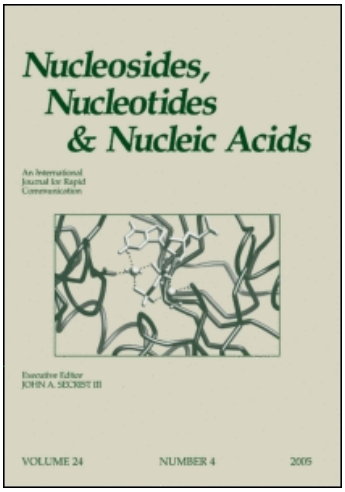

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POTENTIAL ANTIVIRAL AGENTS. PART II. SYNTHESIS AND ANTIVIRAL EVALUATION OF PYRAZINONES SUBSTITUTED WITH ACYCLIC CHAINS.

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Abstract: The synthesis of a series of 4'-substituted hydroxybutyl pyrazine analogues of the anti-herpes compound, acyclovir, is described. The compounds were characterized with ^{1}H and ^{13}C nmr, mass and IR spectroscopy. Antiviral (HSV-1, CMV, Cox B4, HIV-1) properties of these compounds were examined. None of these compounds were active against these viruses.

Since the discovery of 9-[2-(hydroxyethoxy)methyl]guanine (acyclovir)[1], a selective antiherpes virus agent, considerable interest has been focused on the synthesis of novel acyclic analogues of nucleosides.[2] As a result of this research, a number of hydroxyalkylated derivatives of guanine have been identified as potential antiviral drugs.[3] Recently, certain 6-substituted acyclic pyrimidine nucleosides related to acyclovir, such as 1-[2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) have been shown to be selective inhibitors of human immunodeficiency virus in various human lymphocytes.[4] With this last family of compounds, it has been found that an intact hydroxyl is not necessary for its antiviral activity.[5]

After having synthesised several pyrazinic analogues of acyclovir and evaluated their antiviral potential[6], several modifications of these molecules were studied - in particular, the transformation of the 4' position of the hydroxybutyl chain of

hydroxyalkylated pyrazinones by azidation (**6a,b,c** and **7a,b,c**) and by glycosylation (**9a,b,c** and **11a,b,c**) [Scheme]. The synthesis and antiviral activites (HSV-1, CMV, Cox B4, vaccine, HIV-1) in cell cultures of this series of alkyl pyrazinones will be reported herein.

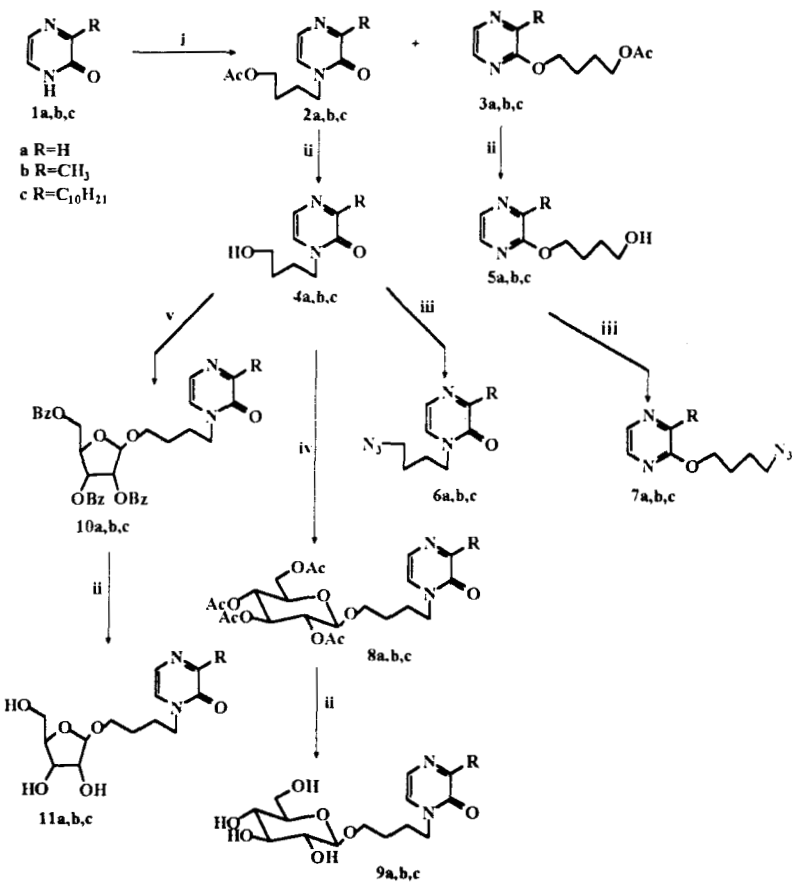
Results and Discussion

The 3-substituted pyrazinones (**1a,b**) were synthesised according to Jones method[7] and **1c** using a modified method described in our preceding paper.[8]

Starting from **1a-c**, the synthesis of compounds **6a-c**, **7a-c** and **10a-c** and **11a-c** is outlined in Scheme I. Compounds **2a-c** and **3a-c** were prepared by reacting sodium hydride with the appropriate pyrazinone followed by the addition of bromobutylacetate using the conditions previously described[6]. Deacetylation of compounds **2a-c** and **3a-c** with sodium methoxide occurred readily; **4a-c** and **5a-c** were recovered in quasi quantitative yields.

Compounds **6a-c** and **7a-c** were prepared by the initial mesylation of alkyl pyrazinones in the presence of mesyl chloride in anhydrous pyridine at 0°C and were used without further purification. Azidation was carried out in DMF at 100°C in the presence of NaN_3. After purification, the obtained yields are comparable to literature values (38-65% overall yield).

