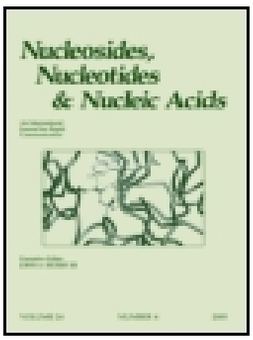

Nucleosides, Nucleotides and Nucleic Acids

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Nucleic Acid Components and Their Analogs: Design and Synthesis of Novel Cytosine Thioglycoside Analogs

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ABSTRACT

The synthesis of a new category of novel cytosine 4-thioglycoside analogs has been first accomplished. The main step of this strategy is the synthesis of sodium pyrimidine-4-thiolate through the condensation of 2-cyano-*N*-arylacetamides with sodium cyanocarbonimidodithioate, followed by coupling with α-bromo-sugars to afford the corresponding cytosine 4-thioglycoside analogs. The free thioglycosides were also prepared. Subsequent studies on the application of this strategy for the preparation of other potent pyrimidine thioglycosides are reported.

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Pyrimidine thioglycosides; antimetabolites; 2-cyano-*N*-arylacetamides; sodium cyanocarbonimidodithioate

Introduction

Nucleoside analogs have been in clinical use and have become fundamental drugs for treating viral infections and cancer.[1] Thioglycosides are versatile building blocks in synthetic carbohydrate chemistry.[2,3] It is worthwhile to note that various thioglycosides are considered as glycosyltransferases inhibitors.[4] Pyrimidine nucleoside analogs are components of solid tumor and hematological malignancy therapies.[5,6] The antitumor and antiviral potencies of many pyrimidine and purine nucleosides have been evaluated.[7] During our studies on the design and synthesis of nucleoside derivatives, a method for the synthesis of thioglycosides bearing a functionalized pyrimidine or pyridine ring was desired.[8–11] That method could generate various analogs of pyrimidine nucleosides with new hydrogen-bonding patterns.[12–15] Such compounds might display pharmaceutically pivotal roles and useful antimetabolite potency.[16] The synthesis of novel substituted pyridine thioglycosides which showed antagonistic potency have been described.[17] In addition, the significant use of dihydropyridine thioglycosides as inhibitors of protein glycosylation were reported.[18] These remarkable bioactivities motivated us to develop a new strategy for the preparation of pyrimidine thioglycosides. Continuing our

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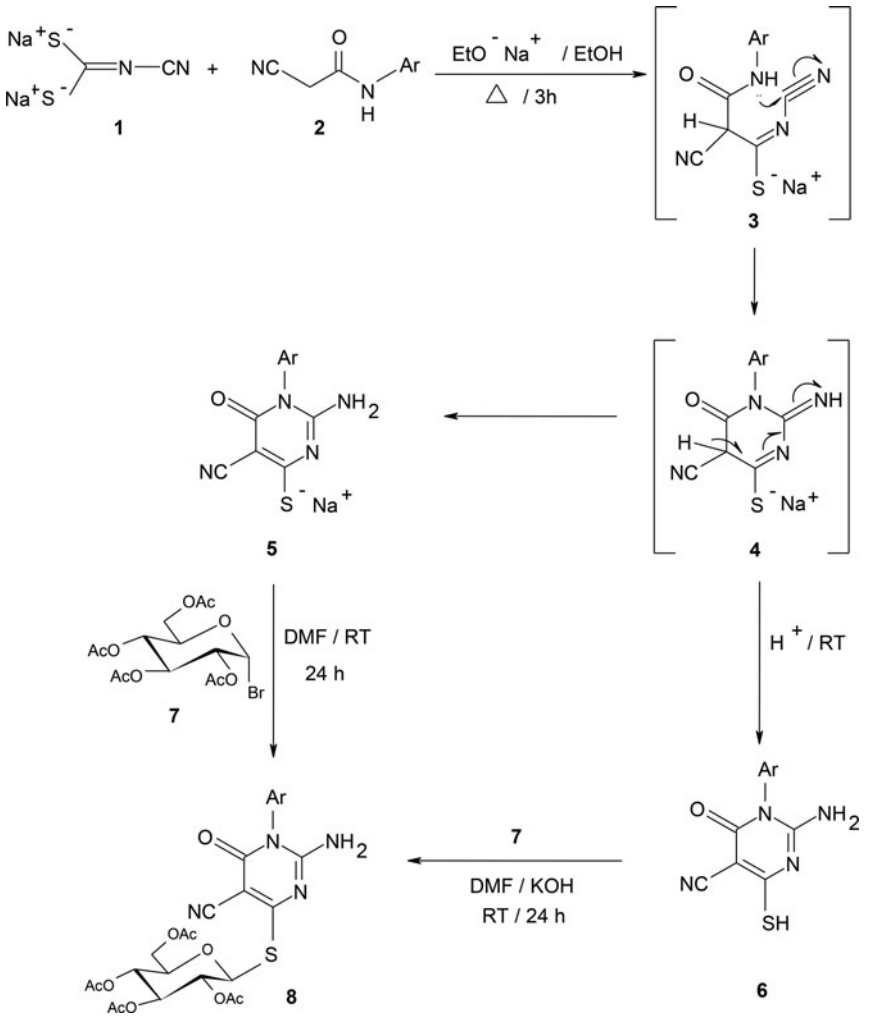
efforts for the development of cost-effective and simple methodologies, novel synthesis of cytosine thioglycoside analogs are reported. This new efficient strategy has been applied to various functionalized pyrimidine thioglycosides in high yields. This is the first approach to be accomplished for the synthesis of this new ring system.

