered after filtration of the reaction mixture followed by evaporation of the filtrate.

In order to obtain the compound **8a**, **1a** was stirred with NaH in DMF at 80°C, followed by the addition of bromobutylacetate at room temperature. A mixture of the desired product, **7a**, and the O-alkylated analogue **9a** was obtained in a 1:1 ratio. A study of the effect of the temperature was undertaken to enhance the proportion of **7a** [Table 1].

An increase in the reaction temperature (140°C) leads to a decrease in the ratio of **7a/9a** (0.8:1). A decrease in the temperature (-20°C) leads to an increase of the **7a/9a** ratio (1.8:1). The overall yield, however, decreases to 44%. The best results were observed by addition of NaH at 22°C to the reaction mixture. In that case a total yield of 89% was obtained with a ratio **7a/9a** of 3:1. These reaction conditions were used for the synthesis of **7b,c** and **9b,c**. Deacetylation of compounds **7a,b,c** and **9a,b,c** with sodium methoxide gave **8a,b,c** and **10a,b,c** in quantitative yields.

Biological Evaluation:

Compounds **3**, **6**, **8** and **10** were tested for their *in vitro* inhibitory effects on the replication of a number of DNA viruses (herpes simplex virus type 1, human cytomegalovirus, vaccinia virus) and RNA viruses (Coxsackie virus B4, HIV-1) [Table 2].Only compound **3c** (Cox B4) and **6c** (CMV) demonstrate marginal activity while some cell toxicity was observed for **6c**.

TABLE 1 : The effect of temperature on the alkylation of **1a**.

Temperature (°C)	Overall Yield [§] (%)	7a / 9a
-20	44	1.8
22	89	3.1
80	76	1.1
140	64	0.8

[§] Isolated by flash column chromatography.

TABLE 2 : Antiviral effects of derivatives of 3-decyl-2-pyrazinones[(a)].

(a) for abreviations see experimental

	Toxicity	Antiviral effect				
	MTT CC50 (μM)	IC 50 (μM)				
		HSV-1	CMV	Cox B4	Vaccine	HIV
3c	>100	>100	>100	100	>100	>100
6c	93	>100	50	>100	>100	>100
8c	nd	>10	>10	nd	nd	>100
10c	nd	>10	>10	nd	nd	>100

*nd: not determined.

EXPERIMENTAL SECTION

Thin-layer chromatography (TLC) was performed on silica gel Kieselgel 60PF_{254} (Merck) plates and visualized in several ways: by an ultraviolet light source at 254 nm and/or 365 nm, by spraying with sulfuric acid (6N) and heating to 200°C, by vaporizing with a fluoresceine solution followed by an aqueous solution of hydrogen peroxide in acetic acid (for compounds containing Br) or by a combination of two or more of these techniques. Silica gel (Merck Kieselgel 60, 15-40 μm) was used for flash column chromatography. Solvents were distilled from appropriate drying agents. ^{1}H and ^{13}C NMR spectra were recorded at 300 (75, ^{13}C) MHz with a Bruker AM-300 spectrometer

or at 200 (50, ^{13}C) MHz with a Bruker Ac-200 spectrometer. Chemical shifts (δ) are expressed in ppm with Me_4Si as internal standard (δ=0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet and br = broad), coupling constants (J) in hertz (Hz) and assignment. Electronic-impact mass spectra (EI) were recorded with a Shimadzu QP1000 mass spectrometer at the "Laboratoire Départemental d'Analyses of Limoges". Chemical-impact mass spectra (CI) were recorded with a Kratos MS580 mass spectrometer; Fast Atom Bombardment (FAB) spectra were recorded on a R10-10 Nermag spectrometer. Both CI and FAB were recorded at the "Laboratoire de Chimie Organique Structurale" of the Université Pierre et Marie Curie (Paris VI). Melting points (°C) were determined with a Köfler block and are uncorrected. Elemental analyses were carried out by Microanalytical Service of the "Université Pierre et Marie Curie (Paris VI)". Rotatory dispersions were measured with a Jasco (DIP-370) polarimeter in a 1 dm quartz cell at 22°C. Infra-red spectra (KBr disk or film) were measured on a Perkin Elmer 1310 grating spectrophotometer and are reported in wave numbers (cm^{-1}). UV spectra were recorded with a Hewlett Packard 8454A diode array spectrophotometer. Wavelengths corresponding to the maximum absorbances, λ_{max}, are expressed in nanometers and the molar absorptivity coefficients, ε in mol^{-1} l cm^{-1}, are expressed as their log values.

1-(2-acetoxyethoxymethyl)-2-pyrazinone (**2a**)

To the 2-pyrazinone (4 mmol, 0.38 g) in freshly distilled dichloroethane (8 mL) was added hexamethyldisilazane (HMDS) (0.9 eq., 0.67 mL) and trimethylchlorosilane (TMSCl) (0.8 eq., 0.40 mL). The solution was heated at reflux for 3 hours and cooled to 0°C. 2-Acetoxyethoxymethyl chloride (1.2 eq., 0.69 mL) was added followed by the slow addition of tin (IV) chloride (1.2 eq., 0.56 mL). The temperature was allowed to warm to room temperature and stirring was continued for 16 hours. The reaction mixture was quenched by the addition of a saturated $NaHCO_3$ solution (15 mL), and extracted with $CHCl_3$ (3 x 40 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed. The product (0.59 g) was adsorbed on Florisil® (4 g) and purified by silica gel chromotography (3.5 cm x 15 cm). Elution with a gradient of $CHCl_3$ / EtOH

gave N^1-(2-acetoxyethoxymethyl) 2-pyrazinone in 52% yield (440 mg). R_f = 0.43 ($CHCl_3$ / EtOH, 95/5, v/v), IR: 3050 (CH ar.), 2950 (CH alk.), 1720 (C=O (acetyl)), 1645 (C=O (pyrazine)), 1580 (C=C), 1230, 1025 (C-O (ether)). UV: (EtOH) λ_{max} (log ε) 316 (3.7). ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, d, J = 1.2, H_3), 7.20 (1H, dd, J = 4.5 - 1.2, H_5), 7.35 (1H, d, J = 4.5, H_6) *N-oxyalkyl* 5.34 (2H, s, $C_{1'}H$), 3.79 (2H, m, $C_{3'}H$), 4.21 (2H, m, $C_{4'}H$), 2.04 (3H, s,CH_3). ^{13}C NMR ($CDCl_3$) δ 156.0 (C_2), 150.3 (C_3), 123.9 (C_5), 126.4 (C_6). *N-oxyalkyl* 76.6 ($C_{1'}$), 68.3 ($C_{3'}$), 62.8 ($C_{4'}$), 170.7 (CO), 20.7 (C (CH_3)). Anal. calcd for $C_9H_{12}O_4N_2$ C 50.94, H 5.70, N 13.20, found C 50.74, H 6.02, N 13.38. MS (DCI/NH_3): *m/z* 213 (MH^+).

Compounds **2b** and **2c** were prepared in a manner similar to that described for **2a** starting from **1b** and **1c** (1 mmol) respectively.

