Toward Developing Therapies against Corona Virus: Synthesis and Anti-Avian Influenza Virus Activity of Novel Cytosine Thioglycoside Analogues

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**ABSTRACT:** A series of pyrimidine and pyrimidine thioglycoside derivatives were newly synthesized using sodium 2-cyano-3-(arylamino)-prop-1-ene-1,1-bis(thiolates) and urea to give the corresponding sodium 6-amino-5-aryl-2-oxo-1,2-dihydropyrimidine-4-thiolates. Stirring of the latter with peracetylated α-D-gluco- and galacto-pyranosyl bromides in DMF afforded the corresponding pyrimidine thioglycosides. On the other hand, treatment of 6-amino-5-aryl-2-oxo-1,2-dihydropyrimidine-4-thiolate salts with hydrochloric acid produced the corresponding pyrimidine-4-thioles, which on stirring with α-D-gluco- and galacto-pyranosyl bromides in sodium hydride and DMF gave the corresponding pyrimidine thioglycosides. Deacetylation of the protected pyrimidine thioglycosides gave the corresponding free pyrimidine thioglycosides. The synthesized compounds have been characterized by 13C NMR, 1H NMR, and IR spectroscopy. The pyrimidine thioglycosides and free pyrimidine thioglycosides were tested against avian influenza H5N1 virus strain and exhibited highest to moderate activity.

1. INTRODUCTION

Decisive routes for the syntheses and expansion of novel drugs are demonstrated via targeting the metabolic pathways. Nucleoside analogues create a significant class of antimetabolic agents used in the treatment of tumors, in addition to numerous viral diseases. Pyrimidinethione nucleosides have major roles in therapeutic chemistry. Numerous pyrimidine-thione products are planned to target the key stages in cellular use. They have fundamental effects in medicinal chemistry and broad uses in biochemistry. Several of those compounds are measured as possible chemotherapeutic agents that have an abundant influence on recent medicinal research. Nucleosides comprising sulfur establish a class of nucleosides present in natural nucleic acids. Among these compounds are some derivatives of 2-thiouridine S2U (Figure 1) that occupy the first anticodon position in the transfer RNAs specific for some amino acids, 2-thiouridines importantly provide translational regulation via codon—anticodon connections. Many approaches for the synthesis of several categories of pyrimidine nucleoside derivatives have been settled. The main value of the pyrimidinethiones prompted their effectiveness against a wide range of dangerous diseases such as microbial, malignancies, cancer, and many antiviral diseases. Accordingly, modern ideas about choosing and designing new compounds have been illustrated. Hence, well-known procedures have been established to develop and discover additional effective drugs.

As a part of our up-to-date plan aimed toward discovering synthetic methods for the preparation of S-glycosylated derivatives of heterocyclic nitrogen bases, we have lately described the synthesis and antiviral activity of a series of heterocyclic S-glycosides that have interesting cytotoxic activity such as pyridine S-glycosides, pyrimidine S-glycosides, imidazole S-glycosides, oxadiazole S-glycosides, pyrazole S-glycosides, triazole S-glycosides, thiazole S-glycosides, and purine S-glycosides. Similar pyrimidine and purine thioglycosides were previously reported. We found that the dihydropyridine S-glycosides presented a strong P-glycoprotein

**Figure 1.** 2-Thiouridine (S2U).
antagonist effect and activity against human cancer cells. In the light of these results and our previous research, the purpose of the present work was to design, prepare, and explore the antiviral activity of pyrimidines linked to sugar moieties through S-glycosidic linkage formation.