Results and discussions

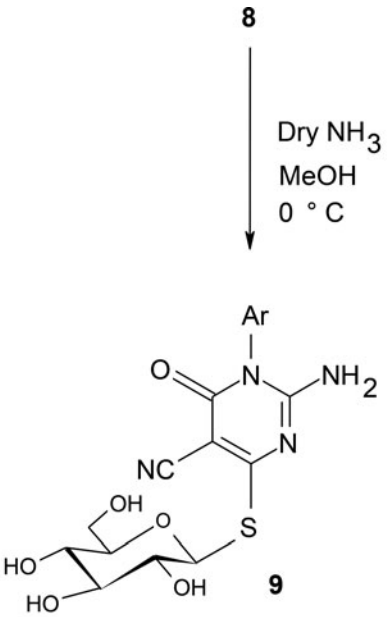
Chemistry

Sodium cyanocarbonimidodithioate salt **1** was furnished upon the reaction of aminomethanenitrile with carbon disulfide in sodium ethoxide. Compound **1** was reacted with 2-cyano-*N*-arylacetamides **2a-d** in the presence of sodium ethoxide



Scheme 1. Synthetic pathway for pyrimidine-4-thioglycosides 8a-d.

for 3 hours to afford the corresponding sodium 2-amino-1-aryl-4-mercapto-6-oxo-1,6-dihydro-pyrimidine-4-thiolate analogs **5a-d** in a relatively quantitative yields. Treatment of the latter with hydrochloric acid afforded the corresponding pyrimidine-4-thiol derivatives **6a-d**. The structures of compounds **6a-d** were established and confirmed on the basis of their spectral data (^{1}H-NMR, IR, ^{13}C-NMR) and elemental analysis. Compounds **6a-d** reacted with halosugars **7** in dimethyl formamide-KOH at room temperature to yield the corresponding *S*-glycosides **8a–d** as outlined in Scheme 1. Compounds **8a-d** can also be prepared through the coupling of pyrimidine-4-thiolate salts **5** with halosugars **7** in dimethylformamide at room temperature. It has been proposed that the *cis*-(α) sugars was reacted by a straightforward SN_2 reaction to afford the β-glycoside derivatives.[19] The structures of **8a-d** were confirmed on the basis of their spectral data (IR, ^{1}H-NMR, ^{13}C-NMR) and elemental analysis. The analytical data for **8a** showed a molecular

