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A convenient synthesis of novel pyranosyl homo-C-nucleosides and their antidiabetic activities

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ABSTRACT

A series of pyranosyl homo-C-nucleosides have been synthesized by reaction of butenonyl C-glycosides (**5a**–**5j**, and **8**) and cyanoacetamide in presence of *t*-BuOK followed by further modifications. The reaction proceeds by Michael addition of cyanoacetamide to the butenonyl C-glycosides and subsequent dehydrative cyclization and oxidative aromatization to give glycosylmethyl pyridones (**6a**–**6j**, **7a**–**7j**, **9,** and **10**). The glycosylmethyl pyridones (**6a**–**6e**) on reaction with $POCl_3$ under reflux gave respective glycosylmethyl pyridines (**11a**–**11e** and **12a**–**12e**) in good yields. The synthesized compounds were screened for their in vitro α-glucosidase, glucose-6-phosphatase and glycogen phosphorylase inhibitory activities. One of the pyridylmethyl homo-C-nucleoside, compound **11d**, displayed 52% inhibition of glucose-6-phosphatase as compared to the standard drug sodium orthovanadate while compound **12a** showed a significant antihyperglycemic effect of 17.1% in the diabetic rats as compared to the standard drug metformin.

1. Introduction

The synthetic interest in nucleoside analogs is due to their capability to interfere with functioning of enzymes, which renders them antiviral, anticancer, antibacterial, insecticidal, fungicidal, and herbicidal, among other known biological activities. The demand and utility of nucleosides and their analogs is continuously increasing due to the spread of HIV, hepatitis B, herpes simplex and other viruses.[1–6] The homo-C-nucleosides, which have a $–CH_2–$ linker between the sugar and heterocyclic moiety are also of great biological significance and are potent chemotherapeutic agents or enzyme inhibitors.[7,8] Further, among the α- and β-anomeric nucleosides, the latter have extensively been studied due to their natural occurrence and numerous biological activities, while the α-nucleosides have received little attention.[9–11]

Diabetes mellitus commonly known as diabetes is a group of metabolic diseases characterized by abnormally high levels of plasma glucose. Inhibition of glycosidases, glucose-6-phosphatase and glycogen phosphorylase are known to reduce the hyperglycemia. Very recently renal SGLT2 (sodium-dependant glucose co-transporter), located on the surface of the epithelial cells and lining the S1 segment of the proximal tubule, is reported to facilitate >90% of renal glucose re-absorption.[12,13] Selective inhibition of SGLT2, therefore, results in preventing glucose re-absorption, which may lead to new antidiabetic drugs with no gastrointestinal side effects. Nucleoside analogues and pyridine-based compounds are known to inhibit the above glycosidases and result in limiting hyperglycemia. Several aryl C-glycosides (dapagliflozin, sergliflozin, LX-4211) and many other heteroaromatic-C-glycosides such as compound **4** are potent SGLT2 inhibitors[13–15] (Fig. 1) and possess very good antidiabetic activities in vivo. The dapagliflozin is in phase III clinical trial for the treatment of diabetes.[14] Further, certain nucleosides and pyridine derivatives are known to inhibit hepatic glycosidases and possess a hypoglycemic effect.[16,17]

A number of methods exist in literature toward the synthesis of aryl β-C-glycosides[18–21] including those clinical candidates for the treatment of diabetes. In general, methods known so far, are based on nucleophilic attack at the anomeric carbon of the sugar, the glycosylidene carbene formation,[22–24] or Wittig-type reaction[25] or substitution of the hydroxyl group at the anomeric carbon with halogen and subsequent reactions such as Reformatsky,[26] Grignard,[27] or free-radical reactions.[28] The methods adopted for the synthesis of antidiabetic aryl β-C-glycosides involve the use of BuLi and restricted reaction conditions. Most of these methods of β-C-glycoside syntheses require a metal-based catalyst and inert atmosphere for successful completion of the reaction. Keeping in mind the above facts and in continuation of our ongoing studies toward the synthesis of β-C-glycosides[29–31] as new antidiabetic agents, we

