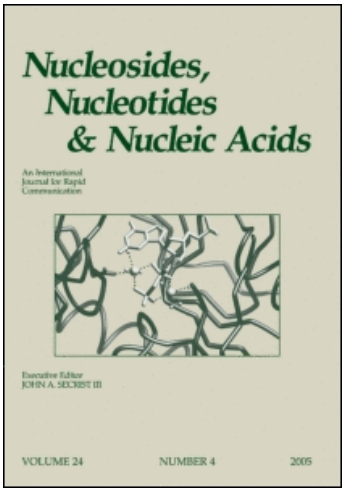

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Synthesis and Antiviral Screening of Some Thieno[2,3-*d*]Pyrimidine Nucleosides

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SYNTHESIS AND ANTIVIRAL SCREENING OF SOME THIENO[2,3-*d*]PYRIMIDINE NUCLEOSIDES

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□ *Some cyclic and acyclic nucleosides of thieno[2,3-d]-pyrimidine derivatives were synthesized* via *the reaction of compounds* ***1*** *and* ***2*** *or* ***3*** *and* ***4*** *with 2-chloroethyl methyl ether or 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. Nucleosides* ***9***, ***10***, ***15***, *and* ***16*** *were tested as antiviral agents against herpes simplex virus type-1 (HSV-1) and hepatitis-A virus (HAV). Compound* ***15*** *showed the highest effect on HSV-1 than the other three compounds, while the four tested compounds did not show any activity against HAV.*

Keywords Cyclic and acyclic nucleosides; Thieno[2,3-*d*]pyrimidine; HSV-1; HAV

INTRODUCTION

Few cyclic thieno[2,3-*d*]pyrimidine nucleosides were reported[1–4] and still very few of their N- and S-acyclic nucleosides were described in the literature.[4,5] Recently, due to the aroused interest to the biologically active pyrimidine and fused heterocyclic pyrimidine nucleosides as potent antiviral agents,[6–9] we have been involved in a program aimed to the synthesis of different fused heterocyclic pyrimidine nucleosides with biological interest,[1,10] and in continuation of these efforts, we report here an efficient synthesis of some thieno[2,3-*d*]pyrimidine nucleosides with promising antiviral activity.

RESULTS AND DISCUSSION

When compounds **1**[11] or **2**[1,11] were treated with phosphorus pentasulfide, they afforded their corresponding pyrimidinethione derivatives

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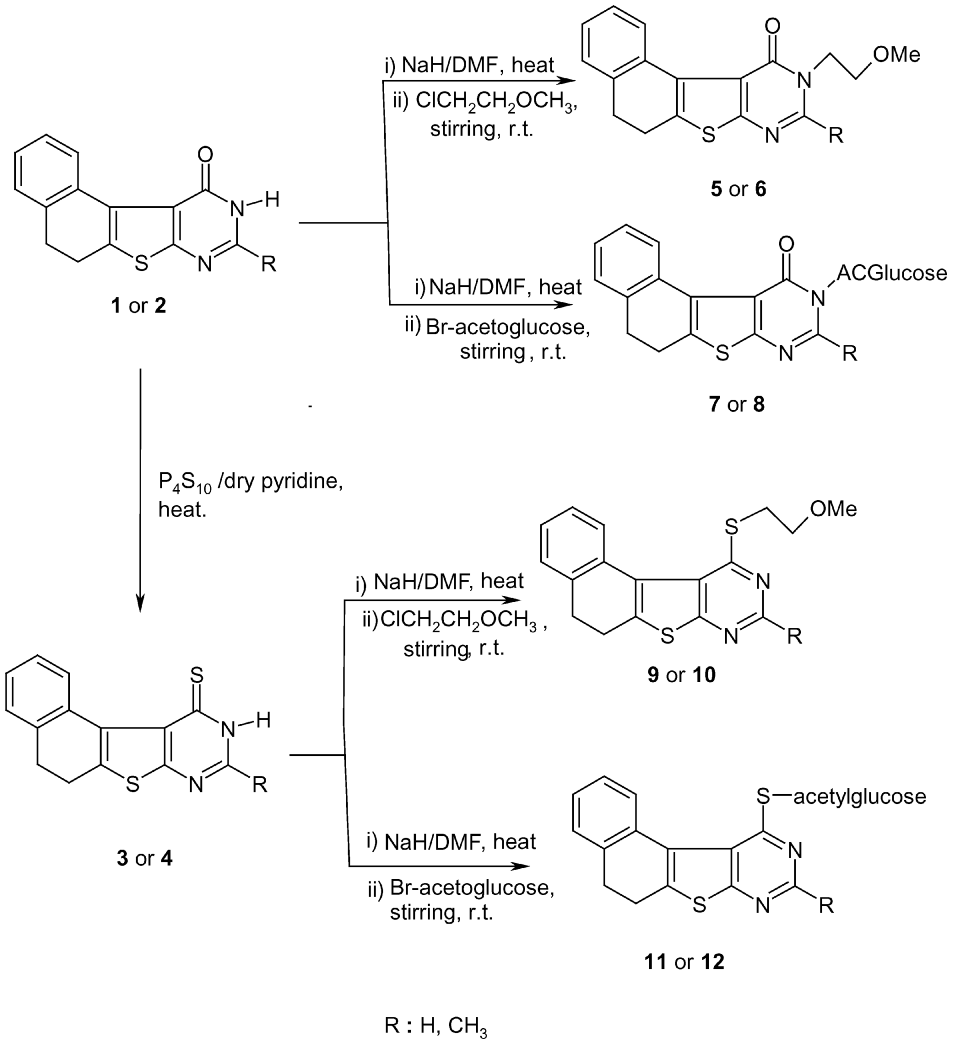


SCHEME 1

3 or **4**, respectively (Scheme 1). The structure of the latter compounds was confirmed with spectral data (see Experimental).

