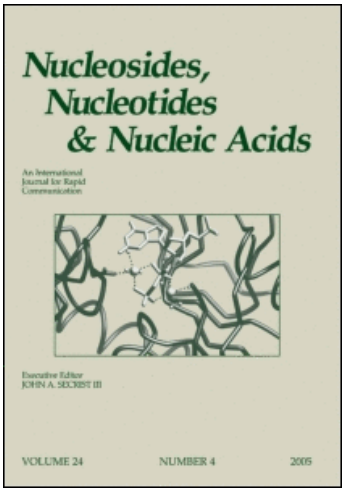

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A Synthetic Strategy to a New Class of Cycloalkane Ring-Fused Pyridine Nucleosides as Potential Anti HIV Agents

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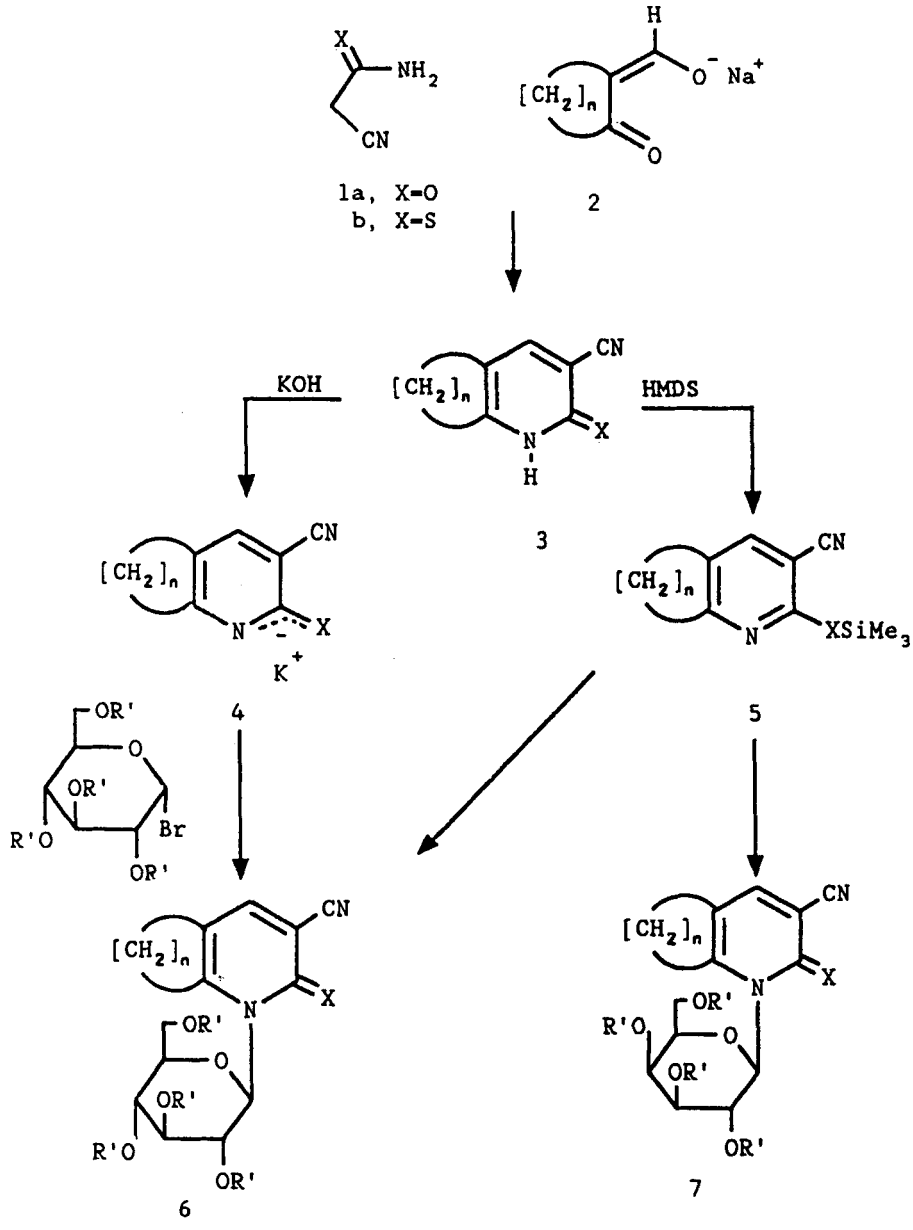
Abstract: Condensation of cyanothioacetamide or cyanoacetamide with sodium salts of 2-formyl-1-cycloalkanones afforded the corresponding cycloalkane ring fused pyridine-2(*1H*)-thiones and -2-pyridones. The latter compounds served as a key intermediates for the synthesis of a new class of cycloalkane ring fused pyridine glycosides.