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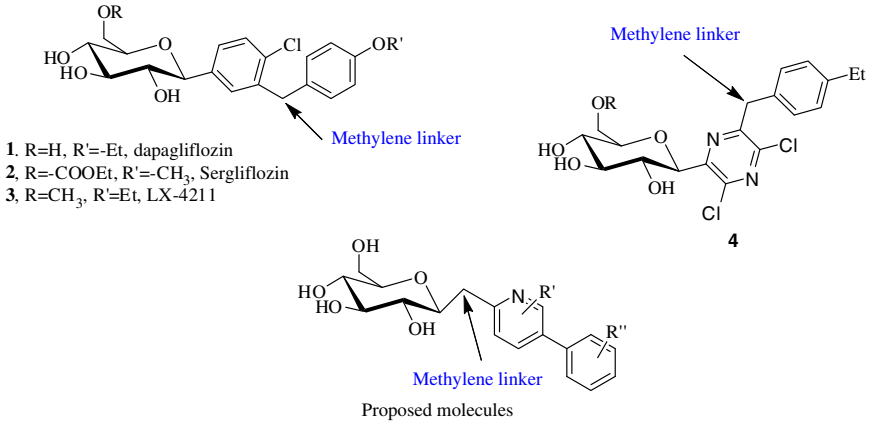


Figure 1. Antidiabetic β-C-glucosides **1–4** in clinical trial and our designed molecules.

were interested in the synthesis of heteroaryl β-C-glycosides as homo-C-nucleoside analogs and evaluating their antidibetic activities.

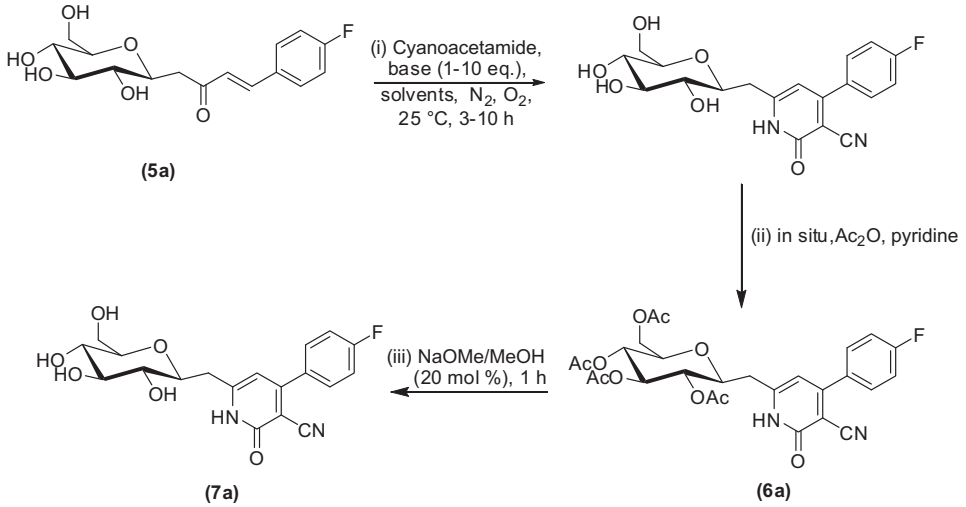
Our method of pyranosyl homo-β-C-nucleoside synthesis involves reaction of the butenonyl C-glycosides with cyanoacetamide followed by further modification of the intermediates. The reaction proceeds by 1,4-conjugate addition (Michael addition) of cyanoacetamide on to the butenonyl C-glycoside to give an intermediate which on dehydrative cyclization and subsequent oxidative aromatization offers the glycopyranosyl methyl pyridine. The latter on refluxing with $POCl_3$ gives the respective pyridylmethyl glycosides. The compounds are evaluated for their antidiabetic potential in vitro. The method adopted in the synthesis is quite simple, eco-friendly, and economical as it involves easily available sugars and reagents.

2. Results and discussion

2.1. Chemistry

The starting butenonyl C-glycosides (**5a–5j**) were prepared from commercially available D-glucose following our method and earlier reported protocols.[29–32] To optimize the reaction conditions, the reaction of 1 equivalent of (*E*)-1-(β-D-glucopyranosyl)-4-(4′-fluorophenyl)-but-3-en-2-one (**5a**) with cyanoacetamide (1–10 equiv) in different organic solvents, under the influence of various inorganic and organic bases, and under an N_2 atmosphere at ambient temperature for 30 min (until the disappearance of starting butenoyl C-glycoside) was carried out. The reaction mixture was brought under the influence of an O_2 atmosphere to carry out oxidative aromatization. The reaction mixture was subsequently acetylated with Ac_2O/pyridine (Scheme 1, Table 1) in order to facilitate the isolation of the pure product by column chromatography. Four equivalents of *t*-BuOK in DMSO at ambient temperature proved to be the most optimum reaction conditions (entry 6) followed by in situ acetylation of the reaction mixture to give the desired compound 3-cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (**6a**) in 53% yield (Table 1). It is appropriate to mention here that many other minor products observed on TLC plate could not be isolated in pure forms despite our several attempts.