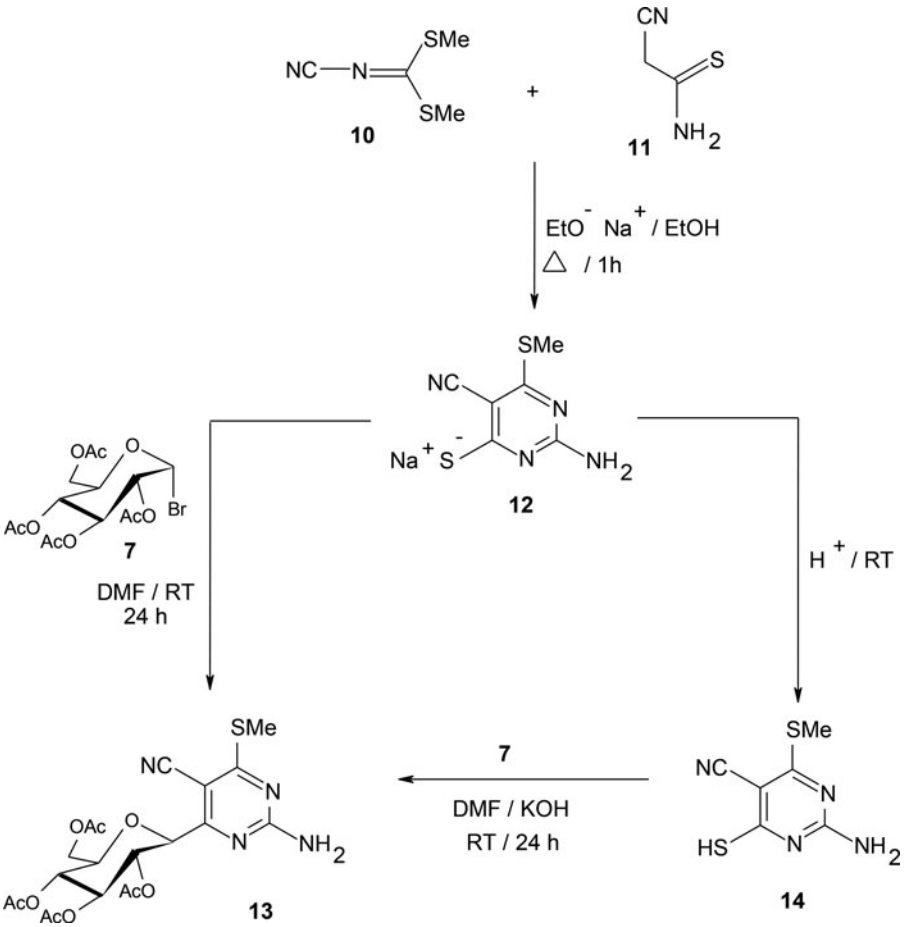


2-6,8	**Ar**		
a,	C_6H_5	c,	4-Cl-C_6H_4
b,	4-H_3C-C_6H_4	d,	$C_{10}H_7$

9	**Ar**		
a,	C_6H_5	b,	4-H_3C-C_6H_4

Scheme 2. Synthetic pathway for pyrimidine-4-thioglycosides 9a,b.

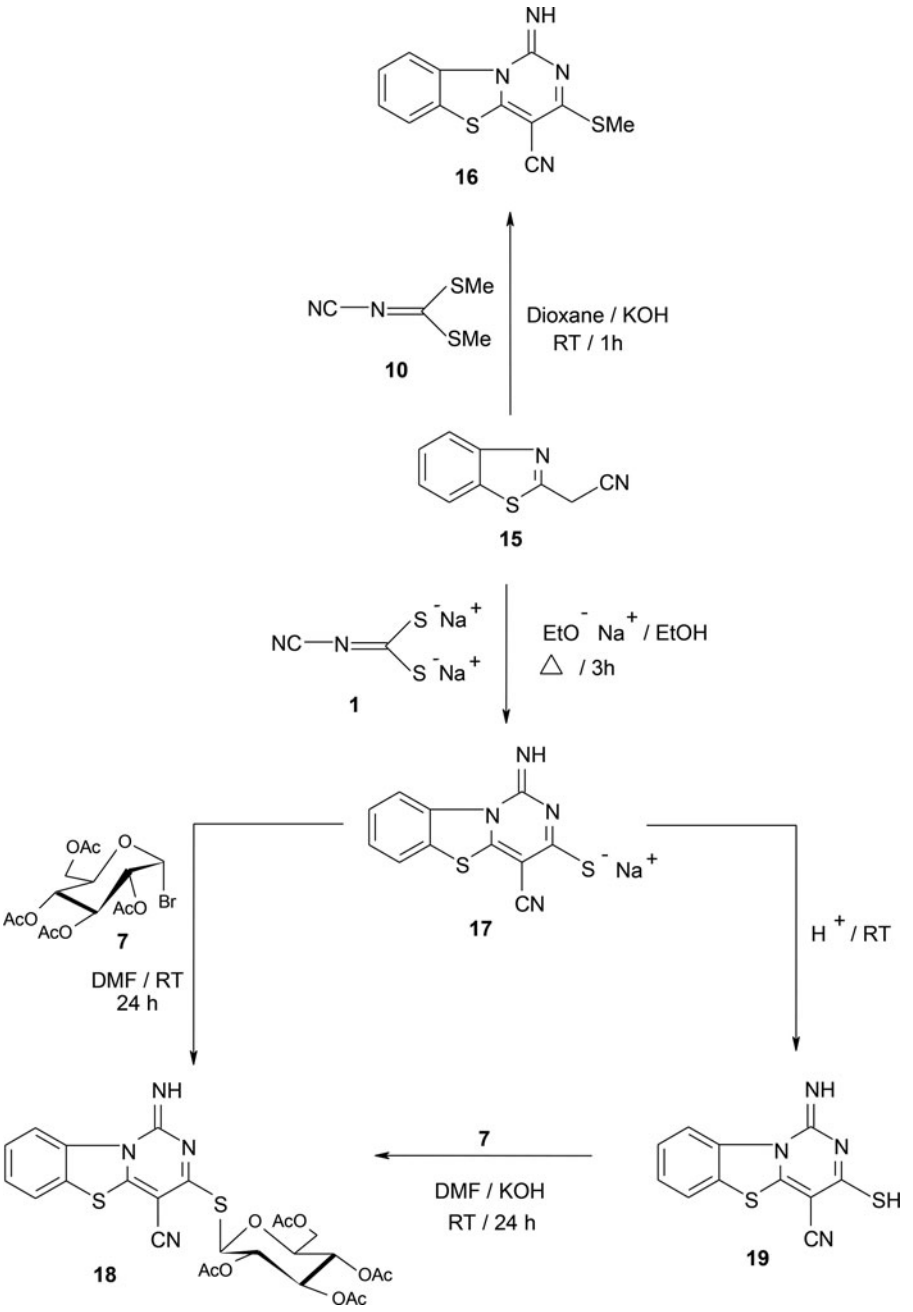
formula $C_{25}H_{26}N_4O_{10}S$, its ^{1}H-NMR spectrum showing the anomeric proton as a doublet at δ 5.85–5.87 ppm with a spin-spin coupling constant of 10.00 Hz for the β-configuration. The other six glucose protons assigned at δ 4.9–5.3 ppm. When glycosides **8a-d** were treated with methanolic ammonia at 0°C, the deprotected analogs **9a,b** were accessed in good yields (Scheme 2), the structures of which were confirmed by their spectral data and elemental analysis. The analytical data for **9b** show the molecular formula $C_{18}H_{20}N_4O_6S$. The ^{1}H NMR spectrum indicates the anomeric proton as doublet at δ 4.61–4.81 ($J_{1,2}$ = 10.00 Hz), showing the existence of only the β-*D*-configuration. The other six-glucose protons exist as a multiplet at δ 3.5–4.12 ppm, while the four hydroxy groups of glucose moiety are assigned at δ 4.35–4.91 ppm (exchangeable by deuterium oxide). Supported by these results, reaction of dimethyl *N*-cyanodithioiminocarbonate **10** with cyanothioacetamide **11** in sodium ethoxide yielded the product **12**. When the latter was reacted with compound **7**, the *S*-glycoside derivative **13** is formed. Its ^{1}H-NMR spectrum showed the anomeric proton as a doublet at δ 5.93–5.95 ppm with a spin-spin coupling constant of 10.00 Hz and a broad band at δ 7.90 ppm which is assignable for an NH_2 group.



