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Assessment of synthetic methods for the preparation of *N*-β-D-glucopyranosyl-N′-substituted ureas, -thioureas and related compounds

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Abstract—Preparation of O-peracetylated *N*-β-D-glucopyranosyl-*N*′-acyl urea derivatives resulted in the formation of anomeric mixtures under the following conditions: acylation of O-peracetylated β-D-glucopyranosyl urea by acyl chlorides in the presence of $ZnCl_2$ in refluxing $CHCl_3$; addition of O-peracetylated β-D-glucopyranosylamine to acyl isocyanates in acetonitrile at rt; addition of carboxamides to in situ prepared O-peracetylated β-D-glucopyranosyl isocyanate in refluxing toluene. Deprotection of O-peracetylated *N*-β-D-glucopyranosyl-*N*′-acyl ureas either under base (NaOMe in MeOH at or below rt) or under acid ($KHSO_4$ or AcCl in MeOH at rt) catalyzed transesterification conditions resulted in unavoidable partial cleavage of the *N*′-acyl moieties. Reaction of β-D-glucopyranosylammonium carbamate with an isocyanate, isothiocyanate or isoselenocyanate in dry pyridine at rt appears as a general method for the preparation of the corresponding β-D-glucopyranosyl ureas, -thio- and -selenoureas, respectively, inclusive *N*′-acyl derivatives.

Keywords: Glucosylurea; Acyl urea; Thiourea; Selenourea

1. Introduction

Inhibition of human liver glycogen phosphorylase is under extensive study with the hope to provide a potential new therapy for type 2 diabetes mellitus. The most populated class of inhibitors comprises glucose derivatives[1,2] most of which bind at the catalytic site as evidenced by X-ray crystallography.[3]

The first potent glucose analogue inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGP*b*) were some *N*-acyl-β-D-glucopyranosylamines **I** (Chart 1). Later, it was demo- nstrated that the elongation of the aglycon[6] especially with another NHCO moiety as in *N*-β-D-glucopyranosyl-*N*′-acyl ureas **III** together with the presence of a large aromatic group (R = 2-naphthyl) rendered these inhibitors into the nanomolar range. In this paper, we summarize our experience in the preparation of *N*-β-D-glucopyranosyl-*N*′-acyl urea derivatives, and propose a simple way for the synthesis of *N*-β-D-glucopyranosyl-N′-substituted ureas **II** and **III** as well as some thio and seleno analogues, which were needed to establish structure–activity relationships. The enzymatic and structural studies will be published elsewhere.[7,8]

2. Results and discussion

The first acyl ureas **III** (R = Me, Ph) tested as inhibitors of GP were those for which the O-peracetylated derivatives were known in the literature.[9] For the preparation of other derivatives, acylation of urea **1**[10] by $ZnCl_2$

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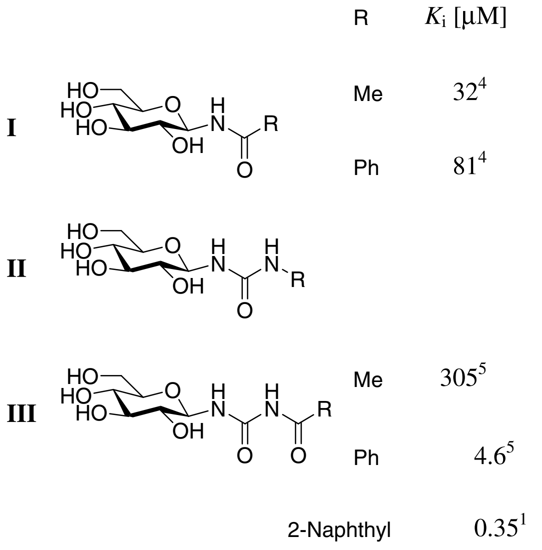
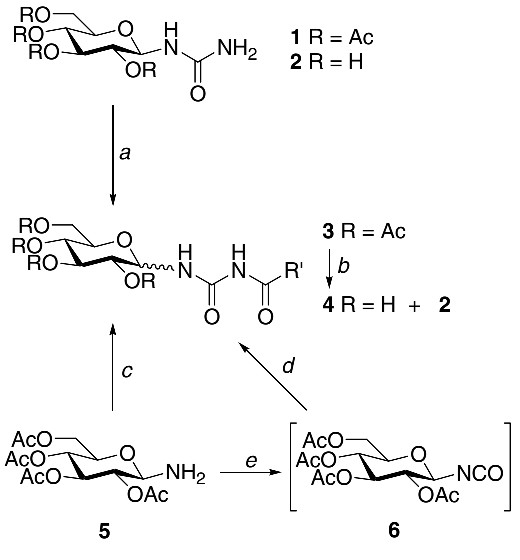


Chart 1. Some representative inhibitors of rabbit muscle glycogen phosphorylase.[4,5]

catalyzed reaction of the corresponding acyl chlorides to give **3** was investigated first[7,8] (Scheme 1, Table 1, Route a). In most of these reactions formation of an anomeric mixture was observed, the separation of which by silica gel column chromatography allowed only the β-anomers to be isolated in low yields because of the very similar mobilities of the isomers. From a larger scale preparation of the 2-naphthoyl urea, it was possible to isolate a small amount of the α-anomer α-**3m**, which was unambigously characterized by MS and NMR methods (see Section 3). To avoid the formation of the undesired by-product, glucopyranosylamine **5** was reacted with acyl isocyanates (Route c) obtained from acyl chlorides with NaOCN catalyzed by $SnCl_4$.[11] In these reactions, too, anomerization was observed in several cases (although, we speculate, probably to a lesser extent as revealed by the higher isolated yields for the β-anomers; compare Routes a and c for **3h** and **3i**). Reactions of the prepared glucopyranosyl isocyanate[12] **6** with carboxamides (Route d) also gave anomeric mixtures from which the β-anomers of **3h** and **3i** could be isolated in satisfactory yields together with some α-**3h** and α-**3i**. At first sight, these anomerizations were surprising since N-acylated glycosylamines and similar derivatives were considered to be configurationally stable (precisely, more stable than glycosylamines).[13] However, it was pointed out that glycosyl ureas underwent both acid- and base-catalyzed anomerization.[14] Loss of anomeric configurational integrity was also reported for an O-perbenzylated glucosyl urea under slightly acidic conditions,[15] and for glucosyl thioureas under slightly basic Zemplén deacetylation conditions.[16] Anomerizations of glycosyl ureas and -carbamates were also observed during formation of glycosyl isocyanates to be reacted with amines.[17] In the light of these literature reports, our observations may be unravelled. The Lewis acidic $ZnCl_2$ may not only activate acid chlorides but can also catalyze iminium ion formation[13,18] and, thereby, anomerization in the reactions of **1**. During the addition of **5** to acyl isocyanates, the glucosylamine itself may anomerize, but even traces of it may act as basic catalysts for the anomerization of the formed ureas. The most difficult is to understand the reaction of **6** with carboxamides because the latter are probably neither acidic nor basic enough to elicit anomerization; since **6** was not purified but used as the crude product of the transformation of **5**, some unreacted glucosylamine might have remained in the mixture to act as a basic catalyst for the anomerization.



Scheme 1. Reagents and conditions: (a) R′–COCl, $ZnCl_2$, $CHCl_3$, reflux; (b) deprotection, see text; (c) R′–CONCO, CH_3CN, Ar, rt; (d) R′–$CONH_2$, $PhCH_3$, reflux; (e) $(Cl_3CO)_2CO$, $NaHCO_3$, CH_2Cl_2, water, rt.

Deprotection of compound **3** was complicated by the propensity of the acyl urea moiety towards splitting off the acyl part.[7,8] Thus, deacetylation under Zemplén conditions at or below room temperature in most cases gave **4** together with **2** within 0.5–1 h. Acid catalyzed transesterification either by using $KHSO_4$ or by using a catalytic amount of AcCl in MeOH slowed down the reaction to 5–12 days, and thus it became easier to follow the transformation by TLC and to detect the optimal time to get the highest yield for **4**. However, even in these reactions, the formation of **2** was to be observed.