1-(2-acetoxyethoxymethyl)-3-methyl 2-pyrazinone **(2b)**

Yield 20% . R_f = 0.55 ($CHCl_3$ / EtOH, 95/5, v/v). IR: 3050 (CH ar.), 2925 (CH alk.), 1720 (C=O (acetyl)), 1650 (C=O (pyrazine)), 1580 (C=C), 1220, 1025 (C-O (ether)). UV: (EtOH) λ_{max} (log ε) 316 (3.8). ^{1}H NMR ($CDCl_3$) δ 7.11 (1H, dd, J = 4.4 - 0.6, H_5), 7.22 (1H, d, J = 4.4, H_6), 2.46 (3H, d, J = 0.6), *N-oxyalkyl* 5.34 (2H, s, $C_{1'}H$), 3.79 (2H, m, $C_{3'}H$), 4.21 (2H, m, $C_{4'}H$), 2.05 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.1 (C_2), 156.2 (C_3), 122.6 (C_5), 124.7 (C_6) 20.8 (CH_3), *N-oxyalkyl* 76.9 ($C_{1'}$), 62.9 ($C_{3'}$), 68.2 ($C_{4'}$), 170.7 (CO), 20.8 (C (CH_3)). Anal. calcd for $C_{10}H_{14}O_4N_2$ C 53.09, H 6.24, N 12.38, found C 53.21, H 6.10, N 12.22. MS (DCI/NH_3): *m/z* 227 (MH^+).

1-(2-acetoxyethoxymethyl)-3-decyl 2-pyrazinone **(2c)**

Yield 35%. R_f = 0.53, ($CHCl_3$ / EtOH, 95/5, v/v). IR: 3050 (CH ar.), 2925 (CH alk.), 1730 (C=O (acetyl)), 1645 (C=O (pyrazine)), 1580 (C=C), 1220, 1030 (C-O (ether)). UV: (EtOH) λ_{max} (log ε) 316 (3.8). ^{1}H NMR ($CDCl_3$) δ 7.10 (1H, br.d, J = 4.3, H_5), 7.26 (1H, d, J = 4.3, H_6), *decyl chain* : 0.88 (3H, t, J = 6.4, H_{10}), 1.26 (14H, br. s, $H_{3\text{-}9}$), 1.69 (2H, br.quint, J = 7.5, H_2), 2.81 (2H, br.t, J = 7.7, H_1), *N-oxyalkyl* 5.35 (2H s, $C_{1'}H$), 3.79 (2H, m, $C_{3'}H$), 4.21 (2H, m, $C_{4'}H$), 2.06 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 162.2 (C_2), 156.0 (C_3), 122.7 (C_5), 124.4 (C_6), *decyl chain* 14.1 (C_{10}), 22.7 (C_9), 29.3

(C_8), 26.5 (C_7), 29.5 (C_{3-6}), 31.7 (C_2), 33.5 (C_1), *N-oxyalkyl.* 77.0 ($C_{1'}$), 68.2 ($C_{3'}$), 63.0 ($C_{4'}$), 170.8 (CO), 20.8 (C (CH_3)). Anal. calcd for $C_{19}H_{32}O_4N_2$ C 64.74, H 9.15, N 7.95, found C 64.65, H 8.97, N 7.75. MS (DCI/NH_3): *m/z* 353 (MH^+).

***1-(2-hydroxyethoxymethyl)-2-pyrazinone* (3a)**

The deacetylation of **2a** (0.1 g, 0.47 mmol) was carried out in the presence of 0.5 eq of sodium methoxide (1M solution in methanol.). The solution was neutralized by addition of Amberlite IRN 77 H^+ resin (Aldrich) and filtered giving N^1-(2-hydroxyethoxymethyl) 2-pyrazinone in 92% yield (74 mg). R_f = 0.29 ($CHCl_3$ / EtOH, 90/10, v/v). F 69.5°C. IR: 3500-3250 (OH), 1650 (C=O), 1580 (C=C). UV: (EtOH) λ_{max} (log ε) 320 (3.7). ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, br s, H_3), 7.24 (1H, dd, *J* = 4.5 - 1.1, H_5), 7.35 (1H, d, *J* = 4.5, H_6) *N-oxyalkyl* 5.35 (2H, s, $C_{1'}H$), 3.72 (2H, m, $C_{3'}H$), 3.72 (2H, m, $C_{4'}H$), 2.65 (1H, br s, OH). ^{13}C NMR ($CDCl_3$) δ 156.1 (C_2), 150.2 (C_3), 123.9 (C_5), 126.6 (C_6). *N-oxyalkyl* 77.2 ($C_{1'}$), 71.5 ($C_{3'}$), 61.5 ($C_{4'}$). Anal. calcd for $C_7H_{10}O_3N_2$ C 49.41, H 5.92, N 16.46, found C 49.29, H 6.00, N 16.40. MS (DCI/NH_3): *m/z* 171 (MH^+).

Compounds **3b** and **3c** were prepared in a manner similar to that described for **3a** starting from **2b** and **2c** (0.15 mmol) respectively.

***1-(2-hydroxyethoxymethyl)-3-methyl 2-pyrazinone* (3b)**

Yield 90%. R_f = 0.47 ($CHCl_3$ / EtOH, 90/10, v/v). IR: 3400-3250 (OH), 1650 (C=O), 1580 (C=C). UV: (EtOH) λ_{max} (log ε) 320 (3.7). ^{1}H NMR ($CDCl_3$) δ 7.11 (1H, br. d, *J* = 4.4, H_5), 7.22 (1H, d, *J* = 4.4, H_6), 2.46 (3H, s, CH_3), *N-oxyalkyl* 5.35 (2H, s, $C_{1'}H$), 3.72 (2H, m, $C_{3'}H$), 3.78 (2H, m, $C_{4'}H$). ^{13}C NMR ($CDCl_3$) δ 159.4 (C_2), 156 (C_3), 122.7 (C_5), 125 (C_6) *chain* 20.8 (CH_3). *N-oxyalkyl.* 77.5 ($C_{1'}$), 61.7 ($C_{3'}$), 71.4 ($C_{4'}$). Anal. calcd for $C_8H_{12}O_3N_2$ C 52.17, H 6.57, N 15.21, found C 52.06, H 6.51, N 15.10. MS (DCI/NH_3): *m/z* 185 (MH^+).