Though a number of drugs have been approved for use in the treatment of AIDS, there continues to be a need for and an interest in the development of new drugs with improved properties. 3'-Azido-3'-deoxythymidine (AZT) and 2',3'-dideoxyinosine (DDI) are nowadays the only anti-HIV agents used in spite of their toxic side effects. This fact shows the need for better drugs to develop this disease. Another new class of anti HIV-1 agents has been identified[1], including 1-(benzyloxymethyl)-5-ethyl-6-(phenylthio) uracil (EBPU) and 1-[(2-

hydroxyethoxy)-methyl]-6-(phenylthio) thymine (HEPT), shows a high selectivity for the HIV-1 reverse transcriptase. As a part of our program directed for development of new simple and efficient procedures for the synthesis of antimetabolites[2-4], we have recently reported different successful approaches for synthesis of mercaptopurine, 5-deaza folic acid and pyrimidine nucleoside analogues[5-7]. We report in this article a novel synthesis of deaza analogues of HEPT and EBPU. The latter compounds will be considered as precursors of modified nucleosides. Thus, it has been found that sodium salts of 2-(hydroxymethylene)-1-cycloalkanones **2** reacted with cyanothio- acetamide or cyanoacetamide **1** to give the condensed 3-cyanopyridine-2(*1H*)-thione or -2-one derivatives **3**.

Compounds **3** can be coupled with different classes of halogenated sugars to give a novel ring system of glycosides, thus, **3** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl bromides in the presence of aqueous potassium hydroxide to give the corresponding condensed pyridine glycosides **6a-h** and **7a-h**. Although the coupling of **3e-h** with the glycosyl bromides could also give the corresponding thioglycosides, the formation of **6e-h** and **7e-h** was proved chemically. Reaction of **3e-h** with hexamethyldisilazane (HMDS) in the presence of ammonium sulphate gave the corresponding 2-trimethylsilylthiopyridines **5**, which were subsequently treated with peracetylated sugars in the presence of redistilled $SnCl_4$ to afford the corresponding *N*-glycosyl compounds. The previous literature reports that Lewis acid-induced coupling reactions of *S*-silylated heterocyclic bases with peracetylated sugars gave the corresponding *N*-nucleosides as the sole product[8-10]. The structures of the reaction products **6a-h** and **7a-h** were established and confirmed by their elemental analyses and spectral data (MS, IR, UV, ^1H NMR, ^{13}C NMR). Thus, the analytical data for **6f** revealed a molecular

formula $C_{24}H_{28}N_2SO_9$ (m/z 520). The ^1H NMR spectrum showed the anomeric proton as a doublet at δ 6.04 with a spin-spin coupling constant of 10.52 Hz which corresponds to the diaxial orientation of 1'-H and 2'-H protons, indicating the presence of only the β-configuration. The other six protons of the glucopyranosyl ring resonated in the δ 3.98-5.56 region, while the four acetoxy groups appear as four singlets at δ 1.98-2.04 and the four methylene of the aglycone resonate at δ 1.78, 1.84, 2.66 and 2.96. The ^{13}C NMR spectrum of **6f** contained a signal at δ 80.8 corresponding to the C-1' atom of the β-configuration. Four signals appeared at δ 169.5-170.1 due to the ester carbonyl carbon atoms, while signals appearing at δ 20.6-20.7 were attributed to the acetoxy methyl carbons. Another five signals at δ 62.1, 68.5, 69.3, 73.5 and 75.3 were assigned to C-6', C-4', C-2', C-3' and C-5', respectively. The UV spectrum of **6f** proved that the reaction had led selectively to the formation of *N*-glucosyl derivatives and excluded substitution at the sulfur atom. Thus, whereas the *S*-methyl derivative of **3f** shows two maxima at 270 and 326 nm, its *N*-glucosyl derivative exhibited three maximum absorption bands at 267, 316 and 404 nm. After deprotection of compounds **6a-h** and **7a-h** with a saturated solution of ammonia in methanol, the final nucleosides **6i-n** and **7i-n** are obtained in almost quantitative yields, the structures of which have been established on the basis of elemental analyses and spectral data. Thus, the analytical data for **7l** revealed a molecular formula $C_{16}H_{20}N_2SO_5$ (m/z 352). The ^1H NMR spectrum shows the anomeric proton as a doublet at δ 5.52 ($J_{1'-2'}$ = 10.39 Hz) indicating the presence of only the β-D-configuration. The signals of the other six galactose protons appear as a multiplet at δ 3.26-3.80, while the signals of the four hydroxy groups are observed at δ 4.42-5.28 (exchangeable by D_2O). The ^{13}C NMR spectrum of **7l** contained a signal at δ 84.0