Because of the above difficulties, we sought for a more simple and direct way of preparation of the target *N*-(β-D-glucopyranosyl)-*N*′-acyl ureas **4**. The choice of reacting glucopyranosylamines with acyl isocyanates seemed straightforward, since the feasibility of analogous reactions with iso(thio)cyanates had been demonstrated.[19,20] However, glycosylamines[13] are available

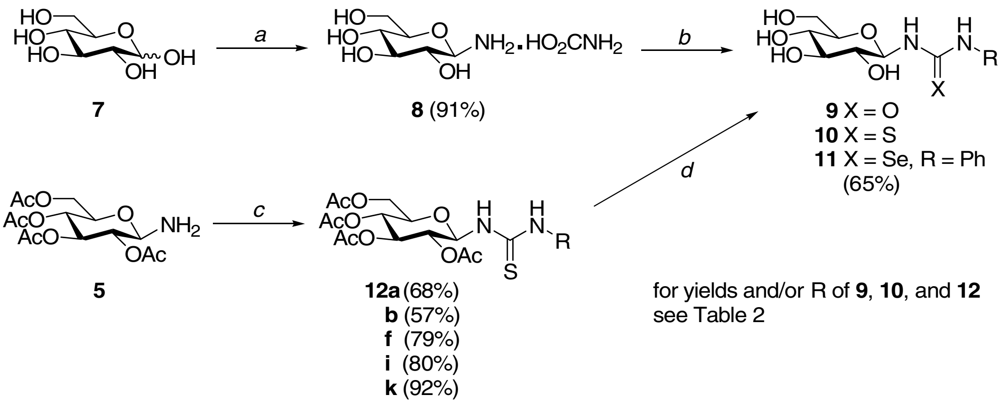
Table 1. Preparation of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-acyl ureas **3** by methods indicated in Scheme 1[7,8]

	R′ in **3**	Route a		Route c		Route d	
		Observed	Isolated	Observed	Isolated	Observed	Isolated
a	*c*-C_6H_{11}	β	40% β				
b	4-NO_2–C_6H_4	αβ	60% β	β	65% β		
c	4-Cl–C_6H_4			β	67% β		
d	3-Cl–C_6H_4			β	90% β		
e	4-AcO–C_6H_4	β	72% β	αβ	20% β		
f	4-Ph–C_6H_4	αβ	43% β				
g	4-Me–C_6H_4	αβ	34% β				
h	4-*t*Bu–C_6H_4	αβ	36% β	αβ	40% β	αβ	51% β 10% α
i	4-CF_3–C_6H_4	αβ	Failed	αβ	40% β	αβ	69% β 9% α
j	$PhCH_2$	β	57% β				
k	Ph_2CH	αβ	14% β				
l	1-Naphthyl	β	73% β				
m	2-Naphthyl	αβ	32% β 1% α				
n	2-Indolyl	β	41% β				
o	2-Pyridyl	αβ	47% β				

by rather lengthy and laborious methods involving, for example, several days or even weeks reaction time, the need for large amounts of reagents, evaporating large volumes of water, using ion exchange and lyophilization.[18,21,22] On the other hand, these compounds can be obtained by a recent new method[23–25] in which the monosaccharide is reacted with ammonium carbamate in methanol, and the glycosylammonium carbamate crystals can be isolated by a simple filtration after 1 day. Thus, β-D-glucopyranosylammonium carbamate (**8**) was obtained from D-glucose (**7**) in 91% yield (Scheme 2) and the salt could be stored in a refrigerator for at least one month.

Although the liberation of the free glucopyranosylamine from the carbamate salt was feasible,[23] the more simple direct use of the salt was envisaged (N-bromoacetylation of the salt was reported[26]). To this end, the reaction of **8** with phenyl isocyanate was investigated in several solvents such as MeOH, acetone, MeOH–Py, acetone–Py and MeOH–Et_3N at rt but satisfactory conversion was to be observed only in dry pyridine. Therefore, reactions of **8** with a series of cyanates and thiocyanates were performed in pyridine at rt to give **9** and **10**, respectively (Table 2). For these reactions, the acyl isocyanates were obtained by oxalyl chloride from the corresponding carboxamides.[27] It has to be noted that the conversions were not complete even after rather long (1 week) reaction times. The yields refer to the amount of the starting carbamate salt **8** without taking into account the incomplete conversion because recovery of **8** was not reasonable. Thus, the real yields must be higher than those given in Table 2. Some thioureas (**10a**,**b**,**f**,**i**,**k**) were obtained by the reaction of acetylated glucopyranosylamine **12** with the corresponding isothiocyanates to give **13a**,**b**,**f**,**i**,**k**, which were deprotected by the Zemplén protocol to give the corresponding compounds **10**.

Carbamate salt **8** was also reacted with phenyl isoselenocyanate to give selenourea **11**[28] in 65% yield (again without taking into account the incomplete conversion of **8**) exhibiting spectral data identical with the reported ones.



Scheme 2. Reagents and conditions: (a) $NH_4O_2CNH_2$ (4 equiv), abs MeOH, 37 °C, 1 day; (b) R–NCX, abs pyridine, rt; (c) R–NCS, CH_2Cl_2, rt; (d) NaOMe, MeOH, rt.

Table 2. *N*-(β-D-glucopyranosyl)-*N*′-substituted ureas **9** and -thioureas **10** prepared from carbamate salt **8**

	R	**9**		**10**	
		Reaction time (day)	Yield (%)	Reaction time (day)	Yield (%)
a	C_6H_5	3	60		86 from **12**
b	2-Cl–C_6H_4	1	53	5	64 from **8** 20 from **12**
c	3-Cl–C_6H_4	3	42		
d	4-Cl–C_6H_4	1	54		
e	2-F–C_6H_4	1	76		
f	4-F–C_6H_4				20 from **8** 97 from **12**
g	4-Br–C_6H_4	2	70		
h	4-NO_2–C_6H_4	1	76		
i	4-MeO–C_6H_4	2	63	8	44 from **12**
j	3-CF_3–C_6H_4	3	46		
k	4-CF_3–C_6H_4				98 from **12**
l	3-CN–C_6H_4	3	45		
m	$C_{10}H_7$ (1-naphthyl)	3	45		
n	$C_{10}H_7$ (2-naphthyl)	3	42		
o	$C_{10}H_7CO$ (2-naphthyl)[a]	3	60		
p	4-*t*Bu–C_6H_4CO[b]	5	19		

[a] **9o** corresponds to **4** (R = $C_{10}H_7$, 2-naphthyl).

[b] **9p** corresponds to **4** (R = 4-*t*Bu–C_6H_4).

In conclusion, the easy availability of glucopyranosylammonium carbamate allowed the preparation of *N*-(β-D-glucopyranosyl)-N′-substituted ureas, -thioureas and a selenourea in two steps from D-glucose. Thus, the synthesis of the highly efficient glycogen phosphorylase inhibitors *N*-(β-D-glucopyranosyl)-*N*′-acyl ureas has been significantly improved facilitating further structure–activity studies.

3. Experimental

3.1. General methods

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with BRUKER 360 (360/90 MHz for $^1H/^{13}C$) or Avance DRX 500 (500/125 MHz for $^1H/^{13}C$) spectrometers. Chemical shifts are referenced to Me_4Si (^1H), or to the residual solvent signals (^{13}C). TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck), and the plates were visualized under UV light and by gentle heating. For column chromatography, Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated under diminished pressure at 40–50 °C (water bath). Aryl isocyanates and -isothiocyanates were purchased from Aldrich or prepared from the corresponding amines,[12] acyl isocyanates[27] and phenyl isoselenocyanate[28] obtained by the literature methods.

3.2. General procedure I for the preparation of *N*-β-D-glucopyranosyl-*N*′-aryl or acyl ureas 9 and -thioureas 10

Carbamate salt **8** was dissolved in dry pyridine (10 mg/2 mL) containing molecular sieves (3 Å), then 1–2 equiv of the corresponding isocyanate, isothiocyanate or acyl isocyanate was added in one portion. The reaction mixture was stirred at rt and monitored by TLC (7:3 or 1:1 $CHCl_3$–MeOH). When TLC showed no more change (conversions were incomplete), the solvent was evaporated. The obtained crude mixture was purified by column chromatography.

3.3. General procedure II for the preparation of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-aryl thioureas 12

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamine[29] (**5**) was dissolved and stirred in dry CH_2Cl_2 (1 g/20 mL) containing molecular sieves (3 Å). After 20 min, 1–1.5 equiv aryl isothiocyanate was added. The mixture was stirred at rt for 1–10 days (TLC, 1:1 EtOAc–hexane). After completion of the reaction, the mixture was filtered over a Celite pad and the solvent evaporated. The residue was purified by crystallization or column chromatography.

3.4. General procedure III for the Zemplén-deacetylation

To a soln of an *O*-acetyl protected compound in dry MeOH (0.10 g/5 mL), 1–2 drops of a ~1 M methanolic NaOMe soln were added, and the reaction mixture was kept at rt until completion of the transformation (TLC, 1:1 or 7:3 CHCl$_3$–MeOH). Amberlyst 15 (H$^+$ form) was then added to remove sodium ions, the resin was filtered off and the solvent removed. If the residue was chromatographically not uniform, it was purified by column chromatography or crystallization.