When the sodium salts of compounds **1** or **2** were treated with 2-chloroethyl methyl ether or 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, they afforded the corresponding acyclic and cyclic nucleosides **5** and **6** or **7** and **8**, respectively (Scheme 1). The structure of these nucleosides were confirmed with spectral data (see Experimental). The IR spectra of the latter compounds revealed that the sites of attack were on the N- and not O-atom (see Experimental). Also, The ^{1}H-NMR spectra of compounds **7** and **8** gave doublet signals characteristic for the anomeric proton of the glucose moiety with spin-spin coupling constant corresponds to the diaxial

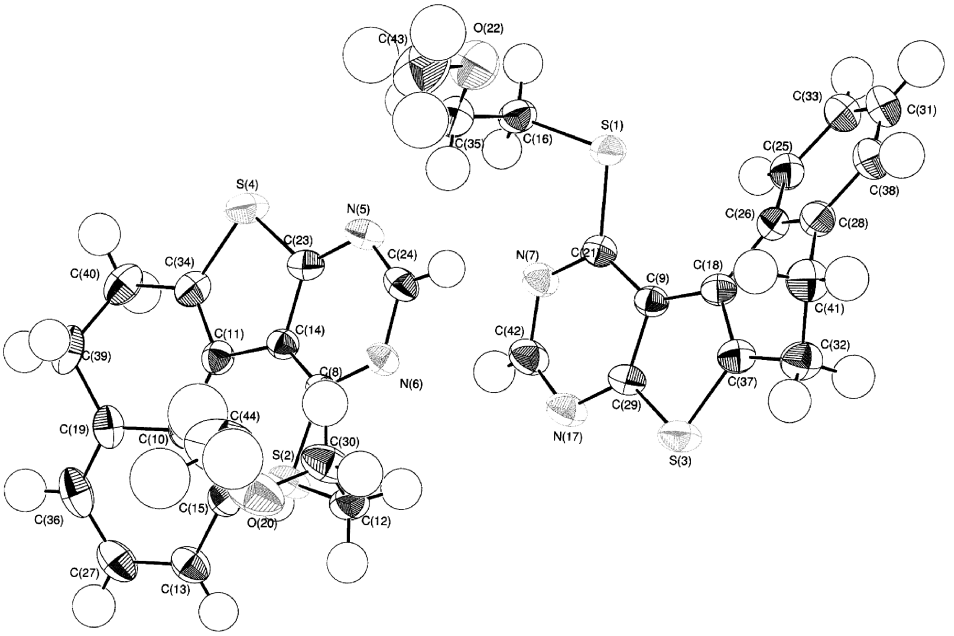


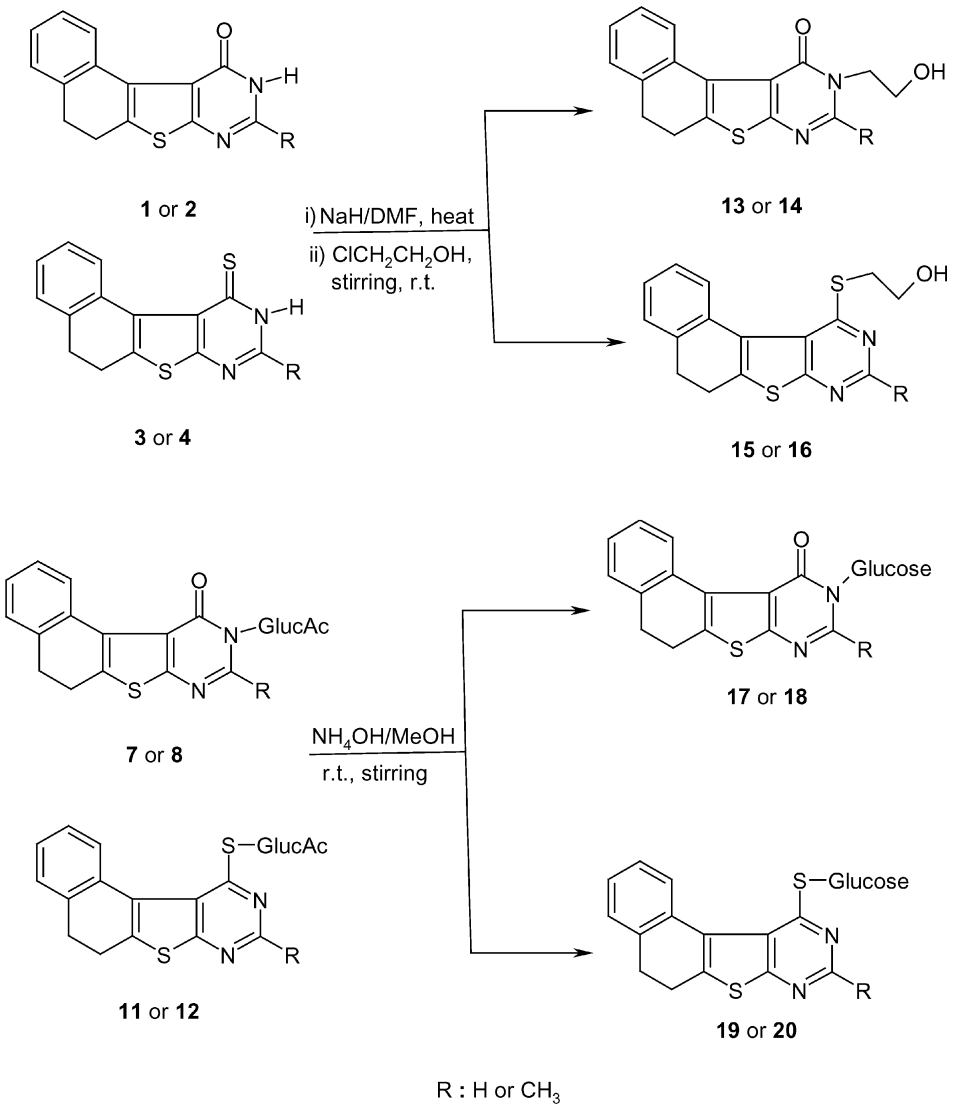
FIGURE 1 Single crystal X-ray structure of compound **9**.

orientation of the H-1′ and H-2′ protons, indicating the presence of only the β-configuration.[12]

Similarly, nucleosides **9**, **10**, **11**, and **12** were obtained by reacting the sodium salts of compounds **3** or **4** with 2-chloroethyl methyl ether or 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (Scheme 1). The ^{13}C-NMR spectra of nucleosides **9–12** (see Experimental) and X-ray analysis of compound **9**, as an example (Figure 1) showed that sites of attack were on the S- and not N-atom.

Deprotection of the acyclic nucleosides **5**, **6**, **9**, and **10** in methanolic ammonia failed, while attempts to deprotect them using alcoholic potassium hydroxide solution, broke the nucleosidic linkage and gave the heterocyclic bases again. To overcome this cleavage, we report here an efficient and convenient method for preparation of the free acyclonucleosides **13**, **14**, **15**, and **16**, by reacting the sodium salts of compounds **1**, **2**, **3**, or **4** directly with 2-chloroethanol (Scheme 2). The spectral data of the latter compounds assigned their structures (see Experimental).

