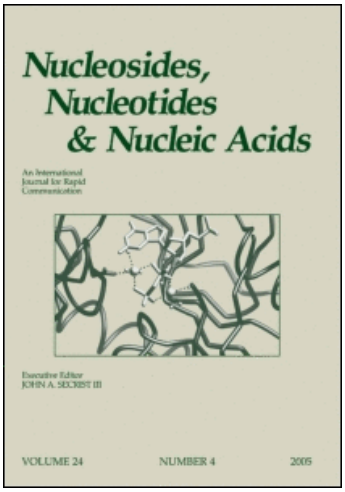

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A NEW CLASS OF BIHETEROCYCLIC THIOGLYCOSIDES FROM PYRIDINE-2-(1*H*)-THIONES

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A NEW CLASS OF BIHETEROCYCLIC THIOGLYCOSIDES FROM PYRIDINE-2-(1*H*)-THIONES

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ABSTRACT

A reported method for preparation of a new class of biheterocyclic thioglycosides via reaction of pyridinethiones with 2,3,4,6-tetra-***O***-acetyl-α-D-gluco- and galactopyranosyl bromides has been studied.

INTRODUCTION

In recent years nucleoside analogues have occupied a significant position in the search for effective antiviral agents, owing to the fact that a large number of unnatural nucleoside derivatives have been shown to inhibit infection caused by viruses.[1–3] The deazapyrimidine nucleosides constitute a class of analogues with potential biological activity.[4] As a part of our program directed towards the development of new, simple and efficient procedures for synthesis of antimetabolites,[5,6] we have recently described that pyridinethione nucleosides exerted inhibitory effects on both DNA and RNA containing viruses.[7] On the basis of these findings,

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it was of interest to prepare modified analogues to search for more effective agents.

RESULTS AND DISCUSSION

This paper describes the synthesis of nonclassical biheterocyclic glycosides. The latter compounds will be considered as precursors of modified glycosides. Thus, it has been found that heating of cyclopentanone, cyclohexanone, cycloheptanone or cyclooctanone with cyanothioacetamide and a catalytic amount of ammonium acetate-acetic acid in benzene for 3 h with azeotropic removal of water gave the corresponding cycloalkylidenecyanothioamides **1** in good yields. Compounds **1** react with quinoline-4-ylidenemalononitrile **2** in refluxing ethanol containing catalytic amounts of piperidine for 2 h to give the corresponding 6-quinolyl-pyridine-2(1*H*)-thiones **5a**–**d**. The structures of compounds **5** were established on the basis of their elemental analysis and spectral data. Thus, structure **5c** is supported by its mass and ^{1}H NMR spectra, the latter included a broad band at δ 14.26 assigned to the NH proton. The formation of **5** from **1** and **2** is assumed to proceed via addition of the active methylene group of **1** to the double bond of **2** to give the intermediate **3**.This Michael adduct then cyclizes via malononitrile elimination to give the intermediate dihydropyridine derivative **4** which is oxidized under the reaction conditions to yield the condensed 6-quinolyl-pyridine-2-(1*H*)-thiones **5**. We also investigated the reaction between the cycloalkylidenemalononitrile **6** and the quinoline-4-ylidenecyanothioacetamide **7** under the same conditions. The products were identified as the same as that obtained from the reaction of **1** and **2** by their m.p.s and spectral data. The mechanism of the reaction of **6** and **7** is assumed to be initiated by an exchange process between the cycloalkylidene group of **6** and the quinolylidene group of **7** to give the intermediate **3** and hence to the products **5** as produced by the reaction of **1** with **2**. Similar mechanism for other analogues was reported by us.[8] Compounds **5** can be coupled with different classes of sugar halides to give a novel ring system of glycosides. As far as we know, this is the first coupling reaction of this type to be reported for this ring system. Thus, it has been found that compounds **5a**–**d** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides **10a,b** in the presence of aqueous potassium hydroxide to give the corresponding *S*-glycosides **11a**–**h**. The structures of the reaction products **11a**–**h** were established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). Thus, the analytical data for **11c** revealed a molecular formula $C_{34}H_{35}N_3O_9S$ (m/z 661). ^{1}H NMR spectroscopy was used to confirm this structure for the product. The ^{1}H NMR spectrum showed the anomeric proton as doublet at δ 6.21 with a spin-spin coupling constant of ($J_{1',2'} = 11.28$ Hz) corresponding to