***1-(2-hydroxyethoxymethyl)-3-decyl 2-pyrazinone* (3c)**

Yield 95%. R_f = 0.48 ($CHCl_3$ / EtOH, 90/10, v/v). IR: 3380-3250 (OH), 2920 (CH alk.), 1645 (C=O), 1580 (C=C). UV: (EtOH) λ_{max} (log ε) 320 (3.7). ^{1}H NMR ($CDCl_3$) δ

7.11 (1H, br.d, J = 4.4, H_5), 7.26 (1H, d, J = 4.4, H_6), *decyl chain* : 0.87 (3H, t, J = 6.4, H_{10}), 1.27 (14H, br. s, $H_{3\text{-}9}$), 1.68 (2H, br.quint, J = 7.5, H_2), 2.80 (2H, br.t, J = 7.8, H_1), *N-oxyalkyl* 5.53 (2H s, $C_{1'}H$), 3.73 (2H, m, $C_{3'}H$), 3.73 (2H, m, $C_{4'}H$), 2.55 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ 162.2 (C_2), 156.0 (C_3), 122.7 (C_5), 124.4 (C_6), *decyl chain* 14.1 (C_{10}), 22.6 (C_9), 29.3 (C_8), 26.5 (C_7), 29.5 ($C_{3\text{-}6}$), 31.7 (C_2), 33.5 (C_1), *N-oxyalkyl* 77.6 ($C_{1'}$), 71.4 ($C_{3'}$), 61.6 ($C_{4'}$). Anal. calcd for $C_{17}H_{30}N_2O_3 \cdot H_2O$ C 62.16, H 9.72, N 8.85, found C 62.32, H 9.52, N 9.00. MS (DCI/NH_3): *m/z* 311 (MH^+).

1-(2 , 3 , 5 tri-O-benzoyl-β-D-ribofuranosyl)-2-pyrazinone **(4a)**

To **1a** (2 mmol, 0.19 g) in dry dichloroethane (8 mL) was added (0.9 eq., 0.33 mL) HMDS and (0.8 eq., 0.20 mL) TMSCl. The reaction mixture was heated at 90°C for 2 hours. After cooling to room temperature, the mixture was evaporated to dryness and a solution of 1-*O*-acetyl-2, 3, 5-tri-*O*-benzoyl β-D-ribofuranose (1 eq., 1 g) in dichloroethane (8 mL) was added followed by $SnCl_4$ (2 eq., 0.46 mL). The solution was stirred at room temperature until tlc indicated the completion of the reaction (3-10 hours depending on pyrazinone). The reaction mixture was quenched by an aqueous saturated $NaHCO_3$ solution and extracted with chloroform. The chloroform solution was dried over $MgSO_4$ and the solvent was removed by evaporation under reduced pressure. The crude product was subjected to preparative tlc using $CHCl_3$ / EtOH ((98/2) x 2, v/v) yielding **4a** (480 mg, 60%) as a foam. R_f = 0.52 ($CHCl_3$/EtOH, 95/5, v/v). IR: 3050 (CH ar.), 1720 (C=O (Bz)), 1645 (C=O (pyrazine)), 1590 (C=C). $[\alpha]_D$: +65.7° (c, 0.95, CH_3Cl). ^1H NMR ($CDCl_3$) δ 7.96 (1H, s, H_3), 7.22 (1H, d, J=4.6, H_5), 7.35-8.13 (17H, m, H_6 and H_{bz}), 6.42 (1H, d, J=4.4, $H_{1'}$), 5.82 (1H, dd, J=5.6-4.4, $H_{2'}$), 5.93 (1H, t, J=5.6, $H_{3'}$), 4.81 (1H, dt, J=5.6-3.5-2.7, $H_{4'}$), 4.89 (1H, dd, J=11.9-2.7, $H_{5'a}$), 4.70 (1H, dd, J=11.9-3.5, $H_{5'b}$). ^{13}C NMR ($CDCl_3$) δ 155.2 (C_2), 150.0 (C_3), 122.8 (C_5), 124.0 (C_6), 88.1 ($C_{1'}$), 74.7 ($C_{2'}$), 70.8 ($C_{3'}$), 80.8 ($C_{4'}$), 63.4 ($C_{5'}$), ***benzoyl groups*** 129.3 (C_1), 128.5, 128.7 ($C_{3,5}$), 129.7, 129.8, 129.9 ($C_{2,6}$), 133.6, 133.7 (C_4), 165.1, 165.2, 166.1 (C_7). Anal. calcd for $C_{30}H_{24}O_8N_2$ C 66.66, H 4.47, N 5.18, found C 66.41, H 4.48, N 5.21. MS (DCI/NH_3): *m/z* 543 (MH^+).

Compounds **4b** and **4c** were prepared in a manner similar to that described for **4a** starting from **1b** (2 mmol) and **1c** (0.8 mmol) respectively.

1-(2 , 3 , 5 tri-O-benzoyl-β-D-ribofuranosyl)-3-methyl-2-pyrazinone **(4b)**

Yield 55%. R_f = 0.42 ($CHCl_3$/EtOH, 98/2, v/v). F 87-89°C. IR: 3050 (CH ar.), 2950 (CH alk.), 1725 (C=O (Bz)), 1645 (C=O ; pyrazine), 1590 (C=C). $[\alpha]_D$: +56.8° (c, 1.02, CH_3Cl). ^1H NMR ($CDCl_3$) δ 7.10 (1H, d, *J*=4.7, H_5), 7.28 (1H, d, *J*=4.7, H_6), 2.45 (3H, s, CH_3), 6.42 (1H, d, *J*=3.9, $H_{1'}$), 5.82 (1H, dd, *J*=5.7-3.9, $H_{2'}$), 5.93 (1H, t, *J*=5.8, $H_{3'}$), 4.80 (1H, dt, *J*=5.8-3.6-2.7, $H_{4'}$), 4.89 (1H, dd, *J*=12.0-2.7, $H_{5'a}$), 4.70 (1H, dd, *J*=12.0-3.6, $H_{5'b}$), 7.35-8.13 (15H, m, H_{Bz}). ^{13}C NMR ($CDCl_3$) δ 158.9 (C_2), 155.4 (C_3), 121.4 (C_5), 122.8 (C_6), 20.7 (C (CH_3)), 88.9 ($C_{1'}$), 74.7 ($C_{2'}$), 70.8 ($C_{3'}$), 80.4 ($C_{4'}$), 63.4 ($C_{5'}$), ***benzoyl groups*** 129.3 (C_1), 128.5, 128.7 ($C_{3,5}$), 129.7, 129.8, 129.9 ($C_{2,6}$), 133.6, 133.7 (C_4), 165.1, 165.2, 166.1 (C_7). Anal. calcd for $C_{31}H_{26}O_8N_2$ C 67.14, H 4.72, N 5.05, found C 67.21, H 4.81, N 5.11. MS (DCI/NH_3): *m/z* 557 (MH^+).