2. RESULTS AND DISCUSSION
It has been found that aromatic amines 1a–d react with ethyl cyanoacetate 2 to give the corresponding acetanilide derivatives 3a–d.25 The synthesis of our desired pyrimidine thioglycosides was carried out by reaction of acetanilide derivatives 3a–d and carbon disulfide in a basic medium (sodium ethoxide) using a simple one-step procedure to give the sodium 2-cyano-3-oxo-3-(arylamino)prop-1-ene-1,1-bis(thiolate) salts 4a–d in high yields (Scheme 1). Repeating the compound 4 with its corresponding urea 6 in boiling ethanol for 8 h results in sodium 6-amino-5-aryl-2-oxo-1,2-dihydropyrimidine-4-thiolate derivatives 7a–d in good yields. Acidification of the latter has led to the creation of the corresponding 3-mercaptopyrimidines 8a–d. Compounds 8a–d could also be synthesized through the reaction of ketene dithioles 5a–d with urea in refluxing ethanol–NaOH. The structures of compounds 8 have been verified by using spectral and chemical measurements. Thus, the 1H NMR spectrum of 8a revealed a signal at δ 13.51 ppm attributed to an SH group, and its 13C NMR spectrum exhibited signals at δ 159.46 and 164.81 ppm attributed to two carbonyl groups. Stirring of compounds 7a–d with the acetylated α-β-gluc- and galacto-pyranosyl bromides 9a,b in dimethylformamide (DMF) at ambient temperature afforded in great yields the corresponding pyrimidine S-glycosides 10a–h (Scheme 1). It has been proposed that the cis-(α) sugars interact via a simple SN2 reaction to give the β-glycoside products.26 Structures of 10a–h were characterized using the spectral data [13C NMR, 1H NMR, and infrared (IR)]. For example, in the 1H NMR spectrum of the 10a anomeric proton, a doublet was found at δ 5.38 ppm with a spin–spin coupling constant of 9.6 Hz, demonstrating the β-configuration. The other six protons of glucose were resonated at δ 3.98–4.93 ppm. Compounds 10a–h can also be synthesized by the reaction of the pyrimidine-4-thioles 8a–d with halo sugars 9 in DMF–sodium hydride at room temperature. When glycosides 10a–h were reacted with NH3–MeOH at room temperature for 10 min, the deacetylated derivatives 11a–h were obtained in good yields (Scheme 2). The structures were characterized using the spectral data and elemental analysis. Thus, in the 1H NMR spectrum of the 11a anomeric proton a doublet was detected at δ 3.98–4.93 ppm. Compounds 11a–h can also be synthesized by the reaction of the pyrimidine-4-thioles 8a–d with halo sugars 9 in DMF–sodium hydride at room temperature. When glycosides 10a–h were reacted with NH3–MeOH at room temperature for 10 min, the deacetylated derivatives 11a–h were obtained in good yields (Scheme 2). The structures were characterized using the spectral data and elemental analysis. Thus, in the 1H NMR spectrum of the 11a anomeric proton a doublet was detected at δ 3.98–4.93 ppm. 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at δ 62.54, 70.63, 73.26, 76.67, and 80.21 were attributed to C-6', C-5', C-4', C-3', and C-2'.

3. CONCLUSIONS

A novel pathway for the synthesis of an important new class of thiopyrimidines and their corresponding thioglycoside analogues has been established. The results presented a new, simple, and clear route for the preparation of the cytosine nucleoside analogues. The ambient temperature reaction conditions, clean and excellent yield reaction products, render this method as a more efficient method among the existing preparation methods for the synthesis of pyrimidine thioglycosides. Further research on the application of this preparation method for the synthesis of other biologically remarkable active glycosides needs to be carried out. These thioglycosides can be used as preliminary compounds for the preparation of other remarkable carbohydrates.

Table 1. Antiviral Activity of the Tested Compounds Measured Using the Plaque Reduction Assay

