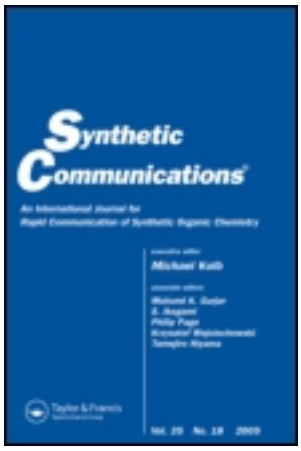

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Adel M. Attia [a] & Galal H. Elgemeie [b]

[a] Department of Chemistry, Faculty of Education, Kafr El-Sheikh, Egypt

[b] Department of Chemistry, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt

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A New Class of Dihydropyridine Thioglycosides via Piperidinium Salts

Adel M. Attia[1] and Galal H. Elgemeie[2,*]

[1]Department of Chemistry, Faculty of Education, Kafr El-Sheikh, Egypt
[2]Department of Chemistry, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt

ABSTRACT

A first reported method for preparation of a new class of thioglycosides via reaction of piperidinium salts of dihydropyridinethiones with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides has been studied. Comparison with the products obtained from silylated thiopyridines is made.

*Correspondence: Galal H. Elgemeie, Department of Chemistry, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt; E-mail: rughe@rusys.cg.net.

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In recent reports from our laboratory, we described the preparation of different novel functionalized pyridinethione glycosides, which revealed antagonistic activity.[1–4] In an ealier brief communication we had already reported the use of dihydropyridinethione glycosides as a substrates or inhibitors in the protein glycosylation process.[5] These common features, encouraged us to develop a new straightforward route for synthesis of these compounds. In the present report, we describe the synthesis of dihydropyridine thioglycosides through reaction of piperidinuim salts of dihydropyridinethiolates with α-halogeno 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 cyanothioacetamide **1** reacted with chalcones **2** in ethanol containing equivalent amounts of piperidine at room temperature to give the corresponding piperidinuim salts of 1,4-dihydropyridine-2-thiones **4**. The structure of **4** was established on the basis of their elemental analysis and spectral data. Compounds **4** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides **5** in acetone at 0°C to give in a high yields the corresponding *S*-glucosides **9a–c** or *S*-galactosides **9d–f**, respectively. It was suggested that the cis(α) sugar reacts by a simple SN_2 reaction to give the β-glycoside product. The structure of the reaction products **9a–f** were established and confirmed by their elemental analyses and spectral data (MS, IR, ^{1}H NMR, ^{13}C NMR). Thus, the analytical data for **9a** revealed a molecular formula $C_{32}H_{32}N_2SO_9$ (M^+ 620). The ^{1}H NMR spectrum showed the anomeric proton as a doublet at *δδ* 6.26 with spin-spin coupling constant of 10.37 Hz which corresponds to the diaxial orientation of H-1′ and H-2′ protons indicating the β-configuration, while the other six glucose protons resonated at *δ* 4.18–5.72. The four acetyl groups appeared as four singlets at *δ* 1.70–2.08. The ^{13}C NMR spectrum of **9a** contained a signal at *δδ* 80.7 corresponding to the C-1′ atom of the β-configuration. Five signals appearing at *δ* 62.1, 68.6, 69.4, 73.5, and 75.5 were assigned to C-6′, C-4′, C-2′, C-3′, and C-5′, respectively. After deprotection of compounds **9a–f** with a saturated solution of ammonia in methanol at 0°C the final glycosides **10a–f** were 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 **10a** reveal the molecular formula $C_{24}H_{24}N_2SO_5$ (M^+ 452). The ^{1}H NMR spectrum shows the anomeric proton as a doublet at *δ* 5.84 (*J* 10.22 Hz) indicating the presence of only the β-D-configuration. The signals of the other six glucose protons appear as a multiplet at *δ* 3.18–3.89, while the signals of the four hydroxy groups of the glucose moiety are observed at *δ* 4.42–5.20 (exchangeable by D_2O). The ^{13}C NMR spectrum of **10a** is characterized by a signal at *δ* 83.3 corresponding to the C-1′ atom of β-D-glucopyranose. Another five

