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Novel synthesis of *S*-glycosides derived from 5,6-di-substituted thieno[2,3-*d*]pyrimidin-4-one-2-thiones

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A synthesis of a new class of thioglycosides by reactions of 5,6-disubstituted thieno[2,3-*d*]pyrimidine-4-one-2-thiones with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or its α-D-galactopyranosyl isomer is described.

Keywords: Thieno[2,3-*d*]pyrimidine-4-one-2-thione; *S*-Nucleosides, α-Bromoacetoglucose; α-Bromoacetogalactose

1. Introduction

Recently, significant progress has been made in the development of antiviral chemotherapy due to the discovery of nucleoside analogues with potential activities [1]. Many modified nucleosides were found to compete with natural nucleosides as substrates for the reverse transcriptase enzyme [2, 3]. The most effective drugs against HIV (Human Immuno Deficiency Virus) are the dideoxy nucleosides AZT (Retrovir, Zidovudine) [4], ddC (Zalcitabine, Hivid) [5], D4T (Stavudine, Zerit), and DdI (Didanosine, Videx) [6] (scheme 1). The first non-nucleoside inhibitor HEPT has been used extensively as a lead compound in the development of more effective drugs against HIV [7, 8]. Compounds such as MKC 442 have been selected for clinical tests (now in phase III) [9–11]. The MKC-442 sulfur derivatives are among the most active compounds against HIV and up to 20 times more active against HIV-1 than AZT [9–11]. Other active pyrimidine and thieno[2,3-*d*] pyrimidine nucleosides have recently been synthesized as antiviral agents against HIV-1 and Herpes simplex virus (HSV-1) [12–14]. However, thioglycosides of thieno[2,3-*d*]pyrimidine are not known in the literature. In extension of our work on *C*-nucleosides [14–16] and thieno-[2,3-*d*]pyrimidines [17–19], I here report preparations of thioglycosides of thieno[2,3-*d*]pyrimidine, which may show enhanced biological activities.

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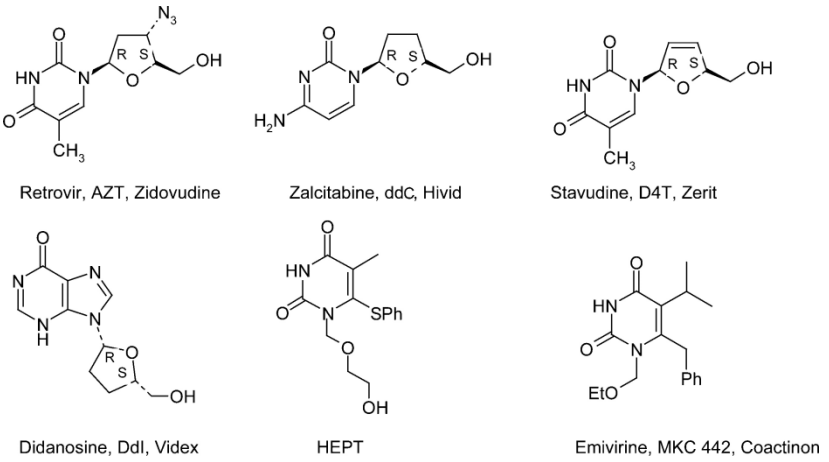
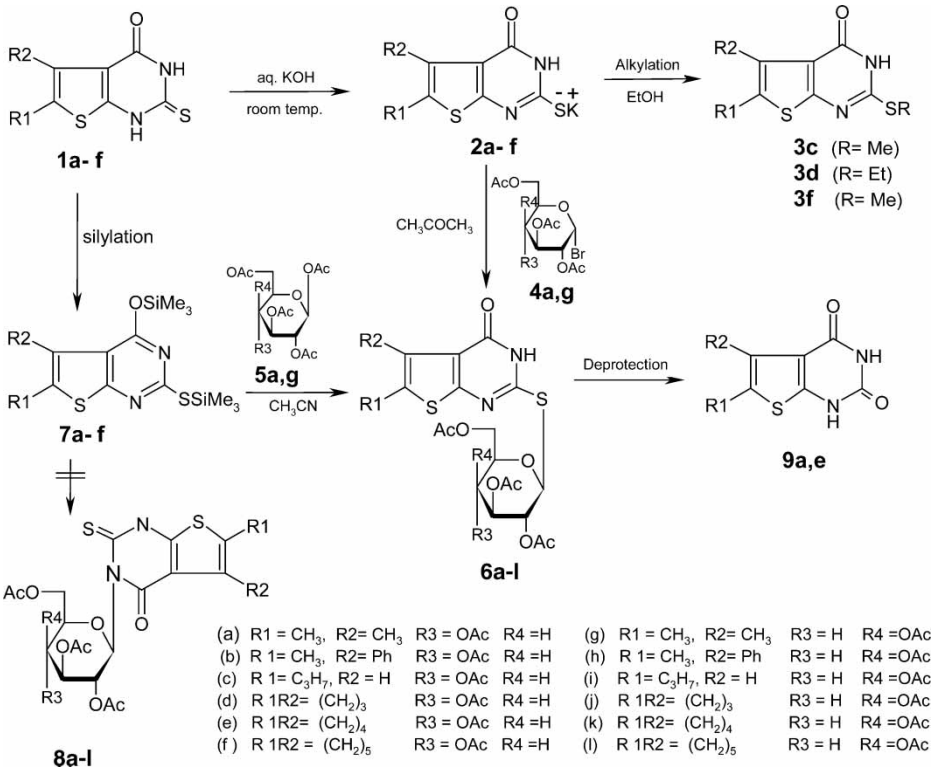