On the other hand, deprotection of the cyclic nucleosides **7**, **8**, **11**, and **12** was achieved with methanolic ammonia to afford their corresponding deacetylated nucleosides **17**, **18**, **19**, and **20**, respectively (Scheme 2). The IR and ^{1}H-NMR spectra of the aforementioned compounds showed signals indicative for the OH groups (see Experimental). Also, the ^{13}C-NMR spectra showed signals characteristic for the glucose ring and the



SCHEME 2

signals of the four carbonyl groups of acetylated glucose were absent (see Experimental).

Antiviral Bioassay

Preparation of Synthetic Compounds for Bioassay. Tested compounds were dissolved as 100 mg each in 1 mL of 10% DMSO in water. The final concentration was 100 μg/μL (stock solution). The dissolved stock solutions were sterilized by addition of 50 μg/mL antibiotic-antimycotic mixture

(10,000 U penicillin G sodium, 10,000 μg streptomycin sulfate, and 250 μg amphotericin B, PAA Laboratories GmbH, Austria).

Cell Culture. African green monkey kidney-derived cells (Vero) and human hepatoma cell line (HepG2) were used. The cells were propagated in Dulbeccos' Minimal Essential Medium, DMEM, supplemented with 10% fetal bovine serum, 1% antibiotic-antimycotic mixture. The *p*H was adjusted at 7.20–7.40 by 7.50% sodium bicarbonate solution. The mixture was sterilized by filtration through 0.2 μm pore size nitrocellulose membrane.

Viruses. Herpes simplex virus type-1 and hepatitis A virus (MBB strain) were obtained from Environmental Virology Lab., Department of Water Pollution Research, National Research Centre.

Cytotoxicity Assay. Cytotoxicity was assayed for both dimethyl sulfoxide (DMSO) and the tested compounds. Serial dilutions were prepared and inoculated on Vero cells grown in 96 well tissue culture plates. The maximum tolerated concentration (MTC) for each compound was determined by both cell morphology and cell viability by staining with tryban blue dye.