Scheme 3. Synthetic pathway for 6-methylthiopyrimidine-4-thioglycoside 13.

Treatment of **12** with hydrochloric acid afforded the corresponding compound **14**. Another way to access compound **13** was accomplished by reacting compound **14** with the compound **7** in DMF-KOH at room temperature (Scheme 3).

A novel pyrimidobenzothiazole derivative **16** was synthesized by reacting *S,S*-dimethyl *N*-cyanodithioimidocarbonate **10** with 2-cyanomethylbenzo[1,2-*b*]thiazole **15** in a dry dioxane solution containing potassium hydroxide at room



Scheme 4. Synthetic pathway for pyrido[6,1-a]benzothiazol-3-thioglycoside 18.

temperature. The structure of **16** was affirmed by its spectral data (^{1}H-NMR, IR, ^{13}C-NMR) and elemental analysis. The mass spectrum of **16** was consistent with the molecular formula $C_{12}H_8N_4S_2$ ($M^+ = 272$). The ^{1}H-NMR spectrum showed a singlet at δ 2.49 ppm assigned to SCH_3 group, multiplet at δ 7.54–8.10 ppm designated for aromatic protons and a broad band at δ 9.30 ppm assigned for an NH group. The ^{13}C-NMR spectrum was depicted by a signal at δ 12.86 ppm attributed to SCH_3 carbon and a signal at δ 115.12 ppm attributed to the CN carbon. Moreover, a signal appeared at δ 120.54–127.93 ppm corresponding to the aromatic carbons, respectively. Sodium cyanocarbonimidodithioate salt **1** was reacted with one equivalent of **15** in the presence of sodium ethoxide to give compound **17**, and further reaction of **17** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **7** yielded 1-imino-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylthio)-pyrido[6,1-*a*]benzothiazol-4-carbonitrile **18** (Scheme 4). The structure of **18** was affirmed by its spectral data and elemental analysis. The ^{1}H-NMR spectrum indicated a singlet at δ 2.40 ppm assigned to the methylthio group, a multiplet at δ 7.19–7.33 ppm assignable for aromatic protons, and a broad band at δ 7.90 ppm assigned for an NH group. The anomeric proton as doublet was shown at δ 6.01–6.03 ($J_{1,2}$ = 10.00 Hz), showing the existence of only the β-*D*-configuration. Treatment of **17** with hydrochloric acid afforded the corresponding compound, 3-(mercapto)-1-imino-pyrido[6,1-*a*]benzothiazol-4-carbonitrile **19**. We obtained compound **18** also by starting with compound **19** and reacting it with **7** in DMF-KOH at room temperature to give the corresponding *S*-glycosides (Scheme 4).

Conclusion

A novel and straightforward approach for the synthesis of the cytosine and pyrimidine thioglycoside analogs has been developed from available starting compounds. Subsequent studies on this innovative method which would represent a major advance in the glycoside syntheses are under way.

Experimental

Chemistry

All melting points were measured on a Gallenkamp melting point apparatus. The ^{1}H NMR and ^{13}C NMR spectra were measured on a Jeol-600 MHz and 500 MHz spectrometer for solutions DMSO-d6 using $Si(CH_3)_4$ as an internal standard at National Research Center, Cairo, Egypt. The mass spectra was measured in the Cairo University. Progress for the reactions was monitored by TLC using aluminum sheets coated with silica gel F254 (Merck). Viewing under a short-wavelength UV lamp effected detection.

General procedure for the synthesis of 6a-d

A solution of substituted acetanilide derivatives (0.01 mol) and disodium *N*-cyanodithioiminocarbonate (0.01 mol) have been refluxed for 3 h in the presence

of sodium ethoxide (0.01 mol) in absolute ethanol (30 mL). After cooling the reaction mixture to room temperature, it was poured into cooled water and treated with hydrochloric acid until the medium became just neutral. The resultant precipitate was collected by filtration and recrystallized.