signals at δ 60.6, 69.4, 73.3, 77.7, and 81.5 are assigned to C-6′, C-4′, C-2′, C-3′, and C-5′, respectively. In another experiment, the glycosides **9a–f** when refluxed in dry ethanol for 3 min, the corresponding aromatized pyridine thioglucosides **8a–c** and thiogalactosides **8d–f** were obtained. In order to investigate the scope of the formation of these glycosides further we studied the coupling of cyanothioacetamide with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides **5** in acetone at room temperature. The reaction proceeded to give the corresponding cyanoacetamidethioglycosides **6**. Compounds **6** reacted with chalcones **2** in dry ethanol containing catalytic amounts of piperidine at 60°C to give the glycosides **8**. The structures of the reaction products **8a–f** were established and confirmed on the basis of their elemental analyses and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). Although the coupling of piperidinium salts **4** with the glycosyl bromides could also give the corresponding *N*-glycosides **7**, the formation of the *S*-glycosides **8** were proved using the ^{13}C NMR spectroscopy which revealed the absence of the thione carbon at δ 178 and appearance of C-2 carbon[6,7] at δ 160 of the same value of the corresponding *S*-methyl derivative **11**. When glycosides **8** were treated with methanolic ammonia at room temperature, the free glycoside derivatives **16a–f** were obtained, the structures of which were established on the basis of elemental analysis and spectral data. With these two dihydropyridine and pyridine thioglycosides as models, it was decided to synthesize these compounds with the silylation method and comparing the products for stereochemical considerations. Thus, in a simple experimental procedure treatment of the piperidinium salts **4** with dilute hydrochloric acid at 30°C converted it to the corresponding pyridine-2(1*H*)thiones **12**. The latter compounds were reacted with hexamethyldisilazane in the presence of ammonium sulfate to give the corresponding 2-trimethylsilylthiopyridines **14**, which was subsequently treated with peracetylated sugars **15** in the presence of redistilled $SnCl_4$ to afford the *S*-glycosyl compounds **8**, which were shown to be the same as those obtained from the reaction of **6** with **2** or from oxidation of by their melting points and spectral data. A suggested mechanism for the formation of the *S*-glycosides **8** by condensation of silylated bases **14** with peracetylated sugars in the presence of Lewis acid catalyst is illustrated in **Chart 3**. In summary, we have achieved a novel synthesis of interesting nonclassical dihydropyridine thioglycosides and their corresponding aromatized forms by the reaction of the piperidinium salts of dihydropyridinethiones with α-halosugars, the nature of the products depends on thermodynamic factors. These nucleosides can be utilized as an excellent starting material for the synthesis of other carbohydrate derivatives and for further biological evaluation studies.

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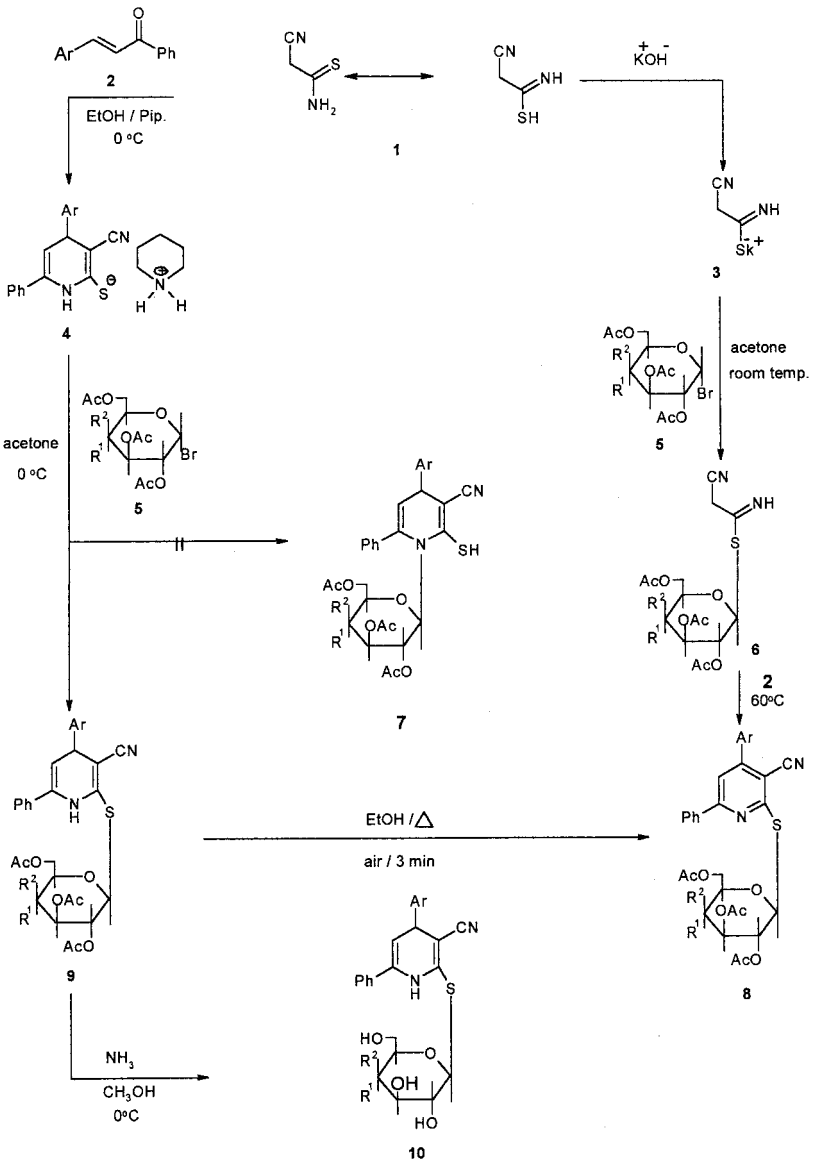
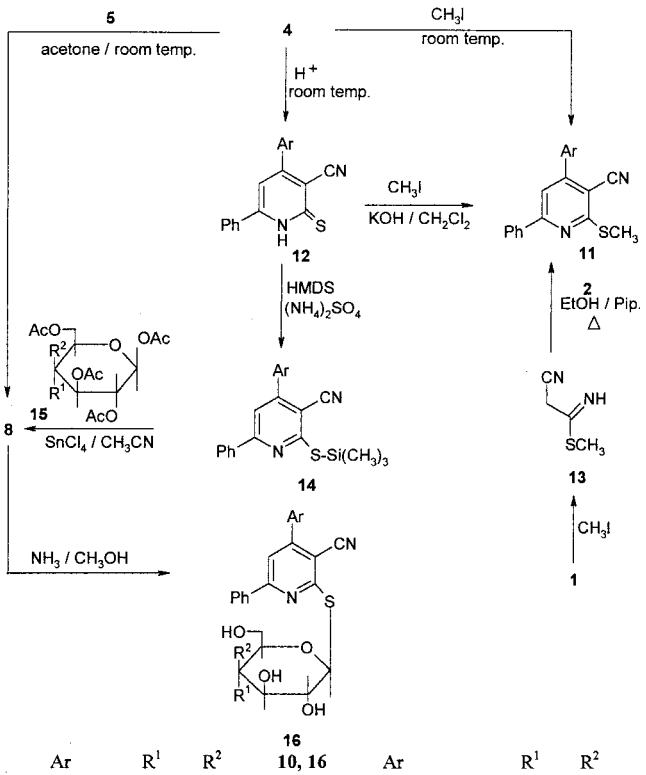


