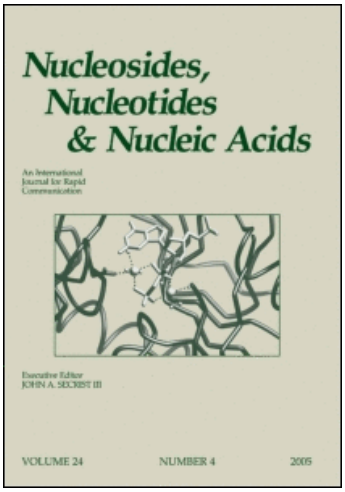

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Nasser A. Hassan[a]; Mohamed I. Hegab[a]; Aymn. E. Rashad[a]; Afaf A. Fahmy[a]; Farouk M. E. Abdel-Megeid[a]
[a] National Research Centre, Dokki, Cairo, Egypt

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME CYCLIC AND ACYCLIC NUCLEOSIDES OF THIENO[2,3-*d*]PYRIMIDINES

Nasser A. Hassan, Mohamed I. Hegab, Aymn. E. Rashad , Afaf A. Fahmy, and Farouk M. E. Abdel-Megeid □ *National Research Centre, Dokki, Cairo, Egypt*

□ *The reaction of compounds* ***1****,* ***2****,* ***3****,* ***4****, or* ***13*** *with 2-chloroethyl methyl ether or 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, afforded some acyclic and cyclic nucleosides of thieno[2,3-d]pyrimidine derivatives. Furthermore, cyclic C-nucleosides* ***24*** *and* ***25*** *were prepared from the reaction of* ***20****,* ***21*** *or from* ***26****,* ***27*** *with D-glucose. The antimicrobial evaluation of some prepared products showed promising antimicrobial activity.*

Keywords Thieno[2,3-*d*]pyrimidines; cyclic and acyclic nucleosides; antimicrobial activity

INTRODUCTION

The synthesis of fused heterocyclic pyrimidine nucleosides have been reported extensively.[1–3] Some of their *N*- and *S*-acyclic nucleosides also were described in the literature.[4–6] *C*-Nucleosides[7–10] and acyclonucleosides[11–14] have been shown to exhibit prominent and versatile biological activities, nevertheless, there is still a great need and interest to prepare more active cyclic and acyclic pyrimidine nucleosides with fewer side effects than those observed for already known derivatives. Thus, in continuation of our previous work on the synthesis of biologically active fused pyrimidines,[15–17] and different nucleoside derivatives,[18–20] we aimed to synthesize some cyclic and acyclic nucleosides related to indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine derivatives with promising antimicrobial activity.

RESULTS AND DISCUSSION

When the sodium salts of compounds **1**[21] or **2**[21] (generated in situ) were coupled with 2-chloroethyl methyl ether or 2,3,4,6-tetra-*O*-acetyl-α-D-