1-(2 , 3 , 5 tri-O-benzoyl-β-D-ribofuranosyl)-3-decyl-2-pyrazinone **(4c)**

Yield 62%. R_f = 0.61 ($CHCl_3$/EtOH, 99/1, v/v). IR: 3050 (CH ar.), 2950-2850 (CH alk.), 1720 (C=O (Bz)), 1645 (C=O ; pyrazine), 1590 (C=C). $[\alpha]_D$: +42.6° (c, 1.5, CH_3Cl). ^1H NMR ($CDCl_3$) δ 6.46 (1H, d, *J*=4.7, H_5), 7.28 (1H, d, *J*=4.7, H_6), 2.78 (2H, t, *J*=7.5, H_1), 1.67 (2H, quint, *J*=7.5, H_2), 1.26 (14H, s, H_{3-9}), 0.88 (3H, t, *J*=6.4, H_{10}), 6.46 (1H, d, *J*=3.9, $H_{1'}$), 5.88 (1H, dd, *J*=5.7-3.9, $H_{2'}$), 5.93 (1H, t, *J*=5.8, $H_{3'}$), 4.82 (1H, ddd, *J*=5.8-3.6-2.7, $H_{4'}$), 4.89 (1H, dd, *J*=12.0-2.7, $H_{5'a}$), 4.70 (1H, dd, *J*=12.0-3.6, $H_{5'b}$), 7.35-8.13 (15H, m, H_{Bz}). ^{13}C NMR ($CDCl_3$) δ 161.9 (C_2), 155.8 (C_3), 120.9 (C_5), 122.8 (C_6), *decyl chain* 14.1 (C_{10}), 22.7 (C_9), 26.5 (2C, C_{7-8}), 29.5 (4C, C_{3-6}), 31.9 (C_2), 33.4 (C_1); 88.6 ($C_{1'}$), 74.9 ($C_{2'}$), 70.8 ($C_{3'}$), 80.4 ($C_{4'}$), 63.3 ($C_{5'}$), ***benzoyl groups*** 129.3 (C_1), 128.5, 128.7 ($C_{3,5}$), 129.7, 129.8, 129.9 ($C_{2,6}$), 113.6, 133.7 (C_4), 165.1, 165.2, 166.1 (C_7). Anal. calcd for $C_{40}H_{44}O_8N_2$ C 70.57, H 6.51, N 4.11, found C 70.65, H 6.54, N 4.13. MS (DCI/NH_3): *m/z* 683 (MH^+).

1-(β-D-ribofuranosyl)-2-pyrazinone **(5a)**

A solution of 1-(2', 3', 5'-tri-O-benzoyl-β-D-ribofuranosyl)-2-pyrazinone (0.46 mmol, 250 mg) **4a** in methanol and sodium methoxide (1M in methanol) was stirred at room temperature. The solution was neutralized with Amberlite IRN-77 resin (H^+), filtered and evaporated to dryness. The resulting oil was partitioned between Et_2O and H_2O and the

aqueous phase was washed once with Et_2O before evaporation. Compound **5a** was obtained in 87% yield (90 mg). R_f = 0.52 $CHCl_3$/EtOH, 75/25, v/v). IR: 3400-3200 (OH), 1645 (C=O), 1590 (C=C). $[\alpha]_D$: -24.7° (c, 0.95, CH_3OH). ^1H NMR ($CDCl_3$) δ 7.99 (1H, d, *J*=1.2, H_3), 8.10 (1H, dd, *J*=4.6-1.2, H_5), 7.41 (1H, d, *J*=4.6, H_6), 6.00 (1H, d, *J*=2.4, $H_{1'}$), 4.15 (1H, m, $H_{2'}$), 4.13 (1H, m, $H_{3'}$), 4.11 (1H, m, $H_{4'}$), 3.96 (1H, dd, *J*=12.4-2.3, $H_{5'a}$), 3.78 (1H, dd, *J*=12.4-2.6, $H_{5'b}$). ^{13}C NMR ($CDCl_3$) δ 157.7 (C_2), 149.0 (C_3), 125.2 (C_5), 126.1 (C_6), 91.6 ($C_{1'}$), 76.8 ($C_{2'}$), 70.3 ($C_{3'}$), 86.2 ($C_{4'}$), 61.4 ($C_{5'}$). Anal. calcd for $C_9H_{12}O_5N_2$ C 47.37, H 5.30, N 12.27, found C 47.28, H 5.41, N 12.21. MS (FAB): *m/z* 229 (MH^+).

Compounds **5b** and **5c** were prepared in a manner similar to that described for **5a** starting from **4b** (0.25 mmol) and **4c** (0.1 mmol) respectively.

***1-(β-D-ribofuranosyl)-3-methyl-2-pyrazinone* (5b)**

Yield 88%. R_f = 0.46, (CH_2Cl_2/EtOH, 8/2, v/v). IR: 3400-3200 (OH), 1645 (C=O), 1590 (C=C). $[\alpha]_D$: +90.6° (c, 0.80, CH_3OH). ^1H NMR ($CDCl_3$) δ 7.95 (1H, d, *J*=4.7, H_5), 7.24 (1H, d, *J*=4.7, H_6), 1.17 (3H, s, CH_3), 6.01 (1H, d, *J*=2.5, $H_{1'}$), 4.13 (1H, m, $H_{2'}$), 4.11 (1H, m, $H_{3'}$), 4.09 (1H, m, $H_{4'}$), 3.94 (1H, dd, *J*=12.4-2.2, $H_{5'a}$), 3.78 (1H, dd, *J*=12.3-2.7, $H_{5'b}$). ^{13}C NMR ($CDCl_3$) δ 157.4 (C_2), 158.2 (C_3), 123.5 (C_5), 124.3 (C_6), 20.3 (C (CH_3)), 91.7 ($C_{1'}$), 76.7 ($C_{2'}$), 70.4 ($C_{3'}$), 86.1 ($C_{4'}$), 61.6 ($C_{5'}$). Anal. calcd for $C_{10}H_{14}O_5N_2$ C 49.58, H 5.83, N 11.26, found C 49.49, H 5.92, N 11.49. MS (FAB): *m/z* 243 (MH^+).

***1-(β-D-ribofuranosyl)-3-decyl-2-pyrazinone* (5c)**

Yield 86%. R_f = 0.55 ($CHCl_3$/MeOH, 85/15, v/v). IR: 3500-3200 (OH), 2950 (CH), 1645 (C=O), 1590 (C=C). $[\alpha]_D$: +65.5° (c, 0.75, CH_3OH). ^1H NMR ($CDCl_3$) δ 7.94 (1H, d, *J*=4.7, H_5), 7.28 (1H, d, *J*=4.7, H_6), 2.75 (2H, t, *J*=7.5, H_1), 1.67 (2H, quint, *J*=7.1, H_2), 1.28 (14H, s, $H_{3\text{-}9}$), 0.89 (3H, t, *J*=6.7, H_{10}), 6.02 (1H, d, *J*=3.6, $H_{1'}$), 4.13 (1H, m, $H_{2'}$), 4.11 (1H, m, $H_{3'}$), 4.09 (1H, m, $H_{4'}$), 3.94 (1H, dd, *J*=12.5-2.3, $H_{5'a}$), 3.78 (1H, dd, *J*=12.5-2.9, $H_{5'b}$). ^{13}C NMR ($CDCl_3$) δ 161.2 (C_2), 157.1 (C_3), 123.6 (C_5), 124.1 (C_6); *decyl chain* 14.4 (C_{10}), 23.7 (C_9), 27.8 (2C, $C_{7\text{-}8}$), 30.5 (4C, $C_{3\text{-}6}$), 33.1(C_2),

34.1 (C_1), 91.7 ($C_{1'}$), 70.4 ($C_{2'}$), 76.8 ($C_{3'}$), 86.1 ($C_{4'}$), 61.6 ($C_{5'}$). Anal. calcd for $C_{19}H_{32}O_5N_2$ C 61.93, H 8.75, N 7.60, found C 61.88, H 8.79, N 7.68. MS (FAB): *m/z* 369 (MH^+).