a diaxial orientation of H-1′ and H-2′ protons indicating the β-configuration. The other six protons of the glucopyranosyl ring resonated in the δ 4.02–5.59 region. The four acetoxy groups appear as four singlets at δ 1.96–2.05 and the five methylene protons of the agylcon resonate at δ 1.35, 1.66, 1.78 and 3.25. ^{13}C NMR spectra were characterized by a signal at δ 80.1 corresponding to the C-1′ atom of the β-D-glucopyranose. The four signals appearing at δ 169.2–170.4 are due to the four acetoxy carbonyl carbon atoms, while the five signals at δ 22.2–22.3 are attributed to the acetate methyl carbons. The five methylene carbon atoms of the aglycone resonated at δ 21.9, 26.2, 27.6, 29.1, 32.8. Another five signals at δ 61.7, 67.8, 69.1, 73.01 and 74.9 were assigned to C-6′, -4′, -2′, -3′ and -5′, respectively. The IR spectrum of compound **11c** was characterized by the presence of acetoxy carbonyl groups at 1752 cm^{-1}. It may be argued that the coupling reaction of **5** with **10** happened on the nitrogen atom to give the corresponding N-glycosides **12a**–**h**. The formation of the *S*-glycosides **11a**–**h** was proven using ^{13}C NMR which revealed the absence of the thione carbon at δ 178 and the appearance of the C-2 carbon at δ 161 of the same value of the corresponding *S*-methyl derivative **14a**–**d**.[9,10] Also, the UV spectra of compounds **11a**–**h** proved that the reaction had led selectively to the formation of *S*-glycosyl derivatives since the corresponding *S*-methyl derivatives **14a**–**d** gave the same UV absoption maxima. Thus, the *S*-methyl derivative of compound **5c** shows three maxima at 216, 268 and 340 nm and its corresponding glucosyl derivative also exhibited three maximum absorption bands at 224, 266 and 340 nm. The protected glycoside **11a**–**h** were deblocked through treatment with methanolic ammonia to give the free glycosides **13a**–**h** after chromatographic purification. TLC of compounds **13a**–**h** showed that a single unique compound was produced, and their structures were confirmed by their elemental analysis and spectral data. Thus, the analytical data for compound **13d** revealed a molecular formula $C_{27}H_{29}N_3O_5S$ (m/z 507). The IR absorption spectra of this compound showed a characteristic band at 3600–3200 cm^{-1} due to the hydroxy groups of the glucose moiety. ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, the ^{1}H NMR spectra revealed the presence of a doublet at δ 5.63 ($J_{1'-2'} = 10.75$ Hz), indicating the presence of only the β-D-glucopyranose. The other six-glucose protons appear as a multiplet at δ 3.45–3.70, while the four hydroxy groups of glucose moiety resonated at δ 5.02, 5.21 and 5.55 (exchangeable by D_2O). ^{13}C NMR spectra were characterized by a signal at δ 84.01 corresponding to the C-1′ atom of β-D glucopyranose. Another five signals, at δ 60.1, 70.1, 72.1, 78.9 and 81.9 were assigned to C-6′, -4′, -2′, -3′, and -5′ of the glucose part, respectively.

In summary, we have achieved a regiospecific synthesis of interesting biheterocyclic glycosides by the reaction of substituted pyridine-2-(1*H*)-thiones with α halosugars. These glycosides can be utilized as an excellent starting material for the synthesis of other carbohydrate derivatives and for biological evaluation studies.