The structure of 3-cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (**6a**) was established on the basis of its spectroscopic data and analysis. The IR spectrum exhibited absorption bands at 3467 cm^{-1}, 1662 cm^{-1} and 1753 cm^{-1} indicating the presence of NH and N–C=O groups of the pyridone ring and carbonyl of the sugar acetyl groups, while an absorption band at 2227 cm^{-1} indicated the presence of cyano (CN) group. ESIMS of the compound displayed *m/z* 559 $[M+H]^+$ peak. In the ^1H NMR spectrum the exchangeable



Scheme 1. Optimization of reaction conditions with compound **5a** and cyanoacetamide.

Table 1
Optimization of reaction between (*E*)-1-(β-D-glucopyranosyl)-4-(4′-fluorophenyl)but-3-en-2-one (**5a**) and cyanoacetamide

Entry	Base	Solvent	Reaction time (h)	Isolated yield (%)
1	*t*-BuOK[a]	THF	10	NR[b]
2	*t*-BuOK[a]	DMF	10	Complex reaction mixture[c]
3	*t*-BuOK[a]	MeOH	10	20
4	*t*-BuOK[a]	CH_2Cl_2	10	NR[b]
5	NaOMe[a]	MeOH	10	15
6	*t*-BuOK[a]	DMSO	3	53
7	Et_3N[a]	DMSO	10	NR[b]
8	DBU	DMSO	10	NR[b]
9	Cs_2CO_3[a]	DMSO	10	NR[b]
10	LiOH[a]	DMSO	10	Complex reaction mixture[c]
11	K_2CO_3[a]	DMSO	10	5
12	*t*-BuOK (1 equiv)	DMSO	10	10
13	*t*-BuOK (3 equiv)	DMSO	10	25
14	*t*-BuOK (10 equiv)	DMSO	3	50

[a] 4 equiv.
[b] NR = No reaction.
[c] Reaction mixture showed a streak on the TLC plate and no desired product was detected.

proton (*NH*) and H-5 of pyridone ring were observed at δ 12.5 (br s) and 6.38 (s), respectively, while the aromatic protons were observed as two multiplets in the range of δ 7.73–7.68 and δ 7.44–7.38. The H-2″, H-3″ and H-4″ sugar ring appeared as a three distinct triplets at δ 5.23 (t, 1H, *J* = 9.45 Hz), δ 4.87 (t, 1H, *J* = 9.72 Hz), δ 4.79 (t, 1H, *J* = 9.57 Hz), respectively. The H-1″ and H-6a″ of the sugar moiety were observed as multiplet in the range of δ 4.12–4.05 while H-6b″ and H-5″ were visible as multiplet in the range of δ 3.97–3.91. The protons of the four sugar acetyl groups were visible as singlets at δ 2.03, δ 2.02, δ 2.01, and δ 1.98. In ^{13}C NMR spectrum the signals for the acetyl carbonyl carbons appeared at δ 170.5, 170.2, 170.1, and 169.9 while C≡N carbon signal was visible at δ 116.2. The aromatic and heteroaromatic carbons were observed in the range of δ 161.7–99.9, while the C-1″, C-2″, C-3″, C-4″, and C-5″ of the puranose sugar appeared at δ 74.7, 73.7, 72.7, 71.7, and δ 68.7, respectively. The two methylene carbons OCH_2 and CH_2 were observed at δ 62.4 and δ 39.9. The four methyl carbons of the acetyl groups were observed at δ 20.8, 20.7, 20.6, and 20.5.