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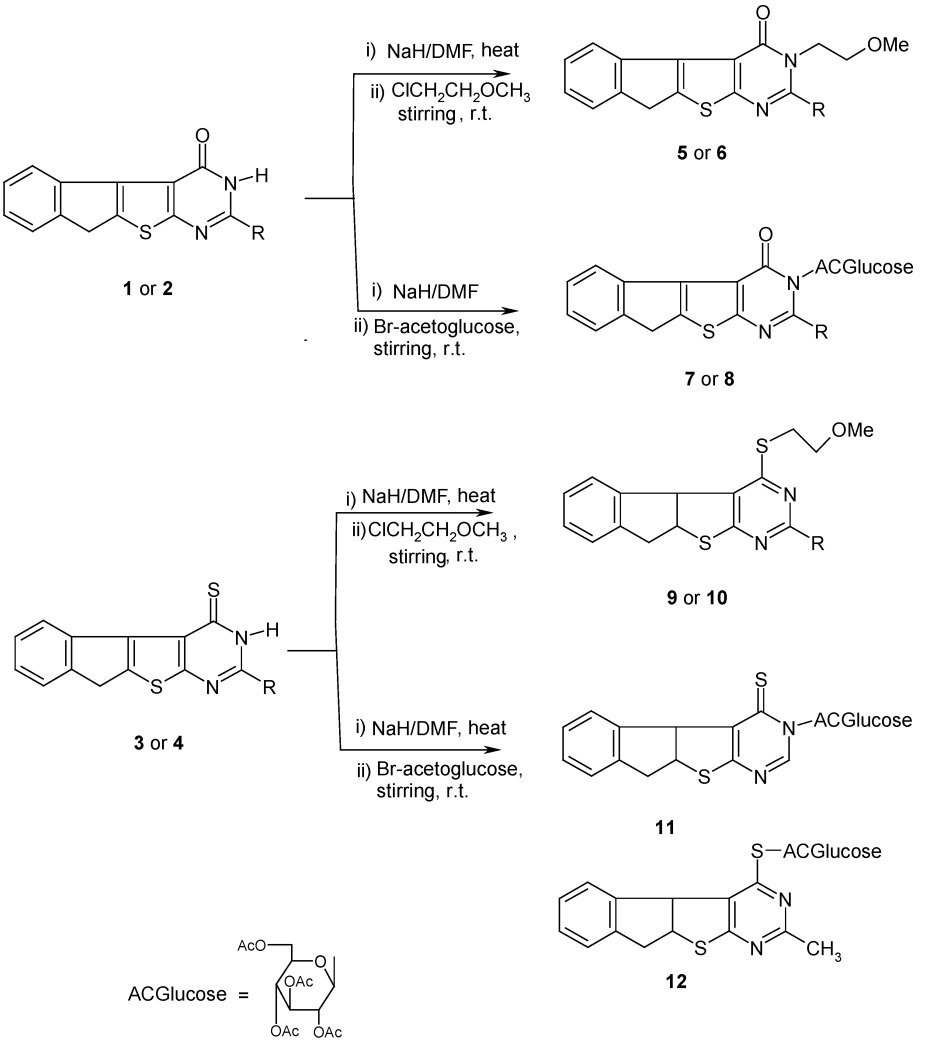
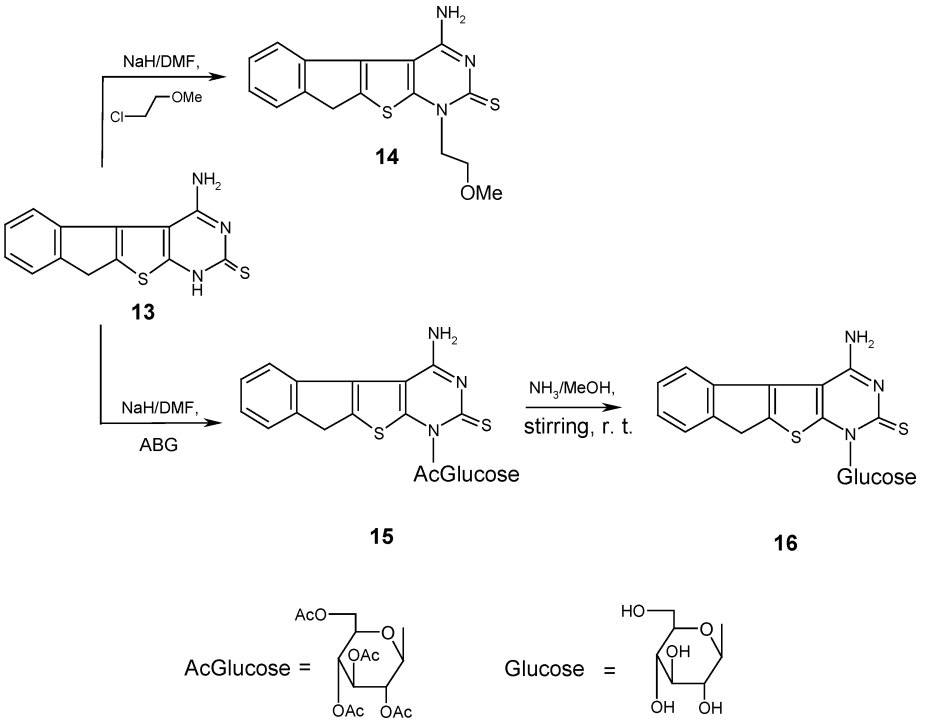
Address correspondence to Aymn. E. Rashad, National Research Centre, El-Behos Street, Dokki, Cairo, 12622 Egypt. E-mail: aymnelzeny@yahoo.com



SCHEME 1

glucopyranosyl bromide, they afforded the corresponding acyclic and cyclic nucleosides **5** and **6** or **7** and **8**, respectively (Scheme 1). The structures of these nucleosides were confirmed with spectral data (see Experimental). The IR spectra of the latter compounds revealed the presence of C=O, which indicates that the sites of attack were on the *N*- and not *O*-atom (see Experimental). Also, The ^{1}H-NMR spectra of the 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



SCHEME 2

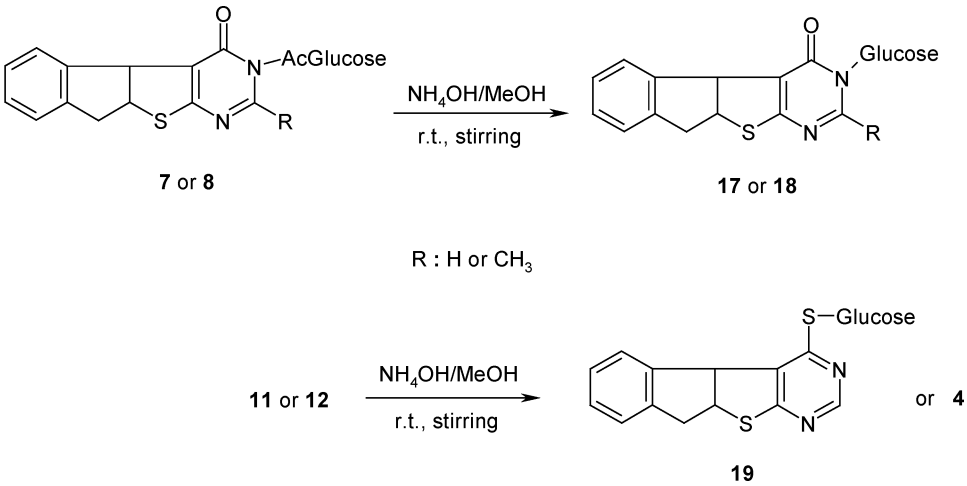
orientation of the H-1′ and H-2′ protons, indicating the presence of only the β-configuration.[22,23]

Similarly, nucleosides **9–12** were obtained (Scheme 1). ^{13}C-spectra of nucleosides **9**, **10**, **12** showed the site of attack to be on the sulfur and not on the nitrogen due to the disappearance of the signal of the C=S group (cf. the Experimental section).