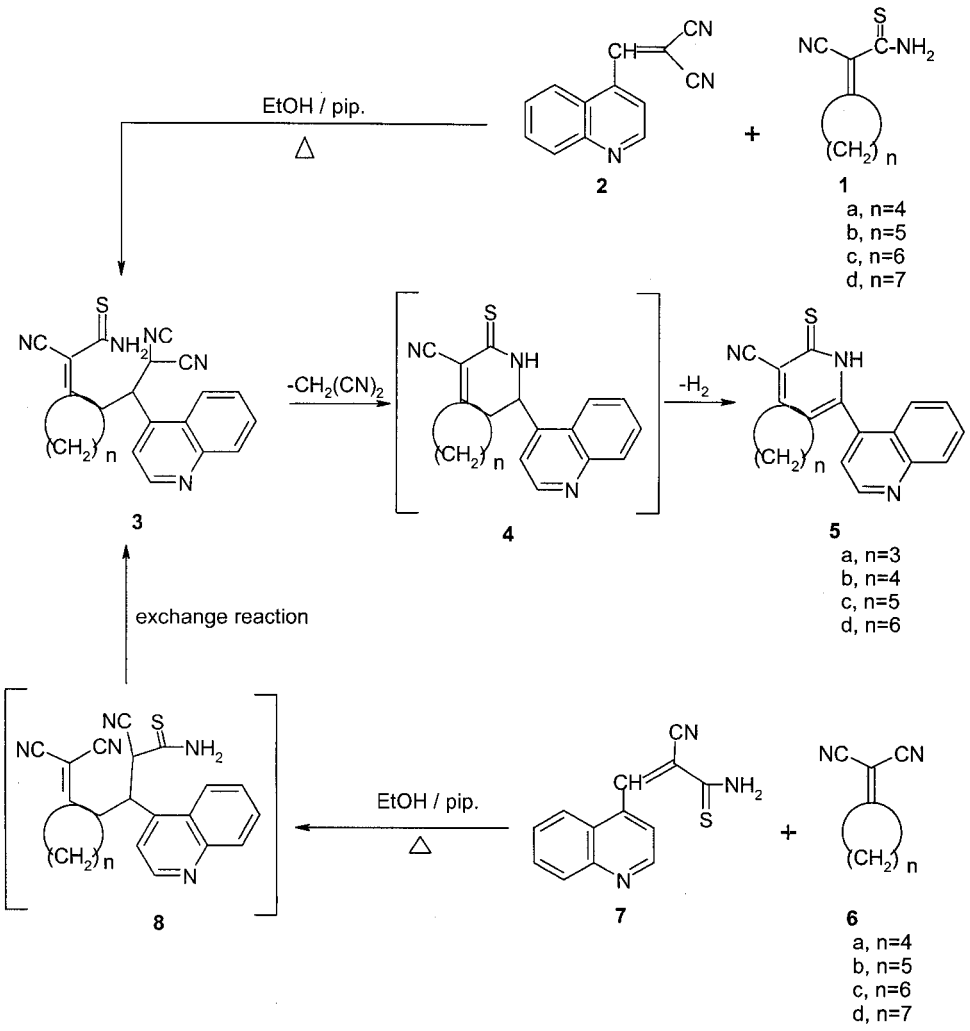

Chart 1.

EXPERIMENTAL

All evaporations were carried out under reduced pressure at 40°C. M.p.s are uncorrected. Aluminun sheets coated with silica gel F_{254} (Merck) were used for TLC. Detection was effected by viewing under a short-wavelength UV lamp. IR spectra were obtained (KBr disk) on a Pye Unicam spectra 1000. ^{1}H NMR and ^{13}C NMR spectra were measured on a Wilmad 270 MHz or on a Vairan 400 MHz spectrometer for solution in $CDCl_3$ or $(CD_3)_2SO$ with $SiMe_4$ as internal standard. *J* Values are given in Hz. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