Compounds **8a-c** were obtained using the method of Koenigs-Knorr[9] which reacts a glycosidic derivative with an alcohol in stoechiometric quantities in the presence of a catalyst ($SnCl_4$, $TiCl_4$,AgTf etc....).[10,11] Thus, **4a, 4b** and **4c** were reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver trifluoromethane sulfonate and s-collidine in dichloromethane protected from light. The s-collidine was added either at the beginning of the reaction according to Vazquez[12] or at the end of the reaction to neutralize the medium; the addition mode did not affect the final yield. After purification, compounds **8a-c** were obtained in approximately 20% yields. Compounds **8a-c** are formed according to the classic anchimeric assistance mechanism of β-glycosylation.[11] In all cases, there was significant acetate transfer from the O-2 to the 4'-hydroxyl of the glycosyl group. This acetate transfer is not uncommon since it has often been reported to compete with glycosylation reactions.[13]



i) NaH, $Br(CH_2)_4OAc$, DMF. ii) MeONa, MeOH. iii) MsCl, pyridine then NaN_3, DMF. iv) 2,3,4,6-tetra-O-acetyl-α-**D**-glucopyranosyl bromide, AgTf, CH_2Cl_2. v)1-O-acetyl-2,3,5-tri-O-benzoyl-β-**D**-ribofura - nose, $SnCl_4$, CH_3CN.

Scheme

Thus even as the desired products were successfully synthesised, the yields of these glycosylation reactions remained the limiting step. Others have also experienced difficulties in glycosylating certain hydroxyl groups[14], in particular, the primary 5'-hydroxyl group of nucleosides using standard conditions for the formation of glycosidic bonds[15,16]. Krepinsky *et al*[16] have postuled that the π-electron systems of the heterocyclic base or the heteroaromatic bonds interact with the unreactive hydroxyl group. They confirmed through semiempirical and *ab initio* molecular modeling

calculations of several nucleoside model compounds that intramolecular hydrogen bonding between the ribosyl O5'—H····O2 of the base is a stabilizing factor in their cytosine model compound. The existence of such intramolecular hydrogen bonding in nucleosides is apparently well documented.[17] In the present case, it is likely that the alcohol function is hydrogen bonded with the 2-keto group.

The removal of the acetyl groups from **8** to give the unprotected compounds **9** proceeded readily with sodium methoxide in nearly quantative yields.[18]

Compounds **10 a,b,c** were obtained using the method of Hannessian.[11] Thus **4a, 4b** and **4c** were reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of Tin(IV) chloride in acetonitrile. After purification, compounds **10 a-c** were obtained with 49, 45 and 42% overall yields respectively. In this case a significative acetylation of aglycone (40%) was also observed.

The removal of benzoyl groups from **10** to give the unprotected compounds **11** proceeded readily with sodium methoxide in nearly quantitative yields.[19]

Biological Evaluation

Most of the prepared compounds 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).

As previously reported, no antiviral activity was observed with compounds substituted with an hydroxybutyl group.[9] Modification of the 4' position of the hydroxylalkyl group by azidation (**6a-c**, **7a-c**) or glycosylation (**9a-c**, **10a-c**) did not improve their activity.

When evaluated in two anti-human immunodeficiency virus (anti-HIV 1) assays, none of the tested compounds showed an antiviral effect at a concentration less than the minimum concentration causing a detectable alteration of MT-4 and CEM host cell viability.

Experimental

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 chromatography. Solvents were distilled from appropriate drying agents. Solutions were concentrated at 1 Torr pressure in a rotary evaporator. ^{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, qt = quintet, m = multiplet and br = broad), coupling constants in hertz (Hz) and assignment. Electronic-impact mass spectra (EI) were recorded with a Shimadzu QP1000 mass spectrometer at the Laboratoire Départemental d'Analyses de 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 Kofler 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.

Compounds **4a-c** and **5a-c** were synthesised according to ref 6.

N^1-(4-azidobutyl)-2-pyrazinone (6a)

To a solution of N^1-(4-hydroxybutyl) 2-pyrazinone **4a** (230 mg, 1.4 mmol) in a minimum of pyridine (4 mL, anhydrous 99.8%) at 0°C was added 4 equivalents of mesyl chloride (0.42 mL). After 1 hour, the solution was quenched with the addition of a

saturated $NaHCO_3$ solution / H_2O (10 mL, 1:1, v/v) and extracted with $CHCl_3$ (3 x 15 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed. The resultant product (258 mg, 78% crude yield) was dissolved in DMF (3 mL). This solution was immersed in an oil bath at 100°C and sodium azide (340 mg ,7 mmol) was added. After 1 hour, the product was extracted with 3 x 20 mL chloroform and the extracts were evaporated. The crude product (141 mg) was purified using preparative tlc (CH_2Cl_2 / EtOH, v/v, 95:5). Pure N^1-(4-azidobutyl) 2-pyrazinone was recovered in an overall yield of 45% (118 mg). R_f = 0.5, (CH_2Cl_2/MeOH, 95/5, v/v). IR: 3070-3050 cm^{-1} (CH (aromatic)), 2950-2850 cm^{-1} (CH), 2180 cm^{-1} (N_3), 1650 cm^{-1} (C=O), 1580 cm^{-1} (C=C (aromatic)). ^1H ($CDCl_3$): δ 8.14 (1H, d, *J*=1.1, H_3), 7.08 (1H d, *J*=4.4-1.1, H_5), 7.32 (1H, d, *J*=4.4, H_6), *N-alkyl*: 3.92 (2H t, *J*=7.1, $H_{1'}$), 1.84 (2H, m, $H_{2'}$), 1.64 (2H, m, $H_{3'}$), 3.35 (2H, t, *J*= 6.5, $H_{4'}$). ^{13}C ($CDCl_3$): δ 156.4 (C_2), 149.8 (C_3), 128.3 (C_5), 123.7 (C_6) *N-alkyl* 48.8 ($C_{1'}$), 25.9 ($C_{2'}$), 26.0 ($C_{3'}$), 50.8 ($C_{4'}$). Anal. calcd. for $C_8H_{11}ON_5$ requires C 49.73, H 5.74, N 36.25, found C 49.57, H 5.75, N 35.99. MS (DCI/NH_3) *m/z* 194 (MH^+).