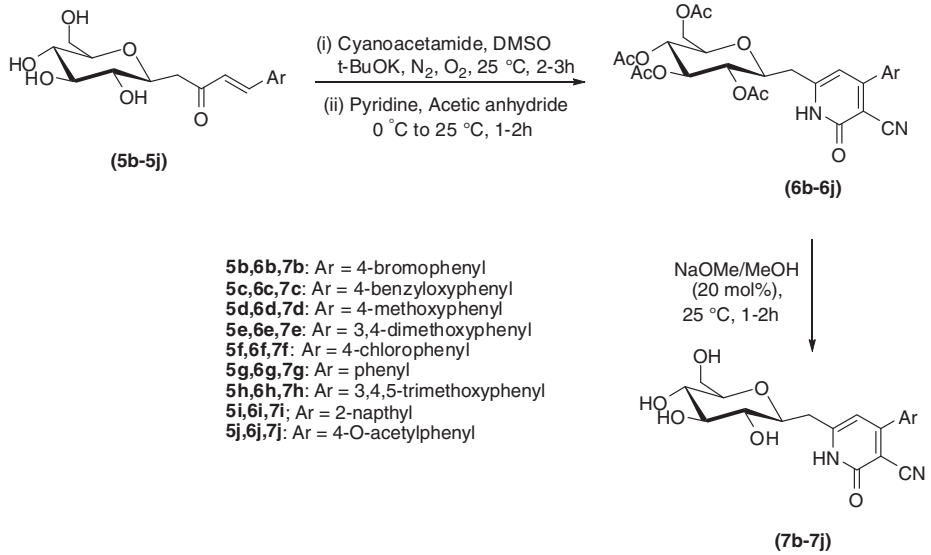
Once the reaction conditions were optimized, the scope of this reaction was studied with different substrates. Thus the reaction of (*E*)-1-(β-D-glucopyranosyl)-4-(aryl)but-3-en-2-ones (**5b–5j**) separately with cyanoacetamide was carried out (Scheme 2) under the above optimized reaction conditions to give the respective 3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridones (**6b–6j**) in moderate to good yields (Scheme 2). Subsequently, deacetylation of compounds **6b–6j** with NaOMe/MeOH afforded the respective 3-cyano-4-phenyl-6-[(β-D-glucopyranosyl) methyl]pyridones (**7b–7j**) in good yields. The structures of all these compounds were in accordance with their spectroscopic data.

Further, in order to enhance the scope of this reaction, a disaccharide derivative, (*E*)-1-(2′,3′,6′,2″,3″,4″,6″-hepta-*O*-acetyl-β-cellobiosyl)-4-(2-napthyl)but-3-en-2-one (**8**),[29] was reacted with cyanoacetamide to give the respective 3-cyano-4-(2′-napthyl)-6-[(2″,3″,6″,2‴,3‴,4‴,6‴-hepta-*O*-acetyl-β-cellobiosyl)methyl]pyridone (**9**) in 54% yield. The deacetylation of the acetyl groups in compound **9** afforded to 3-cyano-4-(2′-napthyl)-6-[(β-cellobiosyl)methyl] pyridone (**10**) in 76% yield (Scheme 3).

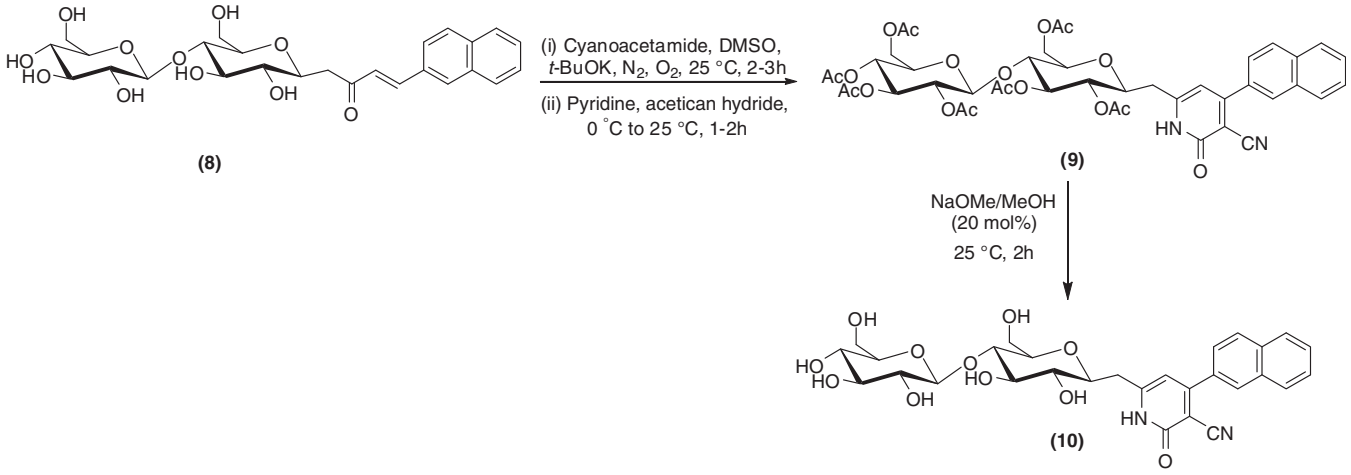
Finally, in order to create structural diversity in the heteroaromatic ring, a few selected 3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridones (**6a–6e**) were reacted with phosphorous oxychloride ($POCl_3$) at 100 °C to afford the respective 2-chloro-3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl] pyridines (**11a–11e**) in good yields (Scheme 4). Deacetylation of the above compounds (**11a–11e**) with NaOMe/MeOH gave respective 2-chloro-3-cyano-4-(aryl)-6-[(β-D-glucopyranosyl)methyl]pyridines (**12a–12e**) in quantitative yields (Scheme 4). The structures of all these compounds were in full agreement with their spectroscopic data.