2-Amino-4-mercapto-6-oxo-1-phenyl-1,6-dihydro-pyrimidine-5-carbonitrile (6a)

Colorless crystals; (EtOH), yield (90%), mp 160°C; IR (KBr, cm-1) υ 3422 (NH_2), 2208 (CN) and 1701 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.38–7.44 (m, 5H, C_6H_5), 9.70 (s, 2H, NH_2), 11.10 (s, 1H, SH). Anal.Calcd. For $C_{11}H_8N_4OS$ (244.27): C, 54.09; H, 3.30; N, 22.94; S, 13.13. Found: C, 54.07; H, 3.30; N, 22.93; S, 13.12.

2-Amino-4-mercapto-6-oxo-1-p-tolyl-1,6-dihydropyrimidine-5-carbonitrile (6b)

Yellow solid; (EtOH), yield (90%), mp 187°C; IR (KBr, cm-1) υ 3375 and 3306 (NH_2), ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.15–7.53 (m, 4H, C_6H_4), 9.70 (s, 2H, NH_2), 10.70 (s, 1H, SH). Anal.Calcd. For $C_{12}H_{10}N_4OS$ (258.30): C, 55.80; H, 3.90; N, 21.69; S, 12.41. Found: C, 55.80; H, 3.90; N, 21.67; S, 12.40.

2-Amino-1-(4-chloro-phenyl)-4-mercapto-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (6c)

Yellow solid; (EtOH), yield (90%), mp 240°C; IR (KBr, cm-1) υ 3453 and 3299 (NH_2), 2209 (CN) and 1658 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.20–7.58 (m, 4H, C_6H_4), 9.20 (s, 2H, NH_2), 11.00 (s, 1H, SH). Anal.Calcd. For $C_{11}H_7ClN_4OS$ (278.72): C, 47.40; H, 2.53; Cl, 12.72; N, 20.10; S, 11.50. Found: C, 47.40; H, 2.51; Cl, 12.71; N, 20.10; S, 11.50.

2-Amino-4-mercapto-1-(naphthalen-1-yl)-6-oxo-1,6-dihydro pyrimidine-5-carbonitrile (6d)

Brown solid; (EtOH), yield (90%), mp 164°C; IR (KBr, cm-1) υ 3322 and 3200 (NH_2), 2193 (CN) and 1670 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.22–7.79 (m, 7H, $C_{10}H_7$), 9.50 (s, 2H, NH_2), 10.80 (s, 1H, SH). Anal.Calcd. For $C_{15}H_{10}N_4OS$ (294.33): C, 61.21; H, 3.42; N, 19.04; S, 10.89. Found: C, 61.20; H, 3.41; N, 19.04; S, 10.88.

General procedure for the synthesis of 8a-d

To a solution of **5** (0.01 mol) in dry DMF (20 mL), a solution of 2′,3′,4′,6′-tetra-*O*-acetyl-α-D-gluco or -galactopyranosyl bromide **7** (0.01 mol) in dry DMF (10 mL) was dropped within 30 min. and the reaction mixture was stirred at room temperature until completion (TLC 24h). Then the reaction mixture was poured onto ice water. A solid product precipitate was filtered off.

2-Amino-5-cyano-1-phenyl-1,6-dihydro-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-pyrimidin-6-one (8a)

Buff solid; (EtOH), yield (75%), mp 186°C; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.93–1.95 (4s, 12H, 4xOAc), 4.90 (m, 3H, 2H-6′ and H-5′), 5.02 (t, 1H, H-4′), 5.04 (t, 1H, H-3′), 5.2–5.3 (t, 1H, H-2′), 5.85–5.87 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 7.28–7.90 (m, 5H, C_6H_5), 8.62 (s, 2H, NH_2). Anal. Calcd. For $C_{25}H_{26}N_4O_{10}S$ (574.56): C, 52.26; H, 4.56; N, 9.75; S, 5.58. Found: C, 52.26; H, 4.56; N, 9.75; S, 5.58.

2-Amino-5-cyano-6-1-p-tolyl-1,6-dihydro-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-pyrimidin-6-one (8b)

White solid; (EtOH), yield (90%), mp 150°C; IR (KBr, cm^{-1}) υ 3448 (NH_2), 2184 (CN) and 1754 (C=O). ^{1}H-NMR (600 MHz, DMSO-d_6): δ 1.88–2.29 (4s, 12H, 4xOAc), 2.35 (s, 3H, CH_3), 4.05–4.07 (m, 3H, 2H-6′ and H-5′), 4.3 (t, 1H, H-4′), 5.04 (t, 1H, H-3′), 5.2–5.3 (t, 1H, H-2′), 5.82–5.84 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 6.90–7.30 (m, 5H, C_6H_5), 8.20 (s, 2H, NH_2). ^{13}C NMR: δ 19.71–19.95 ($4CH_3CO$), 61.03 (C-6′), 67.38 (C-4′), 67.80 (C-2′), 73.14 (C-3′), 74.13 (C-5′), 82.60 (C-1′), 118.5 (CN), 128.51 (Ar-C). Anal. Calcd. For $C_{26}H_{28}N_4O_{10}S$ (588.59): C, 53.06; H, 4.79; N, 9.52; S, 5.45. Found: C, 53.04; H, 4.78; N, 9.51; S, 5.45.