Compounds **6b** and **6c** were prepared in a manner similar to that described for **6a** starting from **4b** and **4c** respectively.

N^1-(4-azidobutyl)-3-methyl 2-pyrazinone (6b)

Yield 65% (168 mg). R_f = 0.49, ($CHCl_3$/MeOH, 95/5, v/v). IR: 3080-3050 cm^{-1} (CH (aromatic)), 2950-2820 cm^{-1} (CH), 2160 cm^{-1} (N_3), 1640 cm^{-1} (C=O), 1580 cm^{-1} (C=C (aromatic). ^1H ($CDCl_3$): δ 6.97 (1H, dd, *J*=4.4-0.6, H_5), 7.18, (1H, d, *J*=4.5, H_6), 2.44, (3H, d, *J*=0.6, H_{methyl}), *N-alkyl*: 3.90 (2H t, *J*=7.0, $H_{1'}$), 1.84 (2H, m, $H_{2'}$), 1.64 (2H, m, $H_{3'}$), 3.34 (2H, t, *J*=6.5, $H_{4'}$). ^{13}C ($CDCl_3$): δ 158.6 (C_2), 156.5 (C_3), 126.8 (C_5), 122.6 (C_6), 20.8 (C_{methyl}), *N-alkyl* : 48.9 ($C_{1'}$), 25.9 ($C_{2'}$), 25.9 ($C_{3'}$), 50.8 ($C_{4'}$). Anal. calcd. for $C_9H_{10}ON_5$ C 52.16, H 6.32, N 33.79, found C 52.16, H 6.34, N 33.63. MS (DCI/NH_3) *m/z* 208 (MH^+).

N^1-(4-azidobutyl)-3-decyl 2-pyrazinone (6c)

Yield 61% (163 mg). R_f = 0.45 (CH_2Cl_2). IR: 3100 cm^{-1} (CH (aromatic)), 2950-2850 cm^{-1} (CH), 2100 cm^{-1} (N_3), 1655 cm^{-1} (C=O), 1600 cm^{-1} (C=C (aromatic)). ^1H ($CDCl_3$)

δ 6.96 (1H, br.d, J = 4.4, H_5), 7.22 (1H, d, J = 4.4, H_6), *decyl chain* : 0.86 (3H, t, J = 6.4, H_{10}), 1.25 (14H, br. s, H_{3-9}), 1.74 (2H, m, H_2), 2.80 (2H, t, J = 7.5, H_1), *N-alkyl* 3.90 (2H t, J = 7.1, $H_{1'}$), 1.85 (2H, m, $H_{2'}$), 1.64 (2H, m, $H_{3'}$), 3.34 (2H, t, J= 6.6, $H_{4'}$). ^{13}C ($CDCl_3$) δ 161.6 (C_2), 155.9 (C_3), 126.4 (C_5), 122.5 (C_6), *decyl chain* 14.0 (C_{10}), 22.7 (C_9), 29.3 (2C, C_{7-8}), 29.5 (4C, C_{3-6}), 31.9 (C_2), 32.5 (C_1), *N-alkyl*. 48.9 ($C_{1'}$), 26.5 ($C_{2'}$), 26.0 ($C_{3'}$), 50.8 ($C_{4'}$). Anal calcd for $C_{18}H_{31}ON_5$ calculated C 64.83, H 9.37, N 21.00, found C 64.95, H 9.51, N 20.91. MS (DCI/NH_3) *m/z* 334 (MH^+).

O-(4-azidobutyl)-2-pyrazinone (7a)

The residue obtained from reaction of mesyl chloride with **5a** (288 mg, 1.7 mmol) was reacted with sodium azide. After one hour and work up, the product (125 mg, 75%) was extracted and purified using preparative tlc with CH_2Cl_2 as eluent. Pure 7a was recovered in 42% yield (70 mg). R_f = 0.65, ($CHCl_3$/EtOH, 95/5, v/v). IR: 2990-2900 cm^{-1} (CH), 2170 cm^{-1} (N_3), 1210 cm^{-1} (C-O-C (aryl alkyl)). ^1H ($CDCl_3$): δ 8.19 (1H, m, H_3), 8.10 (1H, m, H_5), 8.10 (1H, m, H_6), *N-alkyl*: 4.36 (2H, t, J=6.1, $H_{1'}$), 1.85 (2H, m, $H_{2'}$), 1.85 (2H, m, $H_{3'}$), 3.35 (2H, t, J= 6.5, $H_{4'}$). ^{13}C ($CDCl_3$): δ 160.4 (C_2), 140.6 (C_3), 138.3 (C_5), 135.8 (C_6) *N-alkyl* 65.5 ($C_{1'}$), 26.0 ($C_{2'}$), 25.6 ($C_{3'}$), 51.1 ($C_{4'}$). Anal calcd for $C_8H_{11}ON_5$ calculated C 49.73, H 5.74, N 36.25, found C 50.40, H 5.90, N 37.27. MS (DCI/NH_3) *m/z* 194 (MH^+).