3.4.1. *N*-(2,3,4,6-Tetra-*O*-acetyl-β- and α-D-glucopyranosyl)-*N*′-(4-*tert*-butylbenzoyl)urea (3h and α-3h). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamine[29] (**5**, 50 mg, 0.14 mmol) was transformed into the corresponding isocyanate **6** according to the literature method,[12] and this was boiled in dry toluene with 4-*tert*-butylbenzamide (51 mg, 0.28 mmol) for 1 day. The solvent was then removed and the residue purified by column chromatography (1:5 EtOAc–hexane) to give 35 mg (44%) *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4-*tert*-butylbenzoyl)urea **3h**, as the first fraction. Mp: 117–119 °C; [α]$_D$ −39 (*c* 0.20, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 360 MHz): δ (ppm) 9.48 (1H, d, *J* 8.9 Hz, N*H*CONHCOAr), 9.00 (1H, s, NHCON*H*COAr), 7.87 (2H, d, *J* 8.3 Hz, Ar), 7.51 (2H, d, *J* 8.3 Hz, Ar), 5.35 (1H, pseudo t, *J* 9.6, 9.9 Hz, H-3), 5.32 (1H, pseudo t, *J* 8.9, 9.6 Hz, H-1), 5.14 (1H, pseudo t, *J* 8.9, 9.9 Hz, H-4), 5.12 (1H, pseudo t, *J* 9.6, 9.9 Hz, H-2), 4.27 (1H, dd, *J* 4.0, 12.3 Hz, H-6), 4.07 (1H, dd, *J* 1.2, 12.3 Hz, H-6′), 3.81 (1H, ddd, *J* 1.2, 4.0, 8.9 Hz, H-5), 2.06, 2.04, 2.03 (12H, 3s, 4 × OCOC*H*3), 1.35 (9H, s, PhC(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$, 90 MHz): δ (ppm) 170.6, 170.1, 169.8, 169.4, 167.3 (CO), 157.3 (NH*C*ONH), 154.1, 128.8, 127.7, 125.8 (aromatics), 79.0 (C-1), 73.5, 73.0, 70.0, 68.0 (C-2–C-5), 61.6 (C-6), 35.1 (*C*(CH$_3$)$_3$), 31.0 (C(*C*H$_3$)$_3$), 20.7, 20.6, 20.5 (OCO*C*H$_3$). Anal. Calcd for $C_{26}H_{34}N_2O_{11}$ (550.57): C, 56.72; H, 6.22; N, 5.09. Found: C, 56.38; H, 5.96; N, 5.17. The next fraction gave 8 mg (10%) of the title compound **α-3h**, as colourless crystals. Mp: 70–72 °C; [α]$_D$ +88 (*c* 3.89, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 360 MHz): δ (ppm) 10.16 (1H, s, NHCON*H*COAr), 10.05 (1H, d, *J* 7.9 Hz, N*H*CONHCOAr), 8.01 (2H, d, *J* 7.9 Hz, Ar), 7.56 (2H, d, *J* 7.9 Hz, Ar), 6.04 (1H, dd, *J* 5.3, 7.9 Hz, H-1), 5.43 (1H, pseudo t, *J* 9.6, 10.5 Hz, H-3), 5.23 (1H, dd, *J* 5.3, 10.5 Hz, H-2), 5.16 (1H, pseudo t, *J* 9.6, 9.6 Hz, H-4), 4.37 (1H, dd, *J* 1.8, 12.3 Hz, H-6), 4.04 (1H, dd, *J* 3.5, 12.3 Hz, H-6′), 4.00 (1H, ddd, *J* 1.8, 3.5, 9.6 Hz, H-5), 2.06, 2.05, 2.04 (12H, 3s, 4 × OCOC*H*$_3$), 1.37 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (CDCl$_3$, 90 MHz): δ (ppm) 170.5, 169.8, 169.5, 169.4, 168.5 (CO), 157.5 (NH*C*ONH), 154.9, 128.4, 127.9, 125.9 (aromatics), 75.1 (C-1), 70.2, 68.7, 68.3, 68.0 (C-2–C-5), 61.6 (C-6), 35.1 (*C*(CH$_3$)$_3$), 30.9 (C(*C*H$_3$)$_3$), 20.5 (OCO*C*H$_3$).

3.4.2. *N*-(2,3,4,6-Tetra-*O*-acetyl-β- and α-D-glucopyranosyl)-*N*′-(4-trifluoromethyl-benzoyl)urea (3i and α-3i). Prepared from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine[29] (**5**, 200 mg, 0.58 mmol) and 4-trifluoromethyl-benzamide (218 mg, 1.15 mmol) as described in Section 3.4.1. Reaction time 5 h. Column chromatographic purification (1:5 EtOAc–hexane) gave as the first fraction 222 mg (69%) of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4-trifluoromethyl-benzoyl)urea (**3i**) as a white powder. Mp: 109–112 °C; [α]$_D$ −37 (*c* 1.46, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 360 MHz): δ (ppm) 10.16 (1H, s, NHCON*H*COAr), 9.49 (1H, d, *J* 8.9 Hz, N*H*CONHCOAr), 8.15 (2H, d, *J* 8.0 Hz, Ar), 7.79 (2H, d, *J* 8.3 Hz, Ar), 5.38 (1H, pseudo t, *J* 9.2, 9.6 Hz, H-3), 5.27 (1H, t, *J* 8.9, 9.2 Hz, H-1), 5.17 (1H, t, *J* 9.2, 9.6 Hz, H-4), 5.12 (1H, t, *J* 9.2, 9.6 Hz, H-2), 4.25 (1H, dd, *J* 4.3, 12.6 Hz, H-6), 4.02 (1H, dd, *J* 2.2, 12.6 Hz, H-6′), 3.78 (1H, ddd, *J* 2.2, 4.3, 9.6 Hz, H-5), 2.06, 2.05, 2.04, 2.03 (12H, 4s, 4 × OCOC*H*$_3$). ^{13}C NMR (CDCl$_3$, 90 MHz): δ (ppm) 170.5, 170.1, 169.9, 169.4, 166.9 (CO), 154.5 (NH*C*ONH), 134.8 (q, *J* 32 Hz, *C*CF$_3$), 135.1, 128.7, 125.7 (aromatics), 123.4 (q, *J* 273 Hz, *C*F$_3$), 79.1 (C-1), 73.6, 72.8, 70.1, 68.1 (C-2–C-5), 61.6 (C-6), 20.5 (OCO*C*H$_3$). Anal. Calcd for $C_{23}H_{25}F_3N_2O_{11}$ (562.45): C, 49.12; H, 4.48; N, 4.98. Found: C, 49.33; H, 4.26; N, 4.58. The next fraction gave 28 mg (9%) of the title compound **α-3i** as a white powder. Mp: 155–158 °C; [α]$_D$ +75 (*c* 0.84, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 360 MHz): δ (ppm) 10.39 (1H, s, NHCON*H*COAr), 9.87 (1H, d, *J* 7.9 Hz, N*H*CONHCOAr), 8.22 (2H, d, *J* 8.8 Hz, Ar), 7.83 (2H, d, *J* 8.8 Hz, Ar), 6.02 (1H, dd, *J* 5.3, 7.9 Hz, H-1), 5.41 (1H, pseudo t, *J* 9.6, 10.5 Hz, H-3), 5.22 (1H, dd, *J* 5.3, 10.5 Hz, H-2), 5.18 (1H, pseudo t, *J* 9.6, 9.6 Hz, H-4), 4.35 (1H, dd, *J* 3.5, 12.3 Hz, H-6), 4.01 (1H, dd, *J* 2.6, 12.3 Hz, H-6′), 3.97 (1H, ddd, *J* 2.6, 3.5, 9.6 Hz, H-5), 2.07, 2.06, 2.05 (12H, 3s, 4 × OCOC*H*$_3$); ^{13}C NMR (CDCl$_3$, 90 MHz): δ (ppm) 170.6, 169.9, 169.5, 169.4, 167.5 (CO), 154.7 (NH*C*ONH), 135.1 (q, *J* 34 Hz, *C*CF$_3$), 134.5, 128.6, 126.0 (aromatics), 123.2 (q, *J* 289 Hz, *C*F$_3$), 75.3 (C-1), 70.1, 68.7, 68.5, 67.9 (C-2–C-5), 61.4 (C-6), 20.6 (*C*H$_3$).

3.4.3. *N*-(2,3,4,6-Tetra-*O*-acetyl-β- and α-D-glucopyranosyl)-*N*′-(2-naphthoyl)urea (3m and α-3m). To a soln of 2-naphthoyl-chloride (2.93 g, 15 mmol) in dry CHCl$_3$ (40 mL), anhydrous ZnCl$_2$ (160 mg, 1.20 mmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl urea[10] (**1**, 2 g, 5.1 mmol) were added with stirring. The reaction mixture was refluxed until TLC (1:1 EtOAc–hexane) showed complete transformation of **1**. Then, the reaction mixture was poured into ice-water and extracted with chloroform (2×). The organic phases were combined and washed with satd aq Na$_2$CO$_3$ soln and water. After drying, the solvent was evaporated and the residue was purified by column chromatography (1:2 EtOAc–hexane). The main product was 0.88 g (32%) *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(2-naphthoyl)urea. Mp: 184–185 °C; [α]$_D$ −64 (*c* 1.2, CHCl$_3$); ^{1}H NMR (CDCl$_3$ + Me$_2$SO-d_6, 360 MHz): δ (ppm) 10.23 (1H, s, NHCON*H*COAr), 9.65 (1H, d, *J* 8.5 Hz, N*H*CONHCOAr), 8.57 (1H, s, Ar), 8.10–7.6 (6H, m unres., Ar), 5.34 (1H, pseudo t, *J* 9.1 Hz, H-1), 5.33, 5.16, 5.09 (3 × 1H, 3 pseudo t, *J* 9.6 Hz, H-2–H-4), 4.17 (1H, dd, *J* 3.7, 12.6 Hz, H-6), 3.95 (1H, broad d, *J* 12.6 Hz, H-6′), 3.64 (1H, m unres., H-5), 2.03, 2.00 (12H, 2s, 4 × OCOC*H*$_3$); ^{13}C NMR (CDCl$_3$ + Me$_2$SO-*d*$_6$, 90 MHz): δ (ppm) 170.54, 170.03, 169.74, 169.31, 168.11 (CO), 155.04 (NH*C*ONH), 135.47, 132.24, 129.47, 129.25, 128.83, 128.69, 128.56, 127.76, 127.04, 123.79 (aromatics), 78.94 (C-1), 73.46, 72.95, 70.14, 67.99 (C-2–C-5), 61.47 (C-6), 20.53, 20.45 (OCO*C*H$_3$). Anal. Calcd for $C_{26}H_{28}N_2O_{11}$ (544.52): C, 57.35; H, 5.18; N, 5.14. Found: C, 57.38; H, 5.32; N, 5.17. We also isolated 0.03 g (1%) *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-*N*′-(2-naphthoyl)urea **α-3m** as a colourless oil. *R*$_f$ = 0.82 (2:1 EtOAc–hexane); [α]$_D$ +16 (*c* 0.96, CHCl$_3$); ^{1}H NMR (CDCl$_3$): δ (ppm) 10.57 (1H, s, CON*H*CO), 10.18 (1H, d, *J* 6.8 Hz, N*H*), 8.77–8.75, 8.18–7.93, 7.72–7.58 (10H, m, aromatics), 6.11 (1H, pseudo t, *J* 5.9, 6.8 Hz, H-1), 5.51 (1H, pseudo t, *J* 9.9, 9.9 Hz, H-4), 5.31 (1H, dd, *J* 9.6, 5.9 Hz, H-2), 5.23 (1H, pseudo t, *J* 9.9, 9.2 Hz, H-3), 4.40 (1H, dd, *J* 12.0, 3.4 Hz, H-6), 4.13 (1H, dd, *J* 12.0, 1.5 Hz, H-6′), 4.09 (1H, ddd, *J* 9.9, 3.4, 1.5 Hz, H-5), 2.14, 2.11, 2.10, 2.09 (4 × 3H, 4s, C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ (ppm) 171.2, 170.6, 169.9, 169.5, 168.9 (*C*O), 155.4 (NH*C*ONH), 135.9, 135.7, 132.5, 129.6, 129.5, 128.9, 128.2, 127.8, 127.1, 123.6 (aromatics), 75.3 (C-1), 70.4, 68.7, 68.5, 68.2 (C-2–C-5), 61.2 (C-6), 20.6 (*C*H$_3$); ESIMS: *m*/*z* 567.09 ([M+Na]$^+$).