	X	n		X	n	R′		X	n	R′
3a	O	3	**6,7 a**	O	3	Ac	**i**	O	4	H
b	O	4	**b**	O	4	Ac	**j**	O	5	H
c	O	5	**c**	O	5	Ac	**k**	S	3	H
d	O	6	**d**	O	6	Ac	**l**	S	4	H
e	S	3	**e**	S	3	Ac	**m**	S	5	H
f	S	4	**f**	S	4	Ac	**n**	S	6	H
g	S	5	**g**	S	5	Ac				
h	S	6	**h**	S	6	Ac				

corresponding to the C-1' atom of β-D-galactopyranose. Another five signals at δ 60.2, 68.2, 68.8, 74.8 and 79.5 were assigned to C-6', C-4', C-2', C-3' and C-5' of the galactose moiety, respectively. In summary, we have achieved a regiospecific synthesis of 3-deazapyrimidine glycosides by the reaction of condensed pyridine-2(1*H*)-ones and their corresponding thiones with α-halogeno sugars. These glycosides can be utilized as starting materials for the synthesis of other carbohydrate derivatives and for biological evaluation studies.

Experimental

All evaporations were carried out under reduced pressure at 40 ^{o}C. Melting points are uncorrected. TLC aluminium sheets silica gel 60 F_{254} (Merck) was used for thin layer chromatography. Detection was effected by viewing under a short-wavelength UV lamp. IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000. ^{1}H NMR and ^{13}C NMR spectra were measured on a Wilmad 270 MHz or on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Mass spectra were recorded on a double-focusing Varian MAT 112 and Finnigan MAT 8430 spectrometers, low resolution chemical ionization (CI), reagent gas was NH_3. Analytical data were obtained from the Microanalytical data Center at Cairo University. Compounds **3** were prepared following our literature procedures[11].

3-Cyano-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl)cycloalkane ring-fused 2-pyridones and pyridinethiones 6a-h and 7a-h.

General coupling procedures:

Method A. To a solution of compounds **3** (0.01 mol) in aqueous potassium hydroxide [0.56 g, 0.01 mol, in 6 ml of distilled water], was added a solution of

2,3,4,6-tetra-*O*-acetyl-α-D-gluco-or-galactopyranosyl bromide (0.011 mol) in acetone (30 ml). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC (solvent CH_2Cl_2-MeOH in a ratio 1:1; 30 min for **6e-h**, **7e-h** and 12 h for **6a-d**, **7a-d**) then evaporated under reduced pressure at 40 °C and the residue was washed with distilled water to remove the potassium bromide formed. The product was dried and crystallized from ethanol to afford pale yellow crystals.

Method B. Compounds **3** (0.01 mol) were boiled under reflux, with stirring, under anhydrous conditions for 48 hours with hexamethyldisilazane (25 ml) and $(NH_4)SO_4$ (0.02 g). The excess of hexamethyldisilazane was removed under diminished pressure, providing the silylated bases **5** as a colourless oils. To a solution of silylated base in dry MeCN (30 ml) was added a solution of α-D-glucose- or α-D-galactose pentaacetate (0.011 mol) in dry MeCN (10 ml) followed by $SnCl_4$ (1.6 ml). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC (slovent CH_2Cl_2-MeOH in a ratio 1:1; 2 h for **6e-h**, **7e-h** and 6 h for **6a-d** and **7a-d**), then poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude nucleoside which were purified by recrystallization from ethanol to afford pale yellow crystals.

6a : m.p. 260 °C, yield 45 %. IR(KBr) 2226 (CN), 1750 (CO ester), 1660 (CO pyridone) cm^{-1}; m/z 490 (Found: C, 56.5; H, 5.4; N, 5.6. $C_{23}H_{26}N_2O_{10}$ requires C, 56.3; H, 5.3; N, 5.7 %).

6b : m.p. 232 °C, yield 46 %. IR(KBr) 2222 (CN), 1748 (CO ester), 1666 (CO pyridone) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.70 (t, 2H, CH_2), 1.84 (t, 2H, CH_2),

1.98-2.06 (4s, 12H, $4CH_3CO$), 2.44 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 4.12 (m, 2H, 2H-6' and 1H, H-5'), 5.16 (m, 2H, H-4' and H-2'), 5.54 (t, 1H, H-3'), 6.36 (d, $J_{1'-2'}$ = 8.39 Hz, 1H, H-1'), 7.82 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.3-20.5 ($4CH_3$), 21.6-26.6 ($4CH_2$), 61.4 (C-6'), 67.98 (C-4'), 70.3 (C-2'), 71.3 (C-3'), 71.8 (C-5'), 93.3 (C-1'), 99.8 (C-3), 116.6 (CN), 122.2-161.7 (Ar-C), 168.7-169.8 (4CO ester); m/z 504 (Found: C, 57.3; H, 5.6; N, 5.7. $C_{24}H_{28}N_2O_{10}$ requires C, 57.1; H, 5.6; N, 5.6 %).

