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# Synthesis of *N*-tetra-*O*-acetyl-β-D-glucopyranosyl-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas

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ABSTRACT

Some 2-amino-4,6-diarylpyrimidines **2** have been prepared from substituted benzylideneacetophenones and guanidine hydrochloride in the presence of alkali by conventional heating in alcoholic medium and microwave heating in solvent-free conditions. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas **4** have been synthesized by reaction of per-O-acetylated glucopyranosyl isothiocyanate **1** and substituted 2-amino-4,6-diarylpyrimidines **2**. Two different methods have been used, namely, refluxing in anhydrous dioxane and solvent-free microwave-assisted coupling. The second procedure afforded higher yields in much shorter reaction times. The compounds **2** and **4** were tested for their antibacterial and antifungal activities in vitro against *Staphylococcus epidermidis*, *Enterobacter aerogenes* and *Candida albicans* by disc diffusion method.



The pyrimidine structural motif is a fundamental part of nucleic acids and has been associated with a number of biological activities.[1,2] Aminopyrimidine derivatives have displayed interesting antibacterial, antitumour and HIV-I inhibiting activities.[2] Both pyrimidine and aminopyrimidine moieties occur in commercially available drugs such as the anti-atherosclerotic Aronixil®, the anti-histaminic Thonzylamine®, the anti-anxiolytic Buspirone®, and in other medicinally relevant compounds as well.[3]

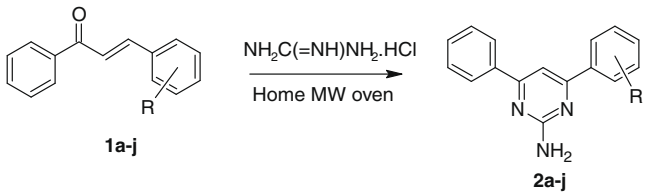
In an other hand, sugar isothiocyanates are among the most versatile synthetic intermediates in carbohydrate chemistry.[4] They play a pivotal role in the preparation of a broad series of functional groups such as amide, isonitrile, carbodiimide and *N*-thiocarbonyl derivatives allowing, simultaneously, the covalent coupling of a quite unrestricted variety of structures to the saccharide part.[5] Moreover, isothiocyanates are important reagents in heterocyclic chemistry, which may be exploited in the synthesis of nucleosides and other *N*-glycosyl structures.[6,7]

One of the most popular and interesting approach in the context of 'green chemistry' is employing microwave energy for conducting chemical transformations, which allows a higher speed of heating, shorter reaction times, is compatible with solvent-free conditions and very often lead to higher selectivities.[8–11]

Thioureas and derivatives are biologically important compounds and are useful fungicides, herbicides[12] and antibacterial agents.[13] They have also found use in organocatalysis.[14,15] Thioureas have been synthesized by the reaction of primary and secondary amines with thiophosgene and isothiocyanates.[4,5,16–19]

Glucopyranosyl thioureas containing heterocycles (such as thiazole, benzothiazole[20] and thiadiazole[21]) were synthesized using conventional heating method. We report herein the preparation of some peracetylated glucopyranosyl thioureas containing the pyrimidine nucleus both under classical heating and solvent-free microwave irradiation conditions.

2-Aminopyrimidines were prepared previously by the reaction of substituted benzylideneacetophenones[22] with guanidine under reflux in ethanol.[3,23] For the purpose of this work, we have prepared new 2-amino-4,6-diarylpyrimidines **2a–j** by ring-closure condensation of substituted benzylideneacetophenones and guanidine hydrochloride in the presence of sodium hydroxide under microwave-assisted conditions and compare the results with the classical procedures (Scheme 1 and Table 1). *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas **4a–j** were subsequently synthesized by the condensation of tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate and the corresponding 2-aminopyrimidines **2a–j**. We performed




**1a-j** and **2a-j:** R= H (**a**), *p*-F (**b**), *p*-Cl (**c**), *m*-Cl (**d**), *p*-Br (**e**), *p*-Me (**f**), *p*-iPr (**g**), *o*-OH (**h**), *p*-OMe (**i**), *m*-OMe (**j**)

**Scheme 1.** Synthetic pathway for 2-amino-4,6-diarylpyrimidines (**2a–j**).

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**Table 1**
2-Amino-4,6-diarylpyrimidines (**2a–j**)

| Entry | R | Yield (%) | | Microwave irradiation time (min) |
|---|---|---|---|---|
| | | A | B | |
| **2a** | H | 72 | 89 | 1 |
| **2b** | *p*-F | — | 86 | 2 |
| **2c** | *p*-Cl | 76 | 85 | 2 |
| **2d** | *m*-Cl | 75 | 83 | 2 |
| **2e** | *p*-Br | 71 | 80 | 2 |
| **2f** | *p*-Me | — | 85 | 1 |
| **2g** | *p*-iPr | — | 85 | 1 |
| **2h** | *o*-OH | 70 | 85 | 1 |
| **2i** | *p*-OMe | 73 | 80 | 1 |
| **2j** | *m*-OMe | — | 83 | 1 |

A: by refluxing; B: under solvent-free condition in modified domestic microwave oven.

this reaction by using two methods: by refluxing in anhydrous dioxane for 8–10 h and by irradiation in a domestic microwave oven for a few minutes in solvent-free condition (Scheme 2 and Table 2). The last method accelerated the reactions and gave higher yields.

We realized that 2-amino-4,6-diphenylpyrimidines with electron-withdrawing group (such $NO_2$, except halogens) cannot be formed; we tried to perform the reaction of benzylideneacetophenones having nitro-group with guanidine, but the reactions were unsuccessful.

In the refluxing cases, 2-aminopyrimidines **2** and peracetylated glucopyranosyl isothiocyanate **3** were dissolved in anhydrous dioxane. After the reaction, the solvent was distilled off, and the resultant sticky residue was triturated with ethanol to afford thioureas **4a–j** that were recrystallized with 1:1 ethanol–toluene. Using MW irradiation, a mixture of 2-aminopyrimidine and peracetylated glucopyranosyl isothiocyanate was grinded together and irradiated in domestic MW oven (750 W). After first several minutes of microwave irradiation (MWI), the reaction mixture became pastry. The reaction yields increased using MW oven from 60–68% to 68–80%. All the obtained thioureas were soluble in common organic solvents (such as ethanol, methanol, toluene, benzene and DMF). Their structures have been confirmed by spectral (IR, NMR and MS) data.

The IR spectra showed characteristic bands at 3522–3410 ($\nu_{NH}$), 1754–1748 ($\nu_{C=O}$), 1594, 1578, 1526, 1495 ($\nu_{C=C}$), 1364–1362 ($\nu_{C=S}$), 1232–1222 and 1070–1041 $cm^{-1}$ ($\nu_{COC}$). The $^1H$ NMR spectra showed resonance signals which are specific for protons in thiourea-NH groups at $\delta$ = 11.16–12.04 ppm. Proton H-1 has its chemical shift at $\delta$ = 6.19–6.21 ppm (in triplet) with couple constants $J_{12}$ = 9.0–9.5 Hz. The resonance signal of H-2 appeared as a triplet at $\delta$ = 5.02–5.06 ppm with $J_{12}$ = 9.0–9.5 Hz. The coupling constant values for the pyranose ring agreed with *trans*-axial H–H disposition and a β-anomeric configuration. The $^{13}C$ NMR spectra showed signals for the thiocarbonyl group at $\delta$ = 181.3–181.4 ppm.[24] The mass spectra showed $M^+$ peak at the respective molecular weights of the compounds. Some of them were subjected to HREIMS to obtain respective molecular weights.