SCHEME 1

2. Results and discussions

Key intermediates for the syntheses of the thioglycosides shown in scheme 2 were the 5,6-disubstituted thieno[2,3-*d*]pyrimidine-4-one-2-thiones (**1**). The heterocycles **1** were routinely prepared by reactions of the β-enamino esters with potassium thiocyanate in presence of concentrated hydrochloric acid according to a reported procedure [20]. Compounds **1** bearing at C-5 and C-6 different functional substituents were found useful for syntheses of the interesting *S*-glycosides. As a model experiment the alkylation of **1** was carried out by reaction of one equivalent of alkyl iodide with the potassium salt **2** generated in situ by the reaction of **1** with alcoholic potassium hydroxide. The structure of the new alkylated products **3** was confirmed by all spectroscopic data. The ^{1}H NMR spectrum of 2-ethylthio-3,5,6,7-tetrahydro-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one **(3d)** as an example showed a triplet at δ 1.42 ppm assigned to the -CH_3 group, and the ^{13}C NMR spectrum showed signals at δ 13.9 (CH_3), 24.7 (SCH_2), and 168.6 (C-2). These data indicate that the site of the alkylation is the sulfur atom rather than the nitrogen atom.

Analogously, coupling of compounds **2a–f** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **(4a)** in acetone afforded the *S*-glycosylated nucleosides **6a–f** in good yields (66–74%) (scheme 2). Thin layer chromatography (chloroform/methanol = 9:1 or ethanol/benzene = 8:2) indicated formation of the pure compounds. The structures of the products **6a–f** were confirmed by elemental analyses and spectral data (MS, IR, ^{1}H NMR, ^{13}C NMR) (see Experimental). For instance, analytical data for compound **6a** revealed a molecular formula $C_{22}H_{26}N_2O_{10}S_2$ (M^+ 542). The ^{1}H NMR spectrum showed the anomeric proton of the glucose moiety as a doublet at δ 5.68 ppm with a coupling constant $^3J = 10.5$ Hz indicating β-configuration of the anomeric center. The other protons of the glucopyranose ring resonated at δ 3.96–5.35 ppm, while the four acetoxy groups appeared as four singlets at 2.02–2.08 ppm. The ^{13}C NMR revealed the absence of a thione carbon atom at about $\delta = 184$ ppm [21]. The resonance of the –N=C–N– carbon atom (C2) at δ 159.41 ppm was identical to the chemical shift of the corresponding carbon atom of compound **3a** [22]. The signals at δ 169.30, 169.37, 170.06, 170.80 ppm are due to the four acetoxy carbonyl carbon atoms, and the four signals at δ 20.57–20.70 ppm are assigned to the acetate methyl carbon atoms. The five signals at δ 61.85, 68.00, 69.23, 73.76, 76.43 ppm were assigned to C-6′, C-4′, C-2′, C-3′, and C-5′, respectively. The IR spectrum of compound **6a** didn't show the signal of a thione group