| comp. no. | concentration (μmol/mL) | initial viral count | viral count PFU/mL | inhibition % | comp. no. | concentration (μmol/mL) | initial viral count | viral count PFU/mL | inhibition % |
|-----------|-------------------------|---------------------|--------------------|--------------|-----------|-------------------------|---------------------|--------------------|--------------|
| 8a        | 0.125                   | 3.1 × 10^6          | 6 × 10^6           | 48.33        | 10g       | 0.125                   | 2.2 × 10^6          | 6 × 10^6           | 63.33        |
|           | 0.25                    | 3.8 × 10^6          | 6 × 10^6           | 36.67        |           | 0.25                    | 2.0 × 10^6          | 6 × 10^6           | 66.67        |
| 8b        | 0.125                   | 6.0 × 10^6          | 6 × 10^6           | 0            | 10h       | 0.125                   | 3.0 × 10^6          | 6 × 10^6           | 50           |
|           | 0.25                    | 3.0 × 10^6          | 6 × 10^6           | 50           |           | 0.25                    | 1.3 × 10^6          | 6 × 10^6           | 75           |
| 8c        | 0.125                   | 3.3 × 10^6          | 6 × 10^6           | 45           | 11a       | 0.125                   | 3.1 × 10^6          | 6 × 10^6           | 48.33        |
|           | 0.25                    | 4.0 × 10^6          | 6 × 10^6           | 33.33        |           | 0.25                    | 2.5 × 10^6          | 6 × 10^6           | 58.33        |
| 8d        | 0.125                   | 3.0 × 10^6          | 6 × 10^6           | 50           | 11b       | 0.125                   | 2.0 × 10^6          | 6 × 10^6           | 66.67        |
|           | 0.25                    | 3.2 × 10^6          | 6 × 10^6           | 46.67        |           | 0.125                   | 2.2 × 10^6          | 6 × 10^6           | 63.33        |
| 10a       | 0.125                   | 3.3 × 10^6          | 6 × 10^6           | 45           | 11c       | 0.125                   | 3.4 × 10^6          | 6 × 10^6           | 43.33        |
|           | 0.25                    | 2.4 × 10^6          | 6 × 10^6           | 60           |           | 0.125                   | 3.2 × 10^6          | 6 × 10^6           | 46.67        |
| 10b       | 0.125                   | 4.6 × 10^6          | 6 × 10^6           | 20           | 11d       | 0.125                   | 4.0 × 10^6          | 6 × 10^6           | 33.33        |
|           | 0.25                    | 1.9 × 10^6          | 6 × 10^6           | 68.33        |           | 0.25                    | 2.4 × 10^6          | 6 × 10^6           | 60           |
| 10c       | 0.125                   | 4.5 × 10^6          | 6 × 10^6           | 25           | 11e       | 0.125                   | 2.0 × 10^6          | 6 × 10^6           | 65.67        |
|           | 0.25                    | 2.5 × 10^6          | 6 × 10^6           | 58.33        |           | 0.25                    | 2.2 × 10^6          | 6 × 10^6           | 63.33        |
| 10d       | 0.125                   | 3.4 × 10^6          | 6 × 10^6           | 43.33        | 11f       | 0.125                   | 3.5 × 10^6          | 6 × 10^6           | 41.67        |
|           | 0.25                    | 2.0 × 10^6          | 6 × 10^6           | 66.67        |           | 0.25                    | 1.7 × 10^6          | 6 × 10^6           | 71.67        |
| 10e       | 0.125                   | 3.0 × 10^6          | 6 × 10^6           | 50           | 11g       | 0.125                   | 3.6 × 10^6          | 6 × 10^6           | 40           |
|           | 0.25                    | 1.9 × 10^6          | 6 × 10^6           | 68.33        |           | 0.25                    | 2.5 × 10^6          | 6 × 10^6           | 58.33        |
| 10f       | 0.125                   | 2.0 × 10^6          | 6 × 10^6           | 66.67        | 11h       | 0.125                   | 3.4 × 10^6          | 6 × 10^6           | 43.33        |
|           | 0.25                    | 1.9 × 10^6          | 6 × 10^6           | 85.33        |           | 0.25                    | 2.0 × 10^6          | 6 × 10^6           | 66.67        |
3.1. Antiviral Activity. The antiviral activity of the synthesized compounds was evaluated with respect to HSN1 influenza virus strain A/Egypt/M7217B/2013 utilizing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxicity (TC50) and plaque reduction assays exploring inhibition and cytotoxicity percentage values. The accumulated inhibition activities and cytotoxicity data (Table 1 and Figures 2 and 3) indicated that most of the compounds demonstrated dose-dependent inhibition behavior.

![Fig. 2. Cytotoxicity of compounds 8a–d, 8b](image)

![Fig. 3. Cytotoxicity of compounds 11a–d](image)

All tested compounds exhibited the highest to moderate activity toward HSN1 virus. Attachment of sugar moieties, especially protected sugars, to the substituted 2-oxo-N-phenyl-1,2-dihydropyrimidine-5-carboxamide derivatives (compounds 10a–h) demonstrated higher inhibition activity than unprotected sugar (compounds 11a–h) against HSN1 virus. However, pyrimidine derivatives incorporated with galacto (compounds 10e–h, 11e–h) showed higher inhibition activity than its gluco analogues (compounds 10a–d, 11a–d). Most active compounds tested in this study contained the 4-chlorophenyl moiety and methoxymethyl at the 4-position, while compounds possessing methyl phenyl and phenyl rings exhibited lower antiviral activity. On the other hand, compounds pyrimidine 4-mercaptop derivatives (compounds 8a–d) demonstrated moderate anti-HSN1 activity.

4. EXPERIMENTAL SECTION

All melting points were measured on an Electrothermal 9100 digital melting point apparatus. The 1H NMR and 13C NMR spectra were measured on a JEOL-500 MHz spectrometer in DMSO-d6 or CDCl3 using Si(CH3)4 as an internal standard at the National Research Centre, Cairo, Egypt. Potential cytotoxicity assay of the newly synthesized compounds was evaluated at the Center of Scientific Excellence for Influenza Viruses, Environmental Research Division, National Research Centre (NRC), Dokki, Cairo 12622, Egypt. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University, Cairo, Egypt. Progress of the reactions was monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel F254 plates with a layer thickness of 0.25 mm (Merck). By viewing under a short-wavelength UV lamp, effective detection can be achieved. Compounds (4a–d, 5a–d) were prepared following our reported procedures.