Compounds **2** and **4** were screened for their antibacterial and antifungal activities in vitro against *Staphylococcus epidermidis*, *Enterobacter aerogenes* and *Candida albicans* by the disc diffusion method. All amines **2** have significant biological activities against *E. aerogenes*, *S. epidermidis* and *C. albicans*. Compounds **2a–j** showed highest antibacterial activity against *S. Epidermidis* (Table 3). Almost all compounds **4** have remarkable biological activity, except compound **4b** which exhibited no antifungal activity against *E. aerogenes* and compound **4g** against *C. albicans*. Especially, the antibacterial activity against *S. epidermidis* was proved significantly in these compounds (Table 4).

In summary, the present new method of formation of 2-amino-4,6-diarylpyrimidines **2** and *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas **4** under microwave irradiation offers several advantages: faster reaction rates (1–2 min for **2** and 5–7 min for **4**) and high yields (80–89% for **2** and 72–83% for **4**), while the conventional method of formation of these thioureas involves longer reaction times (8–10 h and 60–68% for **4**).

## 1. Experimental

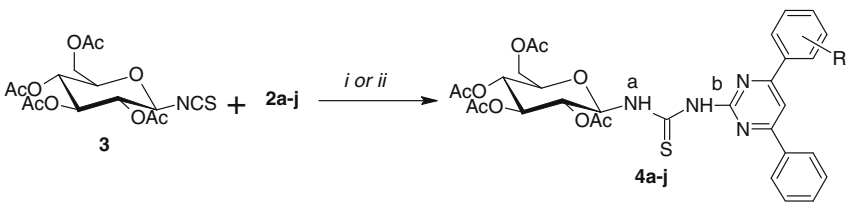
### 1.1. General methods

Melting points were determined on a STUART SMP3 apparatus (BIBBY STERILIN-UK). The FTIR-spectra were recorded on a Magna

**Table 2**
*N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4,6-diarylpyrimidin-2-yl)thioureas (**4a–j**)

| Entry | R | Yield[a] (%) | Refluxing time (h) | Yield[b] (%) | Microwave irradiation time (min) |
|---|---|---|---|---|---|
| **4a** | H | 60 | 8 | 75 | 5 |
| **4b** | *p*-F | — | — | 87 | 5 |
| **4c** | *p*-Cl | 68 | 9 | 76 | 6 |
| **4d** | *m*-Cl | 67 | 10 | 72 | 7 |
| **4e** | *p*-Br | 66 | 9 | 76 | 5 |
| **4f** | *p*-Me | 60 | 8 | 80 | 7 |
| **4g** | *p*-iPr | 68 | 8 | 79 | 6 |
| **4h** | *o*-OH | 60 | 9 | 80 | 6 |
| **4i** | *p*-OMe | 68 | 8 | 77 | 6 |
| **4j** | *m*-OMe | — | — | 83 | 6 |

[a] By refluxing.
[b] By using microwave oven.




**2a-j** and **4a-j:** R= H (**a**), *p*-F (**b**), *p*-Cl (**c**), *m*-Cl (**d**), *p*-Br (**e**), *p*-Me (**f**), *p*-iPr (**g**), *o*-OH (**h**), *p*-OMe (**i**), *m*-OMe (**j**)

*i:* anhydrous dioxane, reflux 8-10 h
*ii:* solvent-free, MW irradiation 5-7 min

**Scheme 2.** Synthetic pathway for *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4,6-diarylpyrimidin-2-yl)thioureas (**4a–j**).

**Table 3**
Response of various micro-organisms to substituted amino-4,6-diarylpyrimidine **2a–j**

| Entry | R | Diameter of zone inhibition[a] (mm) | | |
|---|---|---|---|---|
| | | *E. aerogenes* | *S. epidermidis* | *C. albicans* |
| **2a** | H | 15 | 30 | 20 |
| **2b** | *p*-F | 26 | 30 | 25 |
| **2c** | *p*-Cl | 20 | 29 | 17 |
| **2d** | *m*-Cl | 18 | 30 | 20 |
| **2e** | *p*-Br | 15 | 28 | 15 |
| **2f** | *p*-Me | 23 | 27 | 26 |
| **2g** | *p*-iPr | 22 | 26 | 25 |
| **2h** | *o*-OH | 18 | 23 | 24 |
| **2i** | *p*-OMe | 18 | 29 | 18 |
| **2j** | *m*-OMe | 19 | 25 | 22 |
| Ref. | — | 25[b] | 25[c] | 35[d] |

Ref = [b] ampicillin; [c] methicillin; [d] clotrimazole.
[a] DMF used as control; concentration used = 100 μg/mL of DMF.

**Table 4**
Response of various micro-organisms to substituted *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas **4a–j**

| Entry | R | Diameter of zone inhibition (mm)[a] | | |
|---|---|---|---|---|
| | | *E. aerogenes* | *S. epidermidis* | *C. albicans* |
| **4a** | H | 15 | 27 | 15 |
| **4b** | *p*-F | 17 | 28 | 16 |
| **4c** | *p*-Cl | 0 | 30 | 14 |
| **4d** | *m*-Cl | 13 | 28 | 19 |
| **4e** | *p*-Br | 18 | 30 | 21 |
| **4f** | *p*-Me | 20 | 28 | 20 |
| **4g** | *p*-iPr | 22 | 29 | 22 |
| **4h** | *o*-OH | 20 | 27 | 21 |
| **4i** | *p*-OMe | 23 | 29 | 0 |
| **4j** | *m*-OMe | 22 | 24 | 22 |
| Ref. | — | 35[b] | 35[c] | 45[d] |

Ref = [b] ampicillin; [c] methicillin; [d] clotrimazole.
[a] DMF used as control; concentration used = 100 μg/mL of DMF.

760 FT-IR Spectrometer (NICOLET, USA) in KBr pellets. The $^1$H NMR (500.13 MHz) and $^{13}$C NMR (125.77 MHz) spectra were recorded on an AVANCE500 Spectrometer (BRUKER, Germany) in DMSO-$d_6$ solution; $\delta$ are in ppm compared to TMS as internal reference at 300 K. The assignments of $^1$H and $^{13}$C were confirmed using HMBC and HSQC methods. The high-resolution mass spectra were recorded on AutoSpec Premier instrument (WATERS, USA) using EI. Optical rotations were measured on a POLAX-2L polarimeter (ATAGO-Japan) in DMSO solution. Analytical thin-layer chromatography (TLC) was performed on Silica Gel 60$F_{254}$ No. 5715 (Merck, Germany) with EtOAc and light petroleum (bp 60–90 °C). The spots were visualized by exposure to UV light or by spraying the plates with 10% (v/v) $H_2SO_4$ in EtOH, followed by heating. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **3** was prepared by the reaction of per-O-acetylated-β-D-glucopyranosyl bromide[25] with lead thiocyanate in dried toluene.[20] Other reagents were supplied by Merck and used as received.

In order to perform the reaction in a domestic microwave oven, we have built a modified commercial microwave oven (Tiffany MM17L, power 750 W) in which the round-bottomed flask was attached to a condenser. This condenser was assembled with the flask in microwave oven through a hole on the top. The condenser was protected with a metallic wire mesh connected to the oven body to avoid any microwave leakages. It is also possible to conduct the experiments under controlled atmosphere like nitrogen (Fig. 1, see in Supplementary data).

## 1.2. General procedure for the synthesis of 2-amino-4,6-diarylpyrimidines (2a–j)

*Procedure A (under refluxing condition).* A solution of substituted benzylideneacetophenone **1** (10 mmol) in ethanol (5 mL) was added to a solution of guanidine hydrochloride (15 mmol) and sodium hydroxide (45 mmol) in water (2 mL). The reaction mixture was refluxed for 10 min in the modified domestic microwave oven. The solvent was removed under reduced pressure and the residue was triturated with water and the precipitate was filtered by suction and washed with water until neutral to afford the title compounds **2**, which were recrystallized from 1:1 EtOH-toluene to give ivory-white crystals.