Chart 1.



8,9	Ar	R^1	R^2	10, 16	Ar	R^1	R^2
a	phenyl	OAc	H	a	phenyl	OH	H
b	2-furanyl	OAc	H	b	2-furanyl	OH	H
c	2-thienyl	OAc	H	c	2-thienyl	OH	H
d	phenyl	H	OAc	d	phenyl	H	OH
e	2-furanyl	H	OAc	e	2-furanyl	H	OH
f	2-thienyl	H	OAc	f	2-thienyl	H	OH

Chart 2.

EXPERIMENTAL

Melting points are uncorrected. Aluminum-coated silica gel 60 F_{254} (Merck) sheets were used for thin layer chromatography. IR spectra were collected in the transmission mode on a pye Unicam Spectra-1000 spectrometer. ^1H and ^{13}C NMR spectra were measured in $(CD_3)_2SO$ using $SiMe_4$ as internal reference on a Varian 400 MHz spectrometer. Mass spectra were recorded by EI on a Varian Mat 311A spectrometer and FAB on a kratos MS 50 spectrometer.

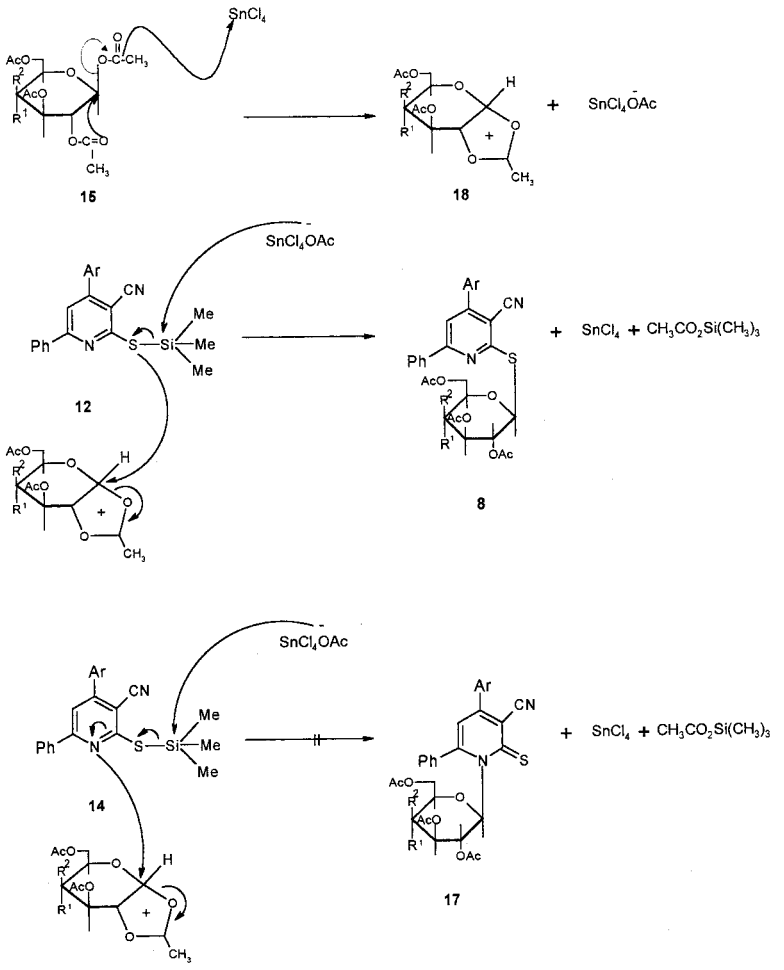


Chart 3.

2,3,4,6-Tetra-*o*-acetyl-β-D-glycopyranosylthiocyanoacetamides (6a,b)

To a solution of thiocyanoacetamide **1** (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 galactopyranosyl bromide **5** (0.11 mol) in acetone 20 mL was added. The reaction mixture was stirred at room temperature until completion (TLC, 1 h), using chloroform: ether 9:1 v/v

(Rf 0.74–0.76 region), 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 chloroform–petroleum ether 40–60 at 0°C to give the yellow products **6**.

6a. Yield 83%, m.p. 147°C. IR 2230 (CN), 1754 (CO ester of glucose). ^{1}H NMR 2.01–2.11(4s, 12H, 4CH_3CO), 3.70 (m, 2H, CH_2), 4.17 (m, 2H, 2H-6′), 4.22 (m, 1H, H-5′), 4.79 (t, 1H, H-4′), 4.84 (m, 1H, H-3′), 5.09 (m, 1H, H-2′), 5.22 (d, $J_{1'\text{-}2'}$ 10.56 Hz, 1H, H-1′), 7.26 (s, 1H, imine NH). *m*/*z* 430 (Found: C, 47.70; H, 5.24; N, 6.68. $C_{17}H_{22}N_2SO_9$ requires C, 47.44; H, 5.11; N, 6.51%).