2.2. Biology

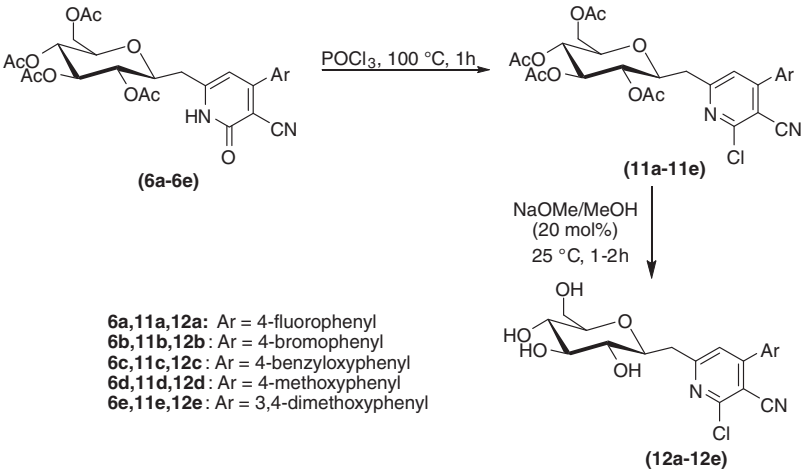
The above-synthesized compounds were screened against the α-glucosidase enzyme, glucose-6-phosphatase and glycogen phosphorylase.[33–36] The compounds dissolved in DMSO were evaluated for their inhibitory potential against the above three enzymes at a



Scheme 2. Synthesis of glycosylmethylpyridones **6b–6j** and **7b–7j**.



Scheme 3. Synthesis of cellobiosylmethylpyridones **9** and **10**.



Scheme 4. Synthesis of glycosylmethylpyridines **11a**–**11e** and **12a**–**12e**.

concentration of 100 μM. Percentage inhibition was calculated with respect to control. The enzyme inhibitory data of screened compounds are shown in Table 2.

As evident from activity results (Table 2) among all the compounds screened, compound **11d** with a 4-methoxyphenyl substituent exhibits good inhibitory activity (52.2% inhibition), while compounds **6h**, **6c**, **7f,** and **12c** display inhibition in the range of 43.3–46% against glucose-6-phosphatase. The compounds **11b** and **12b** exhibited moderate inhibitory activity with 41.3% and 41.8% inhibition against glycogen phosphorylase, respectively.

Out of all the compounds screened above, a few exhibited moderate inhibitory potential for the three enzymes as compared to standard control. Out of curiosity one of the compounds **12a**, with a 4-flurophenyl substituent inhibiting all the three enzymes in vitro was selected for in vivo evaluation in a streptozotocin (STZ) induced diabetic rat model. The in vivo results are shown in Table 3 and Figure 2. It is evident that compound **12a** caused a significant decline by 16.3% (p <0.05 in 5 h) and 17.1% (p <0.05 in 24 h), respectively, in the hyperglycemia of the post sucrose-loaded diabetic rats at 100 mg/kg. The standard drug metformin at the same dose level (100 mg/kg) showed a blood glucose lowering effect of 26.9% (p <0.01 after 5 h) and 21.4% (p <0.01 after 24 h), respectively. The effect of compound **12a**, the standard drug metformin, and a control (no drug) at different time intervals is also shown in Figure 2.

