Pergamon

Tetrahedron 58 (2002) 1399–1405

TETRAHEDRON

Synthesis of thiopyridines and their hydrogenated thioglycosides via piperidinium salts

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Received 21 March 2001; revised 20 November 2001; accepted 13 December 2001

Abstract—The synthesis of several new thiopyridines and their hydrogenated thioglycosides via the reaction of piperidinium salts of dihydropyridinethiones with α-halogeno sugars is described. © 2002 Published by Elsevier Science Ltd.

As part of our search for the synthesis of some antimetabolites,[1,2] we have recently reported different novel functionalised pyridine and pyrimidine nucleosides with HIV and some oncogenic virus antagonistic activity.[3–6] In conjunction with this, we report here a convenient method for the synthesis of thiopyridines and their dihydropyridine thioglycosides through reaction of piperidinium salts of dihydropyridinethiolates with α-bromo sugars. As far as we know this is the first coupling reaction of this type to be reported for glycoside formation. Thus it has been found that arylmethylidene-cyanothioacetamides **1** reacted with both benzoyl acetone and ethyl benzoylacetate **2** in ethanol containing equivalent amounts of piperidine at 0°C to give the corresponding piperidinium salts of 1,4-dihydropyridinethiones **3** (Scheme 1). Compounds **3** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or its α-D-galactopyranosyl isomer in acetone at 0°C to give the corresponding thioglycosides **6** in high yields. The structures of the reaction products **6** were established by elemental analyses and spectral data. In the ^{1}H NMR spectrum of **6a** the anomeric proton H-1′ of the glucopyranosyl moiety gives a doublet at δ 6.04 ppm with a coupling constant J(H1′–H2′) of 10.3 Hz for the diaxial interaction. This large coupling constant is characteristic for a β-glucopyranosyl anomer.[7] The ^{13}C NMR spectrum of **6a** contained a signal at δ 81.8 ppm for the C-1′ of β-D-glucopyranose. Ammonolysis of protected nucleosides **6** with methanolic ammonia at 0°C furnished the corresponding 2-(β-D-glycopyranosylthio)-1,4-dihydro-3-cyanopyridines **7** in yields of 84–86%. TLC of the free thioglycosides **7** showed that a single compound was produced. The ^{1}H NMR spectrum of **7a** showed the anomeric proton as a doublet at δ 5.90 ppm (J=9.0 Hz) indicating the presence of only the β-D-glucopyranose moiety. ^{13}C NMR spectra were characterized by a signal at δ 83.2 ppm corresponding to C-1′ atom of β-D-glucopyranose. In another experiment, the piperidinium salts **3** were reacted with **5** in dry acetone at 30°C to afford the corresponding aromatised pyridine thioglycosides **8** in good yields via a Walden inversion. The structures of **8** were established on the basis of elemental analyses and spectral data. Although the coupling of **3** with **5** could also give the corresponding *N*-glycosides, the formation of *S*-glycosides **8** were proven using ^{13}C NMR spectroscopy which revealed the absence of C=S at δ 179 ppm and appearance of C–S-sugar at 160 ppm, the same value of the corresponding *S*-methyl derivatives[8] **10**. Deprotection of the hydroxy groups in the *S*-glycosides **8** with ammonia in methanol afforded the corresponding 2-(β-D-glycopyranosylthio)-3-cyanopyridines **9** in 85–88% yields after chromatographic purification. With these two dihydropyridine and pyridine thioglycosides as models, it was decided to synthesize these compounds using the potassium salt method and comparing the products for stereochemical considerations. Thus, by a simple experimental procedure, treatment of piperidinium salts **3** with dilute HCl at 30°C converted them to the corresponding 3-cyanopyridine-2(1*H*)-thiones **4** (Scheme 2). The formation of **4** has been proven chemically by the treatment of **1** and **2** in boiling ethanol containing catalytic amounts of piperidine, and the mechanism of this reaction has been previously reported by us.[9] When compounds **4** were subjected to the reaction with bromides **5** in the presence of aqueous potassium hydroxide, the corresponding pyridine thioglycosides **8** were obtained. In summary, the results show that the reaction of **3** with **5** can lead either to pyridine thioglycosides or to the dihydropyridine thioglycosides, the nature of the products depends on thermodynamic factors. The nucleosides **7** and **9** can be utilised as starting materials for the synthesis of other carbohydrate derivatives as deoxy, amino and azido nucleosides.

The compounds **8**, **9** were tested for their antiviral activity against human immunodeficiency virus (HIV-1) in MT-4 cells and against different types of tumour virus; however, no activity was observed.

Keywords: 6-phenyl-3-cyano-2-thiopyridines; 2-(β-D-glycopyranosylthio)-pyridines.