6b. Yield 85%, m.p. 168°C. IR 2228 (CN), 1755 (CO ester of galactose). ^{1}H NMR 1.99–2.09 (4s, 12H, 4CH_3CO), 3.88 (m, 2H, CH_2), 4.09 (m, 2H, 2H-6′), 4.19 (m, 1H, H-5′), 4.55 (t, 1H, H-4′), 4.80 (m, 1H, H-3′), 5.11 (m, 1H, H-2′), 5.27 (d, $J_{1'\text{-}2'}$ 10.0 Hz, 1H, H-1′), 7.20 (s, 1H, imine NH). *m*/*z* 430 (Found: C, 47.62; H, 5.20; N, 6.72. $C_{17}H_{22}N_2SO_9$ requires C, 47.44; H, 5.11; N, 6.51%).

3-Cyano-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D -glycopyranosylthio)-1,4-dihydropyridines (9a–f)

General coupling procedures. A mixture of **1** (0.01 mol) and **2** (0.01 mol) was dissolved 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. The solvent was removed at reduced pressure and the resulting hydrogenated thiopyridines **4** was dissolved in dry acetone (5 mL) and a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyranosyl bromide 6 **5** (0.011 mol) in dry acetone (20 mL) was then added at 0°C. The reaction mixture was stirred until the reaction was judged complete by TLC, using chloroform:ether 4:1 (Rf 0.66–0.70 region), then evaporated under reduced pressure and the residue was crystallized from chloroform- petroleum ether 40–60 at 0°C to give pale yellow crystals.

9a. Yield 72%, m.p. 215°C. IR 2215 (CN), 1748 (CO) cm^{-1}. ^{1}H NMR 1.70–2.08 (4s, 12H, 4CH_3CO), 4.18 (m, 2H, 2H-6′ and 1H, pyridine H-4), 4.38 (m, 1H, H-5′), 5.05 (t, 1H, H-4′), 5.26 (t, H, H-3′), 5.72 (t, 1H, H-2′), 6.26 (d, $J_{1'\text{-}2'}$ 10.37 Hz, 1H, H-1′), 7.62 (m, 5H, Ar-H), 7.78 (m, 3H, Ar-H and 1H, pyridine H-5), 8.04 (s,1H, NH), 8.40 (m, 2H, Ar-H) ppm. ^{13}C NMR 19.9–20.2 (4CH_3), 62.1(C6′), 68.6 (C4′), 69.4 (C2′), 73.5 (C3′), 75.5 (C5′), 80.7 (C1′), 104.2 (C4), 115.1 (C3), 117.2 (CN), 127.8–1158.0 (Ar-C), 159.4 (C2), 169.1–169.6 (4CO) ppm. *m*/*z* 620 (Found: C, 62.08; H, 5.22; N, 4.60. $C_{32}H_{32}N_2SO_9$ requires C, 61.93; H, 5.16; N, 4.51%).

9b. Yield 73%, m.p. 235°C. IR 2213 (CN), 1747 (CO) cm^{-1}. ^{1}H NMR 1.61–2.04 (4s, 12H, $4CH_3CO$), 4.12 (m, 2H, 2H-6′ and 1H, pyridine H-4), 4.35 (m, 1H, H-5′), 5.01(t, 1H, H-4′), 5.22 (t, 1H, H-3′), 5.72 (t, 1H, H-2′), 6.22 (d, $J_{1'-2'}$ 10.44 Hz, 1H, H-1′), 6.84 (q, 1H, furan H-4), 7.79 (m, 3H, Ar-H and 1H, pyridine H-5), 7.90 (d, 1H, furan H-3), 8.09 (d, 1H, furan H-5), 8.16 (s, 1H, NH), 8.27 (d, 2H, Ar-H) ppm. ^{13}C NMR 19.9–20.9 ($4CH_3$), 61.8 (C6′), 68.2 (C4′), 68.8 (C2′), 72.9 (C3′), 75.1(C5′), 80.9 (C1′), 97.6 (C4), 113.1 (C3), 115.8 (CN), 127.6–158.2 (Ar-C), 160.1 (C2), 169.2–169.7 (4CO) ppm. *m*/*z* 610 (Found: C,59.29; H, 5.04; N, 4.73. $C_{30}H_{30}N_2SO_{10}$ requires C, 59.01; H, 4.91; N, 4.59%).