3. Conclusions

In conclusion, we have developed a quite simple and economical method for the synthesis of pyranosyl homo-C-nucleosides exclusively with the β-configuration. The method basically involves Michael addition, dehydrative cyclization and oxidative aromatization reactions. A few of the compounds displayed moderate inhibition of either of α-glucosidase, glucose-6-phosphatase, or glycogen phosphorylase. However, one of the compounds showed antihyperglycemic effect in STZ-induced diabetic rats. These compounds are being selectively exploited for diversification to create a new class of compounds with chemotherapeutic potential.

4. Experimental section

4.1. Chemistry

Commercially available reagent grade chemicals were used as received. All reactions were monitored by TLC on E. Merck Kieselgel 60 F_{254} with detection by UV light or by spraying a 20% $KMnO_4$ aq solution and/or spraying a 4% H_2SO_4 ethanolic solution followed by heating. Column chromatography was performed on silica gel (60–120 mesh E. Merck). IR spectra were recorded as thin films or in KBr solution with a Perkin–Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. The ^1H (200 MHz and

Table 2
α-Glucosidase, glucose-6-phosphatase, and glycogen phosphorylase inhibitory activity of synthesized compounds

S. No.	Compounds	% Activity (100 μM)		
		α-Glucosidase inhibition	Glucose-6-phosphatase inhibition	Glycogen phosphorylase inhibition
1	**6a**	+11.4	−11.9	−26.9
2	**6b**	−13.0	−13.7	−28.7
3	**6c**	+15.6	−45.0	+17.7
4	**6d**	−8.33	+19.1	+0.98
5	**6e**	−13.7	+7.4	+6.1
6	**6f**	−7.50	−6.38	−18.6
7	**6g**	+29.0	−19.4	+20.6
8	**6h**	+12.5	−46.0	−2.94
9	**6i**	+3.30	−21.3	−36.3
10	**6j**	−8.6	+4.9	+14.6
11	**7a**	+3.30	−16.4	−26.1
12	**7b**	−11.2	−21.5	−37.4
13	**7c**	0.0	+4.4	+8.9
14	**7d**	−25.0	0.0	−2.95
15	**7e**	−14.4	−8.03	−18.6
16	**7f**	−8.40	−42.6	−36.3
17	**7g**	+20.3	−25.5	+1.96
18	**7h**	−4.40	−23.4	−25.3
19	**7i**	−20.7	+6.40	+12.8
20	**7j**	−3.3	+5.0	+6.9
21	**9**	−29.7	+5.8	+9.9
22	**10**	0.0	+8.0	+12.4
23	**11a**	−30.4	+29.8	+16.5
24	**11b**	−4.90	−31.3	−41.3
25	**11c**	−7.43	−29.5	−26.9
26	**11d**	−0.86	−52.2	+11.3
27	**11e**	−9.42	−26.9	−32.2
28	**12a**	−22.1	−34.3	−16.5
29	**12b**	+5.43	−35.8	−41.8
30	**12c**	−7.80	−43.3	−6.70
31	**12d**	−9.50	−2.90	+2.61
32	**12e**	−15.5	−17.9	+18.3
33	Acarbose	−39.0	—	—
34	Sodium-*o*-vandate	—	−39.0	—

Table 3
Antihyperglycemic activity of compound **12a** and the standard drug metformin in sucrose-challenged STZ-induced diabetic rats

Compound	Dose (mg/kg)	% Antihyperglycemic activity	
		5 h	24 h
12a	100	16.3[a]	17.1[a]
Metformin	100	26.9[b]	21.4[b]

[a] p <0.05.
[b] p <0.01.

300 MHz) and ^{13}C NMR (50 or 75.5 MHz) spectra were recorded on a Bruker DRX-300 instrument in DMSO, CD_3OD, and $CDCl_3$. Chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as internal reference unless otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet), ddd (doublet of double of doublet), br s (broad singlet); J in hertz. Mass spectra were taken on a JMS-100 TLC (Accutof) atmospheric pressure ionization time-of-flight mass spectrometer (Jeol, Tokyo, Japan) fitted with a DART ion source operated in positive-ion mode. Optical rotations were measured in a 1.0 dm tube with a Rudolph Autopol III polarimeter in MeOH or $CHCl_3$. Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer.