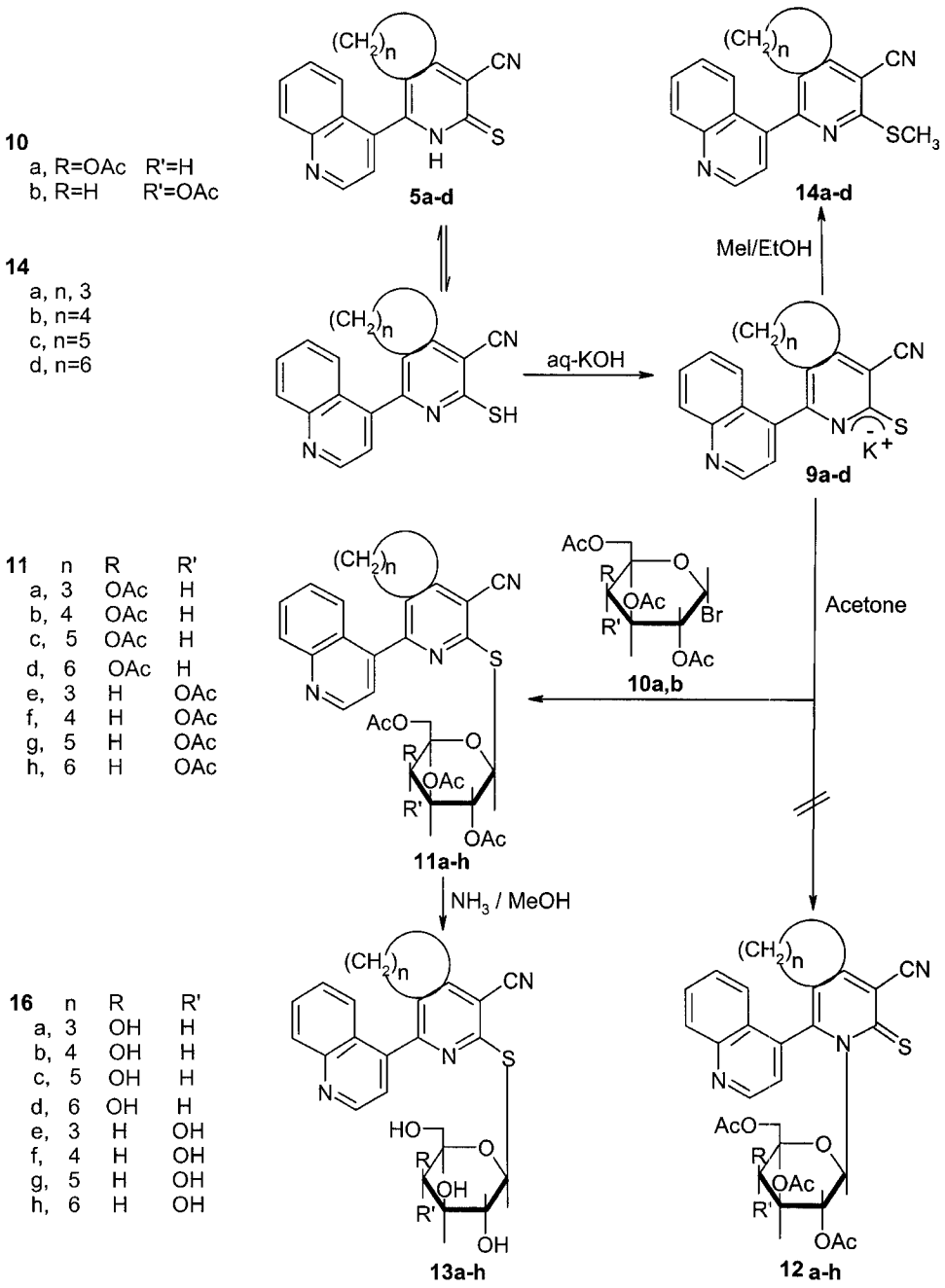

Chart 2.

Cycloalkylidenecyanothioacetamides **1a–d**, quinoline-4-ylidenemalononitrile **2**, cycloalkylidenemalononitriles **6a–d** and quinoline-4-ylidenecyanothioacetamide **7** were prepared following literature procedures.[8]

Cycloalkane Ring-Fused 6-(4-Quinolinyl)-3-cyanopyridine-2-(1*H*)-thiones 5a–d

General Procedures

To a mixture of **1a–d** and **2** or **6a–d** and **7** (0.01 mol each) in ethanol (50 mL), pipridine (1 mL) was added. The mixture was heated under reflux for 2 h and then set aside overnight. The resultant precipitate was filtered off and crystallized from the appropriate solvent.

5a: yellow, from EtOH; m.p: 238–240°C; yield: (70%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN) ^{1}H NMR: 2.00 (m, 2H, CH_2); 2.31 (m, 2H, CH_2); 3.03 (m, 2H, CH_2); 7.83–7.90 (m, 4H, quinolyl-H); 8.16 (d, 2H, quinolyl-H); 14.62 (br, 1H, NH). ^{13}C NMR: 22.3–32.5 ($3 \times CH_2$); 112.8 (C-5); 116.2 (CN); 121 (C-3); 121–132.8 (quinolyl-C); 152.8 (C-4); 155.3 (C-6); 176.1 (C=S). Anal. Calcd for $C_{18}H_{13}N_3S$: C, 71.28; H, 4.29; N, 13.86; S, 10.7. Found: C, 71.5; H, 4.0; N, 14.0; S, 10.9%.

5b: yellow, from EtOH; m.p: 265°C; yield: (80%). IR: ν_{max}/cm^{-1} (KBr) 2220 (CN). ^{1}H NMR: 1.62 (m, 2H, CH_2); 1.83 (m, 2H, CH_2); 2.78 (m, 2H CH_2); 3.07 (m, 2H, CH_2); 7.82–7.89 (m, 4H, quinolyl-H); 8.17 (d, 2H, quinolyl-H). ^{13}C NMR: 21.1–33.4 ($4 \times CH_2$); 114.6 (C-5); 115.7 (CN), 120.8–133.1 (quinolyl-C); 124 (C-3); 150.8 (C-4); 155 (C-6); 175.2 (C=S). Anal. Calcd. for $C_{19}H_{15}N_3S$: C, 71.92; H, 4.73; N, 13.24; S, 10.09. Found: C, 72.1; H, 4.5; N, 12.9; S, 10.2%.

5c: yellow, from EtOH; m.p: 172°C; yield: (75%). IR: ν_{max}/cm^{-1} (KBr) 2220 (CN). ^{1}H NMR: 1.28 (m, 2H, CH_2); 1.65 (m, 2H, CH_2); 1.73 (m, 2H, CH_2); 2.33 (m, 2H, CH_2); 3.06 (m, 2H, CH_2); 7.83–7.89 (m, 4H, quinolyl-H); 8.15 (d, 2H, quinolyl-H); 14.26 (br, 1H, NH). ^{13}C NMR: 24.8–31.9 ($5 \times CH_2$); 112.8 (C-3); 118.1 (CN); 120.1–131.4 (quinolyl-C); 153.1 (C-4); 158.3 (C-6); 176.2 (C=S). MS: m/e = 331. Anal. Calcd. for $C_{20}H_{17}N_3S$: C, 72.50; H, 5.13; N, 12.68; S, 9.66. Found: C, 72.5; H, 5.0; N, 12.5; S, 9.3%.