3.4.4. β-D-Glucopyranosylammonium carbamate (8). D-Glucose (3.0 g, 17 mmol) was dissolved in dry MeOH (84 mL) and ammonium carbamate (5.2 g, 84 mmol) was added. The reaction mixture was stirred for 16 h at 37 °C, then stored at 0 °C for an hour. The product crystallized from the soln. After filtration, it was dried in a vacuum desiccator at ~60 mbar. Yield: 3.64 g (91%), mp: 124–126 °C; [α]$_D$ +17 (*c* 1, water), lit.[23] [α]$_D$ +5.3 (*c* 1, water). NMR data for H-1 and soln behaviour matched those reported.[23]

3.4.5. *N*-(β-D-Glucopyranosyl)-*N*′-phenyl urea (9a). From **8** (0.10 g, 0.41 mmol) and phenyl isocyanate (50 μL, 0.41 mmol) according to General procedure **I**. Purified by column chromatography (2:1 CHCl$_3$–MeOH) to yield 0.07 g (60%) white crystalline product. Mp: 193–195 °C (lit.[30] mp: 223 °C dec); [α]$_D$ −33 (*c* 0.42, Me$_2$SO) (lit.[30] [α]$_D$ −55, water); ^{1}H NMR (D$_2$O): δ (ppm) 7.41–7.16 (5H, m, aromatics), 4.92 (1H, d, *J* 8.9 Hz, H-1), 3.89 (1H, dd, *J* 12.3, 2.2 Hz, H-6), 3.72 (1H, dd, *J* 12.3, 5.2 Hz, H-6′), 3.56 (1H, pseudo t, *J* 9.2, 8.9 Hz, H-3), 3.53 (1H, ddd, *J* 8.9, 5.2, 2.2 Hz, H-5), 3.41 (1H, t, *J* 8.9, 8.9 Hz, H-4), 3.41 (1H, pseudo t, *J* 9.2, 8.9 Hz, H-2); ^{13}C NMR (Me$_2$SO-*d*$_6$): δ (ppm) 154.5 (NH*C*ONH), 137.8, 129.0, 128.3, 125.2, 123.8, 120.2 (aromatics), 80.7 (C-1), 78.1, 77.5, 72.9, 70.0 (C-2–C-5), 60.9 (C-6). Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.30): C, 52.35; H, 6.08; N, 9.39. Found: C, 52.15; H, 5.98; N, 9.56.

3.4.6. *N*-(β-D-Glucopyranosyl)-*N*′-(2-chlorophenyl)urea (9b). From **8** (0.16 g, 0.66 mmol) and 2-chlorophenyl isocyanate (0.10 g, 0.66 mmol) according to General procedure **I**. Purified by column chromatography (2:1 CHCl$_3$–MeOH) to yield 0.12 g (53%) yellowish crystalline product. Mp: 196–198 °C; [α]$_D$ +39 (*c* 0.20, Me$_2$SO); ^{1}H NMR (D$_2$O/CD$_3$OD): δ (ppm) 7.77–7.75 (4H, m, aromatics), 5.17 (1H, d, *J* 9.3 Hz, H-1), 4.22 (1H, dd, *J* 11.9, 1.3 Hz, H-6), 4.05 (1H, dd, *J* 11.9, 5.3 Hz, H-6′), 3.85 (1H, t, *J* 10.6, 9.3 Hz, H-2), 3.80–3.55 (3H, m, H-3, H-4, H-5); ^{13}C NMR (D$_2$O/CD$_3$OD): δ (ppm): 160.4 (NH*C*ONH), 137.2, 133.8, 130.3, 130.0, 129.8, 128.2 (aromatics), 82.3 (C-1), 78.3, 78.0, 73.3, 70.8 (C-2–C-5), 62.0 (C-6). Anal. Calcd for $C_{13}H_{17}ClN_2O_6$ (332.74): C, 46.93; H, 5.15; N, 9.39. Found: C, 46.60; H, 4.98; N, 9.56.

3.4.7. *N*-(β-D-Glucopyranosyl)-*N*′-(3-chlorophenyl)urea (9c). From **8** (0.16 g, 0.67 mmol) and 3-chlorophenyl isocyanate (0.10 g, 0.67 mmol) according to General procedure **I**. Purified by column chromatography (2:1 CHCl$_3$–MeOH) to yield 0.09 g (42%) white crystalline product. Mp: 203–205 °C; [α]$_D$ −18 (*c* 0.10, Me$_2$SO); ^{1}H NMR (CD$_3$OD): δ (ppm) 8.65 (1H, s, NH), 7.66–7.26 (4H, m, aromatics), 7.03 (1H, d, *J* 6.6 Hz NH), 4.79 (1H, pseudo t, *J* 9.2, 6.6 Hz, H-1), 3.83 (1H, dd, *J* 11.9, 2.6 Hz, H-6), 3.62 (1H, dd, *J* 11.9, 2.8 Hz, H-6′), 3.44–3.27 (4H, m, H-2, H-3, H-4, H-5); ^{13}C NMR (CD$_3$OD): δ (ppm): 157.6 (NH*C*ONH), 142.1, 135.4, 131.1, 126.7, 121.1, 118.2 (aromatics), 82.5 (C-1), 79.4, 78.9, 74.1, 71.5 (C-2–C-5), 62.8 (C-6). Anal. Calcd for $C_{13}H_{17}ClN_2O_6$ (332.74): C, 46.93; H, 5.15; N, 9.39. Found: C, 46.68; H, 5.08; N, 9.49.

3.4.8. *N*-(β-D-Glucopyranosyl)-*N*′-(4-chlorophenyl)urea (9d). From **8** (0.16 g, 0.66 mmol) and 4-chlorophenyl isocyanate (0.10 g, 0.66 mmol) according to General procedure **I**. Purified by column chromatography (2:1 CHCl$_3$–MeOH) to yield 0.12 g (54%) white crystalline product. Mp: 240–242 °C; [α]$_D$ +23 (*c* 0.28, Me$_2$SO); ^{1}H NMR (Me$_2$SO-*d*$_6$): δ (ppm) 8.69 (1H, s, NH), 7.42 (2H, d, *J* 8.0 Hz, aromatics), 7.28 (2H, d, *J* 8.0 Hz, aromatics), 6.71 (1H, d, *J* 9.2 Hz, NH), 5.06–5.05 (2H, m, OH), 4.92 (1H, d, *J* 8.9 Hz, OH), 4.65 (1H, pseudo t, *J* 9.2, 8.0 Hz, H-1), 4.52 (1H, s, OH), 3.62 (1H, dd, *J* 11.9, 4.0 Hz, H-6), 3.19 (1H, dd, *J* 11.9, 1.3 Hz, H-6′), 3.10–2.93 (4H, m, H-2, H-3, H-4, H-5); ^{13}C NMR (Me$_2$SO-*d*$_6$): δ (ppm) 154.4 (NH*C*ONH), 138.9, 135.5, 128.5, 128.1, 124.9, 119.3 (aromatics), 80.6 (C-1), 78.2, 77.5, 72.8, 69.9 (C-2–C-5), 60.9 (C-6). Anal. Calcd for

$C_{13}H_{17}ClN_2O_6$ (332.74): C, 46.93; H, 5.15; N, 9.39. Found: C, 46.75; H, 4.92; N, 9.15.