4.1.1. General procedure for the preparation of compounds 6a–6j

To a stirring solution of one of the selected (*E*)-1-(β-D-glucopyranosyl)-4-(aryl)but-3-en-2-ones (**5a–5j**) (3.04 mmol) and cyanoacetamide (3.04 mmol) in DMSO (10 mL), was added

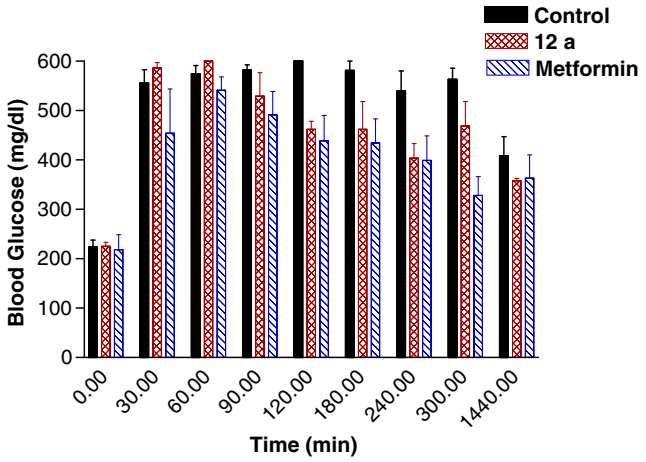


Figure 2. Antihyperglycemic effect of compound **12a** and standard drug metformin on the blood glucose levels of streptozotocin-induced diabetic rats post sucrose load at various time intervals.

4 equiv of *t*-BuOK (12.2 mmol) under nitrogen atmosphere at room temperature. After stirring for 30 min, the N_2 atmosphere was replaced by an O_2 atmosphere, and the reaction was further stirred until the disappearance of starting material was confirmed (TLC). The reaction mixture was then brought to 0 °C and subsequently 50 mL of pyridine was added. To the stirring reaction mixture Ac_2O (24.3 mmol) was slowly added, and stirring was continued until completion of the reaction (TLC). The reaction mixture was extracted with EtOAc/water, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude mass. The latter was purified by column chromatography on silica gel (60–120 mesh) using MeOH–$CHCl_3$ as eluant to give corresponding 3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridones (**6a–6j**).

4.1.1.1. 3-Cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6a). Compound **6a** was obtained by the reaction of (*E*)-1-(β-D-glucopyranosyl)-4-(4′-fluorophenyl)but-3-en-2-one **5a** (0.58 g, 1.78 mmol), cyanoacetamide (0.15 g, 1.78 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL), and Ac_2O (1.0 mL, 10.7 mmol) as white solid (0.52 g, yield 53%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −63.2 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3467 (NH stretching), 2227 (C≡N stretching), 1753 (O–C=O stretching), 1662 cm^{-1} (N–C=O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.5 (br s, 1H, NH), 7.73–7.68 (m, 2H, ArH), 7.44–7.38 (m, 2H, ArH), 6.38 (s, 1H, H-5), 5.23 (t, 1H, J = 9.45 Hz, CH), 4.87 (t, 1H, J = 9.72 Hz, CH), 4.79 (t, 1H, J = 9.57 Hz, CH), 4.12–4.05 (m, 2H, H-1″, H-6″a), 3.97–3.91 (m, 2H, H-6″b, H-5″), 2.91 (dd, 1H, J_1 = 3.0 Hz, J_2 = 15.0 Hz, –C*H*aH–), 2.72 (dd, 1H, J = 5.9 Hz, –C*H*bH–), 2.03, 2.02, 2.01, 1.98 (each singlet, 12H, 4 × –OCOCH$_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 170.5, 170.2, 170.1, 169.9 (OCOCH$_3$), 161.7, 159.3, 152.0, 131.0 (ArCH), 130.9 (ArCH), 116.8 (ArCH), 116.5 (ArCH), 116.2 (C≡N), 107.5, 99.9, 74.7, 73.7, 72.7, 71.7, 68.7, 62.4 (OCH$_2$), 39.9 (CH$_2$), 20.8, 20.7, 20.6, 20.5 (CH$_3$); ESIMS: *m/z* 559 (M+H)$^+$; Anal. Calcd for $C_{27}H_{27}FN_2O_{10}$: C, 58.06; H, 4.87; N, 5.02. Found: C, 58.10; H, 4.93; N, 5.05.