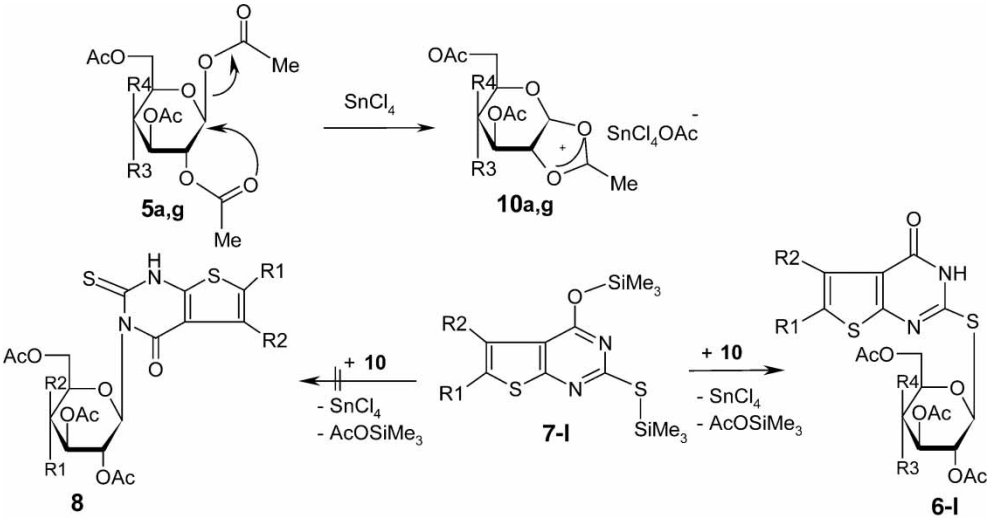


SCHEME 2

but exhibited bands at 1662 cm^{-1} for the C=O group, and at 3280 cm^{-1} for the NH group. Stretching vibration frequencies of the acetate carbonyl groups appeared at 1750–1760 cm^{-1}. The UV spectrum of **6a** proved that the reaction had led selectivity to the formation of *S*-glycoside derivatives and excluded the formation of *N*-glycoside. Both compounds **6a** and the *S*-methyl compound **3a** showed UV absorption maxima at 320 nm. Similarly, the reactions of the heterocyclic bases **1a–f** with 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide **4g** furnished the *S*-glycosated products **6g–l**. The structural assignments of these products are based on their elemental analyses and the spectral data (Experimental).

Furthermore, we developed a preparative alternative for the thieno[2,3-*d*]pyrimidine thioglycosides **6**. Silylations of compounds **1a–f** afforded the silylated products **7a–f**, which reacted with β-D-glucose pentaacetate **5a** or β-D-galactose pentaacetate **5g** in dry acetonitrile in the presence of stannic chloride to furnish the *S*-glycosyl products **6a–l**. A mechanistic proposal for the formation of the *S*-glycosides **6** from the silylated compounds **7** is shown in scheme 3.

Attempted deprotection of **6a,d** with ammonia in methanol did not give the anticipated deacetylated derivatives but furnished compounds **9a,e** by hydrolytic cleavage of the C-S bonds. The spectra of these known products are identical to those reported in the literature [23–26]. Hydrolysis of the *S*-glycoside **6a** with 9% aqueous HCl afforded compound **9a** in agreement with the *S*-glycosidic structure of **6a**. A distinction between the *N*- and *S*-glycosides was possible by comparison of the ^{1}H NMR and ^{13}C NMR spectra with those of literature data of similar compounds [27–34]. ^{13}C=S Chemical shifts of δ 173–176 ppm are reported for 2-thiouracil derivatives, while *S*-substituted 2-thiouracils show chemical shifts of C-2 at δ 158–168 ppm. Some literature data of *N*- and *S*-glycosides are shown in chart 1.



SCHEME 3

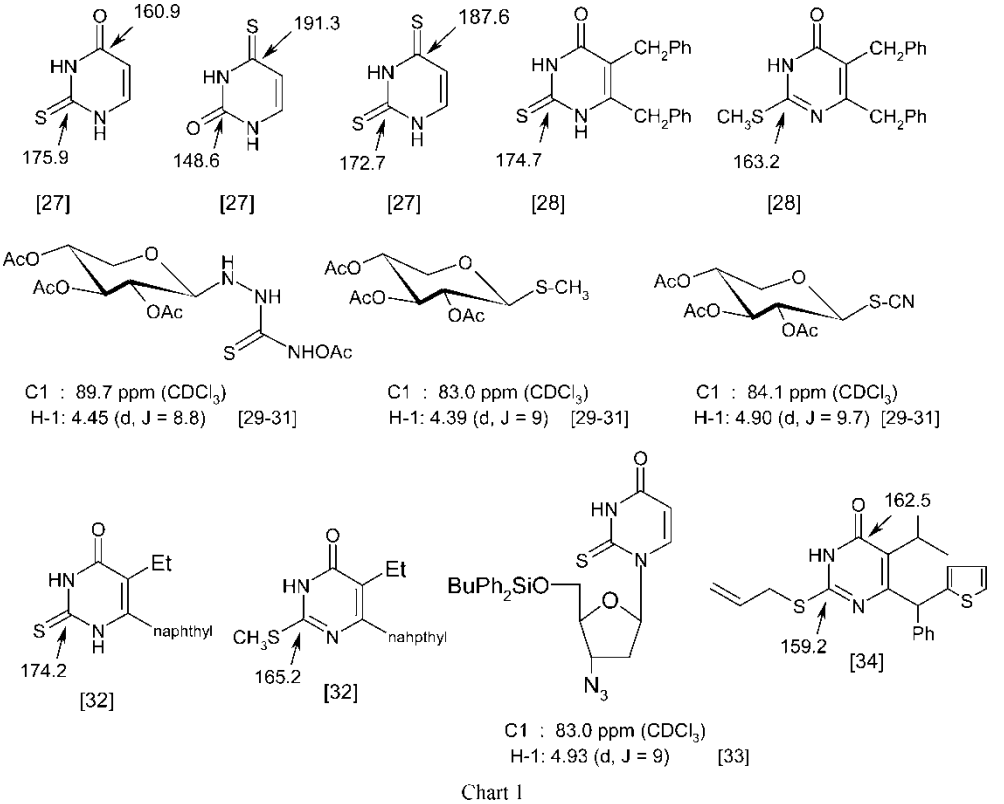


Chart 1

3. Conclusions

This paper presents a facile route for the preparation of a new class of thioglycosides of thieno[2,3-*d*]pyrimidine through the reaction of 5,6-disubstituted thieno[2,3-*d*]pyrimidine-4-one-2-thiones with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or its α-D-galactopyranosyl isomer. The prepared thioglycosides are the first *S*-cyclic nucleosides

described in the literature related to thieno[2,3-*d*]pyrimidine ring system. This should be beneficial for the synthesis of analogues with potentially useful pharmacological properties.