2-Amino-1-(4-chloro-phenyl)-5-cyano-1,6-dihydro-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-pyrimidin-6-one (8c)

Buff solid; (EtOH), yield (26%), mp 170°C; IR (KBr, cm-1) υ 3470 and 3300 (NH_2), 2182 (CN) and 1742 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.9–2.02 (4s, 12H, 4xOAc), 3.98–4.16 (m, 3H, 2H-6′ and H-5′), 4.8 (t, 1H, H-4′), 4.94–4.96 (t, 1H, H-3′), 5.0–5.1 (t, 1H, H-2′), 5.10–5.30 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 7.28–7.55 (m, 5H, C_6H_5), 8.8 (s, 2H, NH_2). Anal. Calcd. For $C_{25}H_{25}ClN_4O_{10}S$ (609.00): C, 49.30; H, 4.14; Cl, 5.82; N, 9.20; S, 5.27. Found: C, 49.30; H, 4.13; Cl, 5.81; N, 9.20; S, 5.27.

2-Amino-5-cyano-1-naphthalen-1-yl-1,6-dihydro-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-pyrimidin-6-one (8d)

Brown solid; (EtOH), yield (24%), mp 200°C; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.90–2.40 (4s, 12H, 4xOAc), 3.98–4.13 (m, 3H, 2H-6′ and H-5′), 4.9–5.1 (t, 1H, H-4′), 5.12–5.3 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 5.34 (t, 1H, H-3′), 5.6–5.8 (t, 1H, H-2′), 7.35–8.05 (m, 8H, $C_{10}H_8$), 8.5 (s, 2H, NH_2). Anal.Calcd. For $C_{29}H_{28}N_4O_{10}S$ (624.62): C, 55.76; H, 4.52; N, 8.97; S, 5.13. Found: C, 55.76; H, 4.52; N, 8.97; S, 5.13.

General procedure for the synthesis of 9a-b

A solution of compounds **8** (0.01 mol) in anhydrous MeOH (10 mL) was added at 0°C to a saturated solution of anhydrous NH_3 in anhydrous MeOH (25 mL). Mixture

was stirred at 0°C for 7 h and then crystallized from EtOH to furnish an analytically pure compound **9**.

2-Amino-5-cyano-1-phenyl-1,6-dihydro-4-(β-D- glucopyranosyl–thio)-pyrimidin-6-one (9a)

White solid; (EtOH), yield (70%), mp 222°C; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.44–3.67 (s, 2H, H-5′, H-6′), 3.71 (s, 1H, H-4′), 3.96 (s, 1H, H-3′), 4.10 (s, 1H, H-2′), 4.30–4.36 (s, 2H, 2′-OH, 3′-OH), 4.58–4.66 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 4.87–4.90 (d, 2H, 4′-OH, 6′-OH), 6.82 (s, br, 2H, NH_2), 7.34–7.56 (m, 5H, C_6H_5). Anal.Calcd. For $C_{17}H_{18}N_4O_6S$ (406.09): C, 50.24; H, 4.46; N, 13.79; S, 7.89. Found: C, 50.24; H, 4.46; N, 13.77; S, 7.87.

2-Amino-5-cyano-6-1-p-tolyl-1,6-dihydro-4-(β-D-glucopyran–osylthio)-pyrimidin-6-one (9b)

Yellow solid; (EtOH), yield (67%), mp 180°C; ^{1}H-NMR (500 MHz, DMSO-d_6): ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.66 (s, 3H, CH_3), 3.51–3.69 (s, 2H, H-5′, H-6′), 3.79 (s, 1H, H-4′), 3.91 (s, 1H, H-3′), 4.12 (s, 1H, H-2′), 4.35–4.38 (s, 2H, 2′-OH, 3′-OH), 4.61–4.81 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 4.91 (d, 2H, 4′-OH, 6′-OH), 6.76 (s, 2H, NH_2), 7.34–7.56 (m, 4H, C_6H_4). Anal.Calcd. For $C_{18}H_{20}N_4O_6S$ (420.44): C, 51.42; H, 4.79; N, 13.33; S, 7.63. Found: C, 51.41; H, 4.79; N, 13.33; S, 7.62.

General procedure for the synthesis of 13,14

A solution of cyanothioacetamide (0.01 mol) and dimethyl *N*-cyanodi thioiminocarbonate (0.01 mol) was heated (50–60°C) for 1 h in the presence of sodium ethoxide (0.01 mol) in absolute ethanol. To a solution of **12** in dry DMF (20 mL), a solution of 2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **7** (0.01 mol) in dry DMF (10 mL) was dropped within 30 min. and the reaction mixture was stirred at room temperature until completion (TLC 24h). The reaction mixture was poured onto ice water. Then a solid product **13** precipitate was filtered off and crystallized. When the solution of **12** (0.01 mol) was poured onto cold water. The mixture was treated with hydrochloric acid until just neutral, then the formed solid **14** was collected by filtration.