9c. Yield 70%, m.p. 244°C. IR 2211(CN), 1746 (CO) cm^{-1}. ^{1}H NMR 1.68–2.05 (4s, 12H, $4CH_3CO$), 4.15 (m, 2H, 2H-6′ and 1H, pyridine H-4), 4.26 (m, 1H, H-5′), 5.05 (t, 1H, H-4′), 5.28 (t, 1H, H-3′), 5.62 (t, 1H, H-2′), 6.18 (d, $J_{1'-2'}$ 10.38 Hz, 1H, H-1′), 7.32 (q, 1H, thiophene H-4), 7.80 (m, 3H, Ar-H and 1H, pyridine H-5), 7.92 (dd, 1H, thiophene H-3), 7.98 (dd, 1H, thiophene H-5), 8.04 (s, 1H, NH), 8.35 (m, 2H, Ar-H) ppm. ^{13}C NMR 19.4–19.8($4CH_3$), 61.6 (C6′), 68.2 (C4′), 68.9 (C2′), 73.0 (C3′), 75.0 (C5′), 80.2 (C1′), 101.3 (C4), 114.0 (C3), 116.2 (CN), 127.3–158.1 (Ar-C), 159.9 (C2), 168.6–169.1 (4CO) ppm. *m*/*z* 626 (Found: C, 57.81; H, 4.97; N, 4.66. $C_{30}H_{30}N_2S_2O_9$ requires C, 57.50; H, 4.79; N, 4.47%).

9d. Yield 73%, m.p. 148°C. IR 2203 (CN), 1753 (CO) cm^{-1}. ^{1}H NMR 1.62–2.04 (4s, 12H, $4CH_3CO$), 4.16 (m, 2H, 2H-6′ and 1H, pyridine H-4), 4.37 (m, 1H, H-5′), 5.04 (t, 1H, H-4′), 5.25 (t, 1H, H-3′), 5.72 (t, 1H, H-2′), 6.28 (d, $J_{1'-2'}$ 10.46 Hz, 1H, H-1′), 7.62 (m, 5H, Ar-H), 7.76 (m, 3H, Ar-H and 1H, pyridine H-5), 8.02 (s, 1H, NH), 8.40 (m, 2H, Ar-H) ppm. ^{13}C NMR 19.8–20.3($4CH_3$), 61.9 (C6′), 68.2 (C4′), 68.8 (C2′), 72.9 (C3′), 75.1 (C5′), 79.9 (C1′), 103.7 (C4), 115.2 (C3), 117.0 (CN), 127.8–158.2 (Ar-C), 160.8 (C2), 169.2–169.6 (4CO) ppm. *m*/*z* 620 (Found: C, 62.24; H, 5.30; N, 4.71. $C_{32}H_{32}N_2SO_9$ requires C, 61.93; H, 5.16; N, 4.51%).

9e. Yield 71%, m.p. 209°C. IR 2212 (CN), 1758 (CO) cm^{-1}. *m*/*z* 610 (Found: C, 59.29; H, 4.98; N, 4.78. $C_{30}H_{30}N_2SO_{10}$ requires C, 59.01; H, 4.91; N, 4.59%).

9f. Yield 72%, m.p. 181°C. IR 2214 (CN), 1750 (CO) cm^{-1}. ^{1}H NMR 1.68–2.12 (4s, 12H, $4CH_3CO$), 4.20 (m, 2H, 2H-6′ and 1H, pyridine H-4), 4.54 (m, 1H, H-5′), 5.28 (t, 1H, H-4′), 5.42 (t, 1H, H-3′), 5.76 (t, 1H, H-2′), 6.24 (d, $J_{1'-2'}$ 10.39 Hz, 1H, H-1′), 7.38 (d, 1H, thiophene H-4), 7.75 (m, 3H, Ar-H and 1H, pyridine H-5), 7.96 (d, 1H, thiophene H-3), 8.00 (d, 1H, thiophene H-5), 8.05(s, 1H, NH), 8.42 (d, 2H, Ar-H) ppm. ^{13}C NMR 19.9–20.4 ($4CH_3$), 61.9 (C6′), 66.3 (C4′), 67.9 (C2′), 70.9

(C3′), 74.4 (C5′), 80.5 (C1′), 101.4 (C4), 114.2 (C3), 116.6 (CN), 127.8–157.3 (Ar-C), 160.1 (C2), 169.3–169.9 (4CO) ppm. *m*/*z* 626 (Found: C, 57.81; H, 4.88; N, 4.70. $C_{30}H_{30}N_2S_2O_9$ requires C, 57.50; H, 4.79; N, 4.47%).

3-Cyano-2-(β-D-glycopyranosylthio)-1,4-dihydropyridines (10a–f)

General procedure for nucleoside deacylation. Dry ammonia gas was passed into a solution of protected glycosides **9** (0.5 g) in 20 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 chloroform:Methanol 9:1 (Rf 0.62–0.66 region). The resulting mixture was then concentrated under reduced pressure to afford a solid residue that was crystallized from methanol–ether at 0°C to furnish colorless crystals.

10a. Yield 81%, m.p. 173°C. IR 3662–3188 (OH), 2206 (CN) cm^{-1}. ^{1}H NMR 3.18–3.89 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, H-2′ and 1H, pyridine H-4), 4.42 (d, 2H, 2′-OH and 3′-OH), 4.98 (d, 1H, 4′-OH), 5.20 (d, 1H, 6′-OH), 5.84 (d, $J_{1'\text{-}2'}$ 10.22 Hz, 1H, H-1′), 7.58 (m, 5H, Ar-H), 7.80 (m, 3H, Ar-H and 1H, pyridine H-5), 7.91 (s, 1H, NH), 8.28 (m, 2H, Ar-H) ppm. ^{13}C NMR 60.6 (C6′), 69.4 (C4′), 73.3 (C2′), 77.7 (C3′), 81.5 (C5′), 83.3 (C1′), 101.8 (C4), 103.3 (C3), 115.5 (CN), 125.4–158.0 (Ar-C), 161.5 (C2) ppm. *m*/*z* 452 (Found: C, 63.92; H, 5.44; N, 6.31. $C_{24}H_{24}N_2SO_5$ requires C, 63.71; H, 5.30; N, 6.19%).