3.4.9. *N*-(β-D-Glucopyranosyl)-*N*′-(2-fluorophenyl)urea (9e). From **8** (0.18 g, 0.75 mmol) and 2-fluorophenyl isocyanate (0.10 g, 0.75 mmol) according to General procedure **I**. Purified by column chromatography (2:1 $CHCl_3$–MeOH) to yield 0.18 g (76%) white crystalline product. Mp: 199–201 °C; $[\alpha]_D$ −10 (*c* 0.20, Me_2SO); ^{1}H NMR (Me_2SO-d_6): *δ* (ppm) 8.51 (1H, s, NH), 8.08–6.93 (4H, m, aromatics), 7.38 (1H, d, *J* 9.2 Hz, NH), 5.14–5.10 (2H, m, OH, H-1), 5.00 (1H, t, *J* 5.3, 5.3 Hz, OH), 4.64 (1H, pseudo t, *J* 6.6, 5.3 Hz, OH), 3.61 (1H, dd, *J* 11.9, 5.3 Hz, H-6), 3.20 (1H, dd, *J* 11.9, 1.3 Hz, H-6′), 3.15–3.00 (3H, m, H-2, H-3, H-5), 2.95 (1H, t, *J* 9.3, 9.3 Hz, H-4); ^{13}C NMR: (Me_2SO-d_6): *δ* (ppm) 154.4 (NH*C*ONH), 151.8 (d, *C*F, *J* 242.4 Hz), 127.9, 124.4, 122.1, 120.5, 115.0 (aromatics), 80.7 (C-1), 78.2, 77.6, 73.0, 69.9 (C-2–C-5), 60.9 (C-6). Anal. Calcd for $C_{13}H_{17}FN_2O_6$ (316.29): C, 49.37; H, 5.42; N, 8.86. Found: C, 49.20; H, 5.58; N, 8.56.

3.4.10. *N*-(β-D-Glucopyranosyl)-*N*′-(4-bromophenyl)urea (9g). From **8** (0.14 g, 0.58 mmol) and 4-bromophenyl isocyanate (0.11 g, 0.58 mmol) according to General procedure **I**. Purified by column chromatography (2:1 $CHCl_3$–MeOH) to yield 0.15 g (70%) white crystalline product. Mp: 187–189 °C; $[\alpha]_D$ +27 (*c* 0.20, Me_2SO); ^{1}H NMR (Me_2SO-d_6): *δ* (ppm) 8.62 (1H, s, NH), 7.43 (2H, d, *J* 7.9 Hz, aromatics), 7.31 (2H, d, *J* 7.9 Hz, aromatics), 6.82 (1H, d, *J* 9.2 Hz, NH), 5.11–5.06 (2H, m, OH), 4.95 (1H, d, *J* 8.9 Hz, OH), 4.70 (1H, pseudo t, *J* 9.2, 9.2 Hz, H-1), 4.52 (1H, s, OH), 3.54 (1H, dd, *J* 11.8, 4.0 Hz, H-6), 3.22 (1H, dd, *J* 11.9, 1.3 Hz, H-6′), 3.15–2.93 (4H, m, H-2, H-3, H-4, H-5); ^{13}C NMR (Me_2SO-d_6): *δ* (ppm) 154.5 (NH*C*ONH), 131.9, 131.5, 126.8, 125.6, 122.3, 118.7 (aromatics), 80.6 (C-1), 78.0, 77.3, 72.5, 69.8 (C-2–C-5), 61.1 (C-6). Anal. Calcd for $C_{13}H_{17}BrN_2O_6$ (377.19): C, 41.40; H, 4.54; N, 7.43. Found: C, 41.12; H, 5.68; N, 7.56.

3.4.11. *N*-(β-D-Glucopyranosyl)-*N*′-(4-nitrophenyl)urea (9h). From **8** (0.05 g, 0.21 mmol) and 4-nitrophenyl isocyanate (0.035 g, 0.21 mmol) according to General procedure **I**. Purified by column chromatography (2:1 $CHCl_3$–MeOH) to yield 0.05 g (76%) white crystalline product. Mp: 169–171 °C; $[\alpha]_D$ −44 (*c* 0.21, Me_2SO); ^{1}H NMR (D_2O): *δ* (ppm) 8.03 (2H, d, *J* 9.3 Hz, aromatics), 7.40 (2H, d, *J* 9.3 Hz, aromatics), 4.87 (1H, d, *J* 9.3 Hz, H-1), 3.83 (1H, dd, *J* 11.9, 1.3 Hz, H-6), 3.67 (1H, dd, *J* 11.9, 5.3 Hz, H-6′), 3.65–3.39 (4H, m, H-2, H-3, H-4, H-5); ^{13}C NMR (D_2O): *δ* (ppm) 156.9 (NH*C*ONH), 145.6, 142.8, 125.8, 125.1, 123.4, 119.3 (aromatics), 81.4 (C-1), 77.9, 77.2, 72.5, 69.9 (C-2–C-5), 61.2 (C-6). Anal. Calcd for $C_{13}H_{17}N_3O_8$ (343.30): C, 45.48; H, 4.99; N, 12.24. Found: C, 45.18; H, 5.18; N, 12.36.

3.4.12. *N*-(β-D-Glucopyranosyl)-*N*′-(4-methoxyphenyl)urea (9i). From **8** (0.10 g, 0.42 mmol) and 4-methoxyphenyl isocyanate (60 μL, 0.46 mmol) according to General procedure **I**. Purified by column chromatography (2:1 $CHCl_3$–MeOH) to yield 0.09 g (63%) white crystalline product. Mp: 192–194 °C; $[\alpha]_D$ +14 (*c* 0.16, Me_2SO); ^{1}H NMR (Me_2SO-d_6): *δ* (ppm) 8.43 (1H, s, NH), 7.30 (2H, d, *J* 9.2 Hz, aromatics), 6.74 (2H, d, *J* 9.2 Hz, aromatics), 6.78 (1H, d, *J* 9.3 Hz, NH), 5.04 (1H, d, *J* 8.9 Hz, OH), 4.92 (1H, d, *J* 8.9 Hz, OH), 4.65 (1H, pseudo t, *J* 9.2, 8.9 Hz, OH), 4.52 (1H, pseudo t, *J* 9.2, 8.9 Hz, OH), 3.69 (4H, m, OCH_3, H-1), 3.61 (1H, dd, *J* 11.9, 3.0 Hz, H-6), 3.38 (1H, dd, *J* 11.9, 1.3 Hz, H-6′), 3.21 (1H, pseudo t, *J* 10.6, 9.3 Hz, H-2), 3.09–2.92 (3H, m, H-3, H-4, H-5); ^{13}C NMR (Me_2SO-d_6): *δ* (ppm) 154.7 (NH*C*ONH), 154.1, 133.1, 119.8, 119.5, 115.6, 113.3 (aromatics), 80.8 (C-1), 78.1, 77.6, 72.9, 69.9 (C-2–C-5), 60.9 (C-6), 55.1 (O*C*H_3). Anal. Calcd for $C_{14}H_{20}N_2O_7$ (328.32): C, 51.22; H, 6.14; N, 8.53. Found: C, 51.02; H, 6.48; N, 8.68.

3.4.13. *N*-(β-D-Glucopyranosyl)-*N*′-(3-trifluoromethylphenyl)urea (9j). From **8** (0.12 g, 0.50 mmol) and 3-trifluoromethylphenyl isocyanate (0.09 g, 0.50 mmol) according to General procedure **I**. Purified by column chromatography (4:1 $CHCl_3$–MeOH) to yield 0.08 g (46%) white crystalline product. Mp: 189–191 °C; $[\alpha]_D$ +17 (*c* 0.21, Me_2SO); ^{1}H NMR (Me_2SO-d_6): *δ* (ppm) 7.95 (1H, s, NH), 7.57–7.20 (4H, m, aromatics), 7.28 (1H, d, *J* 9.3 Hz, NH), 5.12–5.04 (2H, m, OH), 4.68 (1H, t, *J* 9.3, 9.3 Hz, H-1), 4.62 (1H, s, OH), 4.19 (1H, d, *J* 8.9 Hz, OH), 3.99 (1H, dd, *J* 12.1, 2.3 Hz, H-6), 3.58 (1H, dd, *J* 12.1, 4.0 Hz, H-6′), 3.21–2.96 (4H, m, H-2, H-3, H-4, H-5); ^{13}C NMR (Me_2SO-d_6): *δ* (ppm): 154.8 (NH*C*ONH), 141.2, 129.5, 129.4 (q, *C*-CF_3 *J* 31.7 Hz), 124.9 (2), 121.1 (aromatics), 117.3 (q, *C*F_3 *J* 265.3 Hz), 80.6 (C-1), 78.3, 77.6, 72.8, 69.9 (C-2–C-5), 60.8 (C-6). Anal. Calcd for $C_{14}H_{17}F_3N_2O_6$ (366.30): C, 45.91; H, 4.68; N, 7.65. Found: C, 45.51; H, 4.58; N, 7.36.