***1-[1-(1,3-dihydroxy isopropoxy)-2-hydroxyethyl]-2-pyrazinone* (6a)**

To a solution of **5a** (0.44 mmol, 100 mg) in methanol (10 mL) was added 0.5 g each of periodate and borohydride resins. The mixture was stirred at room temperature until reaction was complete (20-27 hours). The intermediate dialdehyde had a higher R_f and the final diol had a lower R_f than the starting compound. The resin beds were filtered and washed with methanol. The methanol filtrate was evaporated under reduced pressure to obtain the desired acyclic product in 94% yield. Pure **6a** was obtained after preparative tlc using CH_2Cl_2 / EtOH (8/2) in 60% yield (60 mg). R_f = 0.44 ($CHCl_3$/EtOH, 75/25, v/v). IR: 3500-3200 (OH), 2950-2850 (CH), 1645 (C=O), 1590 (C=C), 1150 (COC). ^{1}H NMR (CD_3OD) δ 8.02 (H, d, *J*=0.6, H_3), 7.73 (1H, dd, *J*=4.5-0.6, H_5), 7.43 (1H, d, *J*=4.5, H_6), *N-alkyl* 6.02 (1H, t, *J*=4.7, $H_{1'}$), 3.74 (2H, d, *J*=4.7, $H_{2'}$), 3.54 (2H, d, *J*=2.6, $H_{3'}$), 3.70 (1H, quint, *J*=2.6, $H_{4'}$), 3.54 (2H, d, *J*=2.6, $H_{5'}$). ^{13}C NMR (CD_3OD) δ 158.0 (C_2), 149.1 (C_3), 125.1 (C_5), 126.9 (C_6), 85.7 ($C_{1'}$), 63.7 ($C_{2'}$), 62.7 ($C_{3'}$), 83.2 ($C_{4'}$), 62.2 ($C_{5'}$). MS (DCI/NH_3): *m/z* 231 (MH^+).

Compounds **6b** and **6c** were prepared in a manner similar to that described for **6a** starting from **5b** and **5c** (0.25 mmol) respectively.

***1-[1-(1,3-dihydroxy isopropoxy)-2-hydroxyethyl]-3-methyl-2-pyrazinone* (6b)**

Yield 95%. R_f = 0.47 (CH_2Cl_2/EtOH, 75/25, v/v). IR: 3500-3200 (OH), 2950-2850 (CH alk.), 1645 (C=O), 1590 (C=C), 1150 (COC). ^{1}H NMR (CD_3OD) δ 7.61 (1H, dd, *J*=4.7-0.6, H_5), 7.27 (1H, d, *J*=4.7, H_6), 2.38 (3H, d, *J*=0.5, CH_3), *N-alkyl* 6.22 (1H, t, *J*=4.8, $H_{1'}$), 3.74 (2H, d, *J*=4.6, $H_{2'}$), 3.53 (2H, m, $H_{3'}$), 3.71 (1H, m, $H_{4'}$), 3.53 (2H, m, $H_{5'}$). ^{13}C NMR (CD_3OD) δ 158.2 (C_2), 157.7 (C_3), 123.4 (C_5), 124.5 (C_6), 20.5 (C (CH_3)), 85.7 ($C_{1'}$), 62.1 ($C_{2'}$), 62.7 ($C_{3'}$), 82.9 ($C_{4'}$), 63.8 ($C_{5'}$). MS (DCI/NH_3): *m/z* 245 (MH^+).

***1-[1-(1,3-dihydroxy isopropoxy)-2-hydroxyethyl]-3-decyl-2-pyrazinone* (6c)**

Yield 91%. $R_{f\ (triol)}$ = 0.5 ($CHCl_3$/EtOH, 85/15, v/v). IR: 3500-3200 (OH), 2950 (CH

alk.), 1645 (C=O), 1590 (C=C). ^{1}H NMR (CD_3OD) δ 7.59 (1H, br. d, *J*=4.6, H_5), 7.31 (1H, d, *J*=4.6, H_6), 2.75 (2H, t, *J*=7.6, H_1), 1.65 (2H, m, H_2), 1.30 (14H, s, $H_{3\text{-}9}$), 0.89 (3H, t, *J*=6.3, H_{10}), *N-alkyl* 6.22 (1H, t, *J*=4.8, $H_{1'}$), 3.74 (2H, d, *J*=4.6, $H_{2'}$), 3.53 (2H, m, $H_{3'}$), 3.71 (1H, m, $H_{4'}$), 3.53 (2H, m, $H_{5'}$). ^{13}C NMR (CD_3OD) δ 161.2 (C_2), 157.4 (C_3), 123.5 (C_5), 124.6 (C_6); *decyl chain* 14.4 (C_{10}), 23.7 (C_9), 27.6(2C, $C_{7\text{-}8}$), 30.6 (3C, $C_{3\text{-}6}$), 33.1 (C_2), 34.2 (C_1), 85.9 ($C_{1'}$), 63.8 ($C_{2'}$), 62.8 ($C_{3'}$), 82.9 ($C_{4'}$), 62.1 ($C_{5'}$). MS (DCI/NH_3): *m/z* 371 (MH^+).

***1-(4-acetoxybutyl)-2-pyrazinone* (7a) *and 2-O-(4-acetoxybutyl)-2-pyrazinone* (9a)**

To a solution of 2-pyrazinone (10 mmol, 0.96g) in DMF (8 mL) at 0°C was added NaH (50% in oil; 1.2 eq., 0.42g). After 2 hours, 4-acetoxybutyl bromide (1.2 eq., 1.8 mL) was added and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was neutralized, and the product was extracted with $CHCl_3$ (3 x 40 mL). The chloroform layer was washed with water, dried ($MgSO_4$), filtered and evaporated. The residue (2.8 g) was absorbed on Florisil® and purified by chomatography on silica gel (50 g, 3.5 cm x 24 cm) (elution with a gradient of petroleum ether / acetone) giving N^1-(4-acetoxybutyl) 2-pyrazinone (1.41 g, 67%) and O-(4-acetoxybutyl) 2-pyrazinone (0.46 g, 22%) as oils.