Compounds **7b** and **7c** were prepared in a manner similar to that described for 7a starting from **5b** and **5c** (0.06 mmol) respectively.

O-(4-azidobutyl)-3-methyl-2-pyrazinone (7b)

Yield 42% (94 mg). R_f = 0.67, ($CHCl_3$/MeOH, 9/1, v/v). IR: 3080 cm^{-1} (CH (aromatic)), 2950-2870 cm^{-1} (CH (aliphatic)), 2100 cm^{-1} (N_3), 1550 cm^{-1} (C=C), 1170 cm^{-1} (COC). ^1H ($CDCl_3$): δ 7.89 (1H, dd, J=2.9-0.6, H_5), 7.98 (1H, d, J=2.9, H_6), 2.44 (3H, br.s, H_{methyl}), *O-alkyl*: 4.36 (2H t, J=6.1, $H_{1'}$), 1.85 (2H, m, $H_{2'}$), 1.85 (2H, m, $H_{3'}$), 3.35 (2H, t, J=6.5, $H_{4'}$). ^{13}C ($CDCl_3$): δ 158.5 (C_2), 144.8 (C_3), 138.1 (C_5), 133.5 (C_6), 19.2 (C_{methyl}), *O-alkyl* : 65.4 ($C_{1'}$), 26.1 ($C_{2'}$), 25.6 ($C_{3'}$), 51.1 ($C_{4'}$). Anal calcd for $C_9H_{10}ON_5$ C 52.16, H 6.32, N 33.79, found C 52.22, H 6.41, N 33.74. MS (DCI/NH_3) *m/z* 208 (MH^+).

O-(4-azidobutyl)-3-decyl-2-pyrazinone (7c)

Yield 38%. R_f = 0.58, ($CHCl_3$), $R_{f\,(mesyl)}$ = 0.44, (CH_2Cl_2/MeOH, 95/5, v/v). IR: 3080 cm^{-1} (CH (aromatic)), 2950-2870 cm^{-1} (CH (aliphatic)), 2100 cm^{-1} (N_3), 1550 cm^{-1} (C=C), 1170 cm^{-1} (COC). ^1H ($CDCl_3$) δ 6.96 (1H, br.d, *J* = 4.4, H_5), 7.22 (1H, d, *J* = 4.4, H_6), *decyl chain* : 0.86 (3H, t, *J* = 6.4, H_{10}), 1.25 (14H, br. s, $H_{3\text{-}9}$), 1.74 (2H, m, H_2), 2.80 (2H, t, *J* = 7.5, H_1), *N-alkyl* 4.36 (2H t, *J* = 6.0, $H_{1'}$), 1.84 (2H, m, $H_{2'}$), 1.84 (2H, m, $H_{3'}$), 3.37 (2H, t, *J*= 6.6, $H_{4'}$). ^{13}C ($CDCl_3$) δ 158.2 (C_2), 148.4 (C_3), 138.0 (C_5), 135.4 (C_6), *decyl chain* 14.1 (C_{10}), 22.7 (C_9), 29.3 (2C, $C_{7\text{-}8}$), 29.5 (4C, $C_{3\text{-}6}$), 31.9 (C_2), 32.5 (C_1), *N-alkyl.* 65.4 ($C_{1'}$), 26.2 ($C_{2'}$), 25.7 ($C_{3'}$), 54.1 ($C_{4'}$). Anal calcd for $C_{18}H_{31}ON_5$ C 64.83, H 9.37, N 21.00, found C 64.66, H 9.48, N 21.10. MS (DCI/NH_3) *m/z* 334 (MH^+).

N^1-(4-(2'',3'',4'',6''-tetra-O-acetyl-β-D-glucopyranosyloxy)-butyl)-2-pyrazinone (8a)

To a dry system of N^1-(4-hydroxybutyl) 2-pyrazinone (80 mg, 0.36 mmol) in freshly distilled CH_2Cl_2 (6 mL) under Ar and protected from light were added molecular sieves (4Å), 1-bromo 2,3,4,6-tetra-*O*-acetyl-β-**D**-glucopyranose (275 mg, 1.4 eq.) and AgOTf (170 mg, 1.4 eq.). The system was vigorously stirred until completion of reaction as monitered by tlc and neutralized with the addition of s-collidine. The mixture was allowed to stir for an additional 30 minutes and then filtered through celite. The product was purified using preparative silica gel plates with an elution system of toluene/acetone/pet. ether in a 4:5:1 ratio and was recovered in 22% yield (40 mg). R_f = 0.53, (toluene/acetone/pet. ether: 3:6:1, v/v/v). $[\alpha]_D$ +19.1° (0.3, $CHCl_3$). ^1H ($CDCl_3$) δ 8.08 (1H, d, *J* = 1.5, H_3), 7.04 (1H, dd, *J* = 1.5 - 4.3, H_5), 7.25 (1H, d, *J* = 4.3, H_6) *N-alkyl* 3.68 (2H, t, *J* =7.2, $C_{1'}H$), 1.60 (2H, m, $C_{2'}H$), 1.77 (2H, m, $C_{3'}H$), 4.05 (2H, t, *J* = 6.2, $C_{4'}H$), *glucopyranose* 4.44 (1H, d, *J* =8.0, $H_{1''}$), 4.90 (1H, dd, *J* = 8.0-9.5, $H_{2''}$), 5.12 (1H, t, *J* = 9.5, $H_{3''}$), 5.01 (1H, t, *J* = 9.8, $H_{4''}$), 3.63 (1H, m, $H_{5''}$), 4.34 (1H, dd, *J* = 12.3-4.8, $H_{6''a}$), 4.09 (1H, dd, *J* =12.0-2.4, $H_{6''b}$), 2.05-1.95 (12H, 4s, $4H_{Acetyl}$). MS (DCI/NH_3) *m/z* 499 (MH^+).