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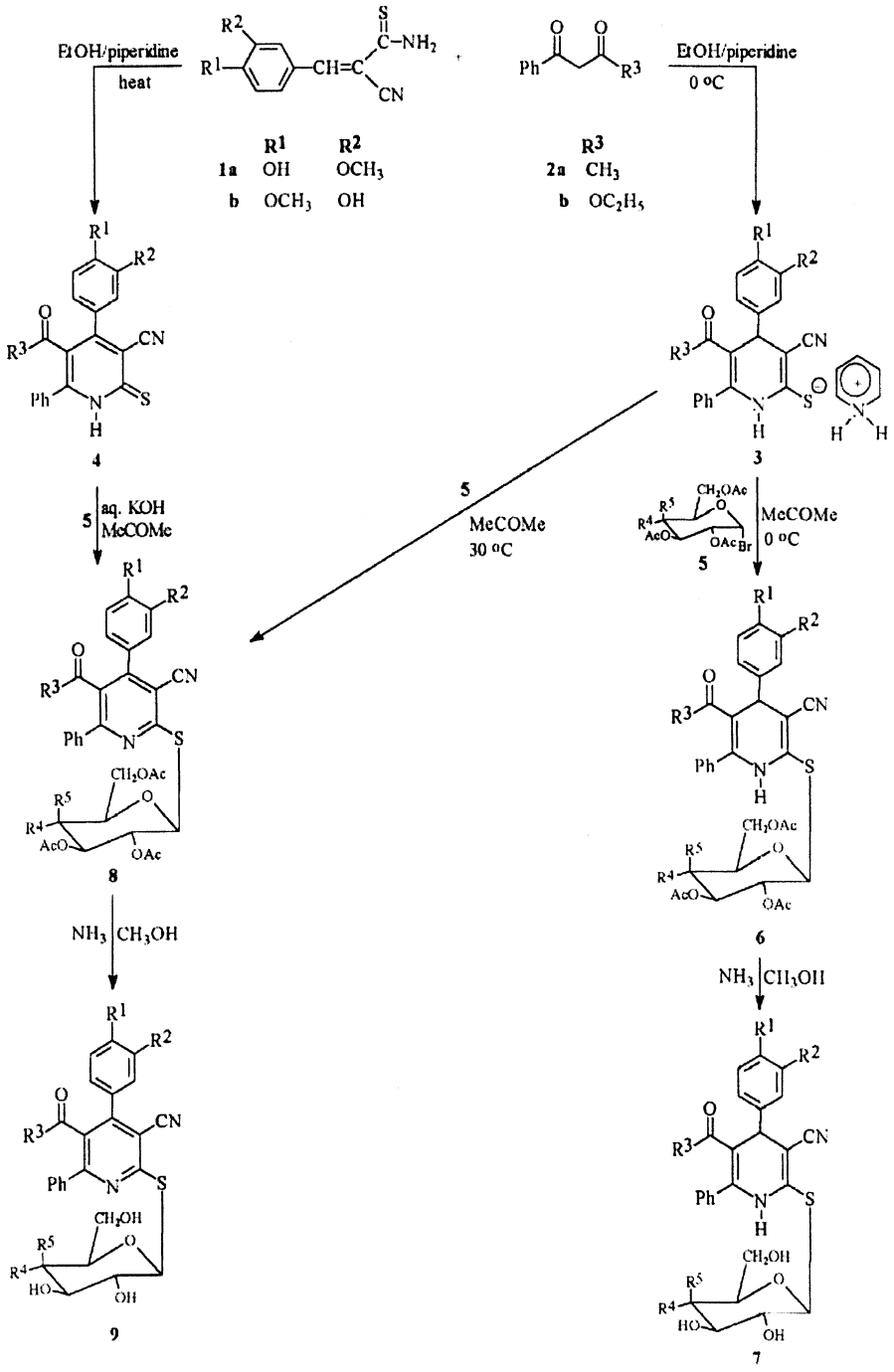
0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(01)01242-X



Scheme 1.

1. Experimental

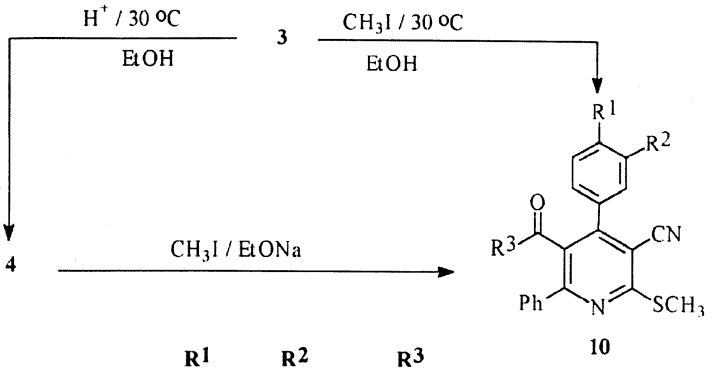
Melting points are uncorrected. TLC was carried out on aluminium sheet silica gel 60 F_{254} (Merck) detected by short UV light. IR spectra were obtained (KBr) using a Pye Unicam spectra 1000. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian 400 MHz spectrometer in DMSO-d_6 using $SiMe_4$ as internal standard. Mass spectra were recorded by EI on a Varian Mat 311 A spectrometer and FAB on a Kratos MS spectrometer.

Compounds **1a**, **1b** were prepared from vanillin and isovanillin following literature procedures.[10]

1.1. 3-Cyano-4,5-disubstituted-6-phenyl-pyridin-2(1*H*)-thiones (4a–d): general procedure

To a mixture of arylmethylenecyanothioacetamides **1** (0.01 mol) and benzoyl acetone **2a** or ethyl benzoylacetate **2b** (0.01 mol) in ethanol (50 mL) a few drops of piperidine were then added. The mixture was heated under reflux for 6 h, and then allowed to stand overnight. The resulting solid product was collected by filtration and crystallised from EtOH–DMF to afford the title compounds **4a–d**.

1.1.1. Compound 4a. Yield 63% as a yellow solid, mp 306°C; IR 3454 (OH and NH), 2210 (CN), 1670



	R1	R2	R3
3,4a	OH	OCH_3	CH_3
b	OH	OCH_3	OC_2H_5
c	OCH_3	OH	CH_3
d	OCH_3	OH	OC_2H_5

	R1	R2	R3	R4	R5
6,8a	OH	OCH_3	CH_3	OAc	H
b	OH	OCH_3	OC_2H_5	OAc	H
c	OCH_3	OH	CH_3	OAc	H
d	OCH_3	OH	OC_2H_5	OAc	H
e	OH	OCH_3	CH_3	H	OAc
f	OH	OCH_3	OC_2H_5	H	OAc
g	OCH_3	OH	CH_3	H	OAc
h	OCH_3	OH	OC_2H_5	H	OAc
7,9a	OH	OCH_3	CH_3	OH	H
b	OH	OCH_3	OC_2H_5	OH	H
c	OCH_3	OH	CH_3	OH	H
d	OCH_3	OH	OC_2H_5	OH	H
e	OH	OCH_3	CH_3	H	OH
f	OH	OCH_3	OC_2H_5	H	OH
g	OCH_3	OH	CH_3	H	OH
h	OCH_3	OH	OC_2H_5	H	OH

Scheme 2.