***1-(4-acetoxybutyl)-2-pyrazinone* (7a)**

Yield 67%. R_f = 0.42 (toluene/acetone, 70/30, v/v). IR: 3050 (CH ar.), 2950 (CH alk.), 1720 (C=O (acetyl)), 1645 (C=O (pyrazine)), 1580 (C=C). UV: ($CHCl_3$) λ_{max} (log ε) 322 (3.7). ^{1}H NMR ($CDCl_3$): δ 8.13 (1H, d, *J*=1.4, H_3), 7.08 (1H dd, *J*=4.3 - 1.4, H_5), 7.31, (1H, d, *J*=4.3, H_6), *N-alkyl*: 3.91 (2H t, *J*=7.0, $H_{1'}$), 1.84 (2H, m, $H_{2'}$), 1.71 (2H, m, $H_{3'}$), 4.10(2H, t, *J*=6.3, $H_{4'}$), 2.04(3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 156.1 (C_2), 149.8 (C_3), 123.8 (C_5), 128.4 (C_6), *N-alkyl*: 63.4 ($C_{1'}$), 25.3 ($C_{2'}$), 25.5 ($C_{3'}$), 49.0 ($C_{4'}$), 171.0 (CO), 20.9 (C (CH_3)). Anal. calcd for $C_{10}H_{14}O_3N_2$ C 57.13, H 6.71, N 13.33, found C 57.06, H 6.76, N 13.38. MS (DCI/NH_3): *m/z* 211 (MH^+).

***2-O-(4-acetoxybutyl)-2-pyrazinone* (9a)**

Yield 22%. R_f = 0.46 (toluene/acetone, 8/2, v/v). IR: 3010 (CH ar.), 2950 (CH alk.), 1720 (C=O (acetyl)), 1540 (C=C), 1220, 1100 (C-O-C (aryl alkyl)). ^{1}H NMR ($CDCl_3$): δ

8.20 (1H, d, J=1.4, H_3), 8.08 (1H dd, J=3.1-1.3, H_5), 8.10 (1H, d, J=3.1, H_6), O-*alkyl*: 4.34 (2H t, J=6.2, $H_{1'}$), 1.84 (2H, m, $H_{2'}$), 1.84 (2H, m, $H_{3'}$), 4.13 (2H, t, J=6.3, $H_{4'}$), 2.04 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 160.2 (C_2), 140.5 (C_3), 136.0 (C_5), 136.4 (C_6), *N-alkyl* : 65.6 ($C_{1'}$), 25.3 ($C_{2'}$), 25.4 ($C_{3'}$), 64.0 ($C_{4'}$), 171.1 (CO), 20.9 (C (CH_3)). Anal. calcd for $C_{10}H_{14}O_3N_2$ C 57.13, H 6.71, N 13.33, found C 56.94, H 6.78, N 13.35. MS (DCI/NH_3): *m/z* 211 (MH^+).

Compounds **7b,c** and **9b,c** were prepared in a manner similar to that described for **7a** and **9a** starting from **1b** (10 mmol) and **1c** (3 mmol) respectively.

***1-(4-acetoxybutyl)-3-methyl 2-pyrazinone* (7b)**

Yield 75%. R_f = 0.49 ($CHCl_3$ / EtOH, 95/5, v/v). IR: 3050 (CH ar.), 2940 (CH alk.), 1720 (C=O (acetyl)), 1630 (C=O (pyrazine)), 1585 (C=C). ^1H NMR ($CDCl_3$): δ 6.96 (1H, dd, J=4.4-0.6, H_5), 7.18, (1H, d, J=4.4, H_6), 2.46, (3H, d, J=0.5, CH_3), *N-alkyl*: 3.91 (2H t, J=7.3, $H_{1'}$), 1.81 (2H, m, $H_{2'}$), 1.72 (2H, m, $H_{3'}$), 4.10 (2H, t, J=6.3, $H_{4'}$), 2.05 (3H, s, $H_{7'}$). ^{13}C NMR ($CDCl_3$): δ 158.5 (C_2), 156.1 (C_3), 122.5 (C_5), 126.7 (C_6), 20.1 (C (CH_3)), *N-alkyl* : 49.0 ($C_{1'}$), 25.3 ($C_{2'}$), 25.5 ($C_{3'}$), 63.4 ($C_{4'}$), 171.0 (CO), 20.9 (C (CH_3)). Anal. calcd for $C_{11}H_{16}N_2O_3$ C 58.91, H 7.19, N 12.49, found C 58.73, H 7.27, N 12.21. MS (DCI/NH_3): *m/z* 225 (MH^+).

***2-O-(4-acetoxybutyl)-3-methyl 2-pyrazinone* (9b)**

Yield 15%. R_f = 0.60 (toluene/acetone, 8/2, v/v). IR: 3050 (CH ar.), 2900 (CH alk.), 1725 (C=O (acetyl)), 1540 (C=C), 1250, 1090 (COC (aryl alkyl)). ^1H NMR ($CDCl_3$): δ 7.87 (1H, br d, J=3.4, H_5), 7.95 (1H, d, J=3.4, H_6), 2.44 (3H, s, CH_3), *O-alkyl*: 4.32 (2H t, J=6.1, $H_{1'}$), 1.81 (2H, m, $H_{2'}$), 1.81 (2H, m, $H_{3'}$), 4.12 (2H, t, J=6.3, $H_{4'}$), 2.03 (3H, s, $H_{7'}$). ^{13}C NMR ($CDCl_3$): δ 159.9 (C_2), 140.2 (C_3), 136.2 (C_5), 135.6 (C_6), 19.0 (C(CH_3)), *O-alkyl*: 65.3 ($C_{1'}$), 25.1 ($C_{2'}$), 25.0 ($C_{3'}$), 63.6 ($C_{4'}$), 170.6 (CO), 20.5 (C (CH_3)). Anal. calcd for $C_{11}H_{16}N_2O_3$ C 58.91, H 7.19, N 12.49, found C 58.72, H 7.26, N 12.22. MS (DCI/NH_3): *m/z* 225 (MH^+).

***1-(4-acetoxybutyl)-3-decyl 2-pyrazinone* (7c)**

Yield 45%. R_f = 0.47 (toluene/acetone, 8/2, v/v). IR: 3050 (CH ar.), 2950 (CH alk.),

1720 (C=O (acetyl)), 1645 (C=O (pyrazine)), 1580 (C=C). ^{1}H NMR ($CDCl_3$) δ 6.95 (1H, br.d, J = 4.4, H_5), 7.21 (1H, d, J = 4.4, H_6), *decyl chain* : 0.85 (3H, t, J = 6.4, H_{10}), 1.23 (14H, br. s, $H_{3\text{-}9}$), 1.73 (2H, br.quint, J = 7.6, H_2), 2.80 (2H, br.t, J = 7.6, H_1), *N-alkyl* 3.90 (2H t, J=7.3, $H_{1'}$), 1.81 (2H, m, $H_{2'}$), 1.81 (2H, m, $H_{3'}$), 4.10 (2H, t, J=6.3, $H_{4'}$), 2.04 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 161.3 (C_2), 155.9 (C_3), 122.5 (C_5), 126.4 (C_6), *decyl chain* 14.1 (C_{10}), 22.6 (C_9), 29.3 (C_8), 26.5 (C_7), 29.5 ($C_{3\text{-}6}$), 31.7 (C_2), 33.5 (C_1), *N-alkyl.* 49.1 ($C_{1'}$), 25.3 ($C_{2'}$), 25.4 ($C_{3'}$), 63.5 ($C_{4'}$), 171.0 (CO), 20.8 (C (CH_3)). Anal. calcd for $C_{20}H_{34}N_2O_3$ C 68.54, H 9.78, N 7.99, found C 68.42, H 9.78, N 7.98. MS (DCI/NH_3): *m/z* 351 (MH^+).