*Procedure B (under microwave-assisted and solvent-free conditions).* Substituted benzylideneacetophenone **1** (10 mmol), guanidine hydrochloride (15 mmol) and sodium hydroxide (45 mmol) were mixed carefully with a little water. The obtained mixture was irradiated under domestic microwave oven. After 1–2 min, the reaction mixture had become dark-yellow, and then the irradiation was continued for the given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then triturated with water and the formed precipitate was filtered by suction and washed with water until neutral to afford the title compounds **2**, which were recrystallized from 1:1 EtOH-toluene to give ivory-white crystals.

### 1.2.1. 2-Amino-4,6-diphenylpyrimidine (2a)

From benzylideneacetophenone (2.08 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 1.78 g, 72% (procedure A); 2.20 g, 89% (procedure B); mp 118–119 °C; IR (KBr) $\nu$/cm$^{-1}$: 3469, 3320, 1601; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.22–8.20 (m, 4H, H-3′ & H5′ and H-3″ & H-5″), 7.70 (s, 1H, H-5), 7.53–7.52 (m, 6H, H-2′, H-4′ & H-6′ and H-2″, H-4″ & H-6″); HREIMS: calcd for $C_{16}H_{13}N_3$: 247.1109, found: 247.0929. Anal. Calcd for $C_{16}H_{12}BrN_3$: C, 77.71; H, 5.30; N, 16.99. Found: 77.86; H, 5.46; N, 17.05.

### 1.2.2. 2-Amino-4-(*p*-fluorophenyl)-6-phenylpyrimidine (2b)

From *p*-fluorobenzylideneacetophenone (2.26 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.78 g, 86% (procedure B); mp 132–133 °C; IR (KBr) $\nu$/cm$^{-1}$: 3493, 3314, 1634; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.30 (s, 1H, H-2′), 8.25–8.23 (m, 2H, H-3″ & H-5″), 8.20 (d, 1H, $J$ = 7.5 Hz, H-4′), 7.78 (s, 1H, H-5), 7.59–7.75 (m, 2H, $J$ = 7.5 Hz & 3.0 Hz, H-5′ & H6′), 7.53–7.52 (m, 3H, H-2″, H-4″ & H-6″), 6.80 (s, 2H, $NH_2$). Anal. Calcd for $C_{16}H_{12}FN_3$: C, 72.44; H, 4.56; N, 15.84. Found: C, 72.60; H, 4.60; N, 15.80.

### 1.2.3. 2-Amino-4-(*p*-chlorophenyl)-6-phenylpyrimidine (2c)

From *p*-chlorobenzylideneacetophenone (2.42 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.14 g, 76% (procedure A); 2.25 g, 85% (procedure B); mp 160–161 °C; IR (KBr) $\nu$/cm$^{-1}$: 3493, 3314, 1634; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.30 (s, 1H, H-2′), 8.25–8.23 (m, 2H, H-3″ & H-5″), 8.20 (d, 1H, $J$ = 7.5 Hz, H-4′), 7.78 (s, 1H, H-5), 7.59–7.75 (m, 2H, $J$ = 7.5 Hz & 3.0 Hz, H-5′ & H6′), 7.53–7.52 (m, 3H, H-2″, H-4″ & H-6″), 6.80 (s, 2H, $NH_2$); HREIMS calcd for $C_{16}H_{12}{}^{35}ClN_3$/$C_{16}H_{12}{}^{37}ClN_3$: 281.0719/283.0690, found: 281.0796/283.0660. Anal. Calcd for $C_{16}H_{12}ClN_3$: C, 68.21; H, 4.29; N, 14.91. Found: C, 68.45; H, 4.31; N, 14.84.

### 1.2.4. 2-Amino-4-(*m*-chlorophenyl)-6-phenylpyrimidine (2d)

From *m*-chlorobenzylideneacetophenone (2.42 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.11 g, 75% (procedure A);

2.34 g, 83% (procedure B); mp 118–119 °C; IR (KBr) $\nu/cm^{-1}$: 3491, 3315, 1634; $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.30 (s, 1H, H-2′), 8.25–8.23 (m, 2H, H-3″ & H-5″), 8.20 (d, 1H, $J$ = 7.5 Hz, H-4′), 7.78 (s, 1H, H-5), 7.59–7.75 (m, 2H, $J$ = 7.5 Hz & 3.0 Hz, H-5′ & H6′), 7.53–7.52 (m, 3H, H-2″, H-4″ & H-6″), 6.80 (s, 2H, $NH_2$); HREIMS calcd for $C_{16}H_{12}{}^{35}ClN_3/C_{16}H_{12}{}^{37}ClN_3$: 281.0719/283.0690, found: 281.0724/283.0745. Anal. Calcd for $C_{16}H_{12}ClN_3$: C, 68.21; H, 4.29; N, 14.91. Found: C, 68.55; H, 4.38; N, 14.87.

#### 1.2.5. 2-Amino-4-(*p*-bromophenyl)-6-phenylpyrimidine (2e)

From *p*-bromobenzylideneacetophenone (2.87 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.31 g, 71% (procedure A); 2.61 g, 80% (procedure B); mp 171–172 °C; IR (KBr) $\nu/cm^{-1}$: 3493, 3294, 3159, 1632; $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.22–8.20 (m, 2H, H-3″ & H-5″), 8.18 (d, 2H, $J$ = 8.5 Hz, H-3′ & H5′), 7.72 (s, 1H, H-5), 7.72 (d, 2H, $J$ = 8.5 Hz, H-2′ & H6′), 7.53–7.51 (m, 3H, $J$ = 3.5 Hz, H-2″, H-4″ & H-6″), 6.76 (s, 2H, $NH_2$); HREIMS calcd for $C_{16}H_{12}{}^{79}BrN_3/C_{16}H_{12}{}^{81}BrN_3$: 325.0215/327.0194, found: 325.3736/327.3077. Anal. Calcd for $C_{16}H_{12}BrN_3$: C, 58.91; H, 3.71; N, 12.88. Found C, 59.11; H, 3.61; N, 12.85.

#### 1.2.6. 2-Amino-4-(*p*-methylphenyl)-6-phenylpyrimidine (2f)

From *p*-methylbenzylideneacetophenone (2.22 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.22 g, 85% (procedure B); mp 127–128 °C; IR (KBr) $\nu/cm^{-1}$: 3363, 3327, 3191, 1642; $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.20–8.18 (m, 2H, H-3″ & H-5″), 8.19 (d, 2H, $J$ = 9.0 Hz, H-3′ & H5′), 7.64 (s, 1H, H-5), 7.52–7.50 (m, 3H, H-2″, H-4″ & H-6″), 7.06 (d, 2H, $J$ = 9.0 Hz, H-2′ & H6′), 6.61 (s, 2H, $NH_2$), 2.41 (s, 3H, $CH_3$); Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 73.20; H, 5.30; N, 15.41.