(CO) cm^{-1}; ^1H NMR 2.28 (s, 3H, CH_3CO), 3.82 (s, 3H, OCH_3), 6.90 (m, 3H, Ar-H), 7.65 (m, 5H, Ar-H), 9.48 (s, 1H, OH), 14.15 (s, br, 1H, NH) ppm; ^{13}C NMR 18.3 (CH_3), 55.9 (OCH_3), 113.4 (C3), 116.9 (CN), 122.5–155.2 (Ar-C), 178.9 (CS), 194.2 (CO) ppm; *m/z* 376 (Found: C, 67.31; H, 4.44; N, 7.69 $C_{21}H_{16}N_2SO_3$ requires C, 67.02; H, 4.25; N, 7.44%).

1.1.2. Compound 4b. Yield 59% as a yellow solid, mp 226°C; IR 3478 (OH and NH), 2222 (CN), 1720 (CO) cm^{-1}; ^1H NMR 1.02 (t, J=6.0 Hz, 3H, CH_3), 3.82 (m, 3H, OCH_3 and 2H, CH_2), 6.88 (m, 3H, Ar-H), 7.50 (m, 5H, Ar-H), 9.64 (s, 1H, OH), 14.22 (s, br, 1H, NH) ppm; ^{13}C NMR 13.7 (CH_3), 56.3 (OCH_3), 62.1 (CH_2), 112.8 (C3), 116.4 (CN), 121.9–154.6 (Ar-C), 166.6 (CO), 179.8 (CS) ppm; *m/z* 406 (Found: C, 65.33; H, 4.60; N, 7.08 $C_{22}H_{18}N_2SO_4$ requires C, 65.02; H, 4.43; N, 6.89%).

1.1.3. Compound 4c. Yield 61% as a yellow solid, mp 230°C; IR 3442 (OH and NH), 2222 (CN), 1670 (CO) cm^{-1}; ^1H NMR 2.24 (s, 3H, CH_3CO), 3.80 (s, 3H, OCH_3), 6.74 (m, 3H, Ar-H), 7.64 (m, 5H, Ar-H), 9.12 (s, 1H, OH), 14.30 (s, br, 1H, NH) ppm; ^{13}C NMR 18.4 (CH_3), 56.0 (OCH_3), 112.2 (C3), 116.9 (CN), 124.8–155.1 (Ar-C), 179.0 (CS), 194.1 (CO) ppm; *m/z* 376 (Found: C, 67.41; H, 4.38; N, 7.70 $C_{21}H_{16}N_2SO_3$ requires C, 67.02; H, 4.25; N, 7.44%).

1.1.4. Compound 4d. Yield 58% as a yellow solid, mp 266°C; IR 3490 (OH and NH), 2218 (CN), 1726 (CO) cm^{-1}; ^1H NMR 1.08 (t, J=7.2 Hz, 3H, CH_3CO), 3.88 (m, 3H, OCH_3 and 2H, CH_2), 6.86 (m, 3H, Ar-H), 7.51 (m, 5H, Ar-H), 9.46 (s, 1H, OH), 14.40 (s, br,1H, NH); ^{13}C NMR 13.6 (CH_3), 56.2 (OCH_3), 61.8 (CH_2), 112.4–154.8 (Ar-C), 164.9 (CO), 179.5 (CS) ppm; *m/z* 406 (Found: C, 65.28; H, 4.56; N, 6.98 $C_{22}H_{18}N_2SO_4$ requires C, 65.02; H, 4.43; N, 6.89%).

1.2. 3-Cyano-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosylthio)-1,4-dihydropyridines (6): general coupling procedures

To a mixture of arylmethylidenecyanothioacetamides **1** (0.01 mol) and **2** (0.01 mol) in dry ethanol (5 mL) a (0.01 mol) of piperidine were then added. The reaction mixture was stirred at 0°C for 1 h, then evaporated under reduced pressure and the resulting piperidinium salt **3** was

dissolved in dry acetone (5 mL) and a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl bromide (0.011 mol) in dry acetone (20 mL) was then added at 0°C. The mixture was stirred until the reaction was judged complete by TLC (6–8 h), using chloroform–ether 4:1, v/v (R_f 0.74–0.76 region), then evaporated under reduced pressure and the residue was crystallized from chloroform–petroleum ether 40–60 at 0°C to give the title compounds **6a**–**h**.

1.2.1. Compound 6a. Yield 71% as a white solid, mp 128°C; $[\alpha]_D$=30.2 (*c* 2, $CHCl_3$); IR 3394 (OH and NH), 2210 (CN), 1752 (CO ester) cm^{-1}; ^1H NMR 1.88–2.08 (4s, 12H, $4CH_3CO$), 2.22 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.08 (m, 2H, 2H-6′), 4.18 (m, 2H, H-5′ and pyridine H-4), 4.82 (t, *J*=7.2 Hz, 1H, H-4′), 5.08 (m, 1H, H-3′), 5.26 (t, *J*=8.7 Hz, 1H, H-2′), 6.04 (d, $J_{1'-2'}$=10.2 Hz, 1H, H-1′), 6.98 (m, 3H, Ar-H), 7.64 (m, 5H, Ar-H), 7.88 (s, 1H, NH), 8.92 (s, 1H, OH) ppm; ^{13}C NMR 18.6 (CH_3 of pyridine), 20.4–22.5 ($4CH_3$), 55.2 (OCH_3), 62.0 (C6′), 68.4 (C4′), 70.6 (C2′), 72.8 (C3′), 75.1 (C5′), 81.8 (C1′), 96.2 (C4), 105.6 (C3), 115.0 (CN), 122.7–157.2 (Ar-C), 159.6 (C2), 169.2–169.8 (4CO), 194.0 (CO of pyridine) ppm; *m/z* 708 (Found: C, 59.66; H, 5.30; N, 4.28 $C_{35}H_{36}N_2SO_{12}$ requires C, 59.32; H, 5.08; N, 3.95%).