10b. Yield 82%, m.p. 208°C. IR 3680–3220 (OH), 2210 (CN) cm^{-1}. *m*/*z* 442 (Found: C, 59.89; H, 5.12; N, 6.50. $C_{22}H_{22}N_2SO_6$ requires C, 59.72; H, 4.97; N, 6.33%).

10c. Yield 83%, m.p. 230°C. IR 3680–3190 (OH), 2211 (CN) cm^{-1}. ^{1}H NMR 3.28–3.86 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, H-2′ and 1H, pyridine H-4), 4.48 (s, 1H, 2′-OH), 5.12 (s, 1H, 3′-OH), 5.24 (s, 1H, 4′-OH), 5.58 (s, 1H, 6′-OH), 5.74 (d, $J_{1'\text{-}2'}$ 10.39 Hz, 1H, H-1′), 7.34 (m, 1H, thiophene H-4), 7.74 (m, 3H, Ar-H and 1H, pyridine H-5), 7.96 (m, 2H, thiophene H-3, H-4 and 1H, NH), 8.26 (m, 2H, Ar-H) ppm. ^{13}C NMR 60.7 (C6′), 69.7 (C4′), 71.7 (C2′), 78.5 (C3′), 81.0 (C5′), 83.9 (C1′), 102.0 (C4), 114.8 (C3), 116.1 (CN), 127.6–158.1 (Ar-C), 162.4 (C2) ppm. *m*/*z* 458 (Found: C, 57.95; H, 4.88; N, 6.34. $C_{22}H_{22}N_2S_2O_5$ requires C, 57.64; H, 4.80; N, 6.11%).

10d. Yield 80%, m.p. 206°C. IR 3730–3240 (OH), 2213 (CN) cm^{-1}. ^{1}H NMR 3.20–3.96 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, H-2′ and 1H, pyridine H-4), 4.64 (d, 2H, 2′-OH and 3′-OH), 5.18 (s, 1H, 4′-OH), 5.42 (s, 1H, 6′-OH), 5.76 (d, $J_{1'\text{-}2'}$ 10.19 Hz, 1H, H-1′), 7.58 (m, 5H,

Ar-H), 7.78 (m, 3H, Ar-H and 1H, pyridine H-5), 7.96 (s, 1H, NH), 8.35 (d, 2H, Ar-H) ppm. ^{13}C NMR 60.5 (C6′), 68.5 (C4′), 69.9 (C2′), 75.0 (C3′), 78.9 (C5′), 84.4 (C1′), 103.3 (C4), 115.6 (C3), 116.4 (CN), 127.4–152.2 (Ar-C), 161.7 (C2) ppm. *m*/*z* 452 (Found: C, 63.93; H, 5.48; N, 6.40. $C_{24}H_{24}N_2SO_5$ requires C, 63.71; H, 5.30; N, 6.19%).

10e. Yield 80%, m.p. 200°C. IR 3690–3230 (OH), 2212 (CN) cm^{-1}. *m*/*z* 442 (Found: C, 60.06; H, 5.12; N, 6.49. $C_{22}H_{22}N_2SO_6$ requires C, 59.72; H, 4.97; N, 6.33%).

10f. Yield 83%, m.p. 240°C. IR 3690–3290 (OH), 2210 (CN) cm^{-1}. ^{1}H NMR 3.38–3.95 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, H-2′ and 1H, pyridine H-4), 4.60 (d, 1H, 2′-OH), 4.72 (t, 1H, 3′-OH), 5.20 (d, 1H, 4′-OH), 5.42 (d, 1H, 6′-OH), 5.76 (d, $J_{1'\text{-}2'}$ 10.18 Hz, 1H, H-1′), 7.34 (t, 1H, thiophene H-4), 7.73 (m, 3H, Ar-H and 1H, pyridine H-5), 7.92 (m, 2H, thiophene H-3, H-5 and 1H, NH), 8.28 (d, 2H, Ar-H) ppm. ^{13}C NMR 60.5 (C6′), 68.5 (C4′), 68.9 (C2′), 74.9 (C3′), 79.9 (C5′), 83.8 (C1′), 100.8 (C4), 114.8 (C3), 115.9 (CN), 127.6–152.2 (Ar-C), 162.6 (C2) ppm. *m*/*z* 458 (Found: C, 57.90; H, 5.02; N, 6.25. $C_{22}H_{22}N_2S_2O_5$ requires C, 57.64; H, 4.80; N, 6.11%).

3-Cyano-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosylthio)-pyridines (8a–f)

General coupling procedures. Method A. The piperidinium salt of dihydropyridinethiones **4** (0.01 mol) was dissolved in dry acetone (5 mL) and a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyranosyl bromide (0.11 mol) in dry acetone (20 mL) was then added at 30°C. The reaction mixture was stirred until the reaction was judged complete by TLC, using chloroform:ether 9:1 v/v (Rf 0.70–0.72 region), then evaporated under reduced pressure and the residue was crystallized from ethanol to give the yellow products **10a–f**.