5d: yellow, from EtOH; m.p: 190°C; yield: (70%). IR: ν_{max}/cm^{-1} (KBr) 2215 (CN). ^{1}H NMR: 1.11 (m, 2H, CH_2); 1.43 (m, 2H, CH_2); 1.81 (m, 2H, CH_2); 2.20 (m, 2H, CH_2); 2.76 (m, 2H, CH_2); 2.99 (m, 2H, CH_2); 7.00–7.94 (m, 4H, quinolyl-H); 8.09 (d, 2H, quinolyl-H); 14.00 (br, 1H, NH). ^{13}C NMR: 22.5–30.2 ($6 \times CH_2$); 110.1 (C-3); 116.9 (CN); 120.8–130.5 (quinolyl-C); 151.0 (C-4); 155.1 (C-6); 174.8 (C=S). MS: m/e = 345. Anal. Calcd. for

$C_{21}H_{19}N_3S$: C, 73.04; H, 5.51; N, 12.17; S, 9.27. Found: C, 72.9; H, 5.3; N, 12.2; S, 9.3%.

3-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-gluco- and galactopyranosylthio)-1-(4-quinolinyl)cycloalkeno[c]pyridine-4-carbonitriles 11a–h

General Procedures

To a solution of condensed 3-cyanopyridine-2-(1*H*)thione **5** (0.01 mol) in aqueous potassium hydroxide [0.56 g (0.01 mol) in distilled water (6 mL)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **10a**,**b** (4.52 g, 0.01 mol) in acetone (30 mL). The reaction mixture was stirred at room temperature until the reaction was judged complete by TLC (30 min to 2 h). The mixture was 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 the appropriate solvent.

11a: buff, from EtOH; m.p: 160°C; yield: (65%). UV: ν_{max} 218, 268, 316. IR: ν_{max}/cm^{-1} (KBr) 2222 (CN). Anal. Calcd. for ($C_{32}H_{31}N_3O_9S$): C, 60.66; H, 4.89; N, 6.63; S, 5.05. Found: C, 60.5; H, 4.6; N, 6.5; S, 4.9%.

11b: yellow, from EtOH; m.p: 140°C; yield: (65%). UV: λ_{max} 220, 262, 340 nm. IR: ν_{max}/cm^{-1} (KBr) 2223 (CN). MS: m/e = 647. Anal. Calcd. for $C_{33}H_{33}N_3SO_9$: C, 61.20; H, 5.10; N, 6.49; S, 4.94. Found: C, 61.5; H, 4.9; N, 6.5; S, 5.0%.

11c: yellow, from EtOH; m.p: 119°C; yield: (65%). UV: λ_{max} 224, 266, 340 nm. IR: ν_{max}/cm^{-1} (KBr) 2224 (CN). ^{1}H NMR: 1.35 (m, 2H, CH_2); 1.66 (m, 2H, CH_2); 1.78 (m, 2H, CH_2); 1.96–2.05 (4s, 12H, 4 × CH_3CO); 2.32 (m, 2H, CH_2); 3.25 (m, 2H, CH_2); 4.02 (m, 2H, H-6′,6″); 4.15 (m, 1H, H-5′); 5.03 (m, 1H, H-4′); 5.16 (d, 1H, H-3′); 5.59 (t, 1H, H-2′); 6.21 (d, $J_{1',2'}$, 11.28 Hz, 1H, H-1′); 7.84–7.89 (m, 4H, quinolyl-H); 8.17 (d, 2H, quinolyl-H) ^{13}C NMR: 21.9 (4 × CH_3); 22.2–32.4 (4 × CH_2); 61.7 (C-6′); 67.8 (C-4′); 69.1 (C-2′); 73.0 (C-3′); 74.9 (C-5′); 80.1 (C-1′); 105 (C-3); 114 (CN); 121–134.1 (quinolyl-C); 131.1 (C-5); 149.8 (C-4); 152.4 (C-6); 155 (C−S); 169.2–170.4 (4 × CO). MS: m/e = 661. Anal. Calcd. for $C_{34}H_{35}N_3O_9S$: C, 61.72; H, 5.29; N, 6.35; S, 4.84. Found: C, 61.6; H, 5.2; N, 6.1; S, 4.7%.

11d: yellow, from EtOH; m.p: 178°C; yield: (65%). UV: λ_{max} 220, 264, 340 nm. IR: ν_{max}/cm^{-1} (KBr) 2226 (CN). Anal. Calcd. for $C_{35}H_{37}N_3SO_9$: C, 62.22; H, 5.48; N, 6.20; S, 4.74. Found: C, 62.5; H, 5.5; N, 5.9; S, 4.8%.