3.4.14. *N*-(β-D-Glucopyranosyl)-*N*′-(3-cyanophenyl)urea (9l). From **8** (0.1 g, 0.83 mmol) and 3-cyanophenyl isocyanate (0.12 g, 0.83 mmol) according to General procedure **I**. Purified by column chromatography (4:1 $CHCl_3$–MeOH) to yield 0.12 g (45%) white crystalline product. Mp: 219–221 °C; $[\alpha]_D$ +1 (*c* 0.21, Me_2SO); ^{1}H NMR (Me_2SO-d_6): *δ* (ppm) 8.50 (1H, s, NH), 7.35–6.78 (4H, m, aromatics), 6.61 (1H, d, *J* 9.3 Hz, NH), 5.03 (1H, d, *J* 8.9 Hz, OH), 4.89 (1H, d, *J* 8.9 Hz, OH), 4.67 (1H, pseudo t, *J* 9.2, 8.9 Hz, OH), 4.51 (1H, pseudo t, *J* 9.2, 8.9 Hz, OH), 3.61 (1H, dd, *J* 11.9, 2.3 Hz, H-6), 3.42 (1H, dd, *J* 11.9, 2.3 Hz, H-6′), 3.33 (1H, t, *J* 9.3, 9.3 Hz, H-1), 3.20 (1H, pseudo t, *J* 10.6, 9.3 Hz, H-2), 3.10–3.02 (2H, m, H-3, H-5), 2.96 (1H, t, *J* 9.3, 9.3 Hz, H-4); ^{13}C NMR (Me_2SO-d_6): *δ* (ppm) 154.5 (NH*C*ONH), 133.6, 132.7, 119.4, 119.2, 113.9, 113.7 (aromatics), 110.5 (*C*N), 80.7 (C-1), 78.0, 77.5, 72.8, 69.9 (C-2–C-5), 60.8 (C-6). Anal. Calcd for $C_{14}H_{17}N_3O_6$ (323.31): C, 52.01; H, 5.30; N, 13.00. Found: C, 51.90; H, 5.28; N, 13.26.

3.4.15. *N*-(β-D-Glucopyranosyl)-*N*′-(1-naphthyl)urea (9m). From **8** (0.05 g, 0.21 mmol) and 1-naphthyl isocyanate (35 μL, 0.21 mmol) according to General procedure **I**. Purified by column chromatography (4:1 $CHCl_3$–MeOH) to yield 0.03 g (45%) mildly brown crystalline product. Mp: 220–222 °C; $[\alpha]_D$ −24 (*c* 0.20, Me_2SO); ^1H NMR (Me_2SO-d_6 + D_2O): δ (ppm) 8.00–7.41 (7H, m, aromatics), 4.70 (1H, d, *J* 8.9 Hz, H-1), 3.66 (1H, dd, *J* 12.3, 1.5 Hz, H-6), 3.43 (1H, dd, *J* 12.3, 4.0 Hz, H-6′), 3.26 (1H, pseudo t, *J* 9.6, 8.9 Hz, H-3), 3.21 (1H, ddd, *J* 8.9, 4.0, 1.5 Hz, H-5), 3.12 (1H, t, *J* 8.9, 8.9 Hz, H-4), 3.07 (1H, pseudo t, *J* 9.6, 8.9 Hz, H-2); ^{13}C NMR (Me_2SO-d_6 + D_2O): δ (ppm) 154.8 (NH*C*ONH), 134.6, 133.6, 128.4, 125.8, 125.7, 125.5, 125.4, 122.3, 121.1, 116.4 (aromatics), 80.8 (C-1), 78.1, 77.5, 73.1, 69.9 (C-2–C-5), 60.9 (C-6). Anal. Calcd for $C_{17}H_{20}N_2O_6$ (348.36): C, 58.61; H, 5.79; N, 8.04. Found: C, 58.40; H, 5.58; N, 8.26.

3.4.16. *N*-(β-D-Glucopyranosyl)-*N*′-(2-naphthyl)urea (9n). From **8** (0.17 g, 0.69 mmol) and 2-naphthyl isocyanate (0.11 g, 0.69 mmol) according to General procedure **I**. Purified by column chromatography (2:1 $CHCl_3$–MeOH) to yield 0.10 g (42%) mildly brown crystalline product. Mp: 238–239 °C; $[\alpha]_D$ −24 (*c* 0.20, Me_2SO); ^1H NMR (Me_2SO-d_6 + D_2O): δ (ppm) 7.92–7.30 (7H, m, aromatics), 4.70 (1H, d, *J* 9.2 Hz, H-1), 3.67 (1H, dd, *J* 12.3, 1.9 Hz, H-6), 3.44 (1H, dd, *J* 12.3, 5.5 Hz, H-6′), 3.28 (1H, pseudo t, *J* 9.2, 8.9 Hz, H-3), 3.22 (1H, ddd, *J* 8.9, 5.5, 1.9 Hz, H-5), 3.10 (1H, t, *J* 8.9, 8.9 Hz, H-4), 3.09 (1H, pseudo t, *J* 9.2, 8.9 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ (ppm) 154.6 (NH*C*ONH), 137.6, 133.7, 128.9, 128.3, 127.4, 126.8, 126.2, 123.7, 119.4, 113.0 (aromatics), 80.8 (C-1), 78.2, 77.6, 72.9, 70.0 (C-2–C-5), 60.9 (C-6). Anal. Calcd for $C_{17}H_{20}N_2O_6$ (348.36): C, 58.61; H, 5.79; N, 8.04. Found: C, 58.55; H, 5.66; N, 8.06.

3.4.17. *N*-(β-D-Glucopyranosyl)-*N*′-(2-naphthoyl)urea (9o). From **8** (0.13 g, 0.54 mmol) and 2-naphthoyl isocyanate (0.11 g, 0.54 mmol) according to General procedure **I**. Purified by column chromatography (2:1 $CHCl_3$–MeOH) to yield 0.10 g (60%) white crystalline product. Mp: 213–214 °C; $[\alpha]_D$ +6.5 (*c* 0.18, Me_2SO); ^1H NMR (Me_2SO-d_6): δ (ppm) 11.02 (1H, s, NH), 9.15 (1H, d, *J* 9.5 Hz, NH), 8.2–7.5 (7H, m, aromatics), 4.84 (1H, pseudo t, *J* 9.5, 8.6 Hz, H-1), 4.01–3.08 (10H, m, 4 × O*H*, H-2, H-3, H-4, H-5, H-6, H-6′); ^{13}C NMR (Me_2SO-d_6) δ (ppm) 168.5 (NH*C*OAr), 153.5 (NH*C*ONH), 134.7, 134.6, 132.1, 130.0, 129.6, 129.4, 129.2, 127.8, 127.6, 126.5 (aromatics), 80.3 (C-1), 78.6, 77.3, 73.2, 69.70 (C-2–C-5), 60.8 (C-6). Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.30): C, 52.35; H, 6.08; N, 9.39. Found: C, 52.55; H, 6.26; N, 9.16.

3.4.18. *N*-(β-D-Glucopyranosyl)-*N*′-(4-*tert*-butylbenzoyl)-urea (9p). From **8** (0.68 g, 2.80 mmol) and 4-*tert*-butylbenzoyl isocyanate (0.28 g, 1.40 mmol) according to General procedure **I**. Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.10 g (19%) pale yellowish oil, R_f 0.08, $CHCl_3$–MeOH, 9:1; $[\alpha]_D$ −31 (*c* 0.16, Me_2SO); ^1H NMR (Me_2SO-d_6): δ (ppm) 10.78 (1H, s, NH), 9.14 (1H, d, *J* 9.2 Hz, NH), 7.92 (2H, d, *J* 9.2 Hz, aromatics), 7.53 (2H, d, *J* 9.2 Hz, aromatics), 5.25 (1H, d, *J* 5.3 Hz, OH), 5.02 (1H, d, *J* 4.0 Hz, OH), 4.94 (1H, d, *J* 5.3 Hz, OH), 4.82 (1H, t, *J* 9.2, 9.2 Hz, H-1), 4.52 (1H, t, *J* 5.3, 5.3 Hz, OH), 3.65 (1H, dd, *J* 11.9, 5.3 Hz, H-6), 3.46 (1H, dd, *J* 11.9, 2.6 Hz, H-6′), 3.32–3.01 (4H, m, H-2, H-3, H-4, H-5), 1.30 (9H, s, $C(CH_3)_3$); ^{13}C NMR (Me_2SO-d_6): δ (ppm) 168.2 (NH*C*OAr) 156.0 (NH*C*ONH), 153.5, 129.5, 128.0 (2), 125.3 (2) (aromatics), 80.2 (C-1), 78.5, 77.2, 73.1, 69.7 (C-2–C-5), 62.8 (C-6), 34.7 ($C(CH_3)_3$), 30.7 ($C(CH_3)_3$). Anal. Calcd for $C_{18}H_{26}N_2O_7$ (382.42): C, 56.54; H, 6.85; N, 7.33. Found: C, 56.40; H, 6.18; N, 7.26.

3.4.19. *N*-(β-D-Glucopyranosyl)-*N*′-phenyl thiourea (10a). From **12a** (0.13 g, 0.27 mmol) according to General procedure **III**. Yield: 0.07 g (86%) pale yellow crystals. Mp: 119–121 °C (lit.[30] mp: 121 °C), $[\alpha]_D$ −24 (*c* 0.23, water); ^1H NMR (D_2O): δ (ppm) 7.48–7.24 (5H, m, aromatics), 5.50 (1H, d, *J* 9.2 Hz, H-1), 3.85 (1H, dd, *J* 11.9, 1.0 Hz, H-6), 3.70 (1H, dd, *J* 11.9, 6.6 Hz, H-6′), 3.51 (1H, ddd, *J* 9.2, 6.6, 1.0 Hz, H-5), 3.54, 3.40, 3.37 (3 × 1H, 3 × pseudo t, *J* 9.2, 9.2 Hz, H-2, H-3, H-4); ^{13}C NMR (D_2O): δ (ppm) 182.9 (*C*S), 130.2 (2), 129.2, 128.3 (2), 127.0 (aromatics), 84.6 (C-1), 77.9, 77.1, 72.5, 69.7 (C-2–C-5), 61.1 (C-6). Anal. Calcd for $C_{13}H_{18}N_2O_5S$ (314.36): C, 49.67; H, 5.77; N, 8.91; S, 10.20. Found: C, 49.22; H, 5.95; N, 8.45; S, 10.33.