6c : m.p. 215 °C, yield 50 %. IR(KBr) 2230 (CN), 1752 (CO ester), 1665 (CO pyridone) cm^{-1}; m/z 518 (Found: C, 58.1; H, 5.9; N, 5.6. $C_{25}H_{30}N_2O_{10}$ requires C, 57.9; H, 5.8; N, 5.4 %).

6d : m.p. 221 °C, yield 54 %. IR (KBr) 2228 (CN), 1755 (CO ester), 1660 (CO pyridone) cm^{-1}; m/z 532 (Found: C, 58.8; H, 6.1; N, 5.5. $C_{26}H_{32}N_2O_{10}$ requires C, 58.6; H, 6.0; N, 5.3 %).

6e : m.p. 140 °C, yield 68 %. IR(KBr) 2223 (CN), 1752 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (t, 2H, CH_2), 1.94-2.08 (4s, 12H, $4CH_3CO$), 2.78(t, 2H, CH_2), 3.00 (t, 2H, CH_2), 3.98 (m, 2H, 2H-6' and 1H, H-5'), 4.92(t, 1H, H-4'), 5.18 (m, 1H, H-2'), 5.52 (t, 1H, H-3'), 6.08 (d, $J_{1'-2'}$ = 10.51 Hz, 1H, H-1'), 8.01 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.3-25.2 ($4CH_3$), 29.7-34.1 ($3CH_2$), 61.8 (C-6'), 68.1 (C-4'), 68.8 (C-2'), 73.0 (C-3'), 74.8 (C-5'), 80.3 (C-1'), 105.0 (C-3), 115.4 (CN), 122.2-165.6 (Ar-C), 169.1-169.7 (4CO); m/z 506 (Found: C, 54.7; H, 5.1; N, 5.6. $C_{23}H_{26}N_2SO_9$ requires C, 54.5; H, 5.1; N, 5.5 %).

6f : m.p. 203 °C, yield 70 %. IR (KBr) 2218 (CN), 1759 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.78 (t, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.98-2.04 (4s, 12H, $4CH_3CO$), 2.66 (t, 2H, CH_2), 2.96 (m, 2H, CH_2), 4.08 (m, 2H, 2H-6' and 1H, H-5'), 4.98 (t, 1H, H-4'), 5.13 (t, 1H, H-2'), 5.50 (t, 1H, H-3'), 6.04 (d, $J_{1'-2'}$ =

10.52 Hz, 1H, H-1'), 7.98 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.6-20.8 ($4CH_3$), 21.9-32.7 ($4CH_2$), 62.1 (C-6'), 68.5 (C-4'), 69.3 (C-2'), 73.5 (C-3'), 75.3 (C-5'), 80.8 (C-1'), 105.0 (C-3), 115.8 (CN), 122.6-162.4 (Ar-C), 169.5-170.1 (4CO); m/z 520 (Found: C, 55.6; H, 5.5; N, 5.6. $C_{24}H_{28}N_2SO_9$ requires C, 55.4; H, 5.4; N, 5.4 %).

6g : m.p. 147 °C, yield 72 %. IR(KBr) 2222 (CN), 1754 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.38 (d, 2H, CH_2), 1.66 (t, 2H, CH_2), 1.82 (t, 2H, CH_2), 1.98-2.12 (4s, 12H, $4CH_3CO$), 2.70 (m, 2H, CH_2), 3.12 (m, 2H, CH_2), 4.15 (m, 2H, 2H-6' and 1H, H-5'), 5.02 (m, 2H, H-4' and H-2'), 5.52 (t, 1H, H-3'), 6.16 (d, $J_{1'-2'}$ = 10.51 Hz, 1H, H-1'), 8.00 (s, 1H, Pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.2-20.3 ($4CH_3$), 25.6-32.7 ($5CH_2$), 61.7 (C-6'), 68.1 (C-4'), 69.0 (C-2'), 73.1 (C-3'), 74.9 (C-5'), 80.3 (C-1'), 104.5 (C-3), 115.4 (CN), 122.2-167.6 (Ar-C), 169.1-169.7 (4CO); m/z 534 (Found: C, 56.4; H, 5.6; N, 5.4. $C_{25}H_{30}N_2SO_9$ requires C, 56.2; H, 5.6; N, 5.2 %).