4. Experimental

The melting points are uncorrected and were measured using an Electro-thermal IA 9100 apparatus. The IR spectra were recorded as potassium bromide pellets on a Nexus 670 spectrophotometer; wave numbers ν (cm^{-1}) are reported. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded with Bruker WM-250 and AC-250 spectrometers (Konstanz University, Germany) and a Jeol-Ex-270 spectrometer (NRC, Cairo-Egypt). Coupling constants J are reported in Hz and chemical shifts in ppm (δ values) against TMS as internal reference. Mass spectra were recorded on EI+Q1 MSLMR UPLR spectrometers. Microanalyses were carried out with a Vario El Elmental apparatus, their results were found to be in good agreement with the calculated values.

4.1 *2,3-Dihydro-5-isopropyl-2-thioxo-thieno[2,3-d]pyrimidin-4(1H)-one (1c)*

A mixture of 2-amino-4-isopropyl-thiophene-3-ethylcarboxylate [35] (21.30 g, 100 mmol) and potassium thiocyanate (9.70 g, 100 mmol) was heated under reflux in dioxane (100 ML) for 30 minutes. The reaction mixture was allowed to cool and then 37% concentrated hydrochloric acid was added. The resultant suspension was refluxed for 4 h, and then poured onto water. The solid product, so formed, was filtered off, dried and subjected to treatment with boiling aqueous solution of NaOH (30%). The clear solution was filtered, neutralized with HCl (37%). The precipitated solid was collected by filtration, washed with hot water (5 × 10 mL), ethanol (3 × 5 mL), dried and crystallized from dioxane to give (13.20 g, 58%) of **1c**; Mp: 174–176 °C; IR (KBr) ν (cm^{-1}): 3239 (NH), 1675 (C=O), 1620 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.18 (d, 6H, $2CH_3$), 3.46 (m, 1H, CH), 6.87 (s, 1H, H-6), 12.32 (br, 1H, NH, D_2O exchangeable), 13.45 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.61 (2 CH_3), 27.87 (CH), 111.40 (C-4a), 115.95 (C-6), 145.60 (C-5), 152.90 (C-7a), 156.90 (C=O), 172.99 (C=S); MS: $m/z = 226$ (M^+); Calcd. (%) for $C_9H_{10}N_2OS_2$ (226.32): C; 47.76, H; 4.45, N; 12.38, S; 28.33. Found: C; 47.77, H; 4.45, N; 12.36, S; 28.32.

5. General procedure for the alkylation of 1c, d, f

To a warm solution of KOH (0.14 g, 2.50 mmol) in EtOH (20 mL) was added **1c, d, f** (2.50 mmol). The mixture was boiled under reflux for 30 minutes. After cooling to room temperature, a solution of iodomethane (0.43 g, 3 mmol) or iodoethane (0.47 g, 3 mmol) in EtOH (5 mL) was added. The reaction mixture was boiled on water bath for 1 h and then stirred at room temperature for 12 h. The separated solid was filtered off, washed with H_2O (3 × 5 mL), cold EtOH (2 × 2 mL), dried and crystallized from EtOH to afford **3c, d, f**.

5.1 *6-Isopropyl-2-methylthio-3H-thieno[2,3-d]pyrimidin-4-one (3c)*

Yield: (0.56 g, 93%). Mp: 181–182 °C; IR (KBr) ν (cm^{-1}): 3230 (NH), 1666 (C=O), 1619(C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.23 (2s, 6H, 2 CH_3), 2.48 (s, 3H, SCH_3), 3.56 (m, 1H, CH), 7.01 (s, 1H, CH-6), 12.52 (br, 1H, NH, D_2O exchangeable). MS: m/z 240

(M^+). Calcd. (%) for $C_{10}H_{12}N_2OS_2$ (240.35): C; 49.97, H; 5.03, N; 11.66, S; 26.68. Found: C; 49.96, H; 5.02, N; 11.65, S; 26.67.