Compounds **8b** and **8c** were prepared in a manner similar to that described for **8a** starting from **4b** and **4c** (0.5 and 0.3 mmol) respectively.

N^1-(4-(2'',3'',4'',6''-tetra-O-acetyl-β-D-glucopyranosyloxy)-butyl)-3-methyl-2-pyrazinone (8b)

Yield 20%. R_f = 0.38, (toluene/acetone/pet. ether, 4:5:1, v/v/v). $[\alpha]_D$ +16.8° (0.33, $CHCl_3$). ^1H ($CDCl_3$) δ 7.02 (1H, d, *J* = 4.4, H_5), 7.20 (1H, d, *J* = 4.4, H_6), 2.47 (3H, s, H_{methyl}), *N-alkyl* 3.90 (2H, t, *J*= 6.2 , $H_{1'}$), 1.83 (2H, m, $H_{2'}$), 1.67 (2H, m, $H_{3'}$), 3.90 (2H, t, $H_{4'}$), *glucopyranose* 4.50 (1H, d, *J* = 8.1, $H_{1''}$), 4.98 (1H, dd, *J* = 8.2-9.3, $H_{2''}$), 5.21 (1H, t, *J* = 9.4, $H_{3''}$), 5.09 (1H, t, *J* = 9.5, $H_{4''}$), 3.70 (1H, m, $H_{5''}$), 4.26 (1H, dd, *J* = 12.1-4.6, $H_{6''a}$), 4.14 (1H, dd, *J* = 12.1-2.8, $H_{6''b}$), 2.08-1.98 (12H, 4s, $4H_{Acetyl}$). MS (DCI/NH_3) *m/z* 513 (MH^+).

N^1-(4-(2'',3'',4'',6''-tetra-O-acetyl-β-D-glucopyranosyl)-butoxy)-3-decyl-2-pyrazinone (8c)

Yield 15%. R_f = 0.40, (toluene/acetone/pet. ether, (6:2:2) x2, v/v/v). $[\alpha]_D$ +47.7° (0.40, $CHCl_3$). ^1H ($CDCl_3$) δ 6.91 (1H, d, *J* = 4.1, H_5), 7.14 (1H, d, *J* = 4.1, H_6), *decyl chain* : 0.85 (3H, t, *J* = 5.4, H_{10}), 1.26 (14H, br. s, H_{3-9}), 1.68 (2H, m, H_2), 2.76 (2H, t, *J* = 7.7, H_1), *N-alkyl* 3.87 (2H t, J= 7.8, $H_{1'}$), 1.83 (2H, m, $H_{2'}$), 1.58 (2H, m, $H_{3'}$), 3.91 (2H, t, *J*=5.3, $H_{4'}$), *glucopyranose* 4.50 (1H, d, *J*=8.3, $H_{1''}$), 4.99 (1H, dd, *J*=9.7-8.3, $H_{2''}$), 5.21 (1H, t, *J*=9.7, $H_{3''}$), 5.08 (1H, t, *J*=9.6, $H_{4''}$), 3.70 (1H, m, $H_{5''}$), 4.27 (1H, dd, *J*=11.7-5.0, $H_{6''a}$), 4.15 (1H, dd, *J*=11.7-3.2, $H_{6''b}$), 2.04-1.97 (12H, 4s, $4H_{Acetyl}$). MS (DCI/NH_3) *m/z* 639 (MH^+).

(4-(β-D-glucopyranosyl) butoxy)-2-pyrazinone (9a)

The deacetylation of the parent compound (40 mg, 0.080 mmol) was carried out in the presence of 0.5 eq of sodium methoxide (1M solution in methanol.). When tlc showed reaction completion, the solution was then neutralized by addition of Amberlite IRN 77 H^+ resin (Aldrich). When neutral pH was reached, the solution was quickly filtered and the resin thoroughly rinsed with methanol. **9a** was obtained in 85% yield (23 mg, 0.068 mmol). R_f = 0.52, ($CHCl_3$/EtOH, 1:2, v/v). $[\alpha]_D$ +35.4° (0.30, $CHCl_3$). ^1H (D_2O/CD_3OD) δ8.04 (1H, d, *J* = 1.4, H_3), 7.61 (1H, dd, *J* = 1.5 - 4.3, H_5), 7.40 (1H, d, *J* = 4.2, H_6) *N-alkyl* 3.59 (2H, t, *J* =7.0, C_1H), 1.88 (2H, m, C_2H), 1.76 (2H, m, C_3H), 3.94 (2H, t, *J* = 6.3, C_4H), *glucopyranose* 4.27 (1H, d, *J* =7.7, $H_{1''}$), 3.97 (1H, dd, *J* =

7.7-7.5, $H_{2''}$), 4.03 (1H, t, J = 7.4, $H_{3''}$), 4.02 (1H, t, J = 7.6, $H_{4''}$), 3.66 (1H, m, $H_{5''}$), 3.86 (1H, dd, J = 11.7-1.7, $H_{6''a}$), 3.81 (1H, dd, J =11.7-2.0, $H_{6''b}$). MS (DCI/NH_3) *m/z* 331 (MH^+).

Compounds **9b** and **9c** were prepared in a manner similar to that described for **9a** starting from **8b** and **8c** (0.06 mmol) respectively.