6h : m.p. 136 °C, yield 74 %. IR(KBr) 2226 (CN), 1755 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.34 (m, 4H, $2CH_2$), 1.76 (m, 4H, $2CH_2$), 1.95-2.08 (4s, 12H, $4CH_3CO$), 2.80 (t, 2H, CH_2), 3.01 (t, 2H, CH_2), 4.06 (m, 2H, 2H-6' and 1H, H-5'), 5.00 (t, 1H, H-4'), 5.18 (t, 1H, H-2'), 5.54 (t, 1H, H-3'), 6.10 (d, $J_{1'-2'}$ = 10.51 Hz, 1H, H-1') 8.00 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.1-20.6 ($4CH_3$), 25.6-34.5 ($6CH_2$), 62.2 (C-6'), 68.5 (C-4'), 69.2 (C-2'), 73.4 (C-3'), 75.2 (C-5'), 80.7 (C-1'), 105.4 (C-3), 115.8 (CN), 122.4-166.0 (Ar-C), 169.5-170.1 (4CO); m/z 548 (Found: C, 57.1; H, 5.9; N, 5.3. $C_{26}H_{32}N_2SO_9$ requires C, 56.9; H, 5.8; N, 5.1 %).

7a : m.p. 267 °C, yield 43 %. IR (KBr) 2228 (CN), 1748 (CO ester), 1664 (CO pyridone) cm^{-1}; m/z 490 (Found: C, 56.4; H, 5.4; N, 5.9. $C_{23}H_{26}N_2O_{10}$ requires C, 56.3; H, 5.3; N, 5.7 %).

7b : m.p. 189 °C, yield 45 %. IR(KBr) 2222 (CN), 1750 (CO ester), 1660 (CO pyridone) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.66 (s, 2H, CH_2), 1.95-2.09 (4s, 12H,

$4CH_3CO$), 2.42 (s, 2H, CH_2), 2.69 (s, 2H, CH_2), 2.80 (s, 2H, CH_2), 4.06 (t, 2H, 2H-6'), 4.47 (s, 1H, H-5'), 5.36 (m, 3H, H-4', H-2' and H-3'), 6.30 (d, $J_{1'-2'}$ = 8.33 Hz, 1H, H-1'), 8.01 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.2-21.7 ($4CH_3$), 24.9-32.3 ($4CH_2$), 61.1 (C-6'), 67.2 (C-4'), 68.0 (C-2'), 70.0 (C-3'), 70.7 (C-5'), 93.0 (C-1'), 99.9 (C-3), 113.1 (CN), 127.6-160.2 (Ar-C), 169.8-169.9 (4CO); m/z 504 (Found: C, 57.2; H, 5.7; N, 5.8. $C_{24}H_{28}N_2O_{10}$ requires C, 57.1; H, 5.6; N, 5.6 %).

7c : m.p. 125 °C, yield 49 %. IR(KBr) 2230 (CN), 1753 (CO ester), 1666 (CO pyridone) cm^{-1}; m/z 518 (Found: C, 58.0; H, 5.9; N, 5.6. $C_{25}H_{30}N_2O_{10}$ C, 57.9; H, 5.8; N, 5.4 %).

7d : m.p. 208 °C, yield 53 %. IR(KBr) 2230 (CN), 1752 (CO ester), 1660 (CO pyridone) cm^{-1}; m/z 532 (Found: C, 58.7; H, 6.0; N, 5.4. $C_{26}H_{32}N_2O_{10}$ requires C, 58.6; H, 6.0; N, 5.3 %).

7e : m.p. 106 °C, yield 68 %. IR(KBr) 2220 (CN), 1748 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.64 (m, 2H, CH_2), 1.90-2.15 (4s, 12H, $4CH_3CO$), 2.77 (s, 2H, CH_2), 3.01 (s, 2H, CH_2), 3.98 (t, 2H, 2H-6'), 4.39 (s, 1H, H-5'), 5.37 (m, 3H, H-4', H-2' and H-3'), 6.06 (d, $J_{1'-2'}$ = 10.51 Hz, 1H, H-1'), 8.03 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.2-25.2 ($4CH_3$), 29.7-34.1 ($3CH_2$), 61.5 (C-6'), 66.4 (C-4'), 67.7 (C-2'), 70.9 (C-3'), 74.0 (C-5'), 80.7 (C-1'), 105.1 (C-3), 115.0 (CN), 133.7-165.6 (Ar-C), 169.2-169.8 (4CO); m/z 506 (Found: C, 54.6; H, 5.2; N, 5.7. $C_{23}H_{26}N_2SO_9$ requires C, 54.5; H, 5.1; N, 5.5 %).