Plaque Reduction Assay. A 6-well plate was cultivated with cell culture (10^5 cell/mL) and incubated for 2 days at 37°C. HSV-1 and HAV were diluted to give 10^4 PFU/mL final concentration for each virus and mixed with the tested compound at the previous concentration and incubated overnight at 4°C. Growth medium was removed from the multiwell plate and virus-compound mixture was inoculated (100 μL/well). After 1 h contact time, the inoculum was aspirated and 3 mL of MEM with 1% agarose was overlaid the cell sheets. The plates were left to solidify and incubated at 37°C until the development of virus plaques. Cell sheets were fixed in 10% formaline solution for 2 h and stained with crystal violet stain. Control virus and cells were treated identically without chemical compound. Virus plaques were counted and the percentage of reduction was calculated.[13]

Results and Discussion. Plaque infectivity assay was carried out to test compounds **9**, **10**, **15**, and **16** for antiviral activity and the results were shown in Figure 2. The test was performed to include the three possibilities for virucidal effect, virus adsorption, and effect on virus replication. Compound **15** showed the highest effect on HSV-1 than the other three compounds, where its antiviral activity increased from 34.20% at concentration of 20 $\mu g/10^5$ cells to 70.30% at concentration of 20 $\mu g/10^5$ cells (Figure 2). On the other hand, the four compounds did not show any activity against HAV.

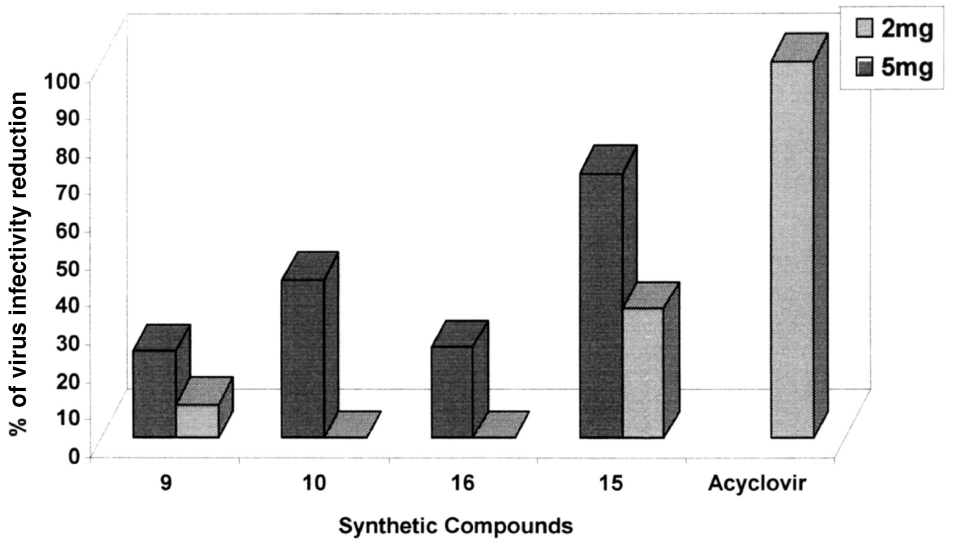


FIGURE 2 Effect of thieno[2,3-*d*]pyrimidine nucleoside derivatives **9**, **10**, **15**, and **16** on Herpes Simplex Virus-1 reduction.

EXPERIMENTAL

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus. IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer, National Research Centre. ^{1}H NMR and ^{13}C NMR spectra were determined on a Jeol-Ex-300 NMR spectrometer and chemical shifts were expressed as parts per million, ppm (δ values), against TMS as internal reference (Cairo University, Faculty of Science). Mass spectra were recorded on EI + Q1 MSLMR UPLR, National Research Centre. Microanalyses were operated using Mario Elmentar apparatus, Organic Microanalysis Unit, National Research Centre, and the results were within the accepted range (± 0.40) of the calculated values. The single crystal for the X-ray diffraction analysis of compound **9** was obtained by slow evaporation of the corresponding ethanol solution. The X-ray determination was performed by the Central Services Laboratory, National Research Centre. Column chromatography was performed on (Merck) Silica gel 60 (particle size 0.06–0.20 mm).

Compounds **1** and **2** prepared here are identical in all respects (mp, physical, and spectral data) with that prepared previously.[1,11]

Preparation of Compounds 3 and 4

General Procedure. Compounds **1** or **2** (1 mmol) were dissolved in dry pyridine (20 mL), phosphorus pentasulfide (2 mmol) was added, and the reaction mixtures were heated under reflux temperature for 3 or 5 h,

poured onto ice-water, neutralized with 2–3 drops of conc. hydrochloric acid (35%), filtered off, dried, and the solids that obtained were recrystallized from dioxane.

5,6-Dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidine-11(10*H*)-thione (3). mp 270–272°C, yield 90%, ^{1}H-NMR (DMSO-d_6, ppm): δ 2.80–2.90 (m, 4H, $2CH_2$), 7.10–7.30 (m, 3H, Ar—H), 8.03 (d, $J = 9$ Hz, 1H, Ar—H), 8.25 (s, 1H, C_9-H), 13.90 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, ppm): δ 25 (C-5), 30 (C-6), 125.50–131.02 (Ar—C), 132.26 (C-11a), 136.20 (C-11b), 140.92 (C-6a), 144.74 (C-7a), 162.66 (C-9), 187.30 (C=S); *m/z* (%): 270 (M^+, 71); calculated for $C_{14}H_{10}N_2S_2$ (270.38): C, 62.19; H, 3.73; N, 10.36; S, 23.72. Found: C, 62.10; H, 3.95; N, 10.43; S, 23.50.