#### 1.2.7. 2-Amino-4-(*p*-isopropylphenyl)-6-phenylpyrimidine (2g)

From *p*-isopropylbenzylideneacetophenone (2.50 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.46 g, 85% (procedure B); mp 141–142 °C; IR (KBr) $\nu/cm^{-1}$: 3363, 3327, 3191, 1642; $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.20–8.18 (m, 2H, H-3″ & H-5″), 8.19 (d, 2H, $J$ = 9.0 Hz, H-3′ & H5′), 7.64 (s, 1H, H-5), 7.52–7.50 (m, 3H, H-2″, H-4″ & H-6″), 7.06 (d, 2H, $J$ = 9.0 Hz, H-2′ & H6′), 6.61 (s, 2H, $NH_2$), 3.02 [septet, 1H, $J$ = 12.0 Hz, 4‴-$CH(CH_3)_2$], 1.28 [d, 6H, $J$ = 12.0 Hz, 4‴-CH($CH_3$)$_2$]; Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 78.74; H, 6.42; N, 14.72.

#### 1.2.8. 2-Amino-4-(*o*-hydroxyphenyl)-6-phenylpyrimidine (2h)

From *o*-hydroxybenzylideneacetophenone (2.24 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 1.84 g, 70%, procedure A; 2.24 g, 85% (procedure B); mp 181–182 °C; IR (KBr) $\nu/cm^{-1}$: 3519, 3362, 3204, 1629; $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.25–8.21 (m, 3H, H-3″, H-5″ & H-3′), 7.86 (s, 1H, H-5), 7.54–7.53 (m, 3H, H-2″, H-4″ & H-6″), 7.37–7.34 (td, 1H, $J$ = 8.5 Hz & 1.25 Hz, H-6′), 7.18 (br, OH & $NH_2$), 6.90 (t, 1H, $J$ = 7.0 Hz, H-5′), 6.90 (dd, 1H, $J$ = 8.5 Hz & 1.25 Hz, H-4′); HREIMS calcd for $C_{16}H_{13}N_3O$: 263.1059, found: 263.0977. Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.69; H, 4.88; N, 15.67.

#### 1.2.9. 2-Amino-4-(*p*-methoxyphenyl)-6-phenylpyrimidine (2i)

From *p*-methoxybenzylideneacetophenone (2.38 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.02 g, 73% (procedure A); 2.22 g, 80% (procedure B); mp 151–152 °C; IR (KBr) $\nu/cm^{-1}$: 3363, 3327, 3191, 1642; $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.20–8.18 (m, 2H, H-3″ & H-5″), 8.19 (d, 2H, $J$ = 9.0 Hz, H-3′ & H5′), 7.64 (s, 1H, H-5), 7.52–7.50 (m, 3H, H-2″, H-4″ & H-6″), 7.06 (d, 2H, $J$ = 9.0 Hz, H-2′ & H6′), 6.61 (s, 2H, $NH_2$), 3.84 (s, 3H, $OCH_3$); HREIMS calcd for $C_{17}H_{15}N_3O$: 277.1215, found: 277.0977. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.83; H, 5.35; N, 15.35.

#### 1.2.10. 2-Amino-4-(*m*-methoxyphenyl)-6-phenylpyrimidine (2j)

From *m*-methoxybenzylideneacetophenone (2.38 g, 10 mmol) and guanidine hydrochloride (1.43 g, 15 mmol). Recrystallized from EtOH/toluene to yield a white solid, 2.29 g, 83% (procedure B); mp 139–140 °C; (KBr) $\nu/cm^{-1}$: 3491, 3315, 1634; $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.30 (s, 1H, H-2′), 8.25–8.23 (m, 2H, H-3″ & H-5″), 8.20 (d, 1H, $J$ = 7.5 Hz, H-4′), 7.78 (s, 1H, H-5), 7.59–7.75 (m, 2H, $J$ = 7.5 Hz & 3.0 Hz, H-5′ & H6′), 7.53–7.52 (m, 3H, H-2″, H-4″ & H-6″), 6.80 (s, 2H, $NH_2$), 3.92 (s, 3H, $OCH_3$); Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.80; H, 5.31; N, 15.39.

### 1.3. General procedure for the synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas (4a–j)

*Procedure A (under refluxing condition).* A solution of 2-amino-4,6-diarylpyrimidine **2** (2 mmol) in anhydrous dioxane (10 mL) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **3** (2 mmol) in anhydrous dioxane (10 mL). The reaction mixture was heated at reflux for 8–10 h. Then the solvent was removed under reduced pressure, and the residue was triturated with ethanol. The precipitate was filtered by suction and recrystallized with 1:1 EtOH-water to afford the title compounds **4** as ivory-white crystals.

*Procedure B (under microwave-assisted and solvent-free conditions).* A mixture of 2-amino-4,6-diarylpyrimidine **2** (2 mmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **3** (2 mmol) was grinded in a 5mL porcelain beaker. Then the mixture was put into a domestic microwave oven (the power output is 750 W). The adjustor of the microwave oven was set to the proper temperature (about 50 °C). The reactants were irradiated for a period of 5–7 min. The mixture became dark-yellow paste in reaction process. The reaction was traced with thin-layer chromatography. The reaction mixture was cooled to room temperature, triturated with ethanol, filtered by suction and recrystallized with ethanol/toluene (1:1) to afford the title compounds **4** as ivory-white crystals.

#### 1.3.1. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diphenylpyrimidin-2′-yl)thiourea (4a)

From 494 mg of **2a** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 763 mg, 60% (procedure A); 954 mg, 75% (procedure B); mp 229–230 °C; $[\alpha]_D^{25}$+46.6 (*c* 1.0, DMSO); IR (KBr) $\nu/cm^{-1}$: 3529, 3422 (m, NH), 1754 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1362 (m, C=S),1231 and 1045 (m, C–O–C); $^1H$ NMR (DMSO-$d_6$): $\delta$ 12.18 (d, 1H, $J$ = 9.5 Hz, $H_a$), 11.11 (s, 1H, $H_b$), 8.32–8.30 (m, 4H, H-2″, H-6″ & H-2‴, H-6‴), 8.29 (s, 1H, H-5′), 7.65–7.60 (m, 6H, H-3″, H-4″, H-5″ & H-3‴, H-4‴, H-5‴), 6.21 (t, 1H, $J$ = 9.5 Hz, H-1), 5.53 (t, 1H, $J$ = 9.5 Hz, H-3), 5.04 (t, 1H, $J$ = 9.25 Hz, H-2), 5.03 (t, 1H, $J$ = 9.5 Hz, H-4), 4.23 (m, 1H, H-5), 4.23 (d, 1H, $J$ = 10.0 Hz, H-6a), 4.07 (d, 1H, $J$ = 10.0 Hz, H-6b), 2.03, 1.99, 1.96, 1,95 (4s, 12H, 4 × $CH_3$CO); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 181.39 (C=S), 169.93, 169.57, 169.50, 169.35 (4C, 4 × $CH_3CO$), 164.97 (C-4′ & C-6′), 157.55 (C-2′), 135.53 (C-1″ & C-1‴), 131.73 (C-4″ & C-4‴), 128.96 (C-3″, C-5″, C-3‴ & C5‴), 127.49 (C-2″, C-6″, C-2‴ & C-6‴), 107.66 (C-5′), 81.72 (C-1), 72.61 (C-5), 72.14 (C-3), 71.48 (C-2), 67.98 (C-4), 61.75 (C-6), 20.43, 20.40, 20.32, 20.23 (4C, 4 × $CH_3$CO); EIMS: *m/z* 635, $[M-H]^+$.