7f : m.p. 184 °C, yield, 70 %. IR(KBr) 2223 (CN), 1753 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.70 (m, 4H, $2CH_2$), 1.91-2.15 (4s, 12H, $4CH_3CO$), 2.73 (t, 2H, CH_2), 2.92 (t, 2H, CH_2), 4.00 (m, 2H, 2H-6' and 1H, H-5'), 5.38 (m, 3H, H-4', H-2' and H-3'), 5.97 (d, $J_{1'-2'}$ = 10.55 Hz, 1H, H-1'), 7.97 (s, 1H, pyridine H-4); ^{13}C NMR-d_6) δ 20.3-21.7 ($4CH_3$), 25.4-32.4 ($4CH_2$), 61.4 (C-6'), 67.6 (C-4'), 68.8 (C-2'), 72.1 (C-3'), 74.1 (C-5'), 80.9 (C-1'), 104.7 (C-3), 115.5 (CN),

121.4-162.0 (Ar-C), 169.3-169.9 (4CO); m/z 520 (Found: C, 55.5; H, 5.4; N, 5.5. $C_{24}H_{28}N_2SO_9$ requires C, 55.4; H, 5.4; N, 5.4 %).

7g : m.p. 113 ^{o}C, yield 71 %. IR(KBr) 2224 (CN), 1753 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.88 (m, 2H, CH_2), 1.99-2.12 (4s, 12H, $4CH_3CO$), 2.81 (t, 2H, CH_2), 3.04 (t, 2H, CH_2), 4.02 (m, 2H, 2H-6'), 4.40 (t, 1H, H-5'), 5.38 (m, 3H, H-4', H-2' and H-3'), 6.08 (d, $J_{1'-2'}$ = 10.59 Hz, 1H, H-1'), 8.00 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.2-20.4 ($4CH_3$), 25.6-32.8 ($5CH_2$), 61.4 (C-6'), 66.5 (C-4'), 67.7 (C-2'), 71.0 (C-3'), 74.1 (C-5'), 80.8 (C-1'), 104.6 (C-3), 115.4 (CN), 122.2-167.6 (Ar-C), 169.3-169.9 (4CO); m/z 534 (Found: C, 56.3; H, 5.7; N, 5.4. $C_{25}H_{30}N_2SO_9$ requires C, 56.2; H, 5.6; N, 5.2 %).

7h : m.p. 102 ^{o}C, yield 73 %. IR(KBr) 2223 (CN), 1753 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.36 (m, 4H, $2CH_2$), 1.78 (m, 4H, $2CH_2$), 1.94-2.15 (4s, 12H, $4CH_3CO$), 2.80 (t, 2H, CH_2), 3.00 (t, 2H, CH_2), 4.01 (m, 2H, 2H- 6'), 4.38 (t, 1H, H-5'), 5.22 (m, 1H, H-4'), 5.40 (t, 1H, H-2'), 5.51 (m, 1H, H-3'), 6.08 (d, $J_{1'-2'}$ = 10.56 Hz, 1H, H-1'), 8.01 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.2-20.3 ($4CH_3$), 25.2-34.9 ($6CH_2$), 61.5 (C-6'), 66.4 (C-4'), 67.7 (C-2'), 70.9 (C-3'), 74.1 (C-5'), 80.8 (C-1'), 105.1 (C-3), 115.4 (CN), 122.2-165.6 (Ar-C), 169.2-169.8 (4CO); m/z 548 (Found: C, 57.0; H, 5.9; N, 5.2. $C_{26}H_{32}N_2SO_9$ requires C, 56.9; H, 5.8; N, 5.1 %).

3-Cyano-1-(β-D-glycopyranosyl)cycloalkane ring-fused 2-pyridones and pyridinethiones 6i-n and 7i-n.

General procedure for nucleoside deacylation.

Dry gaseous ammonia was passed through a solution of protected nucleosides **6a-h** and **7a-h** (0.5 g) in dry methanol (20 ml) at 0 ^{o}C for about 0.5 hour, then the reaction mixture was stirred until judged complete by TLC (benzene-MeOH in a ratio 1:2; 4 h for **6k-n**, **7k-n** and 8 h for **6i,j**, **7i,j**). The mixture was

evaporated under reduced pressure at 40 °C to give a solid residue, which was crystallized from methanol to afford colourless crystals.

6i : m.p. 268 °C, yield 80 %. IR(KBr) 3660-3220 (OH), 2226 (CN), 1660 (CO pyridone) cm^{-1}; m/z 336 (Found: C, 57.3; H, 6.1; N, 8.5. $C_{16}H_{20}N_2O_6$ requires C, 57.1; H, 6.0; N, 8.3 %).

6j : m.p. 246 °C, yield 82 %. IR(KBr) 3760-3294 (OH), 2229 (CN), 1640 (CO pyridone) cm^{-1}; m/z 350 (Found: C, 58.5; H, 6.4; N, 8.2. $C_{17}H_{22}N_2O_6$ requires C, 58.3; H, 6.3; N, 8.0 %).