5.2 *2-Ethylthio-3,5,6,7-tetrahydro-cyclopenta[4,5]thieno[2,3-d]-pyrimidin-4-one (3d)*

Yield: (0.62 g, 98%). Mp: 189–191 °C; IR (KBr) ν (cm^{-1}): 3390 (NH), 1660 (C=O), 1621(C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.42 (t, 3H, CH_3), 2.45 (m, 2H, CH_2), 2.91 (m, 4H, CH_2), 3.06 (m, 2H, CH_2), 9.75 (br, 1H, NH, D_2O exchangeable); ^{13}CNMR (DMSO-d_6) δ (ppm): 13.9 (CH_3), 24.7 (SCH_2), 27.5, 28.6, 28.9 ($3CH_2$), 116.7(C-5), 135.6(C-4a), 139.4 (C-6), 154.5 (C-7a), 158.7 (C=O), 168.6 (C=N). MS: $m/z = 252$ (M^+). Calcd. (%) for $C_{11}H_{12}N_2OS_2$ (252.36): C; 52.36, H; 4.79, N; 11.10, S; 25.41. Found: C; 52.39, H; 4.81, N; 11.10, S; 25.40

5.3 *2-Methylthio-3,5,6,7,8,9-hexahydro-3H,5H-cyclohepta[4,5]-thieno[2,3-d] pyrimidin-4(4H)-one (3f)*

Yield: (0.57 g, 85%). Mp: 259–261 °C; IR (KBr) ν (cm^{-1}): 3448 (NH), 1654 (CO) C7 (SH); $\lambda_{max} = 320$ nm; ^{1}H NMR (DMSO-d_6) (ppm): 1.6 (m, 4H, $2CH_2$), 1.9 (m, 2H, CH_2), 2.5 (s, 3H, CH_3), 2.8 (m, 2H, CH_2), 3.2 (m, 2H, CH_2), 12.3 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 12.7 (CH_3), 26.7, 27.3, 28.8, 31.7 (CH_2), 119.5 (C-5), 134.2 (C-4a), 136.0 (C-6), 155.8 (C-7a), 158.4 (C=N), 161.2 (C=O). MS: (m/z), 266.0 (M^+). Calcd. (%) for $C_{12}H_{14}N_2S_2O$ (266.38): C; 54.10, H; 5.29, N; 10.51, S; 24.07. Found. C; 54.33, H; 5.00, N; 10.50, S; 24.09.

6. Preparation of the acetylated nucleosides (6); general procedure

Method A: To a solution of **1** (5 mmol) in aqueous potassium hydroxide [(0.28 g, 5 mmol) in distilled H_2O (4 mL)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco-or-galacto-pyranosyl bromide **4a** or **4g** (2.14 g, 5.2 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature over night (12 h) and judged to be complete by TLC. The solvent was evaporated under reduced pressure at 40 °C, and the crude product was filtered off and washed with distilled H_2O (3×4 mL) to remove potassium bromide formed. The product was dried, and crystallized from EtOH to afford **6a–l**.

Method B: Compounds **1** (5 mmol) were boiled under reflux, with stirring, under anhydrous conditions for 72 hours with Me_3Si-$SiMe_3$ (HMDS) (50 mL) in the presence $(NH_4)_2SO_4$ (10 mg). The clear solution obtained was cooled and the solvent was evaporated in vacuo to give the silylated compounds **7a–l** as pale yellow oil. To a solution of silylated base in anhydrous MeCN (10 mL) was added a solution of **5a** or **5 g** (5 mmol) in anhydrous acetonitrile (5 mL) followed by addition of $SnCl_4$ (0.8 mL). The reaction mixture was stirred at room temperature for 12 h and judged to be complete by TLC. Then, the mixture was poured into saturated $NaHCO_3$ solution and extracted with EtOAc (100 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to furnish crude nucleosides which were purified by column chromatography (10–25% EtOAc in petroleum ether) to afford the pure nucleosides **6**.

6.1 *5,6-Dimethyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D- glucopyranosy-thio)-3H-thieno-[2,3-d]pyrimidin-4-one (6a)*

Yield (1.87 g, 69%). Mp: 218–220 °C; IR (KBr) ν (cm^{-1}): 3471 (NH), 1746 (CO), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.02–2.08 (4s, 12H, $4CH_3CO$), 2.39 (s, 3H, CH_3), 2.47 (s, 3H,

CH_3), 3.96 (m, 1H, H-5′), 4.21 (m, 2H, H6′, 6″), 5.16 (t, 1H, H-4′), 5.19(m, 1H, H-2′), 5.35 (t, 1H, $J = 9.4$ Hz, H-3′), 5.68 (d, 1H, $J = 10.5$, H-1′), 11.03 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 12.95 (CH_3), 13.01 (CH_3), 20.57–20.70 ($4CH_3$), 61.85 (C-6′), 68.00 (C-4′), 69.23 (C-2′), 73.76 (C-3′), 76.43 (C-5′), 81.93 (C-1′), 121.45 (C-5), 129.45 (C-4a), 129.98 (C-6), 150.22 (C-7a), 159.41 (C-2), 162.49 (C-4), 169.30, 169.37, 170.06, 170.80 (4 C=O); MS: $m/z = 542$ (M^+); Calcd. (%) for $C_{22}H_{26}N_2O_{10}S_2$ (542.59): C; 48.70, H; 4.83, N; 5.16, S; 11.82. Found: C; 48.73, H; 4.81, N; 5.17, S; 11.80.