#### 1.3.2. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*p*-fluorophenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4b)

From 638 mg of **2b** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 1076 mg, 76% (procedure B); mp 223–224 °C ; $[\alpha]_D^{25}$ +65.6 (*c* 1.0, DMSO); IR (KBr) $\nu/cm^{-1}$: 3291 (m, NH), 1755 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1368 (m, C=S),1233 and 1045 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): δ 12.07 (d, 1H, *J* = 9.0 Hz, $H_a$), 11.14 (s, 1H, $H_b$), 8.40 (qd, 2H, *J* = 8.5 Hz, *J* = 1.75 Hz, H-2‴ & H-6‴), 8.31 (s, 1H, H-5′), 8.30 (m, 2H, *J* = 8.5 Hz, H-2″ & H-6″), 7.65–7.60 (m, 3H, H-3″, H-4″ & H-5″), 7.45 (d, 2H, *J* = 8.5 Hz, H-3‴ & H-5‴), 6.19 (t, 1H, *J* = 9.25 Hz, H-1), 5.52 (t, 1H, *J* = 9.5 Hz, H-3), 5.04 (t, 1H, *J* = 9.5 Hz, H-2), 5.02 (t, 1H, *J* = 9.5 Hz, H-4), 4.22–4.20 (m, 2H, H-5 & H-6a), 4.05 (m, 1H, H-6b), 2.03, 1.99, 1.96, 1.95 (4 × *CH*$_3$CO); $^{13}$C NMR (DMSO-$d_6$): δ 181.35 (C=S), 169.92, 169.58, 169.49, 169.33 (4 × *CH*$_3$CO), 165.33 (C-4′), 164.83 & 164.09 ($J_{C-F}$ 371.5 Hz, C-4‴), 163.34 (C-6′), 157.47 (C-2′), 135.48 (C-1″), 132.09 (C-1″), 131.76 (C-1″), 130.12 & 130.04 ($J_{C-F}$ 36 Hz, C-2‴ & C-6‴), 128.97 (C-3‴ & C-5‴), 127.46 (C-2‴ & C-6‴), 116.04 & 115.86 ($J_{C-F}$ 86.5 Hz, C-3‴ & C-5‴), 107.52 (C-5′), 81.74 (C-1), 72.66 (C-5), 72.19 (C-3), 71.39 (C-2), 68.01 (C-4), 61.79 (C-6), 20.41, 20.38, 20.30, 20.21 (4 × CH$_3$*CO*).

#### 1.3.3. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*p*-chlorophenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4c)

From 563 mg of **2c** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 912 mg, 68% (procedure A); 1019 mg, 76% (procedure B); mp 218–219 °C; $[\alpha]_D^{25}$ +76.6 (*c* 1.0, DMSO); IR (KBr) $\nu/cm^{-1}$: 3410 (m, NH), 1750 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1364 (m, C=S), 1222 and 1045 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): δ 12.04 (d, 1H, *J* = 9.0 Hz, $H_a$), 11.16 (s, 1H, $H_b$), 8.35 (d, 2H, *J* = 9.0 Hz, H-2″ & H-6″), 8.33 (s, 1H, H-5′), 8.31 (dd, 2H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-2‴ & H-6‴), 7.69 (d, 2H, *J* = 9.0 Hz, H-3″ & H-5″), 7.63 (dd, 3H, *J* = 8.0 Hz, *J* = 7.5 Hz, H-3‴, H-4‴ & H-5‴), 6.20 (t, 1H, *J* = 9.0 Hz, H-1), 5.52 (t, 1H, *J* = 9.5 Hz, H-3), 5.06 (t, 1H, *J* = 9.25 Hz, H-2), 5.04 (t, 1H, *J* = 9.5 Hz, H-4), 4.22 (t, 1H, *J* = 9.25 Hz, H-5), 4.21 (dd, 1H, *J* = 10.0 Hz, H-6a), 4.05 (dd, 1H, *J* = 10.0 Hz, H-6b), 2.03, 1.99, 1.96, 1.95 (4s, 12H, 4 × C*H*$_3$CO); $^{13}$C NMR (DMSO-$d_6$): δ 181.32 (C=S), 169.88, 169.57, 169.47, 169.30 (4C, 4 × CH$_3$*C*O), 165.02 (C-4′), 163.82 (C-6′), 157.46 (C-2′), 136.56 (C-4″), 135.40 (C-1‴), 134.34 (C-1″), 131.77 (C-4‴), 129.25 (C-3″ & C-5″), 128.97 (C-2″ & C-6″), 128.93 (C-3‴ & C-5‴), 127.47 (C-2‴ & C-6‴), 107.62 (C-5′), 81.17 (C-1), 72.67 (C-5), 72.20 (C-3), 71.38 (C-2), 67.99 (C-4), 61.79 (C-6), 20.39, 20.37, 20.29, 20.21 (4C, 4 × *CH*$_3$CO); HREIMS calcd for $C_{31}H_{31}{}^{37}ClN_4O_9S$: 673.1544, found: 673.5450 $[M+H]^+$·.

#### 1.3.4. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*m*-chlorophenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4d)

From 563 mg of **2d** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 898 mg, 67% (procedure A); 966 mg, 72% (procedure B); mp 190–191 °C; $[\alpha]_D^{25}$ +79.3 (*c* 1.0, DMSO); IR (KBr) $\nu/cm^{-1}$: 3410 (m, NH),1750 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1364 (m, C=S),1223 and 1045 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): δ 12.16 (d, 1H, *J* = 9.5 Hz, $H_a$), 11.22 (s, 1H, $H_b$), 8.40 (s, 2H, H-2″ & H-5), 8.35–8.32 (m, 3H, H-2‴, H-4‴ & H-6‴), 7.70 (m, 1H, H-6″), 7.66–7.60 (m, 4H, H-4″, H-5″ & H-3‴, H-5‴), 6.20 (t, 1H, *J* = 9.5 Hz, H-1), 5.56 (t, 1H, *J* = 9.5 Hz, H-3), 5.06 (t, 1H, *J* = 9.5 Hz, H-4), 5.05 (t, 1H, *J* = 9.5 Hz, H-2), 4.21 (octet, 1H, *J* = 9.5 Hz, *J* = 5.0 Hz, *J* = 2.0 Hz, H-5), 4.22 (dd, 1H, *J* = 12.5 Hz, *J* = 4.75 Hz, H-6a), 4.05 (dd,1H, *J* = 12.5 Hz, *J* = 1.75 Hz, H-6b), 2.03, 1.99, 1.96, 1.95 (4s, 12H, 4 × C*H*$_3$CO); $^{13}$C NMR (DMSO-$d_6$): δ 181.30 (C=S), 169.90, 169.57, 169.45, 169.30 (4C, 4 × CH$_3$*C*O), 165.45 (C-4′), 163.14 (C-6′), 157.46 (C-2′), 137.53 (C-3″), 135.39 (C-1‴), 134.05 (C-1″), 131.86 (C-2″), 131.38 (C-5″), 130.83 (C-4‴), 128.95 (C-3‴ & C-5‴), 127.57 (C-2‴ & C-6‴), 127.09 (C-6″), 126.16 (C-4″), 107.81 (C-5′), 81.63 (C-1), 72.57 (C-5), 71.88 (C-3), 71.53 (C-2), 67.98 (C-4), 61.72 (C-6), 20.39, 20.39, 20.28, 20.17 (4C, 4 × *CH*$_3$CO).