11e: yellow, from EtOH; m.p: 120°C; yield: (80%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN). Anal. Calcd. for $C_{32}H_{31}N_3SO_9$: C, 60.66; H, 4.89; N, 6.63; S, 5.05. Found: C, 60.5; H, 4.6; N, 6.3; S, 4.9%.

11f: yellow, from EtOH; m.p: 117°C; yield: (75%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN). ^{1}H NMR: 1.62 (m, 2H, CH_2); 1.78 (m, 2H, CH_2); 2.05–2.08 (4s, 12H, $4 \times CH_3CO$); 2.71 (m, 2H, CH_2); 2.83 (m, 2H, CH_2); 3.98 (m, 2H, H-6′,6″); 4.18 (m, 1H, H-5′); 5.19 (m, 1H, H-4′); 5.24 (d, 1H, H-3′); 5.59 (t, 1H, H-2′); 6.21 (d, $J_{1',2'}$, 9.9 Hz, 1H, H-1′); 7.84–7.89 (m, 4H, quinolyl-H); 8.30 (d, 2H, quinolyl-H). ^{13}C NMR: 21.2 ($4 \times CH_3$); 24.8–27.11 ($4 \times CH_2$); 61.7 (C-6′); 67.8 (C-4′); 69.1 (C-2′); 74.9 (C-3′); 76.2 (C-5′); 80.1 (C-1′); 105 (C-3); 114 (CN); 121–134.1 (quinolyl-C); 131.1 (C-5); 149.8 (C-4); 152.4 (C-6); 155 (C–S); 169.2–170.4 ($4 \times CO$). MS: m/e = 647. Anal. Calcd for $C_{33}H_{33}N_3SO_9$: C, 61.20; H, 5.10; N, 6.49; S, 4.94. Found: C, 61.0; H, 5.0; N, 7.1; S, 5.1%.

11g: yellow, from EtOH; m.p: 118°C; yield: (70%) IR: ν_{max}/cm^{-1}(KBr) 2222 (CN). Anal. Calcd. for $C_{34}H_{35}N_3SO_9$: C, 61.72; H, 5.29; N, 6.35; S, 4.84. Found: C, 61.6; H, 5.1; N, 6.1; S, 4.6%.

11h: yellow, from EtOH; m.p: 238–240°C; yield: (62%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN). Anal. Calcd. for $C_{35}H_{37}N_3SO$: C, 62.22; H, 5.48; N, 6.20; S; 4.74. Found: C, 62.1; H, 5.6; N, 5.9; S, 4.5%.

3-(β-D-Gluco- and galactopyranosylthio)-1-(4-quinolinyl)cycloalkeno[c]pyridine-4-carbonitriles 13a–h

General Procedures

Dry gaseous ammonia was passed through a solution of protected glycoside **11a**–**h** (0.5 g) in dry methanol (20 mL) at 0°C for ca 0.5 h. Then the mixture was stirred at 0°C until reaction was judged complete (2–6 h). The mixture was evaporated at 40°C to give a solid residue, which was crystallized from the appropriate solvent.

13a: brown, from MeOH; m.p: 211°C; yield: (60%). UV: λ_{max} 217, 272, 340 nm. IR: ν_{max}/cm^{-1} (KBr) 3375 (OH); 2219 (CN). Anal. Calcd. for $C_{24}H_{23}N_3O_5S$: C, 61.39; H, 4.94; N, 9.03; S, 6.88. Found: C, 61.2; H, 5.0; N, 8.7; S, 6.6%.

13b: yellow, from EtOH; m.p: 158°C; yield: (80%). UV: λ_{max} 220, 266, 340 nm. IR: ν_{max}/cm^{-1} (KBr) 3397 (OH); 2222 (CN). ^{1}H NMR: 1.55 (m, 2H, CH_2); 1.78 (m, 2H, CH_2); 2.78 (m, 2H, CH_2); 2.97 (m, 2H, CH_2); 3.29 (m, 2H, H-6′,6″); 3.34 (m, 1H, H-5′); 3.42 (m, 1H, H-4′); 3.50 (m, 1H, H-3′); 3.69 (m,

1H, H-2′), 4.49 (t, 1H, 2′-OH); 5.06 (t, 1H, 3′-OH); 5.24 (t, 1H, 4′-OH); 5.58 (d, 1H, 6′-OH); 5.63 (d, $J_{1',2'}$, 10.4 Hz, 1H, H-1′); 7.79–7.88 (m, 4H, quinolyl-H); 8.16 (d, 2H, quinolyl-H). ^{13}C NMR: 21.7 ($4 \times CH_3$); 22.5–33.2 ($4 \times CH_2$); 61.7 (C-6′); 66.1 (C-4′); 73.2 (C-2′); 78.9 (C-3′); 81.2 (C-5′); 82.1 (C-6′); 104 (C-5); 114 (CN); 122–134.2 (quinolyl-C); 132.0 (C-3); 159.1 (C-4); 154.0 (C-6); 168 (C−S). Anal. Calcd. for $C_{25}H_{25}N_3O_5S$: C, 62.63; H, 5.21; N, 8.76; S, 6.68%. Found: C, 62.5; H, 5.0; N, 8.4; S, 6.5%.