4.1. General Procedure for the Synthesis of Sodium Pyrimidine Thiolates (7a–d).

4.1.1. Method A. An ethanolic solution of urea (10 mmol) was added dropwise for 30 min to sodium 2-cyano-3-oxo-3-(arylamino)prop-1-ene-1,1-bis(thiolates) 4a–d (10 mmol) dissolved in 10 mL of absolute ethanol, and the reaction mixture was heated for 8 h. After the reaction was completed (monitored by TLC), the mixture was cooled and then poured into ice water. The obtained solid was filtered, dried, and recrystallized from ethanol to provide compounds 7a–d.

4.1.2. Method B. To a solution of compounds 8a–d (10 mmol) in ethanol, sodium hydroxide (10 mmol) was added, and the mixture was stirred at 50 °C for 1 h and allowed to cool to room temperature. The formed solid product was collected by filtration and recrystallized from an appropriate solvent.

4.1.2.1. Sodium-6-amino-2-oxo-5-(phenylcarbamoyl)-1,2-dihydropyrimidine-4-thiolate (7a). White solid; (EtOH); yield (85%); mp > 300 °C; IR (KBr, cm-1) v: 3373 (NH2), 3266 (NH), 3029 (CH aromatic), 1682 (C=C), and 1592 (C=C) C12H11N4NaO3S (284.27).

4.1.2.2. Sodium-6-Amino-5-(4-chlorophenylcarbamoyl)-2-oxo-1,2-dihydropyrimidine-4-thiolate (7b). White solid; (EtOH); yield (82%); mp > 300 °C; IR (KBr, cm-1) v: 3356, 3342 (NH2), 3251 (NH), 3036 (CH aromatic), 2972 (CH), 1695 (C=O), 1654 (CO), 1600 (C=C) C12H9ClN4NaO3S (318.71).

4.1.2.3. Sodium-6-Amino-2-oxo-5-(p-tolyllcarbamoyl)-1,2-dihydropyrimidine-4-thiolate (7c). White solid; (EtOH); yield (95%); mp > 300 °C; IR (KBr, cm-1) v: 3351, 3346, (NH2), 3276 (NH), 3252 (NH), 2921 (CH), 1696 (C=O), 1677 (CO), 1594 (C=C) C12H11N4NaO3S (298.30).

4.1.2.4. Sodium-6-Amino-5-(4-methoxyphenylcarbamoyl)-2-oxo-1,2-dihydropyrimidine-4-thiolate (7d). White solid; (EtOH); yield (79%); mp > 300 °C; IR (KBr, cm-1) v: 3356 (NH2), 3267 (NH), 3032 (CH aromatic), 2938 (CH), 1682 (C=O), 1648 (CO), 1602 (C=C) C12H11N4NaO3S (314.30).

4.2. General Procedure for the Synthesis of Pyrimidine Thiolos (8a–d).

4.2.1. Method A. A mixture of sodium 2-cyano-3-oxo-3-(arylamino)prop-1-ene-1,1-bis(thiolates) 5a–d (10 mmol) and urea (10 mmol) in ethanolic sodium hydroxide (10 mL) was refluxed for 3 h. After the reaction was completed, the reaction mixture was concentrated...
and cooled, and the residue was poured into ice water, collected by filtration, dried, and recrystallized from ethanol producing compounds 8a–d.

4.2.2. Method B. To an aqueous solution of compound 7a–d (10 mmol), three drops of HCl (36%) were added at room temperature (25 °C) with stirring, and the obtained white solid was filtered off and crystallized from ethanol to give 8a–d.

4.2.2.1. 6-Amino-4-mercapto-2-oxo-N-phenyl-1,2-dihydropyrimidine-5-carboxamide (8a). White solid; (EtOH); yield (85%); mp 254 °C; IR (KBr, cm⁻¹): ν = 3388 (NH₂), 3272 (NH₂), 3261 (NH), 3035 (CH aromatic), 1682 (C=O), 1646 (CO), 1595 (C=N); ¹H NMR (500 MHz, DMSO-d₆): δ = 7.62 (s, D₂O exh., 2H, NH₂), 7.32–7.63 (m, 3H, CH₂), 10.64 (s, D₂O exh., 1H, NH), 11.28 (s, D₂O exh., 1H, NH), 13.51 (s, D₂O exh., 1H, SH); ¹³C NMR: δ = 81.41 (C-S), 124.63 (2C, Ar–C), 126.82 (2C–Ar–C), 140.54 (5C, Ar–C), 159.46 (CO), 164.81 (CO), 167.26 (C₄–C₆), 169.70 (C₆). Anal. Calcd for C₁₅H₁₁N₄O₂S (296.73): C, 50.31; H, 3.41; N, 22.20; S, 14.19; Found: C, 50.26; H, 3.36; N, 22.19; S, 14.15.