***2-O-(4-acetoxybutyl)-3-decyl 2-pyrazinone* (9c)**

Yield 28%. R_f = 0.65 (toluene/acetone, 8/2, v/v). IR: 3100 (CH ar.), 2950-2850 (CH alk.), 1730 (C=O (acetyl)), 1525 (C=C), 1240, 1090 (COC (aryl alkyl)). ^{1}H NMR ($CDCl_3$) δ 7.88 (1H, br.d, J = 2.8, H_5), 8.00 (1H, d, J = 2.8, H_6), *decyl chain* : 0.88 (3H, t, J = 6.7, H_{10}), 1.26 (14H, br. s, $H_{3\text{-}9}$), 1.70 (2H, br.quint, J = 7.6, H_2), 2.79 (2H, br.t, J = 7.8, H_1), *O-alkyl* 4.34 (2H t, J=6.1, $H_{1'}$), 1.85 (2H, m, $H_{2'}$), 1.85 (2H, m, $H_{3'}$), 4.15 (2H, t, J=6.3, $H_{4'}$), 2.05 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 160.0 (C_2), 149.3 (C_3), 135.9 (C_5), 139.9 (C_6), *decyl chain* 14.1 (C_{10}), 22.6 (C_9), 29.3 (C_8), 27.4 (C_7), 29.5 ($C_{3\text{-}6}$), 31.7 (C_2), 32.5 (C_1), *O-alkyl.* 65.5 ($C_{1'}$), 25.4 ($C_{2'}$), 25.5 ($C_{3'}$), 64.0 ($C_{4'}$), 189.8 (CO), 20.9 (C (CH_3)). Anal. calcd for $C_{20}H_{34}N_2O_3$ C 68.54, H 9.78, N 7.99, found C 68.66, H 9.90, N 7.96. MS (DCI/NH_3): *m/z* 351 (MH^+).

***1-(4-hydroxybutyl)-2-pyrazinone* (8a)**

1-(4-Acetoxybutyl) 2-pyrazinone (0.65g, 3.09 mmol) was dissolved in a 2M solution of sodium methoxide in methanol (5 mL). The reaction was neutralized after 30 minutes by addition of Amberlite IRN 77 H^+ resin. The suspension was then filtered and the resin thoroughly washed with methanol. Evaporation of the solvent yielded N^1-(4-hydroxybutyl) 2-pyrazinone **8a** (90% yield, 450 mg).

R_f = 0.55 ($CHCl_3$ / EtOH, 90/10, v/v). IR: 3400-3200 (OH), 3050 (CH ar.), 2900 (CH alk.), 1640 cm^{-1} (C=O), 1550 cm^{-1} (C=C). UV: (EtOH) λ_{max} (log ε) 310 (3.7). ^{1}H NMR ($CDCl_3$): δ 8.09 (1H, d, J=1.4, H_3), 7.21 (1H, dd, J=4.1-1.4, H_5), 7.33 (1H, d, J=4.1,

H_6), *N-alkyl*: 3.94 (2H t, *J*=7.0, $H_{1'}$), 1.84 (2H, m, $H_{2'}$), 1.57 (2H, m, $H_{3'}$), 3.65 (2H, t, *J*= 6.2, $H_{4'}$), 3.74 (1H, br s, $H_{5'}$). ^{13}C NMR ($CDCl_3$): δ 156.3 (C_2), 148.6 (C_3), 124.0 (C_5), 129.1 (C_6), *N-alkyl* : 49.2 ($C_{1'}$), 28.8 ($C_{2'}$), 25.0 ($C_{3'}$), 61.0 ($C_{4'}$). Anal. calcd for $C_8H_{12}N_2O_2 \cdot$ ¾ H_2O C 52.88, H 7.49, N 15.42, found C 52.79, H 7.15, N 15.33. MS (DCI/NH_3): *m/z* 169 (MH^+).

Compounds **8b**, **8c** and **10a,b,c** were prepared in a manner similar to that described for **8a** starting from **7b**, **7c** and **9a,b,c** respectively.

1-(4-hydroxybutyl)-3-methyl 2-pyrazinone **(8b)**

Yield 92%. R_f = 0.45 ($CHCl_3$ / EtOH, 90/10, v/v). IR: 3500-3200 (OH), 3070 (CH ar.), 2925 (CH alk.), 1630 (C=O), 1570 (C=C). UV: (EtOH) λ_{max} (log ε) 308 (3.7). ^1H NMR ($CDCl_3$): δ 7.02 (1H, d, *J*=4.5, H_5), 7.17 (1H, d, *J*=4.5, H_6), 2.42, (3H, s, CH_3) *N-alkyl*: 3.91 (2H t, *J*=7.3, $H_{1'}$), 1.82 (2H, m, $H_{2'}$), 1.59 (2H, m, $H_{3'}$), 3.66 (2H, t, *J*=6.1, $H_{4'}$), 2.84 (1H, br s, OH). ^1H (CD_3OD): δ 7.43 (1H, dd, *J*=4.5-0.7, H_5), 7.22 (1H, d, *J*=4.5, H_6), 2.38, (3H, d, *J*=0.7, CH_3) *N-alkyl*: 3.98 (2H t, *J*=7.2, $H_{1'}$), 1.81 (2H, m, $H_{2'}$), 1.55 (2H, m, $H_{3'}$), 3.58 (2H, t, *J*=6.3, $H_{4'}$). ^{13}C NMR (CD_3OD): δ 158.5 (C_2), 157.9 (C_3), 123.7 (C_5), 129.7 (C_6), 20.5 (C (CH_3)), *N-alkyl* : 62.3 ($C_{1'}$), 30.5 ($C_{2'}$), 26.3 ($C_{3'}$), 50.6 ($C_{4'}$). Anal. calcd for $C_9H_{14}N_2O_2 \cdot H_2O$ C 49,53, H 7,39, N 12.83, found C 49.68, H 7.47, N 12.71. MS (DCI/NH_3): *m/z* 183 (MH^+).

1-(4-hydroxybutyl)-3-decyl 2-pyrazinone **(8c)**

Yield 90%. R_f = 0.41 ($CHCl_3$ / EtOH, 95/5, v/v). IR: 3350 (OH), 3050 (CH ar.), 2990 (CH), 1620 (C=O), 1565 (C=C). UV: (EtOH) λ_{max} (log ε) 310 (3.8). ^1H NMR ($CDCl_3$) δ 7.00 (1H, br.d, *J* = 4.3, H_5), 7.25 (1H, d, *J* = 4.3, H_6), *decyl chain* : 0.85 (3H, t, *J* = 6.4, H_{10}), 1.27 (14H, br. s, $H_{3\text{-}9}$), 1.79 (2H, m, H_2), 2.80 (2H, t, *J* = 7.5, H_1), *N-alkyl* 3.90 (2H t, *J* = 7.3, $H_{1'}$), 1.70 (2H, m, $H_{2'}$), 1.60 (2H, m, $H_{3'}$), 3.60 (2H, t, *J*= 6.3, $H_{4'}$), 2.20 (1H, br s, OH). ^{13}C NMR ($CDCl_3$) δ 161.4 (C_2), 156.0 (C_3), 122.5 (C_5), 126.5 (C_6), *decyl chain* 14.1 (C_{10}), 22.6 (C_9), 29.4 (C_8), 26.5 (C_7), 29.5 ($C_{3\text{-}6}$), 31.9 (C_2), 33.5 (C_1), *N-alkyl*. 49.3 ($C_{1'}$), 25.3 ($C_{2'}$), 25.3 ($C_{3'}$), 62.0 ($C_{4'}$). Anal. calcd for $C_{18}H_{32}N_2O_2 \cdot$ ¼ H_2O C 69.08, H 10.47, N 8.95, found C 69.21, H 10.49, N 9.07. MS (DCI/NH_3): *m/z* 309 (MH^+).