Method B. 3-Cyanopyridine-2(1*H*)-thiones **12** (0.01 mol) were refluxed by stirring under anhydrous condition for 48 h with hexamethyldisilazane 60 mL and $(NH_4)_2SO_4$ (0.02 g). The clear solution obtained was cooled and the solvent was removed in vacuo. The resulting trimethylsilylated pyridines **14** were dissolved in anhydrous acetonitrile (30 mL), and a solution of β-D-glycopyranose pentaacetate **15** (0.011 mol) in acetonitrile (10 mL) was then added with stirring. The mixture was cooled to 0°C and a solution of $SnCl_4$ (1.6 mL) in acetonitrile (5 mL) was added dropwise and the mixture was stirred until the reaction was judged complete by TLC (4–6 h), then poured into saturated $NaHCO_3$ solution, and extracted with $CHCl_3$. The

organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude glycosides that were purified by recrystallization from ethanol.

Method C. 3-Cyano-1,4-dihydropyridine-2-thioglycosides **9** (0.01 mol) were refluxed in ethanol (30 mL) with stirring under anhydrous condition for 3 min The resulting products were collected by filtration and recrystallized from ethanol.

10a. Yield 70, m.p. 202°C. IR 2216 (CN), 1748 (CO) cm^{-1}. ^1H NMR 1.61–2.06 (4s, 12H, $4CH_3CO$), 4.06 (d, 2H, 2H-6′), 4.42 (m, 1H, H-5′), 5.03 (t, 1H, H-4′), 5.31(t, 1H, H-3′), 5.80 (t, 1H, H-2′), 6.22 (d, $J_{1'\text{-}2'}$ 10.56 Hz, 1H, H-1′), 7.61 (m, 5H, Ar-H), 7.78 (m, 3H, Ar-H), 7.90 (s, 1H, pyridine H-5), 8.44 (m, 2H, Ar-H) ppm. ^{13}C NMR 19.4–22.6 ($4CH_3$), 61.3 (C6′), 66.9 (C4′), 69.3 (C2′), 72.6 (C3′), 74.9 (C5′), 80.1 (C1′), 105.8 (C3), 115.5 (CN), 122.4–154.6 (Ar-C), 161.2 (C2), 168.3–169.4 (4CO) ppm. *m/z* 618 (Found: C, 62.28; H, 5.09; N, 4.61. $C_{32}H_{30}N_2SO_9$ requires C, 62.13; H, 4.85; N, 4.53%).

10b. Yield 68%, m.p. 212°C. IR 2215 (CN), 1746 (CO) cm^{-1}. *m/z* 608 (Found: C, 59.45; H, 4.64; N, 4.82. $C_{30}H_{28}N_2SO_{10}$ requires C, 59.21; H, 4.60; N, 4.60%).

10c. Yield 69%, m.p. 219°C. IR 2210 (CN), 1754 (CO) cm^{-1}. ^1H NMR 1.72–2.08 (4s, 12H, $4CH_3CO$), 4.16 (m, 2H, 2H-6′ and 1H, H-5′), 4.80 (t, 1H, H-4′), 5.12 (t,1H, H-3′), 5.78 (t, 1H, H-2′), 6.28 (d, $J_{1'\text{-}2'}$ 10.32 Hz, 1H, H-1′), 6.98 (dd, 1H, thiophene H-4), 7.46 (m, 3H, Ar-H), 7.81 (m, 1H, thiophene H-3), 7.96 (m, 1H, thiophene H-5 and 1H, pyridine H-5), 8.38 (m, 2H, Ar-H) ppm. *m/z* 624 (Found: C, 57.90; H, 4.62; N, 4.68. $C_{30}H_{28}N_2S_2O_9$ requires C, 57.69; H, 4.48; N, 4.48%).

10d. Yield 71%, m.p. 161°C. IR 2214 (CN), 1748 (CO) cm^{-1}. ^1H NMR 1.58–2.12(4s, 12H, $4CH_3CO$), 4.08 (m, 2H, 2H-6′), 4.58 (t, 1H, H-5′), 5.26 (t, 1H, H-4′), 5.42 (d, 1H, H-3′), 5.68 (dd, 1H, H-2′), 6.25 (d, $J_{1'\text{-}2'}$ 10.62 Hz, 1H, H-1′), 7.58 (m, 5H, Ar-H), 7.78 (m, 3H, Ar-H), 7.92 (s, 1H, pyridine H-5), 8.40 (m, 2H, Ar-H) ppm. *m/z* 618 (Found: C, 62.21; H, 5.14; N, 4.70. $C_{32}H_{30}N_2SO_9$ requires C, 62.13; H, 4.85; N, 4.53%).

10e. Yield 68%, m.p. 213°C. IR 2218 (CN), 1750 (CO) cm^{-1}. ^1H NMR 1.68–2.05 (4s, 12H, $4CH_3CO$), 4.08 (m, 2H, 2H-6′), 4.26 (m, 1H, H-5′), 4.92 (t, 1H, H-4′), 5.14 (t, 1H, H-3′), 5.68 (t, 1H, H-2′), 6.18 (d, $J_{1'\text{-}2'}$ 9.98 Hz, 1H, H-1′), 6.88 (d, 1H, furan H-4), 7.26 (m, 3H, Ar-H), 7.62 (d, 1H, furan H-3), 8.02 (m, 1H, furan H-5 and 1H, pyridine H-5), 8.30 (d, 2H, Ar-H) ppm. *m/z* 608 (Found: C, 59.34; H, 4.78; N, 4.84. $C_{30}H_{28}N_2SO_{10}$ requires C, 59.21; H, 4.60; N, 4.60%).