4.2.2.2. 6-Amino-N-(4-chlorophenyl)-4-mercapto-2-oxo-1,2-dihydropyrimidine-5-carboxamide (8b). White solid; (EtOH); yield (80%); mp 248 °C; IR (KBr, cm⁻¹): ν = 3372 (NH₂), 3260 (NH₂), 3253 (NH), 3038 (CH aromatic), 1689 (C=O), 1649, 1598 (C=N); ¹H NMR (500 MHz, DMSO-d₆): δ = 6.82 (s, D₂O exh., 2H, NH₂), 7.35–7.84 (m, 4H, C₄H₄), 10.85 (s, D₂O exh., 1H, NH), 11.46 (s, D₂O exh., 1H, NH), 13.47 (s, D₂O exh., 1H, SH); ¹³C NMR: δ = 82.32 (C-S), 124.86 (2C–Ar–C), 131.45 (2C–Ar–C), 138.74 (Ar–C), 139.83 (Ar–C), 160.57 (CO), 163.76 (CO), 168.42 (C₄), 170.37 (C₆). Anal. Calcd for C₁₅H₁₀ClN₄O₂S (331.73): C, 44.40; H, 3.16; Cl, 11.90; N, 18.88; S, 10.81. Found: C, 44.40; H, 3.16; Cl, 11.90; N, 18.82; S, 10.65.

4.2.2.3. 6-Amino-4-mercapto-2-oxo-N-p-tolyl-1,2-dihydropyrimidine-5-carboxamide (8c). White solid; (EtOH); yield (85%); mp 234 °C; IR (KBr, cm⁻¹): ν = 3353 (NH₂), 3247 (NH₂), 3235 (NH), 3029 (CH aromatic), 1683 (C=O), 1601 (C=N); ¹H NMR (500 MHz, DMSO-d₆): δ = 2.46 (s, 3H, CH₃), 6.69 (s, D₂O exh., 2H, NH₂), 7.34–7.56 (m, 4H, C₄H₄), 10.23 (s, D₂O exh., 1H, NH), 10.96 (s, D₂O exh., 1H, NH), 13.26 (s, D₂O exh., 1H, SH); ¹³C NMR: δ = 23.15 (CH₃), 80.24 (C-S), 123.63 (2C–Ar–C), 132.26 (2C–Ar–C), 136.45 (Ar–C), 138.37 (Ar–C), 159.84 (CO), 164.34 (CO), 166.75 (C₄), 169.89 (C₆). Anal. Calcd for C₁₅H₁₃N₄O₂S (276.31): C, 52.16; H, 4.38; N, 20.28; S, 11.60. Found: C, 52.13; H, 4.27; N, 20.17; S, 11.54.

4.2.2.4. 6-Amino-4-mercapto-N-(4-methoxyphenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxamide (8d). White solid; (EtOH); yield (79%); mp 222 °C; IR (KBr, cm⁻¹): ν = 3373 (NH₂), 3235 (NH), 3217 (NH), 3039 (CH aromatic), 1672 (C=O), 1651 (CO), 1599 (C=N); ¹H NMR (500 MHz, DMSO-d₆): δ = 3.95 (3H, CH₃), 6.82 (s, D₂O exh., 2H, NH₂), 7.23–7.57 (m, 4H, C₄H₄), 10.54 (s, D₂O exh., 1H, NH), 11.65 (s, D₂O exh., 1H, NH), 13.17 (s, D₂O exh., 1H, SH); ¹³C NMR: δ = 58.26 (CH₃), 85.14 (C₄–C₆), 124.25 (2C–Ar–C), 126.23 (2C–Ar–C), 132.88 (Ar–C), 156.41 (CO), 164.25 (Ar–C), 168.25 (CO), 170.22 (C₆). Anal. Calcd for C₁₅H₁₃N₄O₂S (293.31): C, 49.31; H, 4.14; N, 19.17; S, 10.97. Found: C, 49.19; H, 4.8; N, 19.10; S, 10.83.