6.2 *5-Methyl-6-pheny-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyrano-sylthio)-3H-thieno[2,3-d]pyrimidin-4-one (6b)*

Yield (2.02 g, 67%). Mp: 182–184 °C; IR (KBr) ν (cm^{-1}): 3476 (NH), 1749 (CO), 1666 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.11–2.15 (4s, 12H, $4CH_3CO$), 2.62 (s, 3H, CH_3), 3.99 (m, 1H, H-5′), 4.22 (m, 2H, H6′, 6″), 5.16–5.21 (m, 2H, H-4′+H-2′), 5.37 (t, 1H, H-3′), 5.70 (d, 1H, $J = 10.5$, H-1′), 7.36–7.48 (m, 5H, Ph), 11.80 (br, 1H, NH, exchangeable with D_2O; MS: m/z 604 (M^+). Calcd. (%) for $C_{27}H_{28}N_2O_{10}S_2$ (604.66): C; 53.63, H; 4.67, N; 4.63, S; 10.61. Found: C; 53.64, H; 4.69, N; 4.65, S; 10.61.

6.3 *5-Isopropyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-3H-thieno[2,3-d]pyrimidin-4-one (6c)*

Yield (1.98 g, 71%). Mp: 197–199 °C; IR (KBr) ν (cm^{-1}): 3477 (NH), 1741 (CO), 1667 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.24 (d, 6H, $2CH_3$), 1.98-2.04 (4s, 12H, $4CH_3CO$), 3.41 (sep, 1H, CH), 3.95 (m, 1H, H-5′), 4.17 (m, 2H, H6′, 6″), 5.09 (t, 1H, H-4′), 5.11 (m, 1H, H-2′), 5.28 (t, 1H, $J = 9.4$ Hz, H-3′), 5.62 (d, 1H, $J = 10.5$, H-1′), 7.41 (s, 1H, H-thiophene), 11.89 (br, 1H, NH, D_2O exchangeable); MS: m/z 556 (M^+). Calcd. (%) for $C_{23}H_{28}N_2O_{10}S_2$ (556.62): C; 49.63, H; 5.07, N; 5.03, S; 11.52. Found: C; 49.65, H; 5.09, N; 5.04, S; 11.51.

6.4 *2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylthio)-3,5,6,7-tetrahydro-cyclopenta[4,5]thieno-[2,3-d]pyrimidin-4-one (6d)*

Yield (2.05 g, 74%). Mp: 237–239 °C; IR (KBr) ν (cm^{-1}): 3467 (NH), 1747 (CO), 1667(CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04–2.07 (4s, 12H, $4CH_3CO$), 2.48 (m, 2H, CH_2), 2.96 (t, 2H, CH_2), 3.07 (t, 2H, CH_2), 3.98–4.01 (m, 1H, H-5′), 4.15–4.26 (m, 2H, H6′, 6″), 5.12–5.23 (m, 2H, H-4′+ H-2′), 5.38 (t, 1H, H-3′), 5.80 (d, 1H, $J = 10.5$, H-1′), 11.79 (br, 1H, NH, D_2O exchange-able); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.59–20.75 ($4CH_3$), 27.94 (CH_2), 28.97 (CH_2), 29.52 (CH_2), 61.82 (C-6′), 67.94 (C-4′), 69.11 (C-2′), 73.80 (C-3′), 76.24 (C-5′), 81.59 (C-1′), 117.90 (C-5), 138.25 (C-4a), 140.11 (C-6), 150.28 (C-7a), 159.47 (C-2), 168.53 (C-4), 169.41, 169.45, 170.11, 170.80 (4 CO). Calcd. (%) for $C_{23}H_{26}N_2O_{10}S_2$ (554.60): C; 49.81, H; 4.73, N; 5.05, S; 11.56. Found: C; 49.85, H; 4.72, N; 5.07, S; 11.57.

6.5 *2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylthio)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (6e)*

Yield (1.87 g, 66%). Mp: 211–213 °C; IR (KBr) ν (cm^{-1}): 3461 (NH), 1748 (CO), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04–2.08(4s, 12H, $4CH_3CO$), 1.97 (m, 4H, CH_2), 2.78 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 3.96–3.99 (m, 1H, H-5′), 4.16–4.28 (m, 2H, H6′, 6″), 5.14–5.23 (m, 2H, H-4′+ H-2′), 5.37 (t, 1H, H-3′), 5.78 (d, 1H, $J = 10.5$, H-1′), 11.55 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.57–20.78 ($4CH_3$), 22.23, 22.95, 25.13,

25.36 ($4CH_2$), 61.88 (C-6′), 67.93 (C-4′), 69.17 (C-2′), 73.81 (C-3′), 76.21 (C-5′), 81.63 (C-1′), 120.41 (C-5), 131.42 (C-4a), 133.03 (C-6), 150.52 (C-7a), 159.68 (C-2), 163.48 (C-4), 169.42, 169.47, 170.10, 170.87 (4C=O). Calcd. (%) for $C_{24}H_{28}N_2O_{10}S_2$ (568.63): C; 50.70, H; 4.96, N; 4.93, S; 11.28. Found: C; 50.73, H; 4.97, N; 4.95, S; 11.29.