6k : m.p. 183 °C, yield 83 %. IR(KBr) 3640-3180 (OH), 2220 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.32 (m, 2H, CH_2), 2.74 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.20-3.68 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.44 (t, 1H, 3'-OH), 5.01 (d, 1H, 2'-OH), 5.21 (d, 1H, 4'-OH), 5.53 (d, $J_{1'-2'}$ = 9.63 Hz, 1H, H-1' and 1H, 6'-OH), 7.96 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 25.2-34.3 ($3CH_2$), 60.5 (C-6'), 69.6 (C-4'), 71.7 (C-2'), 78.6 (C-3'), 81.4 (C-5'), 83.6 (C-1'), 104.6 (C-3), 115.8 (CN), 132.7-165.3 (Ar-C); m/z 338 (Found: C, 53.5; H, 5.4; N, 8.5. $C_{15}H_{18}N_2SO_5$ requires C, 53.3; H, 5.3; N, 8.3 %).

6l : m.p. 176 °C, yield 82 %. IR(KBr) 3680-3260 (OH), 2226 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75 (m, 4H, $2CH_2$), 2.70 (t, 2H, CH_2), 2.84 (t, 2H, CH_2), 3.17-3.72 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.43 (t, 1H, 3'-OH), 5.00 (d, 1H, 2'-OH), 5.17 (d, 1H, 4'-OH), 5.46 (d, $J_{1'-2'}$ = 9.61 Hz, 1H, H-1' and 1H, 6'-OH), 7.92 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 21.6-32.4 ($4CH_2$), 60.6 (C-6'), 69.6 (C-4'), 71.8 (C-2'), 78.5 (C-3'), 81.5 (C-5'), 83.5 (C-1'), 103.9 (C-3), 115.7 (CN), 128.8-161.6 (Ar-C); m/z 352 (Found: C, 54.7; H, 5.8; N, 8.1. $C_{16}H_{20}N_2SO_5$ requires C, 54.5; H, 5.7; N, 8.0 %).

6m : m.p. 187 °C, yield 85 %. IR(KBr) 3740-3320 (OH), 2224 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.58 (m, 4H, $2CH_2$), 1.88 (m, 2H, CH_2), 2.78 (t, 2H, CH_2), 3.02 (t, 2H, CH_2), 3.21-3.64 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.38 (t, 1H, 3'-OH), 4.98 (d, 1H, 2'-OH), 5.18 (d, 1H, 4'-OH), 5.42 (d, 1H, 6'-

OH), 5.63 (d, $J_{1'-2'}$ = 9.69 Hz, 1H, H-1'), 7.98 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 25.5-32.7 ($5CH_2$), 60.5 (C-6'), 69.6 (C-4'), 71.8 (C-2'), 78.5 (C-3'), 81.4 (C-5'), 83.5 (C-1'), 103.8 (C-3), 115.8 (CN), 122.4-167.2 (Ar-C); m/z 366 (Found: C, 55.9; H, 6.1; N, 7.8. $C_{17}H_{22}N_2SO_5$ requires C, 55.7; H, 6.0; N, 7.7 %).

6n : m.p. 171 °C, yield 83 %. IR(KBr) 3730-3360 (OH), 2223 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (m, 4H, $2CH_2$), 1.78 (m, 4H, $2CH_2$), 2.74 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 3.18-3.64 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.40 (s, 1H, 3'-OH), 4.96 (s, 1H, 2'-OH), 5.15 (s, 1H, 4'-OH), 5.46 (s, 1H, 6'-OH), 5.58 (d, $J_{1'-2'}$ = 9.65 Hz, 1H, H-1'), 7.96 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 25.2-34.3 ($6CH_2$), 60.5 (C-6'), 69.6 (C-4'), 71.7 (C-2'), 78.6 (C-3'), 81.4 (C-5'), 83.6 (C-1'), 104.5 (C-3), 115.8 (CN), 122.6-165.2 (Ar-C); m/z 380 (Found: C, 57.0; H, 6.5; N, 7.5. $C_{18}H_{24}N_2SO_5$ requires C, 56.8; H, 6.3; N, 7.4 %).

7i : m.p. 245 °C, yield 78 %. IR(KBr) 3660-3210 (OH), 2224 (CN), 1655 (CO pyridone) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.68 (m, 4H, $2CH_2$), 2.42 (t, 2H, CH_2), 2.58 (t, 2H, CH_2), 3.20-3.78 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.50 (t, 1H, 3'-OH), 5.08 (m, 2H, 2'-OH and 4'-OH), 5.48 (d, 1H, 6'-OH), 6.18 (d, $J_{1'-2'}$ = 8.23 Hz, 1H, H-1'), 7.89 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 20.5-26.6 ($4CH_2$), 60.4 (C-6'), 65.7 (C-4'), 68.0 (C-2'), 69.1 (C-3'), 70.8 (C-5'), 91.2 (C-1'), 99.8 (C-3), 116.8 (CN), 122.4-159.7 (Ar-C); m/z 336 (Found: C, 57.2; H, 6.1; N, 8.5. $C_{16}H_{20}N_2O_6$ requires C, 57.1; H, 6.0; N, 8.3 %).