13c: yellow, from MeOH; m.p: 218°C; yield: (60%). UV: λ_{max} 220, 270, 316 nm. IR: ν_{max}/cm^{-1} (KBr) 3387 (OH); 2221 (CN). ^{1}H NMR: 1.34 (s, 2H, CH_2); 1.65 (s, 2H, CH_2); 1.72 (s, 2H, CH_2); 2.29 (m, 2H, CH_2); 3.15 (m, 2H, CH_2); 3.25 (m, 2H, H-6′,6″); 3.34 (m, 1H, H-5′); 3.40 (m, 1H, H-4′); 3.51 (t, 1H, H-3′); 3.68 (t, 1H, H-2′); 4.47 (t, 1H, 2′-OH); 5.05 (t, 1H, 3′-OH); 5.22 (t, 1H, 4′-OH); 5.56 (d, 1H, 6′-OH); 5.65 (d, $J_{1',2'}$, 9.8 Hz, 1H, 1′-H); 7.81–7.88 (m, 4H, quinolyl-H); 8.17 (d, 2H, quinolyl-H). ^{13}C NMR: 25.1–38.1 ($4 \times CH_2$); 61.2 (C-6′); 69.9 (C-4′); 74.1 (C-2′); 80.1 (C-3′); 82.2 (C-5′); 84.5 (C-1′); 106.1 (C-5); 115 (CN), 121.1–130.2 (quinolyl-C), 132.0 (C-3), 151.9 (C-4), 155.8 (C-6); 168 (C−S). MS: m/e = 493. Anal. Calcd. for $C_{26}H_{27}N_3O_5S$: C, 63.28; H, 5.47; N, 8.51; S, 6.40. Found: C, 63.0; H, 5.5; N, 8.2; S, 6.2%.

13d: yellow, from MeOH; m.p: 210°C; yield: (60%). UV: λ_{max} 220; 268; 340 nm. IR: ν_{max}/cm^{-1} (KBr) 3600–3200 (OH); 2221 (CN). ^{1}H NMR: 1.22 (s, 2H, CH_2); 1.33 (m, 2H, CH_2); 1.79 (m, 2H, CH_2); 2.29 (m, 2H, CH_2); 2.73 (s, 2H, CH_2); 2.88 (s, 2H, CH_2); 3.45–3.70 (m, 6H, H-6′,6″, 5′, 4′, 3′, 2′-H); 4.46 (t, 1H, 2′-OH); 5.02 (t, 1H, 3′-OH); 5.21 (d, 1H, 4′-OH); 5.55 (d, 1H, 6′-OH); 5.63 (d, $J_{1',2'}$, 10.75 Hz, 1H, 1′-H); 7.79–7.88 (m, 4H, quinolyl-H); 8.15(d, 2H, quinolyl-H) ^{13}C NMR: 24.8–35.1 ($5 \times CH_2$); 60.1 (C-6′); 70.1 (C-4′); 72.1 (C-2′); 78.9 (C-3′); 81.9 (C-5′); 84.0 (C-1′); 115 (CN); 121.1–130.2 (quinolyl-C), 132.0 (C-5), 149.8 (C-4), 156.0 (C-6); 169 (C−S). MS: m/e = 507. Anal. Calcd. for $C_{27}H_{29}N_3O_5S$: C, 63.90; H, 5.71; N, 8.28; S, 6.31. Found: C, 64.0; H, 5.5; N, 7.9; S, 5.9%.

13e: yellow, from EtOH; m.p: 158°C; yield: (80%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN). Anal. Calcd. for $C_{24}H_{23}N_3O_5S$: C, 60.66; H, 4.89; N, 6.63; S, 5.05. Found: C, 60.4; H, 5.1; N, 6.5; S, 5.1%.