(4-(β-D-glucopyranosyloxy)-butyl)-3-methyl-2-pyrazinone (9b)

Yield 87%. R_f = 0.45, ($CHCl_3$/EtOH, 1:1, v/v) x 2. $[\alpha]_D$ +48.2° (0.40, $CHCl_3$). ^1H (D_2O/CD_3OD) δ 7.23 (1H, dd, J = 4.4-1.8, H_5), 7.34 (1H, d, J = 4.3, H_6), 2.44 (3H, s, H_{methyl}), *N-alkyl* 3.62 (2H, t, J=7.0, $H_{1'}$), 1.87 (2H, m, $H_{2'}$), 1.68 (2H, m, $H_{3'}$), 3.94 (2H, m, $H_{4'}$), *glucopyranose* 4.26 (1H, d, J = 7.8, $H_{1''}$), 3.96 (1H, m, $H_{2''}$), 4.00 (1H, t, J = 7.7, $H_{3''}$), 3.98 (1H, t, J = 7.3, $H_{4''}$), 3.68 (1H, m, $H_{5''}$), 3.87 (1H, dd, J = 11.8-2.4, $H_{6''a}$), 3.79 (1H, dd, J = 11.9-2.5, $H_{6''b}$). MS (DCI/NH_3) *m/z* 345 (MH^+).

(4-(β-D-glucopyranosyloxy)-butyl)-3-decyl-2-pyrazinone (9c)

Yield 92%. R_f = 0.48, ($CHCl_3$/EtOH, 1:1, v/v). $[\alpha]_D$ +39.1° (0.25, CH_3OH). ^1H ($CDCl_3$/CD_3OD) δ 7.51 (1H, d, J = 4.3, H_5), 7.23 (1H, d, J = 4.3, H_6), *decyl chain* : 0.85 (3H, t, J = 5.5, H_{10}), 1.31 (14H, br. s, H_{3-9}), 1.71 (2H, m, H_2), 2.82 (2H, t, J = 7.7, H_1), *N-alkyl* 3.63 (2H t, J= 7.0, $H_{1'}$), 1.87 (2H, m, $H_{2'}$), 1.74 (2H, m, $H_{3'}$), 3.96 (2H, m, $H_{4'}$), *glucopyranose* 4.27 (1H, d, J=7.5, $H_{1''}$), 3.98 (1H, m, $H_{2''}$), 4.05 (1H, t, J=7.6, $H_{3''}$), 4.04 (1H, t, J=7.3, $H_{4''}$), 3.69 (1H, m, $H_{5''}$), 3.83 (1H, dd, J=11.8-2.4, $H_{6''a}$), 3.79 (1H, dd, J=11.9-1.8, $H_{6''b}$). MS (DCI/NH_3) *m/z* 472 (MH^+).

N^1-(4-(2'', 3'', 5''-tri-O-benzoyl-β-D-furanosyloxy)- butyl)-2-pyrazinone (10a)

To a dry system of N^1-(4-hydroxybutyl) 2-pyrazinone **4a** (60 mg, 0.36 mmol) in freshly distilled acetonitrile at O°C were added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (300 mg, 1 eq.) and tin (IV) chloride (2 eq.). After completion of reaction as monitered by tlc, the solution was quenched with the addition of a saturated $NaHCO_3$ solution / H_2O (20 mL, 1:1, v/v) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed. The product was purified using flash chromatography with an elution gradient of ethyl acetate / methanol and was

recovered in 49% yield (180 mg). R_f = 0.41 (CH_2Cl_2/MeOH, 95:5, v/v). ^1H ($CDCl_3$) δ 8.08 (1H, d, *J*=1.0, H_3), 7.10 (1H, br. d, *J*=4.6 Hz, H_5), 7.31 (1H, d, *J*=4.5 H_6), *N-alkyl* 3.87 (2H t, *J*= 7.3, $H_{1'}$), 1.62 (2H, m, $H_{2'}$), 1.80 (2H, m, $H_{3'}$), 3.49 (1H, dt, *J*=9.7-6.1, $H_{4'a}$), 3.83 (1H, dt, *J*=9.7-6.1, $H_{4'b}$), *ribose* 5.23 (1H, s, $H_{1''}$), 5.66 (1H, br. d, *J*=4.9, $H_{2''}$), 5.84 (1H, dd, *J*=6.5-4.9, $H_{3''}$), 4.70 (1H, m, $H_{4''}$), 4.52 (1H, dd, *J*=12.8-6.5, $H_{5''a}$), 4.72 (1H, dd, *J*=12.8-4.1 Hz, $H_{5''b}$), *benzoyl groups* 7.89, 8.02, 8.06 (6H, dd, J=8.5-1.5, $H_{2,6}$), 7.36-7.51 (9H, m, $H_{3,4,5}$). ^{13}C ($CDCl_3$) δ 149.6 (C_2), 149.5 (C_3), 123.4 (C_5), 123.8 (C_6), *N-alkyl* 49.0 ($C_{1'}$), 25.5 ($C_{2'}$), 26.4 ($C_{3'}$), 67.8 ($C_{4'}$), *ribose* 105.6 ($C_{1''}$), 75.5 ($C_{2''}$), 72.4 ($C_{3''}$), 79.0 ($C_{4''}$), 64.8 ($C_{5''}$), *benzoyl groups* 128.9,129.1, 129.2 (C_1), 128.4, 128.5, 128.6 ($C_{3,5}$), 129.7 ($C_{2,6}$), 133.2, 133.4, 133.5 (C_4), 165.3, 165.4, 166.1 (C_7). MS (DCI/NH_3) *m/z* 613 (MH^+).

Compounds **10b** and **10c** were prepared in a manner similar to that described for **10a** starting from **4b** and **4c** (0.65 and 0.50 mmol) respectively.