4.3. General Procedure for the Synthesis of Pyrimidine Thioglycosides (10a–h). 4.3.1. Method A. 2,3,4,6-Tetra-O-acetyl-α-D-galacto-pyranosyl thiose 9a,b (10 mmol) dissolved in dry DMF, which was dropped gradually within 30 min, was added to a solution of compounds 7a–d (10 mmol) in 20 mL of DMF, and the reaction mixture was stirred at room temperature till completion of the reaction (monitored by TLC). Then, the mixture was poured into ice water, and the resulting precipitate was collected by filtration, dried, and crystallized from an appropriate solvent system to give compounds 10a–h.

4.3.2. Method B. Sodium hydride (15 mmol) was added slowly to a 50 mL flask containing the solution of compound 8a–d (10 mmol) in DMF (20 mL), and the reaction mixture was stirred for 30 min at room temperature. Then, a solution of 2,3,4,6-tetra-O-acetyl-α-D-galacto-pyranosyl thiose 9a,b (10 mmol) in DMF was added dropwise to the reaction mixture for 30 min, and the reaction mixture was stirred at room temperature until completion (monitored by TLC). After the reaction was completed, the reaction mixture was poured into ice water and the yielded product was collected by filtration, dried, and crystallized from an appropriate solvent system to give compounds 10a–d.
OAc), 2.32 (s, 3H, CH3), 3.97—3.99 (m, 1H, H-S'), 4.03 (d, J = 4.1 Hz, J = 5.4 Hz), 4.16 (d, J = 1H, J = 4.8 Hz, J = 5.4 Hz), 5.14 (t, J = 1H, J = 4.8 Hz, J = 5.4 Hz), 5.22 (t, J = 1H, J = 4.8 Hz, J = 5.4 Hz), 5.30 (t, J = 1H, J = 4.8 Hz, J = 5.4 Hz), 5.59 (d, J = 1H, J = 4.8 Hz, J = 5.4 Hz), 7.09 (d, J = 2H, J = 8.6 Hz, H-S'), 7.45 (d, J = 2H, J = 7.7 Hz, Ar-H), 8.37 (s, 3H, D2O exch., 1H, NH), 9.22 (s, 3H, D2O exch., 1H, NH); 13C NMR: δ 20.71 (4 × CH3), 29.41 (CH3), 61.81 (C-S), 68.08 (C-S'), 70.22 (C-4), 74.21 (C-3), 75.64 (C-2), 83.84 (C-1'), 91.62 (C-S), 120.40 (2C, Ar-C), 129.69 (2C, Ar-C), 134.52 (Ar-C), 135.31 (Ar-C), 152.71 (C-O), 156.82 (C-O), 166.15 (C-4), 169.51 (C-6), 176.24 (4C=O). Anal. Calc’d for C26H30N4O12S (622.60): C, 50.16; H, 4.86; N, 9.04; S, 5.12.

4.3.2.4. 6-Amino-N-(4-methoxyphenyl)-4-(2′,3′,4′,6′-tetra-1-acetyl-β-d-glucopyranosylthio)-2-oxo-1,2-diarylpiperidine-5-carboxamide (10d). White solid; (EtOH), yield (88%) (method A), (62%) (method B), mp 258—259 °C; H NMR (500 MHz, DMSO-d6): δ 1.98, 1.99, 2.02, 2.06 (4s, 12H, 4 × OAc), 3.87 (s, 3H, OCH3), 3.92–3.94 (m, 2H, 2H-6'), 4.38–4.39 (m, 1H, H-S'), 4.46 (t, 1H, J = 9.2 Hz, J = 9.3 Hz, H-S'), 4.94 (t, 1H, J = 8.6 Hz, J = 8.6 Hz, H-S'), 4.82 (t, 1H, J = 9.4 Hz, J = 9.4 Hz, H-S'), 5.65 (d, 1H, J = 9.4 Hz, H-S'), 7.21 (s, 1D, D2O exch., 2H, NH), 7.38–7.61 (m, 4H, CArH), 8.82 (s, 3D, D2O exch., 1H, NH), 9.87 (s, 3D, D2O exch., 1H, NH); 13C NMR: δ 22.28 (4 × CH3), 56.74 (CH3), 62.45 (C-S), 67.26 (C-S'), 71.63 (C-4'), 73.41 (C-3'), 77.54 (C-2'), 79.42 (C-1'), 92.61 (C-5'), 121.21 (2C, Ar-C), 124.46 (2C, Ar-C), 133.67 (Ar-C), 160.31 (C-O), 162.14 (Ar-C), 163.38 (C-O), 164.51 (C-4), 166.18 (C-6), 173.24 (4C=O). Anal. Calc’d for C26H30N4O12S (622.60): C, 50.16; H, 4.86; N, 9.00; S, 5.15. Found: C, 50.10; H, 4.78; N, 9.04; S, 5.12.