6.6 *2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylthio)-3,5,6,7,8,9-hexahydro-3H,5H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (6f)*

Yield (1.93 g, 66%). Mp: 198–200 °C; IR (KBr) ν (cm^{-1}): 3471 (NH), 1750 (CO), 1665 (CO); $\lambda_{max} = 320$ nm; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.93, 1.97, 2.00, 2.01 (4s, 12H, $4CH_3CO$), 1.58 (m, 4H, $2CH_2$), 1.88 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 3.21 (m, 2H, CH_2), 4.13 (m, 1H, H-5′), 4.14–4.17 (m, 2H, H6′, 6″), 4.99 (t, 1H, H-4′), 5.08 (m, 1H, H-2′), 5.52 (t, 1H, H-3′), 5.97 (d, 1H, $J = 10.5$, H-1′), 11.05 (br, 1H, NH, D_2O exchangeable); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.61 (m, 4H, $2CH_2$), 1.87 (m, 2H, CH_2), 2.00–2.07 (4s, 12H, $4CH_3CO$), 2.80 (m, 2H, CH_2), 3.19 (m, 2H, CH_2), 4.12 (m, 1H, H-5′), 4.11–4.16 (m, 2H, H6′, 6″), 5.12–5.38 (m, 2H, H-4′ + H-2′), 5.37 (t, 1H, H-3′), 5.77 (d, 1H, $J = 10.5$, H-1′), 11.09 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.57-20.71 ($4CH_3$), 26.71 (CH_2), 27.94 (CH_2), 28.97 (CH_2) 29.53 (CH_2), 31.36 (CH_2), 61.82(C-6′), 67.94 (C-4′), 69.11 (C-2′), 73.80 (C-3′), 76.24 (C-5′), 81.59 (C-1′), 117.90(C-5), 138.25 (C-5a), 140.10 (C-6), 150.27 (C-7a), 159.46 (C-2), 168.52 (C-4), 169.41, 169.45, 170.10, 170.80 (4C=O); MS: m/z 582 (M^+). Calcd. (%) for $C_{25}H_{30}N_2O_{10}S_2$ (582.65): C; 51.54, H; 5.19, N; 4.81, S; 11.01. Found: C; 51.56, H; 5.19, N; 4.83, S; 11.02.

6.7 *5,6-Dimethyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyrano-sylthio)-3H-thieno[2,3-d]pyrimidin-4-one (6g)*

Yield (1.70 g, 63%). Mp: 202–204 °C; IR (KBr) ν (cm^{-1}): 3470 (NH), 1743 (CO), 1667 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04–2.09 (4s, 12H, $4CH_3CO$), 2.38 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.89 (m, 1H, H-5′), 4.20 (m, 2H, H6′, 6″), 5.09 (t, 1H, H-4′), 5.11 (m, 1H, H-2′), 5.41 (t, 1H, $J = 9.4$ Hz, H-3′), 5.67 (d, 1H, $J = 10.81$, H-1′), 11.02 (br, 1H, NH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ (ppm): 12.94 (CH_3), 13.01 (CH_3), 20.56–20.69 ($4CH_3$), 60.95 (C-6′), 67.40 (C-4′), 67.25 (C-2′), 73.99 (C-3′), 76.22 (C-5′), 81.95 (C-1′), 121.43 (C-5), 129.41 (C-4a), 129.98 (C-6), 150.24 (C-7a), 159.40 (C-2), 162.48 (C-4), 169.31, 169.37, 170.07, 170.81 (4C=O). Calcd. (%) for $C_{22}H_{26}N_2O_{10}S_2$ (542.59): C; 48.70, H; 4.83, N; 5.16, S; 11.82. Found: C; 48.73, H; 4.81, N; 5.17, S; 11.80.

6.8 *5-Methyl-6-pheny-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galacto-pyranosylthio)-3H-thieno[2,3-d]pyrimidin-4-one (6h)*

Yield (2.32 g, 77%). Mp: 177–197 °C; IR (KBr) ν (cm^{-1}): 3479 (NH), 1748 (CO), 1669 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.13–2.16 (4s, 12H, $4CH_3CO$), 2.61 (s, 3H, CH_3), 3.98 (m, H-5′), 4.21 (m, 2H, H6′, 6″), 5.17–5.30 (m, 2H, H-4′+H-2′), 5.36 (t, H-3′), 5.69 (d, 1H, $J = 10.7$, H-1′), 7.37–7.50 (m, 5H, Ph), 11.88 (br, 1H, NH, D_2O exchangeable). Calcd. (%) for $C_{27}H_{28}N_2O_{10}S_2$ (604.66): C; 53.63, H; 4.67, N; 4.63, S; 10.61. Found: C; 53.64, H; 4.69, N; 4.66, S; 10.62.