2-Amino-6-methylthio-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glu–copyranosylthio)-pyrimidine-5-carbonitrile (13)

Brown solid; (DMF), yield (20%), mp 200°C; IR (KBr, cm-1) υ 3436 and 3367 (NH_2), 2211 (CN) and 1754 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.9–2.8 (4s, 12H, 4xOAc), 4.01–4.08 (m, 3H, 2H-6′ and H-5′), 4.9 (t, 1H, H-4′), 5.02 (t, 1H, H-3′), 5.6–5.8 (t, 1H, H-2′), 5.93–5.95 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 7.9 (s, 2H, NH_2). Anal.Calcd.

For $C_{20}H_{24}N_4O_9S_2$ (528.56): C, 45.45; H, 4.58; N, 10.60; S, 12.13. Found: C, 45.44; H, 4.57; N, 10.60; S, 12.11.

2-Amino-4-mercapto-6-(methylthio)-pyrimidine-5-carbo-nitrile (14)

Brown solid; (EtOH), yield (20%), mp 170°C; IR (KBr, cm-1) υ 3470 and 3300 (NH_2), 2182 (CN) and 1742 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.40 (s, 3H, SCH_3), 7.80 (s, 2H, NH_2), 9.83 (s, 1H, SH). Anal.Calcd. For $C_6H_6N_4S_2$ (198.27): C, 36.35, H, 3.05; N, 28.26; S, 32.35. Found: C, 36.34; H, 3.04; N, 28.26; S, 32.35.

General procedure for the synthesis of 16–19

Dimethyl *N*-cyanodithioiminocarbonate (0.01 mol) was added to a stirred solution of 2-cyanomethylbenzo[1,2-*b*]thiazole **15** (0.01 mol) in a dry dioxane containing potassium hydroxide (0.01 mol). After stirring 1 h at room temperature, the product **16** was filtered and recrystallized from the appropriate solvent. Compound **15** (0.01 mol) was refluxed with disodium *N*-cyanodithioiminocarbonate **1** (0.01 mol) for 3 h in the presence of sodium ethoxide (0.01 mol) in absolute alcohol (30 mL) to yield **17**. To a solution of the latter (0.01 mol) in the presence of dry DMF (20 mL), a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **7** in dry DMF (10 mL) was dropped within 30 min. and the reaction mixture was stirred at room temperature until completion (TLC 24h). Then the product **18** is extracted from the reaction mixture by using ethyl acetate. It is worthy to note that by pouring compound **17** (0.01 mol) on cold water and treating it with hydrochloric acid until the medium became just neutral, compound **19** was formed and collected by filtration.

3-(Methylthio)-1-imino-pyrido[6,1-a]benzothiazol-4-carbonitrile (16)

Yellow solid; (DMF), yield (97%), mp 230°C; IR (KBr, cm-1) υ 3433 (NH), and 2210 (CN). ^{1}H-NMR (600 MHz, DMSO-d_6): δ 2.49 (s, 3H, SCH_3), 7.54–8.10 (m, 4H, C_6H_4), 9.30 (bs, 1H, NH). ^{13}C-NMR (DMSO) δ 12.86 (SCH_3), 115.12 (CN), 138.36–164.34 (Hetero-Ar-C), 120.54–127.93 (Ar-C). MS: $m/z = 272$. Anal.Calcd. For $C_{12}H_8N_4S_2$ (272.35): C, 52.92; H, 2.96; N, 20.57; S, 23.55. Found: C, 52.91; H, 2.95; N, 20.57; S, 23.55.

1-Imino-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-pyrido[6,1-a]benzothiazol-4-carbonitrile (18)

Buff solid; (EtOH), yield (10%), mp 128°C; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.94–1.96 (4s, 12H, 4xOAc), 2.40 (s, 3H, SCH_3), 3.93–4.2 (m, 3H, H-6′ and H-5′), 4.93 (t, 1H, H-4′), 5.11 (t, 1H, H-3′), 5.33 (t, 1H, H-2′), 6.01–6.03 (d, 1H, $J_{1'\text{-}2'} = 10$ Hz, H-1′), 7.19–7.33 (m, 4H, C_6H_4), 7.9 (s, 1H, NH). Anal.Calcd. For $C_{25}H_{24}N_4O_9S_2$

(528.56): C, 51.01; H, 4.11; N, 9.52; S, 10.90. Found: C, 51.00; H, 4.11; N, 9.51; S, 10.90.

3-(Mercapto)-1-imino-pyrido[6,1-a]benzothiazol-4-carbonitrile (19)

Orange solid; (EtOH), yield (90%), mp 120°C; IR (KBr, cm^{-1}) υ 3427 (NH), 2196 (CN), 2920 and 1623 (C=O). Anal.Calcd. For $C_{11}H_6N_4S_2$ (258.32): C, 51.14; H, 2.34; N, 21.69; S, 24.83. Found: C, 51.14; H, 2.34; N, 21.69; S, 24.83.