In the meantime, when the sodium salt of compound **13**[21] was treated with 2-chloroethyl methyl ether or 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, it gave derivatives **14** and **15**, respectively (Scheme 2). The deacetylation of **15** was accomplished by treatment with methanolic ammonia, to afford **16** (Scheme 2). The ^{13}C-NMR spectra of nucleosides **15** and **16** (cf. Experimental section), showed that sites of attack were on the *N*- and not the *S*-atom.

On the other hand, deprotection of nucleosides **7**, **8**, or **11** with ammonia in methanol, afforded the free nucleosides **17–19** (Scheme 3). While, deprotection of nucleoside **12,** with ammonia in methanol, broke the glycosidic linkage and gave compound **4** again. The structures of the latter compounds were confirmed on the basis of their elemental analysis and spectral data (see Experimental section).

The incorporation of an acyclo *C*-nucleoside moiety[7,24,25] to the triazolopyrimidine ring system would probably enhance its biological

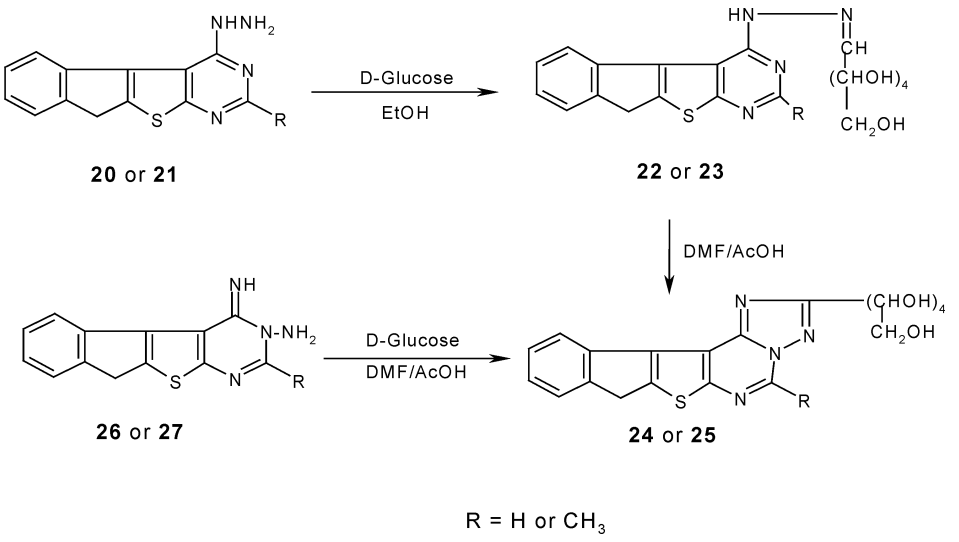


SCHEME 3

activity. Therefore, the condensation of the 4-hydrazino derivatives **20**[21] and **21**[[21] with D-glucose, in the presence of catalytic amounts of glacial acetic acid, gave the corresponding sugar hydrazone derivatives **22** and **23**, respectively. The products revealed absorption bands for (OH+NH), and (C=N) in IR spectra and their ^{1}H NMR spectra showed the presence of the sugar protons, NH, and azo-methine (C<u>H</u> = N) (see Experimental section). Oxidative and thermal dehydrogenative cyclization of the hydrazones and similar aldehydo-sugar hydrazones have been reported to cause annulations of the [1,2,4]triazole ring to the preexisting pyrimidine ring.[7,24,25] So, when compounds **22** and **23**, were heated in dimethylformamide in the presence of glacial acetic acid, underwent thermal dehydrogenative cyclization[25] to afford the annulated [1,2,4]triazolo products **24** and **25**, respectively (Scheme 4). The IR and ^{1}H NMR spectra of compounds **24** and **25**, revealed the absence of the NH, as well as the azo-methine (C<u>H</u> = N) (see Experimental section). The formation of triazolo[1,5-*c*]pyrimidine acyclic *C*-nucleosides **24** and **25** took place presumably via the formation of their corresponding isomeric triazolo[4,3-*c*]pyrimidine acyclic *C*-nucleosides, which underwent a Dimroth-type rearrangement under the conditions of the reaction. This presumption was supported by the reaction of the 4-imino derivatives **26**[21] and **27**,[21] with D-glucose in the presence of glacial acetic acid, which afforded products identical in all respects with the acyclic *C*-nucleosides **24** and **25** respectively (Scheme 4).