2-O-(4-hydroxybutyl)-2-pyrazinone **(10a)**

The deacetylation of **9a** (430 mg, 2 mmol) was carried out in the presence of 2 eq. of sodium methoxide (1M solution in methanol). After completion of reaction, the solution was neutralized by addition of Amberlite IRN 77 H^+ resin (Aldrich), filtered and the resin thoroughly rinsed with methanol. 2-O-(4-hydroxybutyl)-2-pyrazinone **(10a)** was obtained in 90% yield (302 mg). R_f = 0.39 ($CHCl_3$ / EtOH, 92/8, v/v). IR: 3450-3300 (OH), 3050 (CH ar.), 2950 (CH alk.), 1540 (C=C), 1250, 1100 (COC (aryl alkyl)). UV: (EtOH) λ_{max} (log ε) 292 (3.8). ^{1}H NMR (CD_3OD): δ 8.16 (1H, d, *J*=1.4, H_3), 8.13 (1H dd, *J*=1.3-2.8, H_5), 8.07 (1H, d, *J*=2.8, H_6), *N-alkyl*: 4.37 (2H t, *J*=6.4, $H_{1'}$), 1.87 (2H, m, $H_{2'}$), 1.68 (2H, m, $H_{3'}$), 3.61 (2H, t, *J*= 6.3, $H_{4'}$). ^{13}C NMR (CD_3OD): δ 162.1 (C_2), 142.3 (C_3), 136.5 (C_5), 137.1 (C_6), *O-alkyl*. 67.4 ($C_{1'}$), 30.1 ($C_{2'}$), 26.5 ($C_{3'}$), 62.5 ($C_{4'}$). Anal. calcd for $C_8H_{12}N_2O_2$• ¼ H_2O requires C 55.64, H 7.29, N 16.22, found C 55.80, H 7.21, N 16.36. MS (DCI/NH_3): *m/z* 169 (MH^+).

2-O-(4-hydroxybutyl)3-methyl-2-pyrazinone **(10b)**

Yield 92%. R_f = 0.44 ($CHCl_3$ / EtOH, 92/8, v/v). IR: 3500-3200 (OH), 3050 (CH ar.), 2900 (CH alk.), 1540 (C=C), 1250, 1090 (COC (aryl alkyl)). UV: (EtOH) λ_{max} (log ε) 292 (3.8). ^{1}H NMR ($CDCl_3$): δ 7.95 (1H, dd, *J*=2.9-0.6, H_5), 7.91 (1H, d, *J*=2.9, H_6), 2.42 (3H, d, *J*=0.5, CH_3) *O-alkyl*: 4.37 (2H t, *J*=6.2, $H_{1'}$), 1.87 (2H, m, $H_{2'}$), 1.67 (2H, m, $H_{3'}$), 3.62 (2H, t, *J*=6.5, $H_{4'}$). ^{13}C NMR (CD_3OD): δ 160.2 (C_2, 145.8 (C_3), 139.9 (C_5), 135.6 (C_6), 19.0 (C (CH_3)), *O-alkyl* : 67.4 ($C_{1'}$), 26.5 ($C_{2'}$), 30.2 ($C_{3'}$), 62.6 ($C_{4'}$). Anal. calcd for $C_9H_{14}N_2O_2$• H_2O C 53.98, H 8.05, N 13.99, found C 53.89, H 8.14, N 13.67. MS (DCI/NH_3): *m/z* 183 (MH^+).

2-O-(4-hydroxybutyl)3-decyl-2-pyrazinone **(10c)**

Yield 95%. R_f = 0.43 ($CHCl_3$ / EtOH, 98/2, v/v). IR: 3400-3250 (OH), 3050 (CH ar.), 2950 (CH alk.), 1570 (C=C), 1250, 1100 (COC (aryl alkyl)). UV: (EtOH) λ_{max} (log ε) 294 (3.8). ^{1}H NMR (CD_3OD) δ 7.94 (1H, br.d, *J* = 2.9, H_5), 7.96 (1H, d, *J* = 2.8, H_6), *decyl chain*: 0.88 (3H, t, *J*= 6.5, H_{10}), 1.27 (14H, br. s, $H_{3\text{-}9}$), 1.69 (2H, m, H_2), 2.78 (2H, br.t, *J* = 7.7, H_1), *O-alkyl* 4.37 (2H t, *J*=6.3, $H_{1'}$), 1.73 (2H, m, $H_{2'}$), 1.68 (2H, m, $H_{3'}$), 3.62 (2H, t, *J*=6.4, $H_{4'}$). ^{13}C NMR (CD_3OD) δ 160.0 (C_2), 149.3 (C_3), 136.0 (C_5),

139.9 (C_6), *decyl chain* 14.4 (C_{10}), 23.7 (C_9), 30.3 (C_8), 28.6 (C_7), 30.6 ($C_{3\text{-}6}$), 33.0 (C_2), 33.3 (C_1), *O-alkyl.* 67.3 ($C_{1'}$), 30.2 ($C_{2'}$), 26.5 ($C_{3'}$), 62.8 ($C_{4'}$). Anal. calcd for $C_{18}H_{32}N_2O_2 \cdot 2H_2O$ C 62.76, H 9.87, N 8.95, found C 62.98, H 9.69, N 9.00. MS (DCI/NH_3): *m/z* 308 (MH^+).

Biological Methods.

The broad antiviral assays carried out on human embryonic fibroblasts (Cell line: MRC 5) infected with coxsackie virus B4 (Cox B4), Herpes simplex virus type 1 (HSV-1), Human Cytomegalovirus (CMV) and Vaccinia virus were described previously.[14] The antiviral activity is expressed as the IC_{50}, concentration necessary to reduce viral cytopathicity by 50%.

Cytotoxicity (MTT assay)

Cell viability was more evaluated by measuring the activity of mitochondrial dehydrogenase using the MTT assay.[15] The toxicity was expressed as the CC_{50}, the concentration of drugs needed to reduce the number of viable cells by 50%.

Anti HIV 1 assays

The anti HIV 1 activity was tested on CEM-SS and MT_4 cells infected respectively with HIV 1 LAI and HIV 1 IIIB following protocols described previously.[16]

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