References

1. Jordheim, L.P; Durantel, D.; Zoulim, F.; Dumontet, C. Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases. *Nat. Rev. Drug Discov.* **2013,** *12*, 447.
2. Dinkelaar, J.; Witte, M. D.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. NIS/TFA: a general method for hydrolyzing thioglycosides. *Carbohyd. Res.* **2006,** *341*, 1723.
3. Son, S.; Tano, C.; Furuike, T.; Sakairi, N. Pre-activation of fully acetylated dodecyl thioglycosides with BSP–Tf_2O led to efficient glycosylation at low temperature. *Carbohyd. Res.* **2009,** *344*, 285.
4. Komor, R.; Pastuch-Gawołek, G.; Sobania, A.; Jadwiński, M.; Szeja, W. Application of different alpha-1-thioglycosides preparation methods in synthesis of 5-nitro-2-pyridyl-1-thioglycosides substrates in synthesis of conjugates with uridine moiety. Part I. *Acta Pol. Pharm.* **2012,** *69*, 1259.
5. Kananovich, D. G.; Reino, A.; Ilmarinen, K.; Rõõmusoks, M.; Mati Karelson, M.; Lopp, M. A. General approach to the synthesis of 5-S-functionalized pyrimidine nucleosides and their analogues. *Org. Biomol. Chem.* **2014,** *12*, 5634.
6. Galmarini, C. M.; Jordheim, L.; Dumontet, C. Pyrimidine nucleoside analogs in cancer treatment. *Expert Rev. Anticancer Ther.* **2003,** *3*, 717.
7. Yoshimura, Y.; Kitano, K.; Yamada, K.; Sakata, S.; Miura, S.; Ashida, N.; Machida, H. Synthesis and biological activities of 2′-deoxy-2′-fluoro-4′-thioarabinofuranosylpyrimidine and -purine nucleosides. *Bioorg. Med. Chem.* **2000,** *8*, 1545.
8. Abu-Zaied, M.A.; El-Telbani, E.M.; Elgemeie, G. H.; Nawwar, G. A. Synthesis and in vitro anti-tumor activity of new oxadiazole thioglycosides. *Eur. J. Med. Chem.* **2011,** *46*, 229.
9. Elgemeie, G. H.; Zaghary, W.A.; Amin, K. M.; Nasr, T. M. First synthesis of thiophene thioglycosides. *J. Carbohyd. Chem.* **2009,** *28*, 161.
10. Elgemeie, G. H.; Zaghary, W.A.; Amin, K. M.; Nasr, T. M. First synthesis of thienopyrazole thioglycosides. *J. Carbohyd. Chem.* **2008,** *27*, 345.
11. Elgemeie, G. H.; Zaghary, W.A.; Amin, K. M.; Nasr, T. M. A direct route to a new class of acrylamide thioglycosides. *J. Carbohyd. Chem.* **2008,** *27*, 373.
12. Elgemeie, G. H.; Hussein, M. M.; Al-Khursani, S. A. A total synthesis of a new class of biazine thioglycosides. *J. Carbohyd. Chem.* **2004,** *23*, 465.
13. Elgemeie, G. H.; Hussein, M. M.; Jones, P. G. 2-(2′,3′,4′,6′-Tetra-*O*-acetyl-β;-D-glucopyranosylthio)-4-pyridin-4-yl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-carbonitrile. *Acta Cryst.* **2002,** *E58*, 1244.
14. Elgemeie, G. H.; Eltamny, E. H.; Elgawad, I. I.; Mahmoud, N. M. Direct route to novel 2-(β;-D-xylo- and arabinopyranosylthio)dihydropyridine glycosides and their corresponding dehydrogenated forms. *Synth. Commun.* **2009,** *39*, 443.

15. Elgemeie, G. H.; Attia, A. M.; Hussain, B. A. A synthetic strategy to a new class of cycloalkane ring-fused pyridine nucleosides as potential anti-HIV agents. *Nucleosides, Nucleotides and Nucleic Acids.* **1998,** *17*, 855.
16. Elgemeie, G. H.; Mansour, O.A.; Metwally, N.H. Synthesis and anti-HIV activity of different novel nonclassical nucleosides. *Nucleosides, Nucleotides Nucleic Acids.* **1999,** *18*, 113.
17. Elgemeie, G. H.; Mahdy, E. M.; Elgawish, M. A.; Ahmed, M. M.; Shousha, W. G.; Eldin, M. E. A new class of antimetabolites: pyridine thioglycosides as potential anticancer agents. *Z. Naturforsch.* **2010,** *65*, 577.
18. Scala, S.; Akhmed, N.; Rao, U. S.; Paull, K.; Lan, L.; Dickstein, B.; Lee, J.; Elgemeie, G. H.; Stein, W. D.; Bates, S. E. P-Glycoprotein substrates and antagonists cluster into two distinct groups. *Mol. Pharmacol.* **1997,** *51*, 1024.
19. Elgemeie, G. H.; Attia, A. A new class of dihydropyridine thioglycosides via piperdinium salts. *Synth. Commun.* **2002,** *33*, 2243.