3.4.20. *N*-(β-D-Glucopyranosyl)-*N*′-(2-chlorophenyl)thiourea (10b). From **8** (0.20 g, 0.80 mmol) and 2-chlorophenyl isothiocyanate (0.13 mL, 1.04 mmol) or from **13b** (0.23 g, 0.44 mmol) according to General procedures **I** and **III**, respectively. Purified by column chromatography (1:1 $CHCl_3$–MeOH). Yield: 0.29 g (64%) from **8** or 0.07 g (20%) from **12b** pale yellow crystals. Mp: 165–167 °C; $[\alpha]_D$ +71 (*c* 0.05, Me_2SO); ^1H NMR (CD_3OD): δ (ppm) 7.36–7.19 (4H, m, aromatics), 5.37 (1H, d, *J* 9.2 Hz, H-1), 4.33 (1H, dd, *J* 11.9, 1.0 Hz, H-6), 4.18 (1H, dd, *J* 11.9, 6.6 Hz, H-6′), 3.56 (1H, ddd, *J* 9.2, 6.6, 1.0 Hz H-5), 3.44 (1H, pseudo t, *J* 9.2, 9.2 Hz, H-2), 3.35–3.30 (2H, m, H-3, H-4); ^{13}C NMR (CD_3OD): δ (ppm) 173.6 (*C*S), 130.7 (2), 130.5, 129.1, 128.2 (2) (aromatics), 91.4 (C-1), 78.6, 76.5, 73.9, 71.8 (C-2–C-5), 68.4 (C-6). Anal. Calcd for $C_{13}H_{17}ClN_2O_5$ (348.81): C, 40.77; H, 4.91; N, 8.03; S, 9.19. Found: C, 40.55; H, 5.18; N, 8.21; S, 9.01.

3.4.21. *N*-(β-D-Glucopyranosyl)-*N*′-(4-fluorophenyl)thiourea (10f). From **8** (0.20 g, 0.80 mmol) and 4-fluorophenyl isothiocyanate (0.12 mL, 0.82 mmol) or from **12f** (0.15 g, 0.30 mmol) according to General procedures **I** and **III**, respectively. Purified by column chromatography (4:1 $CHCl_3$–MeOH). Yield: 0.13 g (20%) from **8** or 0.09 g (97%) from **12f** yellow crystalline product. Mp: 120–122 °C; $[\alpha]_D$ −182 (*c* 0.08, water); ^1H NMR (D_2O): δ (ppm) 7.26 (d, 2H, *J* 7.9 Hz, aromatics), 7.14 (d, 2H, *J* 7.9 Hz, aromatics), 5.49 (1H, d, *J* 9.2 Hz, H-1), 3.84 (1H, dd, *J* 11.9, 1.0 Hz, H-6), 3.81 (1H, dd, *J* 11.9, 5.3 Hz, H-6′), 3.70 (1H, ddd, *J* 9.2, 5.3, 1.0 Hz H-5), 3.67 (1H, pseudo t, *J* 9.2, 9.2 Hz H-2), 3.54–3.48 (2H, m, H-3, H-4); ^{13}C NMR (D_2O): δ (ppm) 182.2 (*C*S), 162.0 (d, *C*F, *J* 245.3 Hz), 129.3 (2) 116.9, 116.7, 111.9 (aromatics), 78.0 (C-1), 77.9, 77.1, 72.6, 69.8 (C-2–C-5), 61.2 (C-6). Anal. Calcd for $C_{13}H_{17}FN_2O_5S$ (332.35): C, 46.98; H, 5.16; N, 8.43; S, 9.65. Found: C, 46.75; H, 5.38; N, 8.31; S, 9.45.

3.4.22. *N*-(β-D-Glucopyranosyl)-*N*′-(4-methoxyphenyl)-thiourea (10i). From **12i** (0.81 g, 1.58 mmol) according to General procedure **III**. Purified by column chromatography (1:1 $CHCl_3$–MeOH) to yield 0.23 g (44%) pale yellow crystalline product. Mp: 119–121 °C; $[\alpha]_D$ −109 (*c* 0.24, water); ^1H NMR (D_2O): δ (ppm) 7.15 (d, 2H, *J* 7.9 Hz, aromatics), 6.89 (d, 2H, *J* 7.9 Hz, aromatics), 5.48 (1H, d, *J* 9.2 Hz, H-1), 3.82 (1H, dd, *J* 11.9, 1.0 Hz, H-6), 3.67 (1H, dd, *J* 11.9, 5.3 Hz, H-6′), 3.47 (1H, ddd, *J* 9.2, 5.3, 1.0 Hz H-5), 3.52 (1H, pseudo t, *J* 9.2, 9.2 Hz, H-2), 3.41–3.39 (2H, m, H-3, H-4); ^{13}C NMR (D_2O): δ (ppm) 180.2 (*C*S), 128.5 (3), 127.6, 115.2 (2) (aromatics), 83.1 (C-1), 77.9, 77.1, 72.6, 69.8 (C-2–C-5), 61.2 (C-6) 56.1 (O*C*H_3). Anal. Calcd for $C_{14}H_{20}N_2O_6S$ (344.39): C, 48.83; H, 5.85; N, 8.13; S, 9.31. Found: C, 48.62; H, 5.58; N, 8.26; S, 9.05.

3.4.23. *N*-(β-D-Glucopyranosyl)-*N*′-(4-trifluoromethyl-phenyl)thiourea (10k). From **12k** (0.15 g, 0.26 mmol) according to General procedure **III**. Purified by column chromatography (1:1 $CHCl_3$–MeOH) to yield 0.10 g (98%) pale yellow crystalline product. Mp: 190–192 °C; $[\alpha]_D$ −57 (*c* 0.14, water); ^1H NMR (D_2O): δ (ppm) 7.90 (2H, d, *J* 7.9 Hz, ArH), 7.70 (2H, d, *J* 7.9 Hz, ArH), 5.22 (1H, d, *J* 9.2 Hz, H-1), 3.83 (1H, dd, *J* 13.2, 1.5 Hz, H-6), 3.66 (1H, dd, *J* 13.2, 4.0 Hz, H-6′), 3.48–3.37 (4H, m, H-2, H-3, H-4, H-5); ^{13}C NMR (D_2O): δ (ppm) 174.7 (*C*S), 140.3, 132.3 (q, *J* 31.9 Hz, *C*CF_3), 129.6 (2), 125.7 (2) (aromatics), 124.5 (q, *J* 272.9 Hz *C*F_3), 82.7 (C-1), 73.9, 72.7, 70.3, 68.1 (C-2–C-5), 61.5 (C-6). Anal. Calcd for $C_{14}H_{17}F_3N_2O_5S$ (382.36): C, 43.98; H, 4.48; N, 7.33; S, 8.39. Found: C, 43.75; H, 4.38; N, 7.51; S, 8.45.

3.4.24. *N*-(β-D-Glucopyranosyl)-*N*′-phenyl selenourea (11). β-D-Glucopyranosylammonium carbamate **8** was suspended in dry pyridine (0.20 g, 0.83 mmol/8 mL) containing molecular sieves (3 Å). To the suspension (0.15 g, 0.83 mmol), phenyl-isoselenocyanate was added and the mixture was stirred at rt in the dark for 1 day under argon atmosphere (TLC, 4:1 $CHCl_3$–MeOH). Then, the mixture was filtered over a Celite pad and the solvent evaporated. The crude product was purified by column chromatography (4:1 $CHCl_3$–MeOH) to yield 0.15 g (65%) red oil, R_f 0.84 (1:1 $CHCl_3$–MeOH); $[\alpha]_D$ −23 (*c* 0.022, Me_2SO) (lit.[28] $[\alpha]_D$ −19 (*c* 1.4, MeOH)); ^1H NMR (D_2O): δ (ppm) 7.43–7.23 (4H, d, *J* 7.9 Hz, ArH), 5.59 (1H, d, *J* 9.2 Hz, H-1), 3.83 (1H, dd, *J* 11.9, 1.0 Hz, H-6), 3.79 (1H, dd, *J* 11.9, 6.6 Hz, H-6′) 3.69–3.36 (4H, m, H-2, H-3, H-4, H-5); ^{13}C NMR (D_2O): δ (ppm) 181.6 (*C*Se), 149.7, 133.1, 129.5, 127.8, 126.2, 125.1 (aromatics), 87.5 (C-1), 78.1, 77.2, 72.5, 69.8 (C-2–C-5), 61.2 (C-6). ESIMS: *m*/*z* 385.03 ($[M+Na]^+$), $C_{13}H_{18}N_2NaO_5Se$.