9-Methyl-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidine-11(10*H*)thione (4). mp 276–278°C, yield 93%, ^{1}H-NMR (DMSO-d_6, ppm): δ 2.60 (s, 3H, C_9-CH_3), 2.80–2.90 (m, 4H, $2CH_2$), 7.10–7.20 (m, 3H, Ar—H), 8.04 (d, $J = 9$ *Hz*, 1H, Ar—H), 13.70 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, ppm): δ 21.14 (C_9-CH_3), 25.40 (C-5), 30.80 (C-6), 125.53–131.17 (Ar—C), 131.98 (C-11a), 136.07 (C-11b), 139.52 (C-6a), 154.66 (C-7a), 163.48 (C-9), 179.20 (C=S); *m/z* (%): 284 (M^+, 74); calculated for $C_{15}H_{12}N_2S_2$ (284.40): C, 63.35; H, 4.25; N, 9.85; S, 22.55. Found: C, 63.60; H, 4.20; N, 9.98; S, 22.20.

Preparation of Compounds 5 and 6

General Procedure. Compounds **1** and **2** were dissolved in dry dimethylformamide (20 mL), sodium hydride (2 mmol) was added, then the reaction mixtures were stirred at 70°C for 1 h, cooled, then 2-chloroethyl methyl ether (2 mmol) was added, stirring at room temperature was continued for 4 and 6 h, respectively. The reaction mixtures were evaporated under reduced pressure and the residues were purified on silica gel column using petroleum ether 40–60°C: ethyl acetate (4:1) as an eluent to give compounds **5** and **6**, respectively.

10-(2-Methoxyethyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-11-(10*H*)-one (5). From compound **1**: mp 202–204°C; yield 68%; IR (KBr): ν 1695 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ 2.80–2.90 (m, 4H, $2CH_2$), 3.30 (s, 3H, OCH_3), 3.40 (t, $J = 8$ *Hz*, 2H, CH_2O), 3.60 (t, $J = 8$ *Hz*, 2H, CH_2N), 7.30–7.60 (m, 4H, Ar—H), 8.20 (s, 1H, C_9-H); calculated for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36; H, 5.16; N, 8.97; S, 10.26. Found: C, 65.10; H, 5.20; N, 9.10; S, 10.20.

10-(2-Methoxyethyl)-9-methyl-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-d]pyrimidin-11(10*H*)-one (6). From compound **2**: mp 212–214°C; yield 60%; IR (KBr): ν 1705 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ 2.60 (s, 3H, C_9-CH_3), 2.80–2.90 (m, 4H, $2CH_2$), 3.40 (s, 3H, OCH_3), 3.50–3.60 (m, 4H, $2CH_2$), 7.30–7.60 (m, 4H, Ar—H); calculated for $C_{18}H_{18}N_2O_2S$ (326.42): C, 66.23; H, 5.56; N, 8.58; S, 9.28. Found: C, 66.38; H, 5.40; N, 8.63; S, 9.20.

Preparation of Compounds 7 and 8

General Procedure. Compounds **1** and **2** (1 mmol) were dissolved in dry dimethylformamide (20 mL), sodium hydride (2 mmol) was added with stirring at 70°C for 1 h, cooled, a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1 mmol) in dry acetone (10 mL) was added, the reaction mixtures were stirred for 6 and 8 h, then evaporated under reduced pressure at 40°C, and purified on silica gel column using petroleum ether 40–60°C: ethyl acetate (4:1) as an eluent to give products **7** and **8**, respectively.

10-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (7). From compound **1**: mp 235–237°C, yield 65%; IR (KBr): ν 1695–1720 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ 1.80–2.0 (4s, 12H, $4CH_3CO$), 2.80–2.90 (m, 4H, $2CH_2$), 3.90 (m, 2H, 2H-6′), 4.10 (m, 2H, 5′-H, H-4′), 5.20–5.30 (m, 2H, H-3′, H-2′), 6.05 (d, $J_{1',2'} = 9.99$ *Hz*, 1H, H-1′), 7.20–7.50 (m, 4H, Ar—H), 8.10 (s, 1H, C_9—H); calculated for $C_{28}H_{28}N_2O_{10}S$ (584.61): C, 57.53; H, 4.83; N, 4.79; S, 5.84. Found: C, 57.62; H, 4.77; N, 4.46; S, 5.90.

9-Methyl-10-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (8). From compound *2*: mp 243–244°C, yield 58%; IR (KBr): ν 1700–1720 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ 1.80–2.10 (4s, 12H, $4CH_3CO$), 2.60 (s, 3H, C_9—CH_3), 2.80–2.90 (m, 4H, $2CH_2$), 3.95 (m, 2H, 2H-6′), 4.20 (m, 2H, 5′-H, H-4′), 5.10–5.20 (m, 2H, H-3′, H-2′), 6.10 (d, $J_{1',2'} = 9.99$ *Hz*, 1H, H-1′), 7.20–7.50 (m, 4H, Ar—H); calculated for $C_{29}H_{30}N_2O_{10}S$ (598.63): C, 58.19; H, 5.05; N, 4.68; S, 5.36. Found: C, 57.90; H, 5.20; N, 4.56; S, 5.40.