1.2.2. Compound 6c. Yield 74% as a white solid, mp 180°C; $[\alpha]_D$=23.0 (*c* 2, $CHCl_3$); IR 3365 (OH and NH), 2206 (CN), 1752 (CO) cm^{-1}; ^1H NMR 1.90–2.12 (4s, 12H, $4CH_3CO$), 2.18 (s, 3H, CH_3CO), 3.90 (s, 3H, OCH_3), 4.22 (m, 4H, 2H-6′, H-5′ and pyridine H-4), 4.64 (m, 1H, H-4′), 5.06 (t, *J*=5.8 Hz, 1H, H-3′), 5.22 (t, *J*=7.4 Hz, 1H, H-2′), 5.98 (d, $J_{1'-2'}$=10.1 Hz, 1H, H-1′), 6.88 (m, 3H, Ar-H), 7.62 (m, 5H, Ar-H), 7.90 (s, 1H, NH), 8.96 (s, 1H, OH) ppm; *m/z* 708 (Found: C, 59.58; H, 5.22; N, 4.25 $C_{35}H_{36}N_2SO_{12}$ requires C, 59.32; H, 5.08; N, 3.95%).

1.2.3. Compound 6e. Yield 73% as a white solid, mp 162°C; $[\alpha]_D$=38.3 (*c* 2, $CHCl_3$); IR 3394 (OH and NH), 2210 (CN), 1752 (CO) cm^{-1}; ^1H NMR 1.80–2.12 (4s, 12H, $4CH_3CO$), 2.21 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.08 (m, 2H, 2H-6′), 4.22 (m, 2H, H-5′ and pyridine H-4), 4.68 (m, 1H, H-4′), 4.95 (m, 1H, H-3′), 5.18 (t, *J*=8.2 Hz, 1H, H-2′), 6.06 (d, $J_{1'-2'}$=10.1 Hz, 1H, H-1′), 6.98 (m, 3H, Ar-H), 7.63 (m, 5H, Ar-H), 7.95 (s, 1H, NH), 8.99 (s, 1H, OH) ppm; ^{13}C NMR 18.8 (CH_3 of pyridine), 21.2–22.5 ($4CH_3$), 55.6 (OCH_3), 61.8 (C6′), 68.7 (C4′), 71.2 (C2′), 72.0 (C3′), 75.3 (C5′), 83.2 (C1′), 98.8 (C4), 104.9 (C3), 115.6 (CN), 122.0–156.7 (Ar-C), 160.9 (C2), 169.4–169.9 (4CO), 192.3 (CO of pyridine) ppm; *m/z* 708 (Found: C, 59.60; H, 5.14; N, 4.28 $C_{35}H_{36}N_2SO_{12}$ requires C, 59.32; H, 5.08; N, 3.95%).

1.2.4. Compound 6g. Yield 72% as a white solid, mp 148°C; $[\alpha]_D$=42.8 (*c* 2, $CHCl_3$); IR 3380 (OH and NH), 2214 (CN), 1750 (CO) cm^{-1}; ^1H NMR 1.86–2.08 (4s, 12H, $4CH_3CO$), 2.26 (s, 3H, CH_3CO); 3.88 (s, 3H, OCH_3), 4.18 (m, 4H, 2H-6′, H-5′ and pyridine H-4), 4.48 (d, *J*=4.8 Hz, 1H, H-4′), 5.02 (m, 1H, H-3′), 5.50 (m, 1H, H-2′), 6.08 (d, $J_{1'-2'}$=10.0 Hz, 1H, H-1′), 6.88 (m, 3H, Ar-H), 7.52 (m, 5H, Ar-H), 8.90 (s, 1H, NH), 9.46 (s, 1H, OH) ppm; *m/z* 708 (Found: C, 59.70; H, 5.15; N, 4.33 $C_{35}H_{36}N_2SO_{12}$ requires C, 59.32; H, 5.08; N, 3.95%).

1.3. 3-Cyano-2-(β-D-glycopyranosylthio)-1,4-dihydropyridines (7): general procedure for nucleoside deacylation

Dry ammonia gas was passed into a solution of acetylated glycosides **6** (0.5 g) in 10 mL of dry methanol at 0°C for 0.5 h. The reaction mixture was stirred until completion as shown by TLC (10–12 h), using $CHCl_3$–MeOH 9:1, v:v (R_f 0.64–0.68 region). The resulting mixture was then concentrated under reduced pressure at room temperature to afford a solid residue that was crystallized from methanol–ether at 0°C to furnish the title compounds **7**.

1.3.1. Compound 7a. Yield 86% as a colourless crystals, mp 214°C; $[\alpha]_D$=50.2 (*c* 1.5, MeOH); IR 3320 (OH and NH), 2202 (CN) cm^{-1}; ^1H NMR 2.22 (s, 3H, CH_3), 3.28–3.98 (m, 6H, 2H-6′, H-5′, H-4′, H-3′,H-2′ and 3H, OCH_3 and 1H, pyridine H-4), 4.46 (s, 1H, 2′-OH), 4.78 (s, 1H, 3′-OH), 5.12 (s, 1H, 4′-OH), 5.34 (s, 1H, 6′-OH), 5.90 (d, $J_{1'-2'}$=9.0 Hz, 1H, H-1′), 7.38 (m, 3H, Ar-H), 7.69 (m, 5H, Ar-H), 7.98 (s, 1H, NH), 9.42 (s, 1H, OH) ppm; ^{13}C NMR 18.4 (CH_3), 55.2 (OCH_3), 61.8 (C6′), 68.2 (C4′), 70.0 (C2′), 74.9 (C3′), 79.3 (C5′), 83.2 (C1′), 94.8 (C4), 106.2 (C3), 115.4 (CN), 122.8–156.6 (Ar-C), 160.2 (C2), 192.8 (CO) ppm; *m/z* 540 (Found: C, 60.18; H, 5.40; N, 5.48 $C_{27}H_{28}N_2SO_8$ requires C, 60.00; H, 5.18; N, 5.18%).