10f. Yield 70%, m.p. 198°C. IR 2218 (CN), 1750 (CO) cm^{-1}. *m/z* 624 (Found: C, 57.88; H, 4.56; N, 4.68. $C_{30}H_{28}N_2S_2O_9$ requires C, 57.69; H, 4.48; N, 4.48%).

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3-Cyano-2-(β-D-glycopyransosylthio)pyridines (16a–f)

General procedure. Dry ammonia gas was passed into a solution of protected glycosdies **8** (0.5 g) in 20 mL of dry methanol at 0°C for 0.5 h. The reaction mixture was stirred until completion as shown by TLC (8–12 h), using chloroform:methanol 9:1, v/v (Rf 0.66–0.68 region). The resulting mixture was then concentrated under reduced pressure to afford a solid residue that was crystallized from methanol to furnish colorless crystals.

16a. Yield 87%, m.p. 220°C. IR 3600–3180 (OH), 2215 (CN) cm^{-1}. *m/z* 450 (Found: C, 64.24; H, 4.98; N, 6.40. $C_{24}H_{22}N_2SO_5$ requires C, 64.00; H, 4.88; N, 6.22%).

16b. Yield 85%, m.p. 238°C. IR 3600–3220 (OH), 2215 (CN) cm^{-1}. ^{1}H NMR 3.28–3.84 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 4.42 (t, 1H, 2′-OH), 5.12 (d, 2H, 3′-OH and 4′-OH), 5.58 (d, 1H, 6′-OH), 5.72 (d, $J_{1'\text{-}2'}$ 10.12 Hz, 1H, H-1′), 6.80 (m, 1H, furan H-4), 7.58 (m, 3H, Ar-H), 7.75 (d, 1H, furan H-3), 8.00 (m, 2H, furan H-5 and pyridine H-5), 8.28 (m, 2H, Ar-H) ppm. *m/z* 440 (Found: C, 60.12; H, 4.62; N, 6.60. $C_{22}H_{20}N_2SO_6$ requires C, 60.00; H, 4.54; N, 6.36%).

16c. Yield 84%, m.p. 248°C. IR 3660–3200 (OH), 2216 (CN) cm^{-1}. ^{1}H NMR 3.22–3.74 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 4.62 (m, 2H, 2′-OH and 3′-OH), 4.96 (d, 1H, 4′-OH), 5.22 (d, 1H, 6′-OH), 5.82 (d, $J_{1'\text{-}2'}$ 10.08 Hz, 1H, H-1′), 6.92 (m, 1H, thiophene H-4), 7.16 (m, 1H, thiophene H-3), 7.50 (m, 3H, Ar-H), 7.92 (m, 2H, thiophene H-5 and pyridine H-5), 8.30 (m, 2H, Ar-H) ppm. ^{13}C NMR 62.2 (C6′), 67.8 (C4′), 69.8 (C2′), 73.6 (C3′), 75.0 (C5′), 83.1 (C1′), 108.5 (C3), 114.7 (CN), 122.2–156.4 (Ar-C), 161.6 (C2) ppm. *m/z* 456; (Found: C, 58.12; H, 4.50; N, 6.38. $C_{22}H_{20}N_2S_2O_5$ requires C, 57.89; H, 4.38; N, 6.14%).

16d. Yield 89%, m.p. 230°C. IR 3680–3200 (OH), 2213 (CN) cm^{-1}. ^{1}H NMR 3.24–3.68 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 4.61 (t, 1H, 2′-OH), 5.15 (d, 1H, 3′-OH), 5.28 (t, 1H, 4′-OH), 5.59 (t, 1H, 6′-OH), 5.68 (d, $J_{1'\text{-}2'}$ 9.38 Hz, 1H, H-1′), 7.56 (m, 5H, Ar-H), 7.76 (m, 3H, Ar-H), 7.90 (s, 1H, pyridine H-5), 8.28 (m, 2H, Ar-H) ppm. ^{1}H NMR 3.24–3.81 (m, 6H, 2H-6′, H-5′, H-4′, H-3′ and H-2′), 4.60 (d, 1H, 2′-OH), 4.69 (t, 1H, 3′-OH), 5.04 (d, 1H, 4′-OH), 5.43 (d, 1H, 6′-OH), 5.68 (d, $J_{1'\text{-}2'}$ 10.06 Hz, 1H, H-1′), 7.59 (m, 5H, Ar-H), 7.86 (m, 3H, Ar-H and 1H, pyridine H-5), 8.29 (m, 2H, Ar-H) ppm. *m/z* 450 (Found: C, 64.18; H, 5.02; N, 6.48. $C_{24}H_{22}N_2SO_5$ requires C, 64.00; H, 4.88; N, 6.22%).

16e. Yield 85%, m.p. 233°C. IR 3650–3190 (OH), 2218 (CN) cm^{-1}. *m/z* 440 (Found: C, 60.29; H, 4.66; N, 6.60. $C_{22}H_{20}N_2SO_6$ requires C, 60.00; H, 4.54; N, 6.36%).

16f. Yield 87%, m.p. 226°C. IR 3680–3220 (OH), 2212 (CN) cm^{-1}. *m*/z 456 (Found: C, 58.15; H, 4.44; N, 6.30. $C_{22}H_{20}N_2S_2O_5$ requires C, 57.89; H, 4.38; N, 6.14%).

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