Antimicrobial Activity

The in vitro antimicrobial activity of the synthesized compounds was investigated against several pathogenic representative Gram-positive



SCHEME 4

bacteria (*Staphylococcus aureus* ATCC 29231, *Bacillus subtilis,* ATCC 10783, and *Mycobacterium phlei,* ATCC 1014); Gram-negative bacteria (*Escherichia coli* ATCC 11105), and yeast (*Candida albicans* ATCC 10231). All microorganisms used were obtained from the culture collection of the Department of Natural and Microbial Products, National Research Centre, Dokki, Cairo, Egypt. Compounds were tested against *Escherichia coli* and *Staphylococcus aureus* in a nutrient broth, pH = 7.0, against *Bacillus subtilis, Mycobacterium phlei* in the Bacto brain heart infusion broth, pH = 7.0, and against *Candida albicans* in a broth containing 1% peptone, 2% dextrose, pH = 5.7. *Escherichia coli* of known antibiotic sensitivity served for control purposes. Media for disc sensitivity tests were the nutrient agar and Muller-Hinton agar (MHA) purchased from Difico. Nonsterile powder of the tested compound was dissolved in sterile DMSO to yield 2 μg mL^{-1}, and passed through 0.2 μm membrane filters (Millipore Corp, USA). The filtrates were dispensed as 2 mL samples into sterile, small screw-capped vials, frozen and kept stored at −15°C. The vials were refrozen after thawing. Disc diffusion sensitivity test was done in the manner identical to that of Farag et al.[26] DMSO showed no inhibition zones. Streptomycin, Amoxicillin (Bioanalyse, Turkey) and Fusidic acid (Sigma-Aldrich, Milwaukee, WI, USA) were used as reference substances.

Compounds **7**, **11**, **14**, **15**, **19, 22**, and **23** were selected to represent the newly synthesized compounds and tested for their antimicrobial activity. As shown in Table 1, derivative **11** revealed the highest antimicrobial activity than the other tested compounds and the reference drugs.

TABLE 1 Test of the synthesized compounds

C. albicans	*S. aures*	*M. phlei*	*B. subtilis*	*E. coli*	The tested compounds[a]
++++	−	−	++++	++++	**(S)**[b]
−	+	−	−	+++	**(Am)**[c]
++++	+	+++	−	−	**(FA)**[d]
++	+	+	++	+	**7**
++++	++	++	+	++++	**11**
++	+	+	++	++	**14**
+++	−	++	−	+++	**15**
+	+	+	++	+	**19**
+	+	+	+	+	**22**
+	+	+	++	+	**23**

[a] $\gamma = 2\ \mu$g mL–1 in DMSO.
[b] $\gamma = 25\ \mu g/mL^{-1}$.
[c] $\gamma = 4\ \mu g\ mL^{-1}$.
[d] $\gamma = 4\ \mu g/mL^{-1}$.
+++ − Highly sensitive (inhibition zone = 21–25 mm).
++ − Fairly sensitive (inhibition zone = 16–20 mm).
+ − Slightly sensitive (inhibition zone = 10–15 mm).
− Not sensitive.

EXPERIMENTAL

All melting points were uncorrected and measured using Electrothermal IA 9100 apparatus (Shimadzu, Kyoto, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Shimadzu, Japan). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini 180 spectrometer (Varian, Oxford, UK) and chemical shifts were expressed as (ppm) values against TMS as internal reference. Mass spectra were recorded on Gc Ms-QP 1000 EX (Shimadzu, Japan). Microanalyses were performed by Vario El Elementar apparatus, Organic Microanalysis Section, National Research Centre and gave satisfactory values within range of ± 0.3% of the calculated values. Chromatography was performed on (Merck, Darmstadt, Germany) Silica gel 60 (particle size 0.06–0.20 mm).

Compounds **1–4**, **13**, **20**, **21**, **26**, and **27** were prepared as reported before.[16]

Preparation of 5, 6, 9, 10, and 14

General procedure. Compounds **1**, **2, 3**, **4**, or **13** were dissolved in dry dimethylformamide (20 mL), sodium hydride (2 mmol) was added, then the reaction mixtures were stirred at 70°C for 1 hour, cooled, then 2-chloroethyl methyl ether (2 mmol) was added, stirring at room temperature was continued for 6, 8, 3, 4, and 5 hours, 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 to give products **5**, **6**, **9**, **10**, and **14**, respectively.

3-(2-Methoxyethyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-(3*H*)-one (5). From compound **1**: (0.20 g, 67%), m.p. 188–190°C. IR (KBr, ν, cm^{-1}): 1680 (C=O). ^1H NMR (DMSO-d_6, δ ppm): 3.40 (s, 3H, OCH_3), 3.65 (t, 2H, CH_2), 4.10–4.20 (m, 4H, $2CH_2$), 7.10–7.50 (m, 3H, Ar-H), 7.60 (d, J = 10.00 Hz 1H, Ar-H), 8.0 (s, 1H, C_2-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, 64.32; H, 4.48 N, 9.42; S, 10.70.