#### 1.3.5. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*p*-bromophenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4e)

From 652 mg of **2e** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 944 mg, 66% (procedure A); 1087 mg, 76% (procedure B); mp 223–224 °C; $[\alpha]_D^{25}$+89.1 (*c* 1.0, DMSO); IR (KBr) $\nu/cm^{-1}$: 3410 (m, NH),1740 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1363 (m, C=S),1223 and 1045 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): δ 12.03 (d, 1H, *J* = 9.5 Hz, $H_a$), 11.18 (s, 1H, $H_b$), 8.35 (s, 1H, H-5″), 8.31 (dd, 2H, *J* = 8.5 Hz, *J* = 2.0 Hz, H-2‴ & H-6‴), 8.28 (d, 2H, *J* = 9.0 Hz, H-2″ & H-6″), 7.83 (d, 2H, *J* = 9.0 Hz, H-3″ & H-5″), 7.63 (m, 3H, H-3‴, H-4‴ & H-5‴), 6.19 (t, 1H, *J* = 9.5 Hz, H-1), 5.52 (t, 1H, *J* = 9.5 Hz, H-3), 5.05 (t, 1H, *J* = 9.5 Hz, H-2), 5.04 (t, 1H, *J* = 9.5 Hz, H-4), 4.22 (dd, 1H, *J* = 14.5 Hz, H-6a), 4.21 (t, 1H *J* = 9.5 Hz, H-5), 4.05 (dd, 1H *J* = 14.5 Hz, H-6b), 2.03, 1.99, 1.96, 1.95 (4s, 12H, 4 × C*H*$_3$CO); $^{13}$C NMR (DMSO-$d_6$): δ 181.31 (C=S), 169.90, 169.58, 169.48, 169.31 (4C, 4 × CH$_3$*C*O), 165.06 (C-4′), 163.93 (C-6′), 157.48 (C-2′), 135.41 (C-1‴), 134.72 (C-1″), 131.94 (C-3″ & C-5″), 131.80 (C-4‴), 129.46 (C-3‴ & C-5‴), 128.95 (C-2″ & C-6″), 127.49 (C-2‴ & C-6‴), 125.53 (C-4″), 107.60 (C-5′), 81.730 (C-1), 72.66 (C-5), 72.17 (C-3), 71.34 (C-2), 67.97 (C-4), 61.79 (C-6), 20.42, 20.38, 20.30, 20.21 (4C, 4 × *CH*$_3$CO); EIMS: *m/z* 714/716 ($[M]^+$·).

#### 1.3.6. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*p*-methylphenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4f)

From 522 mg of **2f** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 780 mg, 60% (procedure A); 1040 mg, 80% (procedure B); mp 209–210 °C; $[\alpha]_D^{25}$ +56.3 (*c* 1.0, DMSO); IR (KBr) $\nu/cm^{-1}$: 3427 (m, NH),1749 (s, C=O), 1596, 1578, 1529, 1514, 1494 (Ar), 1364 (s, C=S), 1245, 1222 and 1040 (s, C–O–C); $^1$H NMR (DMSO-$d_6$): δ 12.19 (d, 1H, *J* = 9.0 Hz, $H_a$), 11.05 (s, 1H, $H_b$), 8.30 (dd, 2H, *J* = 8.0 Hz, *J* = 1.75 Hz, H-2‴ & H-6‴), 8.24 (s, 1H, H-5), 8.21 (d, 2H, *J* = 8.0 Hz, H-2″ & H6″), 7.60 (m, 3H, H-3‴, H-4‴ & H-5‴), 7.41 (d, 2H, *J* = 8.0 Hz, H-3 & H-5), 6.2 (t, 1H, *J* = 9.25 Hz, H-1), 5.54 (t, 1H *J* = 9.5 Hz, H-3), 5.04 (t, 1H, *J* = 9.5 Hz, H-2), 5.03 (t, 1H, *J* = 9.25 Hz, H-4), 4.25–4.20 (m, 2H, H-6a & H-5), 4.07 (dd, 1H, *J* = 10.5 Hz, *J* = 3.5 Hz, H-6b), 2.41 (s, 3H, C*H*$_3$), 2.03, 1.99, 1.98, 1.96 (4s, 12H, 4 × C*H*$_3$CO); $^{13}$C NMR (DMSO-$d_6$): δ 181.37 (C=S), 169.91, 169.55, 169.48, 169.33 (4C, 4 × CH$_3$*C*O), 164.86 (C-4′), 164.80 (C-6′), 157.50 (C-2′), 141.89 (C-4″), 135.57 (C-1‴), 132.70 (C-1″), 131.46 (C-4‴), 129.55 (C-3″ & C-5″), 128.92 (C-3‴ & C-5‴), 127.43 (C-2‴ & C-6‴), 127.41 (C-2″ & C-6″), 107.21 (C-5′), 99.49 (4-$CH_3$ Ar), 81.78 (C-1), 72.66 (C-5), 72.15 (C-3), 71.48 (C-2), 68.00 (C-4), 61.75 (C-6), 20.99, 20.39, 20.29, 20.20 (4C, 4 × *CH*$_3$CO).

#### 1.3.7. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*p*-isopropylphenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4g)

From 596 mg of **2g** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 922 mg, 68% (procedure A); 1071 mg, 79% (procedure B); mp 151–152 °C; $[\alpha]_D^{25}$ +56.3 (*c* 1.0, DMSO); IR (KBr) $\nu/cm^{-1}$: 3184 (m, NH),1751 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1363 (m, C=S),1220 and 1045 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): δ 12.19 (d, 1H, *J* = 9.0 Hz, $H_a$), 11.05 (s, 1H, $H_b$), 8.31 (dd, 2H, *J* = 9.0 Hz, *J* = 1.75 Hz, H-2‴ & H-6‴), 8.27 (s, 1H, H-5′), 8.26 (d, 2H, *J* = 8.5 Hz, H-2″ & H-6″), 7.64–7.60 (m, 3H, H-3‴, H-4‴ & H-5‴), 7.48 (d, 2H, *J* = 8.5 Hz, H-3″ & H-5″), 6.21 (t, 1H, *J* = 9.0 Hz, H-1), 5.53 (t, 1H, *J* = 9.5 Hz, H-3), 5.05 (t, 1H, *J* = 9.5 Hz, H-2), 5.05 (t, 1H, *J* = 9.25 Hz, H-4), 4.23–4.19 (m, 2H, H-5 & H-6a), 4.07 (m, 1H, H-6b), 3.89 (s, 3H, 4″-$OCH_3$), 3.02 [septet, 1H, *J* = 12.0 Hz, 4‴-*CH*$(CH_3)_2$], 2.04, 1.99, 1.96, 1.95 (4 × *CH*$_3$CO), 1.28 [d, 6H, *J* = 12.0 Hz, 4‴-CH(*CH*$_3$)$_2$]; $^{13}$C NMR (DMSO-$d_6$): δ 181.29 (C=S), 169.77, 169.43, 169.36, 169.22 (4 × *CH*$_3$CO), 164.94 (C-4′),

164.71 (C-6′), 157.45 (C-2′), 152.47 (C-4″), 135.53 (C-1‴), 133.10 (C-1″), 131.55 (C-4‴), 128.85 (C-3‴ & C-5‴), 127.53 (C-3″ & C-5″), 127.36 (C-2‴ & C6‴), 126.82 (C-2″ & C-6″), 107.27 (C-5′), 81.75 (C-1), 72.59 (C-5), 72.47 (C-3), 72.13 (C-2), 67.96 (C-4), 61.69 (C-6), 33.29 [4‴-*CH*($CH_3$)$_2$], 23.45 [4‴-CH(*$CH_3$*)$_2$], 20.29, 20.28, 20.20, 20.12 (4 × $CH_3$*CO*).