6.9 *5-Isopropyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyrano-sylthio)-3H-thieno[2,3-d]pyrimidin-4-one (6i)*

Yield 1.70 g (61%). Mp: 188–190 °C; IR (KBr) ν (cm^{-1}): 3469 (NH), 1745 (CO), 1661 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 (d, 6H, $2CH_3$), 1.91–2.08 (4s, 12H, $4CH_3CO$), 3.40 (sep, 1H, CH), 3.94 (m, H-5′), 4.16 (m, H-H6′, 6″), 5.09 (t, H-4′), 5.12 (m, H-2′), 5.26 (t, $J = 9.4$ Hz, H-3′), 5.60 (d, 1H, $J = 10.5$, H-1′), 7.40 (s, 1H, H-thiophene), 11.81 (br, 1H, NH, D_2O exchangeable); MS: m/z 556 (M^+). Calcd. (%) for $C_{23}H_{28}N_2O_{10}S_2$ (556.62): C; 49.63, H; 5.07, N; 5.03, S; 11.52. Found: C; 49.65, H; 5.09, N; 5.03, S; 11.53.

6.10 *2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosylthio)-3,5,6,7-tetrahydrocyclopenta[4,5]thieno[2,3-d]pyrimidin-4-one (6j)*

Yield (2.13 g, 77%). Mp: 194–196 °C; IR (KBr) ν (cm^{-1}): 3467 (NH), 1747 (CO), 1667 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.05–2.09 (4s, 12H, $4CH_3CO$), 2.47 (m, 2H, CH_2), 2.97 (t, 2H, CH_2), 3.07 (t, 2H, CH_2), 3.95–3.98 (m, 1H, H-5′), 4.14–4.27 (m, 2H, H6′, 6″), 5.15–5.24 (m, 2H, H-4′+ H-2′), 5.36 (t, 1H, H-3′), 5.77 (d, 1H, $J = 10.5$, H-1′), 11.60 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.95 (CH_2), 25.09 (CH_2), 25.49 (CH_2), 20.55–20.73 ($4CH_3$), 61.80 (C-6′), 67.93 (C-4′), 69.18 (C-2′), 73.80 (C-3′), 76.26 (C-5′), 81.60 (C-1′), 120.43 (C-5), 131.50 (C-4a), 133.03 (C-6), 150.52 (C-7a), 159.69 (C-2), 163.49 (C-4), 169.39, 169.40, 170.11, 170.66 (4C=O). Calcd. (%) for $C_{23}H_{26}N_2O_{10}S_2$ (554.60): C; 49.81, H; 4.73, N; 5.05, S; 11.56. Found: C; 49.80, H; 4.74, N; 5.09, S; 11.58.

6.11 *2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosylthio)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (6k)*

Yield (2.01 g, 71%). Mp: 166–168 °C; IR (KBr) ν (cm^{-1}): 3466 (NH), 1746 (CO), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04–2.09 (4s, 12H, $4CH_3CO$), 1.96 (m, 4H, CH_2), 2.77 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 3.95–4.01 (m, 1H, H-5′), 4.14–4.29 (m, 2H, H6′, 6″), 5.15–5.27 (m, 2H, H-4′+ H-2′), 5.39 (t, H-3′), 5.78 (d, 1H, $J = 10.5$, H-1′), 11.55 (br, 1H, NH, D_2O exchangeable); MS: m/z 568 (M^+). Calcd. (%) for $C_{24}H_{28}N_2O_{10}S_2$ (568.63): C; 50.70, H; 4.96, N; 4.93, S; 11.28. Found: C; 50.71, H; 4.96, N; 4.95, S; 11.29.

6.12 *2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosylthio)-3,5,6,7,8,9-hexahydro-3H,5H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (6l)*

Yield (2.07 g, 71%); Mp: 185–187 °C; IR (KBr) ν (cm^{-1}): 3460 (NH), 1751 (CO), 1651 (CO); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.99–2.12 (4s, 12H, $4CH_3CO$), 1.59 (m, 4H, $2CH_2$), 1.87 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.94 (m, 1H, H-5′), 4.00 (m, 2H, H6′, 6″), 5.13 (t, 1H, H-4′), 5.30 (m, 1H, H-2′), 5.33 (t, 1H, H-3′), 5.93 (d, 1H, $J = 10.65$, H-1′), 11.12 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.56–20.73 ($4CH_3$), 26.72 (CH_2), 27.91 (CH_2), 28.00 (CH_2) 29.57 (CH_2), 31.33 (CH_2), 61.02 (C-6′), 67.34 (C-4′), 68.0 (C-2′), 78.80 (C-3′), 79.24 (C-5′), 81.89 (C-1′), 117.88 (C-5), 138.23 (C-5a), 139.90 (C-6), 150.26 (C-7a), 159.63 (C-2), 168.49 (C-4), 169.33 (C=O), 169.35 (C=O), 170.20 (C=O), 170.80 (C=O). Calcd. (%) for $C_{25}H_{30}N_2O_{10}S_2$ (582.65): C; 51.54, H; 5.19, N; 4.81, S; 11.01. Found: C; 51.56, H; 5.19, N; 4.83, S; 11.02.

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