2-Methyl-3-(2-methoxyethyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-(3*H*)-one (6). From compound **2**: (0.20 g, 67%), m.p. 194–196°C. IR (KBr, ν, cm^{-1}): 1684 (C=O).^1H NMR (DMSO-d_6, δ ppm): 2.60 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3), 3.60 (t, 2H, CH_2), 4.10–4.20 (m, 4H, $2CH_2$), 7.10–7.40 (m, 3H, Ar-H), 7.60 (d, J = 10.00 Hz 1H, Ar-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, 65.28; H, 5.28 N, 9.02; S, 10.11.

4-(2-Methoxyethyl)thioindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (9). From compound **3**: (0.25 g, 80%), m.p. 132–134°C. ^1H NMR ($CDCl_3$, δ ppm): 3.40 (s, 3H, OCH_3), 3.50 (t, 2H, CH_2OMe), 3.70 (t, 2H, NCH_2), 4.20 (s, 2H, CH_2), 7.10–7.50 (m, 3H, Ar-H), 8.10 (d, J = 10.90 Hz 1H, Ar H), 8.60 (s, 1H, C_2-H). ^{13}C NMR ($CDCl_3$, δ ppm): 28.34 (C-9), 58.27 (OCH3), 69.90 (CH_2), 76.54 (CH_2), 122.80 (C-4b), 123.50 (C-4a), 127.90–133.90 (Ar C), 134.70 (C-9a), 138.29 (C-10a), 152.60 (C-2), 167.13 (C-4); 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, 4.38 N, 9.02; S, 20.11.

2-Methyl-4-(2-methoxyethyl)thioindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (10). From compound **4**: (0.25 g, 80%), m.p. 168–169°C. ^1H NMR ($CDCl_3$, δ ppm): 2.40 (s, 3H, CH_3), 3.44 (s, 3H, OCH_3), 3.50 (t, 2H, CH_2OMe), 3.73 (t, 2H, NCH_2), 4.30 (s, 2H, CH_2), 7.10–7.50 (m, 3H, Ar-H), 8.10 (d, J = 10.90 Hz 1H, Ar H). ^{13}C NMR ($CDCl_3$, δ ppm): 18.25 (CH_3), 28.15 (C-9), 58.40 (OCH_3), 69.96 (CH_2), 76.94 (CH_2), 122.75 (C-4b), 123.58 (C-4a), 127.62–133.35 (Ar-C), 134.70 (C-9a), 138.29 (C-10a), 168.10 (C-4); calculated for $C_{17}H_{16}N_2OS_2$ (328.46): C, 62.17; H, 4.91; N, 8.53; S, 19.32. Found: C, 61.97; H, 4.98 N, 8.52; S, 19.19.

4-Amino-1-(2-methoxyethyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyramidine-2(1*H*)-thione (14). From compound **13**: (0.19 g, 58%), m.p. 212–214°C. ^1H NMR ($CDCl_3$, δ ppm): 3.30 (s, 3H, OCH_3), 3.40–3.60 (m, 6H, $3CH_2$), 7.20 (s, 2H, NH_2, D_2O exchangeable), 7.30–7.60 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d_6, δ ppm): 29.70 (C-9), 57.95 (OCH_3), 69.00 (CH_2OCH_3), 70.60 (CH_2N), 108 (C-10a), 122.40–135.61 (Ar-C), 138.25 (C-9a), 150.85 (C-4b), 159.10 (C-4a), 168.98 (C-4), 175.50 (C=S); calculated for $C_{16}H_{15}N_3OS$ (329.43): C, 58.10; H, 4.50; N, 12.76; S, 19.45. Found: C, 58.36; H, 4.56; N, 12.46; S, 19.48.

Preparation of 7, 8, 11, 12, and 15

General procedure. Compounds **1**, **2, 3**, **4**, or **13** (1 mmol) were dissolved in dry dimethylformamide (20 mL), then sodium hydride (2 mmol) were added with stirring at 70°C for 1 hour, cooled, 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide (0.452 g, 1 mmol) was added with stirring for 5, 7, 3, 4, and 2 hours, respectively. The reaction mixture was evaporated under reduced pressure and the residues were purified on silica gel column using pet. ether 40–60°C: ethyl acetate (4:1) as an eluent to give products **7**, **8**, **11**, **12**, and **15**, respectively.

3-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (7). From compound **1**: (0.25 g, 36%), m.p. 235–237°C. IR (KBr, ν, cm^{-1}): 1680, 1715 (C=O). ^1H NMR ($CDCl_3$, δ ppm): 1.90–2.20 (4s, 12H, $4CH_3CO$), 4.00–4.30 (m, 4H, CH_2 and 6′-H_2), 5.20–5.60 (m, 4H, 5′-H, 4′-H, 3′-H, and 2′-H), 6.30 (d, $J_{1',2'} = 9.99$ Hz, 1H, 1′-H), 7.20–7.50 (m, 3H, Ar H), 8.10 (d, $J = 10.80$ Hz, 1H, Ar-H), 8.20 (s, 1H, C_2-H); calculated for $C_{27}H_{26}N_2O_{10}S$ (570.58): C, 56.84; H, 4.59; N, 4.91; S, 5.62. Found: C, 56.75; H, 4.56; N, 4.96; S, 5.59.