1.3.2. Compound 7c. Yield 85% as a colourless crystals, mp 218°C; $[\alpha]_D$=22.6 (*c* 1.5, MeOH); IR 3390 (OH and NH), 2205 (CN) cm^{-1}; ^1H NMR 2.24 (s, 3H, CH_3), 3.28–4.09 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, H-2′ and 3H, OCH_3 and 1H, pyridine H-4), 4.58 (s, 1H, 2′-OH), 4.80 (t, *J*=7.2 Hz, 1H, 3′-OH), 5.05 (m, 2H, 4′-OH and 6′-OH), 5.92 (d, *J*=9.7 Hz, 1H, H-1′), 7.31 (m, 3H, Ar-H), 7.82 (m, 5H, Ar-H), 8.03 (s, 1H, NH), 9.12 (s, 1H, OH) ppm; *m/z* 540 (Found: C, 60.38; H, 5.40; N, 5.54 $C_{27}H_{28}N_2SO_8$ requires C, 60.00; H, 5.18; N, 5.18%).

1.3.3. Compound 7e. Yield 84% as a colourless crystals, mp 206°C; $[\alpha]_D$=29.1 (*c* 1.5, MeOH); IR 3406 (OH and NH), 2202 (CN) cm^{-1}; ^1H NMR 2.20 (s, 3H, CH_3), 3.26–4.02 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, H-2′ and 3H, OCH_3 and 1H, pyridine H-4), 4.42 (s, 1H, 2′-OH), 4.66 (m, 2H, 3′-OH and 4′-OH), 5.11 (m, 1H, 6′-OH), 5.88 (d, *J*=8.8 Hz, 1H, H-1′), 7.18 (m, 3H, Ar-H), 7.60 (m, 5H, Ar-H), 7.86 (s, 1H, NH), 9.23 (s, 1H, OH) ppm; ^{13}C NMR 18.0 (CH_3), 55.6 (OCH_3), 62.2 (C6′), 67.8 (C4′), 71.9 (C2′), 74.2 (C3′), 79.0 (C5′), 83.9 (C1′), 96.8 (C4), 105.9 (C3), 114.7 (CN), 122.5–157.4 (Ar-C), 162.1 (C2), 194.0 (CO) ppm; *m/z* 540 (Found C, 60.35; H, 5.26; N, 5.41 $C_{27}H_{28}N_2SO_8$ requires C, 60.00; H, 5.18; N, 5.18%).

1.3.4. Compound 7g. Yield 85% as a colourless crystals, mp 213°C; $[\alpha]_D$=25.5 (*c* 1.5, MeOH); IR 3400 (OH and NH), 2215 (CN) cm^{-1}; ^1H NMR 2.28 (s, 3H, CH_3), 3.30–4.04 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, H-2′ and 3H, OCH_3 and 1H, pyridine H-4), 4.48 (d, *J*=8.4 Hz, 1H, 2′-OH), 4.76 (m, 2H, 3′-OH and 4′-OH), 5.02 (d, *J*=6.8 Hz, 1H, 6′-OH), 5.86 (d, $J_{1'-2'}$=9.6 Hz, 1H, H-1′), 7.08 (m, 3H, Ar-H), 7.70 (m, 5H, Ar-H), 8.12 (s, 1H, NH), 9.45 (s, 1H, OH) ppm; *m/z* 540 (Found: C, 60.28; H, 5.30; N, 5.34 $C_{27}H_{28}N_2SO_8$ requires C, 60.00; H, 5.18; N, 5.18%).

1.4. 3-Cyano-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glyco-pyranosylthio) pyridines (8): general coupling procedures

Method A. To a mixture of arylmethylidenecyanothioacetamides **1** (0.01 mol) and **2** (0.01 mol) in dry ethanol (5 mL), a 0.01 mol of piperidine was added. The reaction mixture was stirred at 0°C for 1 h, then evaporated under reduced pressure at room temperature and the resulting piperidinium salt **3** was dissolved in dry acetone (5 mL) and a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl bromide (0.011 mol) in dry acetone (20 mL) was then added at 30°C. The mixture was stirred until the reaction was judged complete by TLC, using chloroform–ether 4:1, v/v (R_f 0.70–0.74 region), then evaporated under reduced pressure and the residue was crystallized from ethanol to give the title compounds **8a**–**h**.

Method B. To a solution of 3-cyano-4,5-disubstituted-6-phenyl-pyridin-2(1*H*)thiones **4** (0.01 mol) in aqueous potassium hydroxide [0.56 g (0.01 mol) in 6 mL of distilled water], a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galacto-pyranosyl bromide **5** (0.011 mol) in acetone (30 mL) was added. The reaction mixture was stirred at room temperature until completion (TLC, 1–2 h), then evaporated under reduced pressure and the residue was washed with distilled water to remove the formed potassium bromide. The resulting product was dried and crystallized from ethanol to afford the title compounds **8a**–**h**.

1.4.1. Compound 8a. Yield 72% as a white solid, mp 113°C; $[\alpha]_D$=21.9 (*c* 2, $CHCl_3$); IR 3418 (OH), 2222 (CN), 1752 (CO ester) cm^{-1}; ^1H NMR 1.89–2.08 (4s, 12H, $4CH_3CO$), 2.26 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.03 (m, 2H, 2H-6′ and 1H, H-5′), 5.01 (t, *J*=9.1 Hz, 1H, H-4′), 5.19 (t, *J*=5.6 Hz, 1H, H-3′), 5.56 (t, *J*=6.7 Hz, 1H, H-2′), 6.20 (d, $J_{1'-2'}$=10.4 Hz, 1H, H-1′), 6.66 (m, 3H, Ar-H), 7.44 (m, 5H, Ar-H), 9.44 (s, br, 1H, OH) ppm; ^{13}C NMR 17.8 (CH_3), 20.5–23.2 ($4CH_3$), 55.5 (OCH_3), 61.3 (C6′), 68.3 (C4′), 70.4 (C2′), 73.3 (C3′), 75.2 (C5′), 80.3 (C1′), 105.5 (C3), 115.5 (CN), 122.3–154.9 (Ar-C), 158.6 (C2), 169.4–169.9 ($4COCH_3$), 195.3 (CO) ppm; *m/z* 706 (Found: C, 59.70; H, 4.84; N, 4.22 $C_{35}H_{34}N_2SO_{12}$ requires C, 59.49; H, 4.81; N, 3.96%).