### 1.3.8. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(o-hydroxyphenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4h)

From 526 mg of **2h** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 782 mg, 60% (procedure A); 1043 mg, 80% (procedure B); mp 248–249 °C; $[\alpha]_D^{25}$ +76.3 (*c* 1.0, DMSO); IR (KBr) $\nu$/cm$^{-1}$: 3585 (m, NH), 1754 (s, C=O), 1597, 1530, 1495 (Ar), 1368 (m, C=S), 1222 and 1059 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): $\delta$ 12.12 (d, 1H, *J* = 9.5 Hz, $H_a$), 11.85 (s, 1H, $H_b$), 11.83 (s, 1H, OH), 8.34 (s, 1H, H-5′), 8.31 (dd, 1H, *J* = 8.5 Hz, *J* = 1.5 Hz, H-6″), 8.24–8.23 (m, 2H, H-3‴ & H-5‴), 7.68–7.62 (m, 3H, H-2‴, H-4‴ & H-6‴), 7.55 (td, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, H-4″), 7.02 (d, 1H, *J* = 7.5 Hz, H-5″), 7.00 (d, 1H, *J* = 8.0 Hz, H-3″), 6.20 (t, 1H, *J* = 9.25 Hz, H-1), 5.52 (t, 1H *J* = 9.5 Hz, H-3), 5.02 (m, 2H, H-2 & H-4), 4.23–4.18 (m, 2H, H-5 & H-6a), 4.05 (m, 1H, H-6b), 2.03, 2.00, 1.98, 1.95 (4s, 12H, 4 × *$CH_3$*CO); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 181.37 (C=S), 169.90, 169.51, 169.46, 169.31 (4C, 4 × $CH_3$CO), 166.13 (C-4′), 163.55 (C-6′), 159.22 (C-2′), 155.91 (C-2″), 135.48 (C-1‴), 133.68 (C-6″), 131.77 (C-4″), 129.14 (C-4‴), 129.07 (C-3‴ & C-5‴), 127.37 (C-2‴ & C-6‴), 119.22 (C-5″), 118.36 (C-1″), 117.93 (C-3″), 107.15 (C-5′), 81.63 (C-1), 72.61 (C-5), 72.15 (C-3), 71.42 (C-2), 67.96 (C-4), 61.73 (C-6), 20.40, 20.36, 20.28, 20.20 (4 × *$CH_3$*CO).

### 1.3.9. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*p*-methoxyphenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4i)

From 554 mg of **2i** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 906 mg, 68% (procedure A); 1026 mg, 77% (procedure B); mp 213–214 °C; $[\alpha]_D^{25}$ +84.0 (*c* 1.0, DMSO); IR (KBr) $\nu$/cm$^{-1}$: 3434 (m, NH), 1750 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1364 (m, C=S), 1223 and 1045 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): $\delta$ 12.22 (d, 1H, *J* = 9.0 Hz, $H_a$), 11.06 (s, 1H, $H_b$), 8.32 (d, 2H, *J* = 9.5 Hz, H-2″ & H-6″), 8.30 (td, 2H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-2‴ & H6‴), 8.25 (s, 1H, H-5′), 7.64–7.60 (m, 3H, H-3‴, H-4‴ & H-5‴), 7.15 (d, 2H, *J* = 9.0 Hz, H-3″ & H-5″), 6.19 (t, 1H, *J* = 9.25 Hz, H-1), 5.52 (t, 1H *J* = 9.5 Hz, H-3), 5.04 (t, 1H, *J* = 9.5 Hz, H-2), 5.02 (t, 1H, *J* = 9.5 Hz, H-4), 4.21 (m, 1H, H-6a), 4.20 (m, 1H, H-5), 4.05 (m, 1H, H-6b), 3.89 (s, 3H, O*$CH_3$*), 2.03, 1.98, 1.96, 1.95 (4s, 12H, 4 × *$CH_3$*CO); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 181.33 (C=S), 169.91, 169.53, 169.48, 169.34 (4C, 4 × $CH_3$CO), 164.68 (C-4′), 164.38 (C-6′), 162.26 (C-2′), 157.49 (C-4″), 135.66 (C-1‴), 131.58 (C-1″), 129.32 (C-3‴ & C-5‴), 128.93 (C-2″ & C-6″), 127.78 (C-4‴), 127.39 (C-2‴ & C-6‴), 114.32 (C-3″ & C-5″), 106.74 (C-5′), 81.71 (C-1), 72.59 (C-5), 72.11 (C-3), 71.48 (C-2), 67.97 (C-4), 61.77 (C-6), 55.48 (*C*$H_3$O-Ar), 20.42, 20.39, 20.31, 20.21 (4C, 4 × *$CH_3$*CO); HREIMS calcd for $C_{32}H_{34}N_4O_{10}S$: 666.1996, found: 665.0209 ([M−H]$^{+\cdot}$).

### 1.3.10. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[4′-(*m*-methoxyphenyl)-6′-phenyl-pyrimidin-2′-yl]thiourea (4j)

From 554 mg of **2j** and 778 mg of **3**. Recrystallized from EtOH-toluene to yield ivory-white crystals, 1105 mg, 83% (procedure B); mp 165–166 °C; $[\alpha]_D^{25}$ +54.0 (*c* 1.0, DMSO); IR (KBr) $\nu$/cm$^{-1}$: 3434 (m, NH),1756 (s, C=O), 1594, 1578, 1526, 1495 (Ar), 1356 (m, C=S),1228 and 1045 (m, C–O–C); $^1$H NMR (DMSO-$d_6$): $\delta$ 12.24 (d, 1H, *J* = 9.5 Hz, $H_a$), 11.12 (s, 1H, $H_b$), 8.32 (d, 2H, *J* = 8.0 Hz, H-2‴ & H-6‴), 8.31 (s, 1H, H-5′), 7.92 (d, 1H, *J* = 7.5 Hz, H-2″), 7.87 (s, 1H, H-6″), 7.65–7.60 (m, 3H, H-3‴, H-4‴ & H-5‴), 7.53 (t, 1H, *J* = 8.0 Hz, H-5′), 7.21 (dd, 1H, *J* = 8.0 Hz, *J* = 2.5 Hz, H-4″), 6.20 (t, 1H, *J* = 9.25 Hz,H-1), 5.54 (t, 1H *J* = 9.75 Hz, H-3), 5.03 (d, 2H, *J* = 9.5 Hz, H-2 & H-4), 4.24 (ddd, 1H, *J* = 12.0 Hz, *J* = 2.5 Hz, *J* = 2.0 Hz, H-6a), 4.19 (dd, 1H, *J* = 12.0 Hz, *J* = 5.0 Hz, H-5), 4.07 (dd, 1H, *J* = 12.0 Hz, *J* = 2.0 Hz, H-6b), 3.92 (s, 3H, O*$CH_3$*), 2.04, 1.99, 1.950, 1.94 (4s, 12H, 4 × *$CH_3$*CO); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 181.24 (C=S), 169.79, 169.41, 169.34, 169.23 (4C, 4 × $CH_3$CO), 165.08 (C-4′), 164.56 (C-6′), 159.82 (C-2′), 157.39 (C-3″), 136.87 (C-1″), 135.48 (C-1‴), 131.62 (C-5″), 129.99 (C-4‴), 128.47 (C-3‴ & C-5‴), 127.45 (C-2‴ & C-6‴), 119.80 (C-6″), 117.28 (C-4″), 112.80 (C-2″), 107.67 (C-5′), 81.70 (C-1), 72.57 (C-5), 71.97 (C-3), 71.54 (C-2), 68.01 (C-4), 61.70 (C-6), 55.34 (*C*$H_3$O-Ar), 20.29, 20.27, 20.17, 20.08 (4C, 4 × *$CH_3$*CO).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.09.002.