2-Methyl-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (8). From compound **2**: (0.19 g, 33%), m.p. 200–202°C. IR (KBr, ν, cm^{-1}): 1685, 1710 (C=O). ^1H NMR ($CDCl_3$, δ ppm): 1.90–2.20 (4s, 12H, $4CH_3CO$), 2.70 (s, 3H, C_2-CH_3), 4.00–4.45 (m, 5H, CH_2, 5′-H, and 6′-H_2), 5.20–5.60 (m, 3H, 4′-H, 3′-H, and 2′-H), 6.50 (d, $J_{1',2'} = 9.99$ Hz, 1H, 1′-H), 7.10–7.60 (m, 4H, Ar-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, 57.71; H, 4.75; N, 4.91; S, 5.69.

3-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine-4(3*H*)-thione (11). From compound **3**: (0.20 g, 35%), m.p. 210–212°C. ^1H NMR ($CDCl_3$, δ ppm): 1.80–2.20 (4s, 12H, $4CH_3CO$), 4.10–4.50 (m, 5H, CH_2, 5′-H,and 6′-H_2), 5.30–5.60 (m, 3H, 4′-H, 3′-H, and 2′-H), 6.40 (d, $J_{1',2'} = 9.72$ Hz, 1H, 1′-H), 7.50–7.70 (m, 3H, Ar-H), 8.30 (d, $J = 10.80$ Hz, 1H, Ar-H), 8.95 (s, 1H, C_2-H); calculated for $C_{27}H_{26}N_2O_9S_2$ (586.64): C, 55.28; H, 4.47; N, 4.78; S, 10.93. Found: C, 55.41; H, 4.50; N, 4.66; S, 10.89.

2-Methyl-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)thioindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (12). From compound **4** : (0.20 g, 34%), m.p. 250–252°C. ^1H NMR ($CDCl_3$, δ ppm): 1.90–2.20 (4s, 12H, $4CH_3CO$), 2.90 (s, 3H, C_2-CH_3), 4.00–4.30 (m, 4H, CH_2 and 6′-H_2), 5.10–5.40 (m, 4H, 5′-H, 4′-H, 3′-H, and 2′-H), 6.30 (d, $J_{1',2'} = 10.80$ Hz, 1H, 1′-H), 7.10–7.50 (m, 3H, Ar-H), 8.20 (d, $J = 10.52$ Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, δ ppm): 14.00 (CH_3), 20.63, 22.64, 22.93, 23.68 ($4COCH_3$), 25.78 (C-9), 61.90 (C-6′), 67.65 (C-4′), 68.90 (C-2′), 72.65 (C-5′), 73.96 (C-3′), 80.09 (C-1′), 123.25–163.52 (Ar-C), 169.39, 169.55, 170.13, 170.52 (4C=O of acetyl);

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, 55.85; H, 4.56; N, 4.76; S, 10.79.

4-Amino-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)indeno[1′,2′:4,5] thieno[2,3-*d*]pyrimidine-2(1*H*)-thione (15). From compound **13**: (0.20 g, 34%), m.p. 224–226°C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.80–2.20 (4s, 12H, $4CH_3CO$), 3.80–4.30 (m, 5H, CH_2, 5′-H, 6′-H_2), 5.00–5.40 (m, 3H, 4′-H, 3′-H, and 2′-H), 5.80 (d, $J_{1',2'} = 10.12$ Hz, 1H, 1′-H), 5.90 (s, 2H, NH_2, D_2O exchangeable), 7.10–7.40 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, δ ppm): 20.39, 20.42, 22.42, 23.23 ($4COCH_3$), 29.79 (C-9), 61.74 (C-6′), 67.40 (C-4′), 68.86 (C-2′), 73.21 (C-5′), 75.04 (C-3′), 81.17 (C-1′), 108.91–165.71 (Ar-C), 169.30, 169.59, 170.02, 170.25 (4C = O of acetyl), 185.82 (C=S); calculated for $C_{27}H_{27}N_3O_9S_2$ (601.66): C, 53.90; H, 4.52; N, 6.98; S, 10.66. Found: C, 53.75; H, 4.56; N, 6.96; S, 10.59.

Deprotection of Compounds 7, 8, 11, 12 and 15

General procedure. Compounds **7**, **8**, **11**, **12** and **15** (1 mmol) were dissolved in 30 mL dry methanol, then ammonium hydroxide solution (30 mL) were added at 0°C with stirring for 1/2 hout, then at room temperature until deprotection was completed (detected with *tlc*).