Preparation of Compounds 9 and 10

General Procedure. Compounds **9** and **10** were prepared from **3** and **4** as described for **5** and **6**.

11-(2-Methoxy-ethylsulfanyl)-5,6-dihydronaphtho[1′,2′: 4,5]thieno[2,3-*d*]pyrimidine (9). From compound **3**: mp 102–104°C; yield 78%; ^{1}H-NMR ($CDCl_3$, ppm): δ 2.86–2.97 (m, 4H, $2CH_2$), 3.37 (s, 3H, OCH_3), 3.54 (t, $J = 7$ *Hz*, 2H, CH_2O), 3.69 (t, $J = 7.5$ *Hz*, 2H, CH_2N), 7.20–7.40 (m, 3H, Ar—H),

7.80 (d, $J=8$ *Hz*, 1H, Ar—H), 8.25 (s, 1H, C_9-H); ^{13}C-NMR ($CDCl_3$, ppm): δ 25.56 (C-5), 29.78 (C-6), 29.78 (OCH_3), 58.89 ($\underline{C}H_2O$), 71.21 ($\underline{C}H_2N$), 125.94–128.02 (Ar—C), 130.97 (C-11a), 135.94 (C-11b), 141.24 (C-6a), 151.34 (C-7a), 162.98 (C-9), 166.22 (C-11); calculated for $C_{17}H_{16}N_2OS_2$ (328.46): C, 62.17; H, 4.91; N, 8.53; S, 19.52. Found: C, 62.10; H, 4.85; N, 8.63; S, 19.60.

11-(2-Methoxy-ethylsulfanyl)-9-methyl-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (10). From compound **4**: mp 110–112°C; yield 80%; ^{1}H-NMR ($CDCl_3$, ppm): δ 2.73 (s, 3H, C_9-CH_3), 2.80–2.97 (m, 4H, $2CH_2$), 3.40 (s, 3H, OCH_3), 3.50 (t, $J=7.5$ *Hz*, 2H, CH_2O), 3.70 (t, $J=8$ *Hz*, 2H, CH_2N), 7.20–7.40 (m, 3H, Ar—H), 7.80 (d, $J=8$ *Hz*, 1H, Ar—H); ^{13}C-NMR ($CDCl_3$, ppm): δ 25.43 (C_9-CH_3), 25.57 (C-5), 28.46 (C-6), 30.18 (OCH_3), 58.85 ($\underline{C}H_2O$), 71.26 ($\underline{C}H_2N$), 123.60–128.56 (Ar—C), 131.18 (C-11a), 135.90 (C-11b), 139.74 (C-6a), 160.80 (C-7a), 162.44 (C-9), 167.04 (C-11); calculated for $C_{18}H_{18}N_2OS_2$ (342.48): C, 63.13; H, 5.30; N, 8.18; S, 18.72. Found: C, 63.10; H, 5.10; N, 8.34; S, 18.60.

Preparation of Compounds 11 and 12

General Procedure. Compounds **11** and **12** were prepared from **3** and **4** as described for **7** and **8**.

10-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosulfanyl)-5,6-dihydronaphtho-[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (11). From compound **3**: mp 160–162°C, yield 76%; ^{1}H-NMR ($CDCl_3$, ppm): δ 2.02–2.20 (4s, 12H, 4 CH_3CO), 2.80–3.0 (m, 4H, $2CH_2$), 3.60–3.70 (m, 3H, 2H-6′, H-5′), 5.10–5.40 (m, 3H, H-4′, H-3′, H-2′), 6.26 (d, $J_{1',2'}=9$ *Hz*, 1H, H-1′), 7.20–7.30 (m, 3H, Ar—H), 8.05 (d, $J=8$ *Hz*, 1H, Ar—H); 8.80 (s, 1H, C_9-H); ^{13}C-NMR ($CDCl_3$, ppm): δ 25.60–26.40 ($4CH_3$), 29.60 (C-5), 29.80 (C-6), 62.30 (C-6′), 68.38 (C-4′), 69.40 (C-2′), 70.10 (C-3′), 74.59 (C-5′), 80.12 (C-1′), 123.87–160.62 (Ar—C), 167.80–170.70 (4CO); calculated for $C_{28}H_{28}N_2O_9S_2$ (600.67): C, 55.99; H, 4.70; N, 4.66; S, 10.68. Found: C, 56.30; H, 4.77; N, 4.46; S, 10.54.