1.4.2. Compound 8b. Yield 70% as a white solid, mp 118°C; $[\alpha]_D$=36.4 (*c* 2, $CHCl_3$); IR 3382 (OH), 2222 (CN), 1748 (CO ester) cm^{-1}; ^1H NMR 0.82 (t, *J*=7.9 Hz, 3H, CH_3), 1.75–2.05 (4s, 12H, $4CH_3CO$), 3.78 (s, 3H, OCH_3), 3.94 (m, 2H, CH_2), 4.15 (m, 2H, 2H-6′ and 1H, H-5′), 4.99 (t, *J*=3.8 Hz, 1H, H-4′), 5.23 (t, *J*=5.6 Hz, 1H, H-3′), 5.60 (t, *J*=8.0 Hz, 1H, H-2′), 6.15 (d, $J_{1'-2'}$= 10.4 Hz, 1H, H-1′), 7.48 (m, 3H, Ar-H), 7.76 (m, 5H, Ar-H), 9.32 (s, br, 1H, OH) ppm; *m/z* 736 (Found: C, 58.98; H, 4.94; N, 4.06 $C_{36}H_{36}N_2SO_{13}$ requires C, 58.69; H, 4.89; N, 3.80%).

1.4.3. Compound 8c. Yield 71% as a white solid, mp 127°C; $[\alpha]_D$=38.0 (*c* 2, $CHCl_3$); IR 3430 (OH), 2226 (CN), 1750 (CO ester) cm^{-1}; ^1H NMR 1.85–2.02 (4s, 12H, $4CH_3CO$), 2.26 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.28 (m, 2H, 2H-6′ and 1H, H-5′), 4.93 (m, 2H, H-4′ and H-3′), 5.11 (t, *J*=6.2 Hz, 1H, H-2′), 6.26 (d, $J_{1'-2'}$=8.4 Hz, 1H, H-1′), 6.80 (m, 3H, Ar-H), 7.48 (m, 5H, Ar-H), 9.32 (s, br, 1H, OH) ppm; *m/z* 706 (Found: C, 59.81; H, 4.86; N, 4.08 $C_{35}H_{34}N_2SO_{12}$ requires C, 59.49; H, 4.81; N, 3.96%).

1.4.4. Compound 8d. Yield 70% as a white solid, mp 148°C; $[\alpha]_D$=30.8 (*c* 2, $CHCl_3$); IR 3442 (OH), 2222 (CN), 1752 (CO ester) cm^{-1}; ^1H NMR 0.84 (t, *J*=7.0 Hz, 3H, CH_3), 1.76–2.03 (4s, 12H, $4CH_3CO$), 3.84 (s, 3H, OCH_3), 3.96 (m, 2H, CH_2), 4.11 (m, 2H, 2H-6′ and 1H, H-5′), 5.02 (t, *J*=4.6 Hz, 1H, H-4′), 5.25 (t, *J*=5.5 Hz, 1H, H-3′), 5.66 (t, *J*=5.2 Hz, 1H, H-2′), 6.16 (d, $J_{1'-2'}$= 10.5 Hz, 1H, H-1′), 7.08 (m, 3H, Ar-H), 7.78 (m, 5H, Ar-H), 9.20 (s, br, 1H, OH) ppm; ^{13}C NMR 13.2 (CH_3), 20.2–20.4 ($4CH_3CO$), 55.6 (OCH_3), 61.6 (CH_2), 61.9 (C6′), 68.2 (C4′), 68.8 (C2′), 72.9 (C3′), 75.0 (C5′), 80.2 (C1′), 106.3 (C3), 115.2 (CN), 125.9–157.0 (Ar-C), 159.3 (C2), 166.1 (CO), 169.4–169.8 ($4COCH_3$) ppm; *m/z* 736 (Found: C, 58.90; H, 4.95; N, 4.07 $C_{36}H_{36}N_2SO_{13}$ requires C, 58.69; H, 4.89; N, 3.80%).

1.4.5. Compound 8e. Yield 72% as a white solid, mp 147°C; $[\alpha]_D$=12.9 (*c* 2, $CHCl_3$); IR 3454 (OH), 2222 (CN), 1752 (CO ester) cm^{-1}; ^1H NMR 1.90–2.14 (4s, 12H, $4CH_3CO$), 2.32 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.15 (m, 2H, 2H-6′ and 1H, H-5′), 5.28 (t, *J*=3.8 Hz, 1H, H-4′), 5.39 (t, *J*=6.6 Hz, 1H, H-3′), 5.51 (t, *J*=6.8 Hz, 1H, H-2′), 6.18 (d, $J_{1'-2'}$=10.4 Hz, 1H, H-1′), 6.84 (m, 3H, Ar-H), 7.59 (m, 5H, Ar-H), 9.41 (s, 1H, OH) ppm; *m/z* 706 (Found: C, 59.68; H, 5.02; N, 4.20 $C_{35}H_{34}N_2SO_{12}$ requires C, 59.49; H, 4.81; N, 3.96%).

1.4.6. Compound 8f. Yield 71% as a white solid, mp 120°C; $[\alpha]_D$=26.7 (*c* 2, $CHCl_3$); IR 3494 (OH), 2222 (CN), 1748 (CO ester) cm^{-1}; ^1H NMR 0.82 (t, *J*=7.3 Hz, 3H, CH_3), 1.75–2.14 (4s, 12H, $4CH_3CO$), 3.78 (s, 3H, OCH_3), 3.96 (m, 2H, CH_2), 4.12 (m, 2H, 2H-6′ and 1H, H-5′), 4.45 (t, *J*=9.2 Hz, 1H, H-4′), 5.24 (t, *J*=5.7 Hz, 1H, H-3′), 5.38 (t, *J*=7.2 Hz, 1H, H-2′), 6.14 (d, $J_{1'-2'}$=10.8 Hz, 1H, H-1′), 6.86 (m, 3H, Ar-H), 7.55 (m, 5H, Ar-H), 9.40 (s, br, 1H, OH) ppm; ^{13}C NMR 13.3 (CH_3), 20.3–21.1 ($4CH_3CO$), 55.9 (OCH_3), 61.8 (CH_2), 61.9 (C6′), 66.2 (C4′), 68.5 (C2′), 71.8 (C3′), 74.2 (C5′), 80.4 (C1′), 106.3 (C3), 115.8 (CN), 121.6–157.2 (Ar-C), 158.8 (C2), 166.3 (CO), 169.5–170.1 ($4COCH_3$) ppm; *m/z* 736 (Found: C, 58.98; H, 5.13; N, 3.98 $C_{36}H_{36}N_2SO_{13}$ requires C, 58.69; H, 4.89; N, 3.80%).