4-Amino-1-(β-D-glucopyranosyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine-2(1*H*)-thione (16). From compound **15**: (48%) oil. IR (KBr, ν, cm^{-1}): 3180–3415 (NH_2+OH).^{1}H NMR (DMSO-d_6, δ ppm): 3.00–3.40 (m, 3H, 5′-H and 6′-H_2), 3.50–4.10 (m, 5H, CH_2, 4′-H, 3′-H, and 2′-H), 4.30, 4.50, 4.80, 5.20 (4OH, all of them are D_2O exchangeable), 6.90 (d, $J_{1',2'} = 10.20$ Hz, 1H, 1′-H), 7.10–7.60 (m, 6H, 4 Ar-H and NH_2, D_2O exchangeable); calculated for $C_{19}H_{19}N_3O_5S_2$ (433.51): C, 52.64; H, 4.42; N, 6.69; S, 14.79. Found: C, 52.69; H, 4.50; N, 6.61; S, 14.72.

3-(β-D-Glucopyranosyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyramidine-3(2*H*)-one (17). From compound **7**: (54%) oil. IR (KBr, ν, cm^{-1}): 3180–3250 (OH), 1710 (C=O).^{1}H NMR (DMSO-d_6, δ ppm): 3.00–3.10 (m, 1H, 5′-H), 3.30–4.20 (m, 7H, CH_2, 6′-H2, 4′-H, 3′-H, and 2′-H), 4.50–5.20 (m, 4H, 2′-OH, 3′-OH, 4′-OH, and 6′-OH, all of them are D_2O exchangeable), 6.60 (d, $J = 10.00$ Hz, 1H, 1′-H), 7.00–7.60 (m, 5H, 4Ar-H and C_2-H); calculated for $C_{19}H_{18}N_2O_6S$ (402.43): C, 56.71; H, 4.51; N, 6.96; S, 7.97. Found: C, 56.68; H, 4.45; N, 6.82; S, 8.07.

2-Methyl-3-(β-D-glucopyranosyl)indeno[1′,2′:4,5]thieno[2,3-*d*] pyrimidine-3(2*H*)-one (18). From compound **8**: (51%) oil. IR (KBr, ν, cm^{-1}): 3210–3265 (OH), 1710 (C=O).^{1}H NMR (DMSO-d_6, δ ppm): 2.90 (s, 3H, C_2-CH_3), 3.00–3.10 (m, 1H, 5′-H), 3.30–4.20 (m, 7H, CH_2, 6′-H_2, 4′-H, 3′-H, and 2′-H), 4.50–5.20 (m, 4H, 2′-OH, 3′-OH, 4′-OH, and 6′-OH, all of them are D_2O exchangeable), 6.60 (d, $J = 10.00$ Hz, 1H, 1′-H), 7.00–7.60 (m, 5H, 4Ar-H

and C_2-H); calculated for $C_{20}H_{20}N_2O_6S$ (416.40): C, 57.68; H, 4.84; N, 6.73; S, 7.70. Found: C, 57.75; H, 4.80; N, 6.81; S, 7.62.

3-(β-D-Glucopyranosyl)indeno[1′,2′:4,5]thieno[2,3-*d*]pyramidine-3(2*H*)-thione (19). From compound **11**: (59%) oil. ^{1}H NMR (DMSO-d_6, δ ppm): 3.00–3.10 (m, 1H, 5′-H), 3.30–4.20 (m, 7H, CH_2, 6′-H_2, 4′-H, 3′-H, and 2′-H), 4.50–5.20 (m, 4H, 2′-OH, 3′-OH, 4′-OH, and 6′-OH, all of them are D_2O exchangeable), 6.60 (d, J = 10.00 Hz, 1H, 1′-H), 7.00–7.60 (m, 5H, 4 Ar-H and C_2-H). ^{13}C NMR (DMSO-d_6, δ ppm): 30.00 (C-9), 61.00 (C-6′), 70.00 (C-4′), 73.00 (C-2′), 75.00 (C-5′), 78.00 (C-3′), 82.00 (C-1′), 95.00–160.00 (Ar-C), 173 (C=S); calculated for $C_{19}H_{18}N_2O_5S_2$ (418.49): C, 54.53; H, 4.34; N, 6.69; S, 15.32. Found: C, 54.48; H, 4.29; N, 6.75; S, 15.38.

Aldehydo-D-glucose{indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-yl}-hydrazones 22 and 23

General procedure. A solution of compound **20** (0.254 g, 1 mmol) or **21** (0.268 g, 1 mmol) in 20 mL ethanol was added to a solution of D-glucose (0.180 g, 1 mmol) in the least amount of water (2 mL), then glacial acetic acid (1/2 mL) was added with stirring at reflux temperature for 1 hour, kept to cool, then the crystalline products which separated were filtered off, washed with ethanol, and recrystallized from ethanol/water (1:1) to give the corresponding hydrazone derivatives **22** and **23**, respectively.

Aldehydo-D-glucose{indeno[1′,2′:4,5]thieno[2,3-d]pyrimidin-4-yl}-hydrazone (22). From compound **20**: (0.25 g, 60%), m.p. 176–178°C. IR (KBr, ν, cm^{-1}): 3350–3300 (NH, OH), 1580 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.00–4.10 (m, protons of the alditol + CH_2 congregated with the water absorption),[7,8,19] 4.90 (m, 1H, OH, D_2O exchangeable), 6.70–7.40 (m, 4H, Ar-H), 7.80 (d, 1H, HC=N), 8.50 (s, 1H, NH, D_2O exchangeable). MS, m/z (%): 415 (M^+, 2.15); calculated for $C_{19}H_{20}N_4O_5S$ (416.46): C, 54.80; H, 4.84; N, 13.45; S, 7.70. Found: C, 54.95; H, 4.78; N, 13.53; S, 7.76.