4.3.2.5. 6-Amino-(2′,3′,4′,6′-tetra-acteryl-β-d-galactopyranosylthio)-2-oxo-N-phenyl-1,2-diarylpiperidine-5-carboxamide (10e). White solid; (EtOH), yield (88%) (method A), (82%) (method B), mp 258—259 °C; IR (KBr, cm−1): ν = 3346 (NH), 3234 (NH), 3028 (CH aromatic), 2986 (2H-6'), 2920 (C=O), 1662 (C=O), 1616 (C-4), 1595 (C=O), 1653 (C-3'), 1614 (C-2'), 1589 (C=O), 1539 (C=O), 1330 (C=O), 1272 (C=O), 1245 (C-3'), 1224 (2C, Ar-C), 1141 (s, 3D, D2O exch., 1H, NH); 13C NMR: δ 22.67 (4 × CH3), 26.34 (CH3), 62.18 (C-6), 67.12 (C-4'), 68.95 (C-3'), 72.26 (C-3'), 76.22 (C-2'), 79.31 (C-1'), 92.42 (C-5), 124.25 (2C, Ar-C), 134.36 (2C, Ar-C), 139.18 (Ar-C), 140.62 (Ar-C), 160.81 (C-O), 164.34 (C-O), 165.93 (C-4), 170.26 (C-6), 170.62 (C=O). Anal. Calc’d for C26H30N4O12S (622.60): C, 51.48; H, 4.98; N, 9.24; S, 5.29. Found: C, 51.36; H, 4.90; N, 9.18; S, 5.22.

4.3.2.8. 6-Amino-N-(4-methoxyphenyl)-4-(2′,3′,4′,6′-tetra-1-acetyl-β-d-galactopyranosylthio)-2-oxo-1,2-diarylpiperidine-5-carboxamide (10h). White solid; (EtOH), yield (87%) (method A), (82%) (method B), mp 261—262 °C; IR (KBr, cm−1): ν = 3378 (NH), 3244 (NH), 3046 (CH aromatic), 2977 (CH), 1746 (C=O), 1671 (C=O), 1604 (C=N); H NMR (500 MHz, DMSO-d6): δ 1.97, 1.98, 2.01, 2.05 (4s, 12H, 4 × OAc), 3.91 (s, 3H, OCH3), 3.96—3.99 (m, 2H, 2H-6'), 4.24–4.27 (m, 1H, H-S'), 4.68 (t, 1H, J = 3.3 Hz, H-S'), 4.95 (t, 1H, J = 3.3 Hz, H-S'), 5.54 (d, 1H, J = 9.6 Hz, H-S'), 6.37 (t, 1H, J = 9.6 Hz, H-S'), 7.23–7.26 (m, 4H, CArH), 10.68 (s, 3D, D2O exch., 1H, NH), 11.41 (s, 3D, D2O exch., 1H, NH); 13C NMR: δ 23.14 (4 × CH3), 55.54 (CH3), 62.14 (C-6), 66.53 (C-3'), 70.82 (C-4'), 74.66 (C-3'), 76.21 (C-2'), 79.87 (C-1'), 93.23 (C-5), 123.46 (2C, Ar-C), 125.12 (2C, Ar-C), 132.83 (Ar-C), 162.16 (C-O), 164.11 (Ar-C), 165.26 (C-O), 166.92 (C=O), 168.16 (C-6), 174.16 (4C=O). Anal. Calc’d for C26H30N4O12S (622.60): C, 50.16; H, 4.86; N, 9.00; S, 5.15. Found: C, 50.10; H, 4.78; N, 9.04; S, 5.12.

4.4. General Procedure for the Synthesis of Unprotected Pyrimidine Thiglycosides (11a—h). In a 50 mL Quickfit flask, tetracyacetated glycoside (10 ml) was dissolved in 20 mL of dry methanol, and then ammonia gas was allowed to pass through the solution at 0 °C for 10 min. Then, the mixture was left to stir until the reaction was completed (monitored by TLC) using CHCl3/MeOH 9:1. The mixture was concentrated to afford a solid residue, which was washed several times with boiling chloroform. The residue was dried, purified by column chromatography using chloro-
form/methanol (9:1), and crystallized from an appropriate solvent to give corresponding compounds 11a–h.