1.4.7. Compound 8g. Yield 70% as a white solid, mp 140°C; $[\alpha]_D$=21.9 (*c* 2, $CHCl_3$); IR 3440 (OH), 2225 (CN), 1748 (CO ester) cm^{-1}; ^1H NMR 1.80–2.12 (4s, 12H, $4CH_3CO$), 2.30 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.16 (m, 2H, 2H-6′ and 1H, H-5′), 4.86 (d, *J*=5.8 Hz, 1H, H-4′), 5.29 (m, 2H, H-3′ and H-2′), 6.12 (d, $J_{1'-2'}$=9.6 Hz, 1H, H-1′), 6.88 (m, 3H, Ar-H), 7.40 (m, 5H, Ar-H), 9.24 (s, 1H, OH) ppm; *m/z* 706 (Found: C, 59.80; H, 4.96; N, 4.24 $C_{35}H_{34}N_2SO_{12}$ requires C, 59.49; H, 4.81; N, 3.96%).

1.4.8. Compound 8h. Yield 72% as a white solid, mp 136°C; $[\alpha]_D$=35.1 (*c* 2, $CHCl_3$); IR 3406 (OH), 2222 (CN), 1746 (CO ester) cm^{-1}; ^1H NMR 0.88 (t, *J*=7.7 Hz, 3H, CH_3), 1.76–2.02 (4s, 12H, $4CH_3CO$), 3.90 (s, 3H, OCH_3), 4.04 (m, 2H, CH_2), 4.18 (m, 2H, 2H-6′ and 1H, H-5′), 4.70 (t, *J*=6.3 Hz, 1H, H-4′), 5.12 (m, 1H, H-3′), 5.39 (m, 1H, H-2′), 6.20 (d, $J_{1'-2'}$=9.8 Hz, 1H, H-1′), 6.95

(m, 3H, Ar-H), 7.66 (m, 5H, Ar-H), 9.22 (s, 1H, OH) ppm; *m/z* 736 (Found: C, 58.88; H, 5.13; N, 4.12 $C_{36}H_{36}N_2SO_{13}$ requires C, 58.69; H, 4.89; N, 3.80%).

1.5. 3-Cyano-2-(β-D-glycopyranosylthio)-pyridines (9): general procedure

Dry gaseous ammonia was passed through a solution of protected nucleoside **8** (0.5 g) in dry methanol (20 mL) at 0°C for 0.5 h. The reaction mixture was stirred till complete as shown by TLC (10–12 h) using $CHCl_3$–MeOH 9:1, v:v (R_f 0.66–0.68). The resulting mixture was then concentrated under reduced pressure to afford a solid residue that was crystallised from methanol to furnish the title compounds **9**.

1.5.1. Compound 9a. Yield 83% as a colourless crystal, mp 198°C; $[\alpha]_D$=45.4 (*c* 1.5, MeOH); IR 3394 (OH), 2210 (CN) cm^{-1}; ^1H NMR 2.20 (s, 3H, CH_3), 3.32–3.93 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′ and 3H, OCH_3), 4.65 (s, 1H, 2′-OH), 4.82 (s, 1H, 3′-OH), 5.06 (s, 1H, 4′-OH), 5.46 (s, 1H, 6′-OH), 5.61 (d, $J_{1'-2'}$=8.1 Hz, 1H, H-1′), 7.07 (m, 3H, Ar-H), 7.76 (m, 5H, Ar-H), 9.49 (s, 1H, OH) ppm; ^{13}C NMR 17.8 (CH_3), 55.7 (s, 3H, OCH_3), 61.6 (C6′), 68.5 (C4′), 68.8 (C2′), 74.9 (C3′), 80.3 (C5′), 84.1 (C1′), 105.6 (C3), 115.3 (CN), 124.8–157.0 (Ar-C), 161.8 (C2), 194.0 (CO) ppm; *m/z* 538 (Found: C, 60.50; H, 4.97; N, 5.38 $C_{27}H_{26}N_2SO_8$ requires C, 60.22; H, 4.83; N, 5.20%).

1.5.2. Compound 9b. Yield 84% as a colourless crystal, mp 216°C; $[\alpha]_D$=22.8 (*c* 1.5, MeOH); IR 3360 (OH), 2210 (CN) cm^{-1}; ^1H NMR 0.82 (t, *J*=7.0 Hz, 3H, CH_3), 3.26–3.68 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 3.80 (s, 3H, OCH_3), 3.94 (m, 2H, CH_2), 4.72 (s, 1H, 2′-OH), 5.09 (s, 1H, 3′-OH), 5.24 (s, 1H, 4′-OH), 5.50 (s, 1H, 6′-OH), 5.58 (d, $J_{1'-2'}$=9.9 Hz, 1H, H-1′), 6.92 (m, 3H, Ar-H), 7.34 (m, 5H, Ar-H), 9.51 (s, 1H, OH) ppm; *m/z* 568 (Found: C, 59.44; H, 5.04; N, 4.98 $C_{28}H_{28}N_2SO_9$ requires C, 59.15; H, 4.92; N, 4.92%).

1.5.3. Compound 9c. Yield 83% as a colourless crystal, mp 211°C; $[\alpha]_D$=18.2 (*c* 1.5, MeOH); IR 3394 (OH), 2210 (CN) cm^{-1}; ^1H NMR 2.28 (s, 3H, CH_3), 3.36–3.93 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′ and 3H, OCH_3), 4.58 (t, *J*=6.6 Hz, 2H, 2′-OH and 3′-OH), 4.82 (s, 1H, 4′-OH), 5.32 (s, 1H, 6′-OH), 5.78 (d, $J_{1'-2'}$=8.8 Hz, 1H, H-1′), 7.13 (m, 3H, Ar-H), 7.81 (m, 5H, Ar-H), 9.16 (s, 1H, OH) ppm; *m/z* 538 (Found: C, 60.48; H, 5.01; N, 5.51 $C_{27}H_{26}N_2SO_8$ requires C, 60.22; H, 4.83; N, 5.20%).