Aldehydo-D-glucose{2-methylindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-yl}hydrazone (23). From compound **21**: (0.30 g, 70%), m.p. 174–176°C. IR (KBr, ν, cm^{-1}): 3340–3200 (NH, OH), 1580 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.60 (s, 3H, C_2-CH_3), 3.20–3.60 (m, protons of alditol congregated with the water absorption), 4.00 (s, 2H, CH_2), 4.30–4.60 (m, 3H, 3OH, all of them are D_2O exchangeable), 5.30 (s, 1H, OH, D_2O exchangeable), 7.10–7.60 (m, 3H, Ar-H), 8.00 (d, J = 10.60 Hz, 1H, Ar-H), 8.90 (d, 1H, HC = N), 11.40 (s, 1H, NH, D_2O exchangeable), ^{13}C NMR (DMSO-d_6, ppm): 22.00 (CH_3), 28.50 (C-9), 63.50, 70.92, 71.37, 71.46, 73.04 (alditol-C), 120.75 (HC = N), 123.70–157.30 (Ar-C); calculated for $C_{20}H_{22}N_4O_5S$ (430.49): C, 55.80; H, 5.15; N, 13.01; S, 7.45. Found: C, 55.94; H, 4.98; N, 13.52; S, 7.49.

2-(D-Gluco-pentitol-1-yl)indeno[1′,2′:4,5]thieno[3,2-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine Derivatives 24 and 25

General procedure. *Method A*. A mixture of compound **22** (0.416 g, 1 mmol) or compound **23** (0.430 g, 1 mmol) in dimethylformamide (20 mL), glacial acetic acid (1 mL) was heated at 70°C with stirring for 2 hours, cooled, poured into water, filtered, dried, and recrystallized from ethanol to give the corresponding triazolo derivatives **24** and **25**, respectively. *Method B*. A solution of compounds **26** (0.254 g, 1 mmol) or **27** (0.268 g, 1 mmol) in dimethylformamide (20 mL) was added to the solution of D-glucose (0.180 g, 1 mmol) in the least amount of water (2 mL), then glacial acetic acid (1 mL) was added with stirring at 70°C for 4 hours, then the reaction mixture was cooled, poured into water, filtered, dried, and recrystallized from ethanol to give the corresponding triazolo derivatives **24** and **25**, respectively.

2-(D-Gluco-pentitol-1-yl)indeno[1′,2′:4,5]thieno[3,2-*e*][1,2,4]triazolo-[1,5-*c*]pyrimidine (24). From compound **22** or from **26**; (0.31 g, 75% from method A and 0.33 g, 80% from method B); m.p. 240–242°C,. IR (KBr, ν, cm^{-1}): 3350–3300 (OH), 1610 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.40 (m, 2H, CH_2OH, D_2O exchangeable), 3.60–3.90 (m, protons of alditol congregated with the water absorption), 4.00 (s, 2H, CH_2), 4.40–4.50 (m, 2H, 2OH, D2O exchangeable), 4.70 (d, 1H, OH, D_2O exchangeable), 5.20 (d, 1H, OH, D2O exchangeable), 7.10–7.50 (m, 3H, Ar H), 8.10 (d, J = 11.20 Hz, 1H, Ar-H), 8.90 (s, 1H, C_5-H); calculated for $C_{19}H_{18}N_4O_5S$ (414.44): C, 55.06; H, 4.38; N, 13.52; S, 7.74. Found: C, 54.98; H, 4.29; N, 13.75; S, 7.82.

2-(D-Gluco-pentitol-1-yl)-5-methylindeno[1′,2′:4,5]thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (25). From compound **23** or from **27** (0.30 g, 70% from method A and 0.32 g, 75% from method B); m.p. 192–194°C. IR (KBr, ν, cm^{-1}): 3364–3336 (OH), 1614 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.60 (s, 3H, C_5-CH_3), 3.30–3.70 (m, protons of alditol congregated with the water absorption), 4.00 (s, 2H, CH_2), 4.40–4.50 (m, 3H, 3OH, all of them are D_2O exchangeable), 5.10 (d, 1H, OH, D_2O exchangeable), 5.50 (d, 1H, OH, D_2O exchangeable), 7.10–7.50 (m, 3H, Ar H), 8.50 (d, J = 11 Hz 1H, Ar-H); ^{13}C NMR (DMSO-d_6, δ ppm): 30.00 (CH_3), 29.80 (C-8), 37.00 (CH_2), 63.00, 69.00, 71,96 (CHOH), 120.00–158.00 (Ar-C). MS, m/z (%): 278 (8.10), 253.0 (100), 211 (16.00); calculated for $C_{20}H_{20}N_4O_5S$ (428.47): C, 56.07; H, 4.70; N, 13.08; S, 7.48. Found: C, 56.12; H, 4.61; N, 12.96; S, 7.56.

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