3.4.25. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-phenyl thiourea (12a). From **5** (0.50 g, 1.44 mmol) and phenyl isothiocyanate (0.26 mL, 1.5 equiv) according to General procedure **II**. Purified by column chromatography (1:1 EtOAc–hexane) to yield 0.47 g (68%) white crystalline product. Mp: 131–133 °C (lit.[29] mp: 135 °C), $[\alpha]_D$ −19 (*c* 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 9.08 (1H, s, NH), 7.48–7.18 (5H, m, aromatics), 6.90 (1H, d, *J* 6.6 Hz, NH), 5.86 (1H, pseudo t, *J* 9.2, 9.2 Hz), 5.35 (1H, pseudo t, *J* 10.5, 9.2 Hz), 5.03 (1H, pseudo t, *J* 10.5, 9.2 Hz), 4.95 (1H, pseudo t, *J* 9.2, 9.2 Hz), (H-1, H-2, H-3, H-4), 4.32 (1H, dd, *J* 13.2, 4.0 Hz, H-6), 4.08 (1H, dd, *J* 13.2, 1.2 Hz, H-6′), 3.86 (1H, ddd, *J* 9.2, 4.0, 1.2 Hz, H-5), 2.06, 2.04, 2.01, 1.99 (4 × 3H, 4s, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 181.7 (*C*S), 170.5, 170.5, 169.6, 169.4 (*C*O), 135.6, 129.5, 129.5, 127.1, 124.9, 124.9, (aromatics), 82.5 (C-1), 73.1, 72.5, 70.1, 67.9 (C-2–C-5), 61.4 (C-6), 20.4, 20.3 (3) (CH_3). Anal. Calcd for $C_{21}H_{26}N_2O_9S$ (482.51): C, 52.28; H, 5.43; N, 5.81; S, 6.65. Found: C, 52.20; H, 5.35; N, 5.90; S, 6.71.

3.4.26. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(2-chlorophenyl)thiourea (12b). From **5** (0.50 g, 1.44 mmol) and 2-chlorophenyl isothiocyanate (0.37 mL, 1.5 equiv) according to General procedure **II**. Purified by column chromatography (2:3 EtOAc–hexane) to yield 0.59 g (79%) white crystalline product. Mp: 144–146 °C; $[\alpha]_D$ +48, (*c* 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.14 (1H, s, NH), 7.51–7.23 (4H, m, aromatics), 6.71 (1H, d, *J* 9.2 Hz, NH), 5.76 (1H, t, *J*

9.2, 9.2 Hz), 5.35 (1H, pseudo t, *J* 10.5, 9.2 Hz), 5.05 (1H, t, *J* 10.5, 9.2 Hz), 4.90 (1H, t, *J* 9.2, 9.2 Hz), (H-1, H-2, H-3, H-4), 4.33 (1H, dd, *J* 13.2, 4.0 Hz, H-6), 4.10 (1H, dd, *J* 13.2, 1.2 Hz, H-6′), 3.87 (1H, ddd, *J* 9.2, 4.0, 1.2 Hz, H-5), 2.06, 2.05, 2.03, 2.00 (4 × 3H, 4s, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 182.5 (*C*S), 171.1, 170.6, 169.8, 169.6 (*C*O), 132.8, 130.5, 130.4, 129.1, 128.1, 128.0 (aromatics), 83.1 (C-1), 73.5, 72.5, 70.4, 68.2 (C-2–C-5), 61.6 (C-6), 20.7, 20.6, 20.5 (2) (CH_3). Anal. Calcd for $C_{21}H_{25}ClN_2O_9S$ (516.96): C, 48.79; H, 4.87; N, 5.42; S, 6.20. Found: C, 48.65; H, 5.02; N, 5.22; S, 6.07.

3.4.27. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopranosyl)-*N*′-(4-fluorophenyl)thiourea (12f). From **5** (0.50 g, 1.44 mmol) and 4-fluorophenyl isothiocyanate (0.22 mL, 2.16 mmol) according to General procedure **II**. Purified by column chromatography (1:1 EtOAc–hexane) to yield 0.67 g (92%) white crystalline product. Mp: 191–193 °C; $[\alpha]_D$ +18 (*c* 0.29, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.63 (1H, s, NH), 7.20 (2H, d, *J* 7.9 Hz, aromatics), 7.12 (2H, d, *J* 7.9 Hz, aromatics), 6.68 (1H, d, *J* 9.2 Hz, NH), 5.81 (1H, t, *J* 9.2, 9.2 Hz), 5.36 (1H, t, *J* 9.2, 9.2 Hz), 5.06 (1H, t, *J* 9.2, 9.2 Hz), 4.93 (1H, t, *J* 9.2, 9.2 Hz), (H-1, H-2, H-3, H-4), 4.32 (1H, dd, *J* 11.9, 4.0 Hz, H-6), 4.09 (1H, dd, *J* 11.9, 1.5 Hz, H-6′), 3.86 (1H, ddd, *J* 9.2, 4.0, 1.5 Hz, H-5), 2.07, 2.03, 2.01 (2) (4 × 3H, 4s, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 182.2 (*C*S), 170.9, 170.6, 169.7, 169.4 (*C*O), 162.0 (d, *C*F, *J* 246.1 Hz), 132.1, 127.8, 127.6, 116.7, 116.5 (aromatics), 82.9 (C-1), 73.5, 72.4, 70.4, 68.1 (C-2–C-5), 61.5 (C-6), 20.6 (2), 20.4 (2) (CH_3). Anal. Calcd for $C_{21}H_{25}FN_2O_9S$ (500.50): C, 50.40; H, 5.03; N, 5.60; S, 6.41. Found: C, 50.15; H, 5.33; N, 5.36; S, 6.17.

3.4.28. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4-trifluoromethyl-phenyl)thiourea (12k). From **5** (1.00 g, 2.88 mmol) and 4-trifluoromethylphenyl isothiocyanate (0.46 mL, 2.88 mmol) according to General procedure **II**. Purified by column chromatography (1:1 EtOAc–hexane) to yield 1.81 g (80%) white crystalline product. Mp: 112–114 °C; $[\alpha]_D$ +32 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 11.08 (1H, d, *J* 9.2 Hz, NH), 9.21 (1H, s, NH), 7.99 (2H, d, *J* 7.9 Hz, aromatics), 7.78 (2H, d, *J* 7.9 Hz, aromatics), 5.78 (1H, pseudo t, *J* 9.2, 9.2 Hz), 5.39 (1H, pseudo t, *J* 10.6, 9.2 Hz), 5.20 (1H, pseudo t, *J* 10.6, 9.2 Hz), 5.13 (1H, t, *J* 9.2, 9.2 Hz), (H-1, H-2, H-3, H-4), 4.32 (1H, dd, *J* 13.2, 5.3 Hz, H-6), 4.14 (1H, dd, *J* 13.2, 1.2 Hz, H-6′), 3.87 (1H, ddd, *J* 9.2, 5.3, 1.2 Hz, H-5), 2.07, 2.04, 2.03, 1.99 (4 × 3H, 4s, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 182.4 (*C*S), 170.6, 170.1, 170.0, 169.9 (*C*O), 134.8 (q, *C*-CF_3, *J* 31.7 Hz), 128.2 (2), 126.1 (2), 121.7 (aromatics), 123.2 (q, *C*F_3, *J* 272.9 Hz), 77.8 (C-1), 77.8, 77.2, 72.9, 69.9 (C-2–C-5), 61.2 (C-6), 20.7, 20.5 (3) (CH_3). Anal. Calcd for $C_{22}H_{25}F_3N_2O_9S$ (550.51): C, 48.00; H, 4.58; N, 5.09; S, 5.82. Found: C, 48.22; H, 4.78; N, 5.36; S, 5.47.

3.4.29. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4-methoxy-phenyl)thiourea (12i). From **5** (1.00 g, 2.88 mmol) and 4-methoxy-phenylisocyanate (0.33 mL, 4.32 mmol) according to General procedure **II**. Purified by column chromatography (1:1 EtOAc–hexane) to yield 0.81 g (57%) colourless oil, R_f 0.27 (1:1 EtOAc–hexane); $[\alpha]_D$ +14 (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.65 (1H, s, NH), 7.12 (2H, d, *J* 7.9 Hz, aromatics), 6.93 (2H, d, *J* 7.9 Hz, aromatics), 6.57 (1H, d, *J* 9.2 Hz, NH), 5.83 (1H, pseudo t, *J* 9.2, 9.2 Hz), 5.34 (1H, pseudo t, *J* 9.2, 9.2 Hz), 5.02 (1H, pseudo t, *J* 9.2, 9.2 Hz), 4.91 (1H, pseudo t, *J* 9.2, 9.2 Hz), (H-1, H-2, H-3, H-4), 4.30 (1H, dd, *J* 11.9, 4.0 Hz, H-6), 4.10 (1H, dd, *J* 11.9, 2.4 Hz, H-6′), 3.84–3.80 (4H, m, H-5, OCH_3), 2.05, 2.04, 2.02, 1.99 (4 × 3H, 4s, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) 182.1 (*C*S), 171.0, 170.5, 169.6, 169.4 (*C*O), 127.3 (3), 126.7, 114.8 (2) (aromatics), 82.8 (C-1), 73.3, 72.5, 70.3, 68.0 (C-2–C-5), 60.2 (C-6), 55.3 (O*C*H_3), 20.8, 20.4, 20.3 (2) (CH_3). Anal. Calcd for $C_{22}H_{28}N_2O_{10}S$ (512.54): C, 51.56; H, 5.51; N, 5.47; S, 6.26. Found: C, 51.35; H, 5.19; N, 5.28; S, 6.09.

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