9-Methyl-10-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosulfanyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (12). From compound **4**: mp 168–170°C, yield 81%; ^{1}H-NMR ($CDCl_3$, ppm): δ 2.01–2.10 (4s, 12H, 4 CH_3CO), 2.78 (s, 3H, C_9-CH_3), 2.89–2.91 (m, 4H, $2CH_2$), 3.90–4.22 (m, 3H, 2H-6′, H-5′), 5.10–5.42 (m, 3H, H-4′, H-3′, H-2′), 6.25 (d, $J_{1',2'}=7.50$ *Hz*, 1H, H-1′), 7.20–7.30 (m, 3H, Ar—H), 7.60 (d, $J=8$ *Hz*, 1H, Ar—H); ^{13}C-NMR ($CDCl_3$, ppm): δ 25.40–26.60 ($4CH_3$), 26.95 (C_9-CH_3), 29.60 (C-5), 29.80 (C-6), 61.30 (C-6′), 68.80 (C-4′), 69.70 (C-2′), 71.40 (C-3′), 74.94 (C-5′), 81.20 (C-1′), 124.80–160.60 (Ar—C), 167.80–170.60 (4CO); calculated for

$C_{29}H_{30}N_2O_9S_2$ (614.70): C, 56.67; H, 4.92; N, 4.56; S, 10.43. Found: C, 56.90; H, 4.97; N, 4.50; S, 10.40.

Preparation of Compounds 13–16

General Procedure. To a solution of dry dimethylformamide (20 mL) containing (1 mmol) of compounds **1**, **2**, **3**, or **4**, sodium hydride (2 mmol) was added, then the reaction mixtures were stirred at 70°C for 1 h, cooled, then 2-chloroethanol (2 mmol) was added and stirred at room temperature for 4, 5, 3, and 6 h, respectively. The reaction mixtures were evaporated under reduced pressure and the residues were recrystallized from ethanol to give compounds **13**, **14**, **15**, and **16**, respectively.

10-(2-Hydroxyethyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-11(10*H*)-one (13). From compound **1**: mp 180–182°C; yield 60%; IR (KBr): ν 3100–3200 (OH), 1695 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ 2.80–2.90 (m, 4H, $2CH_2$), 3.50–3.60 (m, 4H, $2CH_2$), 4.30 (bs, 1H, OH, D_2O exchangeable), 7.30–7.60 (m, 4H, Ar—H), 8.15 (s, 1H, C_9-H); calculated for $C_{16}H_{14}N_2O_2S$ (298.37): C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.58; H, 4.90; N, 9.43; S, 10.44.

10-(2-Hydroxyethyl)-9-methyl-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-11(10*H*)-one (14). From compound **2**: mp 202–204°C; yield 62%; IR (KBr): ν 3130–3250 (OH), 1705 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ 2.60 (s, 3H, C_9-CH_3), 2.80–2.90 (m, 4H, $2CH_2$), 3.50–3.65 (m, 4H, $2CH_2$), 4.60 (bs, 1H, OH, D_2O exchangeable), 7.30–7.60 (m, 4H, Ar—H); calculated for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.39; H, 5.16; N, 8.97; S, 10.26. Found: C, 65.48; H, 5.34; N, 8.72; S, 10.20.

11-(2-Hydroxy-ethylsulfanyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]-pyrimidine (15). From compound **3**: mp 112–4°C; yield 70%; IR (KBr): ν 3200–3350 (OH); ^{1}H-NMR ($CDCl_3$, ppm): δ 2.86–2.97 (m, 4H, $2CH_2$), 3.70–4.09 (m, 4H, $2CH_2$), 4.90 (bs, 1H, OH, D_2O exchangeable), 7.20–7.30 (m, 3H, Ar—H), 8.09 (d, J= 10 *Hz*, 1H, Ar—H), 8.25 (s, 1H, C_9-H); ^{13}C-NMR ($CDCl_3$, ppm): δ 25.56 (C-5), 29.78 (C-6), 60.89 ($\underline{C}H_2O$), 71.21 ($\underline{C}H_2N$), 125.94–166.20 (Ar—C); calculated for $C_{16}H_{14}N_2OS_2$ (314.43): C, 61.12; H, 4.49; N, 8.91; S, 20.39. Found: C, 61.20; H, 4.66; N, 8.70; S, 20.14.

11-(2-Hydroxy-ethylsulfanyl)-9-methyl-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (16). From compound **4**: mp 118–120°C; yield 84%; IR (KBr): ν 3170–3300 (OH); ^{1}H-NMR ($CDCl_3$, ppm): δ 2.70 (s, 3H, C_9—CH_3), 2.80–2.90 (m, 4H, $2CH_2$), 3.80–4.10 (m, 4H, $2CH_2$), 4.96 (bs, 1H, OH, D_2O exchangeable), 7.20–7.40 (m, 3H, Ar—H), 7.80 (d, J= 10.20 *Hz*,

1H, Ar—H); ^{13}C-NMR ($CDCl_3$, ppm): δ 25.43 (C_9-CH_3), 25.57 (C-5), 28.46 (C-6), 62.85 ($\underline{C}H_2O$), 71.26 ($\underline{C}H_2N$), 125.60–168.24 (Ar—C); calculated for $C_{17}H_{16}N_2OS_2$ (328.46): C, 62.17; H, 4.91; N, 8.53; S, 19.52. Found: C, 62.20; H, 4.76; N, 8.40; S, 19.68.