1.5.4. Compound 9d. Yield 82% as a colourless crystal, mp 203°C; $[\alpha]_D$=16.9 (*c* 1.5, MeOH); IR 3382 (OH), 2210 (CN) cm^{-1}; ^1H NMR 0.84 (t, *J*=7.7 Hz, 3H, CH_3), 3.19–3.79 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 3.85 (s, 3H, OCH_3), 3.94 (m, 2H, CH_2), 4.79 (s, 1H, 2′-OH), 5.16 (d, *J*=5.0 Hz, 1H, 3′-OH), 5.31 (s, 1H, 4′-OH), 5.59 (s, 1H, 6′-OH), 5.63 (d, $J_{1'-2'}$=8.3 Hz, 1H, H-1′), 7.07 (m, 3H, Ar-H), 7.76 (m, 5H, Ar-H), 9.50 (s, 1H, OH) ppm; *m/z* 568 (Found: C, 59.58; H, 5.20; N, 5.08 $C_{28}H_{28}N_2SO_9$ requires C, 59.15; H, 4.92; N, 4.92%).

1.5.5. Compound 9e. Yield 80% as a colourless crystal, mp 203°C; $[\alpha]_D$=24.6 (*c* 1.5, MeOH); IR 3394 (OH), 2210 (CN) cm^{-1}; ^1H NMR 2.30 (s, 3H, CH_3), 3.20–3.71 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 3.87 (s, 3H, OCH_3), 4.44 (t, *J*=6.1 Hz, 1H, 2′-OH), 4.83 (d, *J*=9.6 Hz, 1H, 3′-OH), 5.25 (m, 1H, 4′-OH), 5.48 (m, 1H, 6′-OH), 5.90 (d, $J_{1'-2'}$=9.5 Hz, 1H, H-1′), 7.18 (m, 3H, Ar-H), 7.79 (m, 5H, Ar-H), 9.20 (s, 1H, OH) ppm; *m/z* 538 (Found: C, 60.56; H, 4.90; N, 5.39 $C_{27}H_{26}N_2SO_8$ requires C, 60.22; H, 4.83; N, 5.20%).

1.5.6. Compound 9f. Yield 80% as a colourless crystal, mp 185°C; $[\alpha]_D$=28.4 (*c* 1.5, MeOH); IR 3370 (OH), 2222 (CN) cm^{-1}; ^1H NMR 0.83 (t, *J*=8.1 Hz, 3H, CH_3), 3.39–3.71 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 3.85 (s, 3H, OCH_3), 3.96 (m, 2H, CH_2), 4.34 (s, 1H, 2′-OH), 4.98 (d, *J*=5.9 Hz, 2H, 3′-OH and 4′-OH), 5.22 (s, 1H, 6′-OH), 5.62 (d, $J_{1'-2'}$=10.2 Hz, 1H, H-1′), 6.94 (m, 3H, Ar-H), 7.55 (m, 5H, Ar-H), 9.63 (s, 1H, OH) ppm; *m/z* 568 (Found: C, 59.41; H, 4.95; N, 5.05 $C_{28}H_{28}N_2SO_9$ requires C, 59.15; H, 4.92; N, 4.92%).

1.5.7. Compound 9g. Yield 81% as a colourless crystal, mp 190°C; $[\alpha]_D$=29.0 (*c* 1.5, MeOH); IR 3370 (OH), 2222 (CN) cm^{-1}; ^1H NMR 2.32 (s, 3H, CH_3), 3.18–3.80 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 3.86 (s, 3H, OCH_3), 4.50 (m, 2H, 2′-OH and 3′-OH), 4.99 (s, 1H, 4′-OH), 5.43 (s, 1H, 6′-OH), 5.78 (d, $J_{1'-2'}$=9.0 Hz, 1H, H-1′), 7.13 (m, 3H, Ar-H), 7.66 (m, 5H, Ar-H), 9.28 (s, 1H, OH) ppm; ^{13}C NMR 18.1 (CH_3), 55.2 (OCH_3), 60.8 (C6′), 68.3 (C4′), 69.5 (C2′), 73.7 (C3′), 79.8 (C5′), 83.9 (C1′), 105.1 (C3), 114.7 (CN), 123.1–158.4 (Ar-C), 162.5 (C2), 190.6 (CO) ppm; *m/z* 538 (Found: C, 60.46; H, 4.94; N, 5.48 $C_{27}H_{26}N_2SO_8$ requires C, 60.22; H, 4.83; N, 5.20%).

1.5.8. Compound 9h. Yield 80% as a colourless crystal, mp 196°C; $[\alpha]_D$=20.7 (*c* 1.5, MeOH); IR 3370 (OH), 2210 (CN) cm^{-1}; ^1H NMR 0.86 (t, *J*=7.1 Hz, 3H, CH_3), 3.22–3.75 (m, 6H, 2H-6′, H-5′, H-4′; H-3′ and H-2′), 3.80 (s, 3H, OCH_3), 3.98 (m, 2H, CH_2), 4.48 (s, 1H, 2′-OH), 5.04 (s, 1H, 3′-OH), 5.55 (d, *J*=9.6 Hz, 2H, 4′-OH and 6′-OH), 5.93 (d, *J*=8.7 Hz, 1H, H-1′), 7.08 (m, 3H, Ar-H), 7.63 (m, 5H, Ar-H), 9.18 (s, 1H, OH) ppm; *m/z* 568 (Found: C, 59.60; H, 5.13; N, 4.98 $C_{28}H_{28}N_2SO_9$ requires C, 59.15; H, 4.92; N, 4.92%).

Acknowledgements

The author is deeply indebted to Dr J. P. Bader, Dr V. L. Narayanan and Dr M. R. Boyd, AIDS Department and Drug Synthesis and Chemistry Branch of Health and Human Services, NIH for their valuable in vitro anti-HIV and anti-tumour activity studies for our samples.

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