7j : m.p. 213 °C, yield 79 %. IR(KBr) 3680-3240 (OH), 2228 (CN), 1660 (CO pyridone) cm^{-1}; m/z 350 (Found: C, 58.5; H, 6.4; N, 8.2. $C_{17}H_{22}N_2O_6$ requires C, 58.3; H, 6.3; N, 8.0 %).

7k : m.p. 218 °C, yield 82 %. IR(KBr) 3660-3380 (OH), 2227 (CN) cm^{-1}, ^1H NMR (DMSO-d_6) δ 1.70 (m, 2H, CH_2), 2.72 (t, 2H, CH_2), 2.89 (t, 2H, CH_2),

3.30-3.74 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.48 (m, 2H, 3'-OH and 2'-OH), 4.94 (d, 1H, 4'-OH), 5.34 (d, 1H, 6'-OH), 5.51 (d, $J_{1'-2'}$ = 9.55 Hz, 1H, H-1'), 7.93 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 25.2-34.3 ($3CH_2$), 60.1 (C-6'), 68.3 (C-4'), 68.7 (C-2'), 74.9 (C-3'), 79.5 (C-5'), 84.1 (C-1'), 104.6 (C-3), 115.9 (CN), 132.7-165.2 (Ar-C); m/z 338 (Found: C, 53.5; H, 5.5; N, 8.5. $C_{15}H_{18}N_2SO_5$ requires C, 53.3; H, 5.3; N, 8.3 %).

7l : m.p. 236 °C, yield 84 %. IR(KBr) 3740-3340 (OH), 2225 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.80 (m, 4H, $2CH_2$), 2.76 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.26-3.80 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.48 (m, 2H, 3'-OH and 2'-OH), 4.88 (d, 1H, 4'-OH), 5.22 (d, 1H, 6'-OH), 5.52 (d, $J_{1'-2'}$ = 10.39 Hz, 1H, H-1'), 7.92 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 21.5-32.4 ($4CH_2$), 60.2 (C-6'), 68.2 (C-4'), 68.8 (C-2'), 74.8 (C-3'), 79.5 (C-5'), 84.0 (C-1'), 104.0 (C-3), 115.7 (CN), 122.3-161.6 (Ar-C); m/z 352 (Found: C, 54.7; H, 5.8; N, 8.1. $C_{16}H_{20}N_2SO_5$ requires C, 54.5; H, 5.7; N, 8.0 %).

7m : m.p. 205 °C, yield 83 %. IR(KBr) 3700-3290 (OH), 2228 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.58 (m, 4H, $2CH_2$), 1.83 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.00 (t, 2H, CH_2), 3.21-3.86 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.49 (m, 2H, 3'-OH and 2'-OH), 4.91 (d, 1H, 4'-OH), 5.32 (d, 1H, 6'-OH), 5.60 (d, $J_{1'-2'}$ = 10.33 Hz, 1H, H-1'), 7.98 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 25.5-32.7 ($5CH_2$), 60.2 (C-6'), 68.3 (C-4'), 68.8 (C-2'), 74.9 (C-3'), 79.5 (C-5'), 80.0 (C-1'), 103.9 (C-3), 115.8 (CN), 122.1-167.2 (Ar-C); m/z 366 (Found: C, 55.9; H, 6.1; N, 7.9. $C_{17}H_{22}N_2SO_5$ requires C, 55.7; H, 6.0; N, 7.7 %).

7n : m.p. 226 °C, yield 84 %. IR(KBr) 3720-3380 (OH), 2227 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (m, 4H, $2CH_2$), 1.78 (m, 4H, $2CH_2$), 2.82 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 3.22-3.80 (m, 6H, 2H-6', H-5', H-4', H-3' and H-2'), 4.44 (m, 2H, 3'-OH and 2'-OH), 4.88 (d, 1H, 4'-OH), 5.28 (d, 1H, 6'-OH), 5.55 (d, $J_{1'-2'}$ = 10.36 Hz, 1H, H-1'), 7.99 (s, 1H, pyridine H-4); ^{13}C NMR (DMSO-d_6) δ 25.2-34.3 ($6CH_2$), 60.1 (C-6'), 68.2 (C-4'), 68.7 (C-2'), 74.9 (C-3'), 79.5

(C-5'), 84.1 (C-1'), 104.6 (C-3), 115.8 (CN), 122.3- 165.2 (Ar-C); m/z 380 (Found: C, 56.9; H, 6.4; N, 7.6. $C_{18}H_{24}N_2SO_5$ requires C, 56.8; H, 6.3; N, 7.4 %).

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