N^1-(4-(2'',3'',5''-tri-O-benzoyl-β-D-furanosyloxy)- butyl)-3-methyl-2-pyrazinone (10b)

Yield 45% (190 mg). R_f 0.53 (EtOAc). ^1H ($CDCl_3$) δ 7.03 (1H,br.d, *J*=4.5, H_5), 7.18 (1H, d, *J*=4.5, H_6), C-alkyl 2.49 (3H, s, CH_3), *N-alkyl* 3.87 (2H t, *J*= 7.3, $H_{1'}$), 1.60 (2H, m, $H_{2'}$), 1.80 (2H, m, $H_{3'}$), 3.49 (1H, dt, *J*=9.7-6.1, $H_{4'a}$), 3.83 (1H, dt, *J*=9.7-6.1, $H_{4'b}$), *ribose* 5.23 (1H, s, $H_{1''}$), 5.66 (1H, br. d, *J*=4.9, $H_{2''}$), 5.84 (1H, dd, *J*=6.5-4.9, $H_{3''}$), 4.70 (1H, m, $H_{4''}$), 4.52 (1H, dd, *J*=12.8-6.6, $H_{5''a}$), 4.72 (1H, dd, *J*=12.8-4.1 , $H_{5''b}$), *benzoyl groups* 7.89, 8.02, 8.06 (6H, dd, *J*=8.5-1.5, $H_{2,6}$), 7.36-7.51 (9H, m, $H_{3,4,5}$). ^{13}C ($CDCl_3$) δ 149.5 (C_2), 149.6 (C_3), 123.4 (C_5), 123.8 (C_6),C-alkyl 20.6 (CH_3), *N-alkyl* 49.0 ($C_{1'}$), 25.5 ($C_{2'}$), 26.4 ($C_{3'}$), 67.8 ($C_{4'}$), *ribose* 105.6 ($C_{1''}$), 75.5 ($C_{2''}$), 72.4 ($C_{3''}$), 79.0 ($C_{4''}$), 64.8 ($C_{5''}$), *benzoyl groups* 128.9,129.1, 129.2 (C_1), 128.4, 128.5, 128.6 ($C_{3,5}$), 129.7 ($C_{2,6}$), 133.2, 133.4, 133.5 (C_4), 165.3, 165.4, 166.1 (C_7). MS (DCI/NH_3) m/z 627 MH^+.

N^1-(4-(2'',3'',5''-tri-O-benzoyl-β-D-furanosyloxy)- butyl)-3-decyl-2-pyrazinone (10c)

Yield 42% (158 mg). R_f 0.53 (CH_2Cl_2/EtOH, 95/5, v/v). ^1H ($CDCl_3$) δ 7.03 (1H,br.d, *J*=4.5, H_5), 7.18 (1H, d, *J*=4.5, H_6), C-alkyl 2.83 (2H,br.t, *J*=7.8, CH_2), 1.7 (2H, m,

CH_2),1.3 (14H, br.s, CH_2) 0.88 (3H, br.t, J=7.4, CH_3), *N-alkyl* 3.88 (2H t, J= 7.3, $H_{1'}$), 1.70 (4H, m, $H_{2',3'}$), 3.49 (1H, dt, J=9.7-6.1, $H_{4'a}$), 3.83 (1H, dt, J=9.7-6.1, $H_{4'b}$), *ribose* 5.23 (1H, s, $H_{1''}$), 5.66 (1H, br. d, J=4.9, $H_{2''}$), 5.84 (1H, dd, J=6.5-4.9, $H_{3''}$), 4.70 (1H, m, $H_{4''}$), 4.52 (1H, dd, J=12.8-6.6, $H_{5''a}$), 4.72 (1H, dd, J=12.8-4.1 , $H_{5''b}$), *benzoyl groups* 7.89, 8.00, 8.06 (6H, dd, J=8.5-1.5, $H_{2,6}$), 7.36-7.51 (9H, m, $H_{3,4,5}$). ^{13}C ($CDCl_3$) δ 155.8 (C_2), 161.3 (C_3), 121.3 (C_5), 127.3 (C_6),C-alkyl 33.2 (C_1), 31.9 (C_2), 29.3, 29.4, 29.6, 26.7, 22.8 ($C_{3\text{-}9}$), 14.1 (C_{10}), *N-alkyl* 49.3 ($C_{1'}$), 25.5 ($C_{2'}$), 26.4 ($C_{3'}$), 67.8 ($C_{4'}$), *ribose* 105.6 ($C_{1''}$), 75.5 ($C_{2''}$), 72.5 ($C_{3''}$), 79.0 ($C_{4''}$), 64.8 ($C_{5''}$), *benzoyl groups* 128.9,129.1, 129.2 (C_1), 128.4, 128.5, 128.6 ($C_{3,5}$), 129.7 ($C_{2,6}$), 133.2, 133.4, 133.5 (C_4), 165.3, 165.4, 166.1 (C_7). MS (DCI/NH_3) m/z 753 MH^+.

Compoud **11a**, **11b** and **11c** were prepared in a manner similar to that described for 9a starting from **10a**, **10b** and **10c** (0.39, 0.20 and 0.50 mmol) respectively.