13f: yellow, from EtOH; m.p: 169°C; yield: (70%). IR: ν_{max}/cm^{-1} (KBr) 3480–3333 (OH); 2221 (CN). ^{1}H NMR: 2.51 (m, 2H, CH_2); 2.65 (m, 2H, CH_2); 2.86 (m, 2H, CH_2); 3.31 (m, 2H, CH_2); 3.97 (m, 2H, H-6′,6″); 3.42 (m, 1H, H-5′); 4.55 (m, 1H, H-4′); 5.12 (m, 1H, H-3′); 5.12 (m, 1H, H-2′); 5.48 (t, 1H, 2′-OH); 5.58 (t, 1H, 3′-OH); 5.68 (t, 1H, 4′-OH); 5.69 (d, 1H, 6′-OH); 5.72 (d, $J_{1',2'}$, 9.9 Hz, 1H, 1′-H); 7.55–7.55 (m, 4H, quinolyl-H); 8.35 (d, 2H, quinolyl-H). ^{13}C NMR: 24.8–35.1 ($5 \times CH_2$); 60.1 (C-6′); 70.1 (C-4′); 72.1 (C-2′); 78.9 (C-3′); 81.9 (C-5′); 84.0 (C-1′); 115 (CN); 121.1–130.2 (quinolyl-C),

132.0 (C-5), 149.8 (C-4), 156.0 (C-6); 169 (C–S). Anal. Calcd. for $C_{25}H_{25}N_3O_5S$: C, 61.1; H, 5.09; N, 8.55; S, 6.52. Found: C, 61.4; H, 5.1; N, 8.5; S, 6.2%.

13g: yellow, from EtOH; m.p: 155°C; yield: (65%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN). Anal. Calcd. for $C_{26}H_{27}N_3O_5S$: C, 63.28; H, 5.74; N, 8.51; S, 6.40. Found: C, 62.9; H, 5.5; N, 8.3; S, 6.0%.

13h: yellow, from EtOH; m.p: 150°C; yield: (70%). IR.: ν_{max}/cm^{-1} (KBr) 2222 (CN). Anal. Calcd. for $C_{27}H_{29}N_3O_5S$: C, 63.90; H, 5.71; N, 8.28; S, 6.3. Found: C, 64.1; H, 5.5; N, 7.9; S, 5.9%.

3-(Methylthio)-1-(4-quinolinyl)-cycloalkeno[c]pyridine-4-carbonitriles 14a–d

General Procedures

To a solution of condenced 3-cyanopyridine-2(1*H*) thione **5** (0.01 mol) in ethanol (30 mL) was added aqueous potassium hydroxide [0.56 g (0.01 mol) in distilled water (1 mL)]. The reaction mixture was stirred at room temperature until the reaction mixture was judged complete (30 min to 3 h). A solution of methyl iodide (0.01 mol) was added and the reaction mixture was heated at reflux for 3 h. The mixture was left to cool at room temperature and the resultant precipitate was filtered off and crystallized from the appropriate solvent.

14a: yellow, from EtOH; m.p: <300°C; yield: (60%). IR: ν_{max}/cm^{-1} (KBr) 2221 (CN). MS: m/e = 331. Anal. Calcd. for $C_{19}H_{15}N_3S$: C, 71.92; H, 4.73; N, 13.24; S, 10.09. Found: C, 71.7; H, 4.5; N, 13.6; S, 9.7%.

14b: buff, from EtOH; m.p: <300°C; yield: (70%). UV: λ_{max} 216, 267, 348 nm. IR: ν_{max}/cm^{-1} (KBr) 2220 (CN). ^{1}H NMR: 2.51 (m, 2H, CH_2); 2.58 (m, 4H, $2CH_2$); 2.63 (s, 3H, SCH_3); 2.83 (m, 2H, CH_2); 7.33–7.52 (m, 4H, quinolyl-H); 8.34–8.37 (d, 2H, quinolyl-H). ^{13}C NMR: 13.23 ($2 \times CH_2$); 24.25 (SCH_3); 26.64 ($2 \times CH_2$); 104.1 (C-3); 115.27 (CN); 125.42–132.67 (quinolyl-C); 142.7 (C-5); 145.5 (C-4); 154.2 (C-6); 160.93 (C-2). MS: m/e = 331. Anal. Calcd. for $C_{20}H_{17}N_3S$: C, 72.50; H, 5.13; N, 12.68; S, 9.66. Found: C, 72.1; H, 5.4; N, 12.9; S, 10.0%.

14c: yellow, from EtOH; m.p: 260–262°C; yield: (60%). UV: λ_{max} 216, 268, 340 nm. IR: ν_{max}/cm^{-1} (KBr) 2220 (CN). Anal. Calcd. for $C_{21}H_{19}N_3S$: C, 73.04; H, 5.50; N, 12.17; S, 9.27. Found: C, 73.2; H, 5.5; N, 12.6; S, 9.5%.

14d: yellow, from EtOH; m.p: 240–242°C; yield: (63%). IR: ν_{max}/cm^{-1} (KBr) 2220 (CN). Anal. Calcd. for $C_{22}H_{21}N_3S$: C, 73.53; H, 5.84; N, 11.69; S, 8.91. Found: C, 73.2; H, 5.5; N, 11.4; S, 8.7%.

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