Preparation of Compounds 17–20

General Procedure. To a solution of dry methanol (20 mL) containing (1 mmol) of compounds **7**, **8**, **11**, or **12**, ammonium hydroxide solution (3 mL, 35%) was added, then the reaction mixtures were stirred at room temperature for 2, 4, 3, and 3 h, respectively. The reaction mixtures were evaporated under reduced pressure at 40°C and the residues were purified on silica gel column using chloroform:methanol (4:1) as an eluent to give products **17**, **18**, **19**, and **20**, respectively.

10-(α-D-Glucopyranosyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (17). From compound **7**: mp 202–204°C, yield 66%; IR (KBr): ν 3200–3500 (OH), 1705 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ, 2.80–2.90 (m, 4H, $2CH_2$), 3.10–3.60 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, and H-2′), 3.70 (m, 2H, HO-3′, HO-4′, D_2O exchangeable), 4.30 (m, 2H, HO-2′, HO-6′, D_2O exchangeable), 6.25 (d, $J_{1',2'} = 7.50$ *Hz*, 1H, H-1′), 7.20–7.30 (m, 4H, Ar—H), 8.09 (d, $J = 10$ *Hz*, 1H, Ar—H); calculated for $C_{20}H_{20}N_2O_6S$ (416.46): C, 57.68; H, 4.84; N, 6.73; S, 7.70. Found: C, 57.50; H, 4.77; N, 6.86; S, 7.87.

9-Methyl-10-(α-D-glucopyranosyl)-5,6-dihydronaphtho[1′,2′:4,5]thieno-[2,3-*d*]pyrimidine (18). From compound **8**: mp 218–219°C, yield 80%; IR (KBr): ν 3200–3500 (OH), 1715 (CO); ^{1}H-NMR ($CDCl_3$, ppm): δ 2.78 (s, 3H, C_9-CH_3), 2.89–2.91 (m, 4H, $2CH_2$), 3.10–3.60 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, and H-2′), 3.70 (m, 2H, HO-3′, HO-4′, D_2O exchangeable), 4.30 (m, 2H, HO-2′, HO-6′, D_2O exchangeable), 6.25 (d, $J_{1',2'} = 7.50$ *Hz*, 1H, H-1′), 7.20–7.30 (m, 4H, Ar—H); calculated for $C_{21}H_{22}N_2O_6S$ (430.48): C, 58.59; H, 5.15; N, 6.51; S, 7.45. Found: C, 58.71; H, 4.97; N, 6.58; S, 7.40.

10-(α-D-Glucopyranosulfanyl)-5,6-dihydronaphtho[1′, 2′:4,5]thieno[2,3-*d*]pyrimidine (19). From compound **11**; mp 192–194°C, yield 76%; IR (KBr): ν 3200–3500 (OH); ^{1}H-NMR (DMSO-d_6, ppm): δ 2.80–3.0 (m, 4H, $2CH_2$), 3.10–3.60 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, and H-2′), 3.70 (m, 2H, HO-3′, HO-4′, D_2O exchangeable), 4.30 (m, 2H, HO-2′, HO-6′, D_2O exchangeable), 6.25 (d, $J_{1',2'} = 7.50$ *Hz*, 1H, H-1′), 7.20–7.30 (m, 4H, Ar—H), 8.09 (d, $J = 10$ *Hz*, 1H, Ar—H); ^{13}C-NMR (DMSO-d_6, ppm): δ 25 (C-5), 28 (C-6), 60.40 (C-6′), 70 (C-4′), 71 (C-2′), 76 (C-3′), 78 (C-5′), 81.30 (C-1′), 107.60–164.24 (Ar—C); calculated for $C_{20}H_{20}N_2O_5S_2$ (432): C, 55.94; H, 4.66; N, 6.48; S, 14.83. Found: C, 55.43; H, 4.77; N, 6.46; S, 14.74.

9-Methyl-10-(α-D-glucopyranosyl)-5,6-dihydrothionaphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (20). From compound **12**: mp 196–198°C, yield 81%; IR (KBr): ν 3200–3500 (OH); ^{1}H-NMR (DMSO-d_6, ppm): δ 2.78 (s, 3H, C_9–CH_3), 2.89–2.91 (m, 4H, $2CH_2$), 3.10–3.60 (m, 6H, 2H-6′, H-5′, H-4′, H-3′, and H-2′), 3.70 (m, 2H, HO-3′, HO-4′, D_2O exchangeable), 4.30 (m, 2H, HO-2′, HO-6′, D_2O exchangeable), 6.25 (d, $J_{1',2'} = 7.50$ *Hz*, 1H, H-1′), 7.20–7.30 (m, 4H, Ar—H); ^{13}C-NMR (DMSO-d_6, ppm): δ 22.43 (C_9–CH_3), 25 (C-5), 28 (C-6), 60.40 (C-6′), 70 (C-4′), 71 (C-2′), 76 (C-3′), 79.40 (C-5′), 81.60 (C-1′), 107.60–164.24 (Ar—C); calculated for $C_{21}H_{22}N_2O_5S_2$ (446.55): C, 56.49; H, 4.97; N, 6.27; S, 14.36. Found: C, 56.34; H, 4.90; N, 6.40; S, 14.42.

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