N^1 (4-β-D-ribofuranosyloxy)-butyl)-2-pyrazinone (11a)

Yield 89% (105 mg). R_f 0.28 ($CHCl_3$/MeOH, 80/20, v/v). ^1H ($CDCl_3$) δ 8.04 (1H, d, J=0.9, H_3), 7.6 (1H, dd, J=0.9-4.5 Hz, H_5), 7.4 (1H, d, J=4.5, H_6), *N-alkyl* 4.0 (2H t, J= 7.6, $H_{1'}$), 1.6 (2H, m, $H_{2'}$), 1.84 (2H, m, $H_{3'}$), 3.43 (1H, dt, J=6.3-6.2, $H_{4'a}$), 3.80 (1H, dt, J=6.3-6.2, $H_{4'b}$), *ribose* 4.84 (1H, s, $H_{1''}$), 3.87 (1H, d, J=4.9, $H_{2''}$), 4.05 (1H, dd, J=6.9-4.9, $H_{3''}$), 3.94 (1H, td, J=6.9-3.6, $H_{4''}$), 3.54 (1H, dd, J=12.1-6.9, $H_{5''a}$), 3.74 (1H, dd, J=12.1-3.6 Hz, $H_{5''b}$). ^{13}C ($CDCl_3$) δ 157.2 (C_2), 148.2 (C_3), 124.5 (C_5), 130.6 (C_6), *N-alkyl* 49.5 ($C_{1'}$), 25.7 ($C_{2'}$), 26.6 ($C_{3'}$), 67.2 ($C_{4'}$), *ribose* 107.8 ($C_{1''}$), 75.3 ($C_{2''}$), 71.6 ($C_{3''}$), 83.8 ($C_{4''}$), 63.9 ($C_{5''}$). MS (DCI/NH_3) *m/z* 301 (MH^+).

N^1-(4-β-D-ribofuranosyloxy)-butyl)-3-methyl-2-pyrazinone (11b)

Yield 86% (67 mg). R_f 0.35 (CH_2Cl_2/EtOH, 80/20, v/v). ^1H ($CDCl_3$) δ 7.6 (1H, d, J=4.5 Hz, H_5), 7.4 (1H, d, J=4.5, H_6), C-alkyl 2.30 (3H, s, CH_3), *N-alkyl* 4.1 (2H t, J= 7.6, $H_{1'}$), 1.65 (2H, m, $H_{2'}$), 1.88 (2H, m, $H_{3'}$), 3.43 (1H, dt, J=6.5-6.5, $H_{4'a}$), 3.80 (1H, dt, J=6.5-6.5, $H_{4'b}$), *ribose* 4.82 (1H, s, $H_{1''}$), 3.88 (1H, d, J=4.9, $H_{2''}$), 4.05 (1H, dd, J=6.7-4.9, $H_{3''}$), 3.94 (1H, td, J=6.7-3.6, $H_{4''}$), 3.54 (1H, dd, J=12.2-6.7, $H_{5''a}$), 3.74 (1H, dd, J=12.2-3.6 Hz, $H_{5''b}$). ^{13}C ($CDCl_3$) δ 157.2 (C_2), 158.2 (C_3), 124.5 (C_5), 130.6 (C_6), C-

alkyl 20.5 (CH_3), *N-alkyl* 49.5 ($C_{1'}$), 25.7 ($C_{2'}$), 26.6 ($C_{3'}$), 67.2 ($C_{4'}$), *ribose* 107.8 ($C_{1''}$), 75.3 ($C_{2''}$), 71.6 ($C_{3''}$), 83.8 ($C_{4''}$), 63.9 ($C_{5''}$). MS (DCI/NH_3) *m/z* 315 (MH^+).

N^1-(4-β-D-ribofuranosyloxy)-butyl)-3-decyl-2-pyrazinone (11c)

Yield 79% (79 mg). R_f 0.53 (CH_2Cl_2/EtOH, 80/20, v/v). ^1H ($CDCl_3$) δ 7.25 (1H,d, *J*=4.5, H_5), 7.43 (1H, d, *J*=4.5, H_6), C-alkyl 2.75 (2H, t, *J*=7.8, CH_2), 1.7 (2H, m, CH_2),1.3 (14H, br.s, CH_2), 0.89 (3H, t, *J*=7.0, CH_3), *N-alkyl* 3.97 (2H t, *J*= 7.6, $H_{1'}$), 1.7 (2H, m, $H_{2'}$), 1.8 (2H, m, $H_{3'}$), 3.42 (1H, dt, *J*=6.3-6.4, $H_{4'a}$), 3.8 (1H, dt, *J*=6.3-6.4, $H_{4'b}$), *ribose* 4.87 (1H, s, $H_{1''}$), 3.87 (1H, d, *J*=4.9, $H_{2''}$), 4.05 (1H, dd, *J*=7.0-4.9, $H_{3''}$), 3.92 (1H, td, *J*=3.6-7 0, $H_{4''}$), 3.54 (1H, dd, *J*=12.2-7.0, $H_{5''a}$), 3.72 (1H, dd, *J*=12.2-3.6 , $H_{5''b}$. ^{13}C ($CDCl_3$) δ 156.6 (C_2), 160.5 (C_3), 122.9 (C_5), 128.6 (C_6),C-alkyl 33.4 (C_1), 32.1 (C_2), 29.7, 29.6, 29.5, 29.4, 26.8 ($C_{3\text{-}9}$), 13.5 (C_{10}), *N-alkyl* 49.6 ($C_{1'}$), 25.7 ($C_{2'}$), 26.7 ($C_{3'}$), 67.2 ($C_{4'}$), *ribose* 107.8 ($C_{1''}$), 71.6 ($C_{2''}$), 63.9 ($C_{3''}$), 83.8 ($C_{4''}$), 63.9 ($C_{5''}$). MS (DCI/NH_3) m/z 441 MH^+.

Biological Methods

The 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 previousely.[19] The antiviral activity is expressed as the IC_{50} concentration necessary to reduce viral cytopathicity by 50%.

Cytotoxicity (MTT assay)

Cell viability was evaluated by measuring the activity of mitochondrial dehydrogenase using the MTT assay.[20]

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.[21]

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