4.4.1. 6-Amino-4-β-D-galactopyranosylthio-2-oxo-N-phenyl-1,2-dihydropyrimidine-5-carboxamide (11a). White solid; (EtOH), yield (72%), mp 175 °C; IR (KBr, cm⁻¹): ν 3379 (OH), 3322, 3255 (NH₂), 3246 (NH), 3028 (CH aromatic), 2946 (CH), 1678 (CO), 1648 (C=C), 1601 (C=C); ¹H NMR (500 MHz, DMSO-d₆): δ 3.67–3.88 (m, 2H, H-2', H-6'), 6.42 (1H, J₁–J₂ = 9.1 Hz, H-2'), 9.69 (s, 1H, NH₂), 7.25–7.86 (m, 5H, 5H-4', 5H-5'); ¹³C NMR: 61.35 (C-6), 124.16 (2c, Ar-C), 130.22 (2c, Ar-C), 156.41 (C), 160.41 (C), 170.62 (C-6).

4.4.2. 6-Amino-4-β-D-galactopyranosylthio-2-oxo-1,2-dihydropyrimidine-5-carboxamide (11b). White solid; (EtOH), yield (70%), mp 166 °C; IR (KBr, cm⁻¹): ν 3453 (OH), 3362, 3284 (NH₂), 3257 (NH), 3041 (CH aromatic), 2934 (CH), 1672 (CO), 1659 (C=C), 1603 (C=C); ¹H NMR (500 MHz, DMSO-d₆): δ 3.52–3.56 (m, 2H, H-2', H-6'), 6.41–6.46 (1H, J₁–J₂ = 9.2 Hz, H-2'), 4.61 (1H, J₁–J₂ = 5.4 Hz, D₂O exch., 6'-OH), 4.82 (1H, J₁–J₂ = 9.8 Hz, D₂O exch., 6'-OH), 8.21 (C-2'), 80.21 (C-3'), 90.28 (C-5), 124.16 (2c, Ar-C), 131.43 (2c, Ar-C), 132.52 (Ar-C), 142.14 (Ar-C), 162.17 (C), 164.23 (C), 165.39 (C), 169.96 (C). Anal. Calc. for C₁₇Hₑ₂N₂O₅S (454.45): C, 47.57; H, 4.88; N, 12.33; S, 7.04. Found: C, 47.54; H, 4.80; N, 12.24; S, 7.04%.

4.4.3. 6-Amino-4-β-D-galactopyranosylthio-2-oxo-N-p-tolyl-1,2-dihydropyrimidine-5-carboxamide (11c). White solid; (EtOH), yield (68%), mp 169 °C; IR (KBr, cm⁻¹): ν 3352 (OH), 3327, 3259 (NH₂), 3216 (NH), 3041 (CH aromatic), 1672 (CO), 1649 (C=C), 1598 (C=C); ¹H NMR (500 MHz, DMSO-d₆): δ 3.91 (s, 3H, OCH₃), 3.16–3.19 (m, 2H, 2H-6'), 3.26–3.29 (m, 2H, H-5', H-4'), 3.48 (1H, J₁–J₂ = 7.9 Hz, J₂–J₃ = 8.6 Hz, H-3'), 3.62 (1H, J₁–J₂ = 10.2 Hz, J₂–J₃ = 7.9 Hz, H-2'), 4.82 (1H, J₁–J₂ = 5.4 Hz, D₂O exch., 6'-OH), 9.33 (d, 1H, J = 5.4 Hz, D₂O exch., OH), 5.14 (d, 1H, J = 4.4 Hz, D₂O exch., OH), 5.46 (d, 1H, J = 5.2 Hz, D₂O exch., OH), 6.58 (s, D₂O exch., 2H, NH₂), 7.23–7.48 (m, 4H, C₆H₄), 8.62 (s, D₂O exch., 1H, NH), 9.56 (s, D₂O exch., 1H, NH); ¹³C NMR: δ 56.97 (CH₃), 60.81 (C-6'), 68.54 (C-5'), 72.84 (C-4'), 75.24 (C-3'), 76.65 (C-2'), 84.16 (C-1'), 92.53 (C-5), 120.23 (2c, Ar-C), 124.16 (2c, Ar-C), 135.22 (Ar-C), 157.46 (C), 163.45 (Ar-C), 161.96 (C=C), 167.13 (C-4), 170.62 (C-6). Anal. Calc. for C₁₉H₁₄N₂O₅S (458.45): C, 47.57; H, 4.88; N, 12.33; S, 7.04. Found: C, 47.45; H, 4.80; N, 12.24; S, 7.04%.
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dissolved in 200 μL of 5 mg/mL stock solution) was added to each

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