## References

1. (a) Sayle, K. L.; Bentley, J.; Boyle, F. T.; Calvert, A. H.; Cheng, Y.; Curtin, N. J.; Endicott, J. A.; Golding, B. T.; Hardcastle, I. R.; Jewbury, P.; Mesguiche, V.; Newell, D. R.; Noble, M. E. M.; Parsons, R. J.; Pratt, D. J.; Wang, L. Z.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3079–3082; (b) Balasankar, T.; Nagarajan, S. *Heterocycl. Commun.* **2004**, *10*, 465–468.
2. (a) Chandrasekaran, S.; Nagarajan, S. *Il Farmaco* **2005**, *60*, 279–282; (b) Cocco, M. T.; Congiu, C.; Liliu, V.; Onnis, V. *Bioorg. Med. Chem.* **2006**, *14*, 366–372; (c) Gadhachanda, V. R.; Wu, B.; Wang, Z.; Kuhen, K. L.; Caldwell, J.; Zondler, H.; Walter, H.; Havenhand, H. M.; He, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 260–265.
3. (a) El-Hashash, M. A.; Mahhmoud, M. R.; Madboli, S. A. *Indian J. Chem.* **1993**, *32B*, 449–453; (b) Wustrow, D.; Akunne, H.; Belliotti, T.; Davis, M. D.; Heffner, T.; Kesten, S.; Meltzer, L.; Pugsley, T.; Wise, L. *Eur. Neuropsychopharm.* **1996**, *6*, S4; (c) Rashinkar, G. S.; Pore, S. B.; Mote, K. B.; Salunkhe, R. S. *Indian J. Chem.* **2009**, *48B*, 606–610.
4. (a) Witczak, Z. J. In *Adv. Carbohydr. Chem. Biochem.*, Tipson, S., Ed.; Academic Press: New York, 1986; Vol. 44, pp 91–145.; (b) Lindhorst, T. K.; Kieburg, C. *Synthesis* **1995**, 1228–1230; (c) Jiménez Blanco, J. L.; Sylla, B.; Ortiz-Mellet, C.; García Fernández, J. M. *J. Org. Chem.* **2007**, *72*, 4547–4550; (d) Kühne, M.; Györgydeák, Z.; Lindhorst, T. K. *Synthesis* **2006**, 949–951.
5. (a) García-Fernández, J. M.; Ortiz-Mellet, C. *Sulfur Rep.* **1996**, *19*, 61–159; (b) García-Fernández, J. M.; Ortiz-Mellet, C.. In *Adv. Carbohydr. Chem. Biochem.*; Horton, D., Ed.; Academic Press: New York, 2000; Vol. 55, pp 36–135.
6. (a) Naito, T.; Sano, M. *Chem. Pharm. Bull.* **1961**, *9*, 709–714; (b) Ukita, T.; Hamada, A.; Yoshida, M. *Chem. Pharm. Bull.* **1964**, *12*, 454–459; (c) Ogura, H.; Takahashi, H. *Heterocycles* **1977**, *8*, 125–146.
7. (a) Camarasa, M. J.; Fernandez-Resa, P.; Garcia-Lopez, M. T.; de las Heras, F. G.; Mendez-Castrillon, P. P.; San Felix, A. *Synthesis* **1984**, 509–510; (b) Prata, C.; Mora, N.; Lacombe, J.-M.; Maurizis, J.-C.; Pucci, B. *Carbohydr. Res.* **1999**, *321*, 4–14.
8. (a) Abramovitch, R. A. *Org. Prep. Proc. Int.* **1991**, *23*, 683–712; (b) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
9. (a) Loupy, A. *Microwaves in Organic Synthesis*, 2nd ed.; Wiley and Sons: Weinheim, 2006; (b)Kingston, H. M., Haswell, S. J., Eds.Microwave-Enhanced Chemistry: Fundamental, Sample Preparation, and Applications; American Chemical Society: New York, 1997.
10. (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Roussel, J. *Tetrahedron Lett.* **1986**, *27*, 279; (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432; (c) Gabriel, C.; Gabriel, S.; Grant, E.; Halstead, B. S. J.; Mingos, D. *Chem. Soc. Rev.* **1997**, *27*, 213–224.
11. (a) Chen, S.-T.; Sookkheo, B.; Phutrahul, S.; Wang, K.-T. *Methods Biotechnol.* **2001**, *15*, 373; (b) Soderberg, E.; Westman, J.; Oscarson, S. *J. Carbohydr. Chem.* **2001**, *20*, 397; (c) Lidstorm, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
12. Walpole, C.; Ko, S. Y.; Brown, M.; Beattie, D.; Campbell, E.; Dickenson, F.; Ewan, S.; Hughes, G. A.; Lemaira, M.; Lerpiniere, J.; Patel, S.; Urban, L. *J. Med. Chem.* **1998**, *41*, 3159–3173.
13. (a) Chalina, E. G.; Chakarova, L. *Eur. J. Med. Chem.* **1998**, *33*, 975–983; (b) Stark, H.; Purand, K.; Ligneau, X.; Rouleau, A.; Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1996**, *39*, 1157–1163.
14. (a) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293–4296; (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (c) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064.
15. (a) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351–367; (b) Staab, H. A.; Walther, G. *Leibigs Ann. Chem.* **1962**, *657*, 98–103; (c) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468.

16. (a) Mohanta, P. K.; Dhar, S.; Samal, S. K.; Ila, H.; Junjappa, H. *Tetrahedron* **2000**, *56*, 629–637; (b) Aoyama, T.; Murata, S.; Nagata, Y.; Takido, T.; Kodamari, M. *Tetrahedron Lett.* **2005**, *46*, 4875–4878.
17. (a) Rodríguez-Lucena, D.; Benito, J. M.; Ortiz-Mellet, C.; García Fernández, J. M. *Chem. Commun.* **2007**, 831–833; (c) Jiménez Blanco, J. L.; Bootello, P.; Gutiérrez Gallego, R.; Ortiz-Mellet, C.; García Fernández, J. M. *Synthesis* **2007**, 2545–2558.
18. (a) Sharma, S. *Synthesis* **1978**, 803–820; (b) Bhandari, K.; Srivatsava, S.; Shankar, G. *Bioorg. Med. Chem.* **2004**, *12*, 4189–4196; (c) Kodomari, M.; Suzuki, M.; Tanigawa, K.; Aoyama, T. *Tetrahedron Lett.* **2005**, *46*, 5841–5843.
19. (a) Schroeder, D. C. *Chem. Rev.* **1955**, *55*, 181–228; (b) Sridevi, G.; Rao, J.; Reddy, K. K. *Synth. Commun.* **1989**, *19*, 965–972; (c) Yavari, I.; Sayyed-Alangi, S. Z.; Sabbaghan, M.; Hajinasiri, R.; Iravani, N. *Monatsh. Chem.* **2008**, *139*, 1025–1028.
20. Bama, K. B.; Rajani, K. G. *Indian J. Chem.* **1988**, *27B*, 1157–1158.
21. Liu, Y.-H.; Cao, L.-H. *Carbohydr. Res.* **2008**, *343*, 615–625.
22. (a) Furniss, B. A.; Hannaford, A. J.; Smith, P. W.; Tatchell, A. R. *Vogel's Text-Book of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: Harlow, 1989; (b) Oyedapo, A. O.; Makanju, V. O.; Adewunmi, C. O.; Iwalewa, E. O.; Adenowo, T. K. *Afr. J. Trad. CAM* **2004**, *1*, 55; (c) Adewunmi, C. O.; Ogungbamila, F. O.; Oluwadiya, J. O. *Planta. Med.* **1987**, *53*, 110.
23. El-Hashash, M. A.; Mahhmoud, M. R.; Madboli, S. A. *Indian J. Chem.* **1993**, *32B*, 449–452.
24. E. Pretsch, P. Buhlmann, C. Affolter, *Structure Determination of Organic Compounds*, 2nd ed., Springer: Berlin, 2000, p 152, 236..
25. Lemieux, R. L.. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic: New York, 1963; Vol. 2, pp 221–222.