4.1.1.2. 4-(4′-Bromophenyl)-3-cyano-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6b). Compound **6b** was obtained by the reaction of compound **5b** (0.69 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL), and Ac_2O (1.0 mL, 10.70 mmol) as a white solid

(0.6 g, yield 54%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −118.36 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3466 (NH stretching), 2225 (C≡N stretching), 1753 (O–C=O stretching), 1660 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 12.5 (br s, 1H, NH), 7.61–7.56 (m, 2H, ArH), 7.48–7.44 (m, 2H, ArH), 6.20 (s, 1H, H-5), 5.17 (t, 1H, *J* = 9.3 Hz, CH), 5.01–4.87 (m, 2H, 2 × CH), 4.10–4.07 (m, 2H, H-1″, H-6″a), 3.84–3.83 (m, 1H, H-6″b), 3.68–3.67 (m, 1H, H-5″), 2.84–2.75 (m, 2H, $-CH_2-$), 2.01, 1.97, 1.94, 1.89 (each singlet, 12H, 4 × $-OCOCH_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 170.4, 170.3, 170.3, 169.8 ($OCOCH_3$), 162.0, 149.7, 132.5 (ArH), 130.9, 130.0, 129.3, 128.4 (ArH), 76.0, 75.9, 74.1, 71.7, 68.7 (OCH_2), 35.9 (CH_2), 21.0, 20.9 (CH_3); ESIMS: *m/z* 621 $(M+2)^+$; Anal. Calcd for $C_{27}H_{27}BrN_2O_{10}$: C, 52.35; H, 4.39; N, 4.52. Found: C, 52.30; H, 4.41; N, 4.57.

4.1.1.3. 4-(4′-Benzyloxyphenyl)-3-cyano-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6c). Compound **6c** was obtained by the reaction of compound **5c** (0.74 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL), and Ac_2O (1.0 mL, 10.7 mmol) as a white solid (0.6 g, yield 52%); mp 215–217 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ +25.68 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3472 (NH stretching), 2225 (C≡N stretching), 1753 (O–C=O stretching), 1660 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 12.3 (br s, 1H, NH), 7.62–7.60 (m, 5H, ArH), 7.44–7.33 (m, 3H, ArH), 7.09–7.06 (m, 1H, ArH), 6.24 (s, 1H, H-5), 5.23–5.13 (m, 3H, OCH_2, and CH), 4.97 (t, 1H, *J* = 9.8 Hz, CH), 4.87 (t, 1H, *J* = 9.2 Hz, CH), 4.19–4.04 (m, 2H, H-1″, H-6″a), 3.85–3.82 (m, 2H, H-6″b, H-5″), 2.84–2.58 (m, 2H, CH_2), 2.05, 2.03, 2.02, 2.01 (each singlet 4 × $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 170.4, 170.1, 169.7 ($OCOCH_3$), 163.1, 161.1, 160.2, 149.3, 136.6, 130.2 (ArCH), 129.0, 128.5 (ArCH), 127.8 (ArCH), 116.6 (CN), 115.5 (ArCH), 108.4, 99.4, 74.2, 73.0, 72.6, 71.7, 70.4, 68.7, 62.4 (OCH_2), 35.9 (CH_2), 21.0, 20.9, 20.8 (CH_3); ESIMS: *m/z* 647 $(M+H)^+$; Anal. Calcd for $C_{34}H_{34}N_2O_{11}$: C, 63.15; H, 5.30; N, 4.33. Found: C, 63.19; H, 5.33; N, 4.38.

4.1.1.4. 3-Cyano-4-(4′-methoxyphenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6d). Compound **6d** was obtained by the reaction of compound **5d** (0.60 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.60 g, 7.14 mmol), pyridine (10 mL), and Ac_2O (1.0 mL, 10.70 mmol) as a white solid (0.6 g, yield 60%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ +16.4 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3470 (NH stretching), 2224 (C≡N stretching), 1754 (O–C=O stretching), 1658 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, DMSO) δ = 7.62 (d, 2H, *J* = 8.7 Hz, ArH), 7.02 (d, 2H, *J* = 8.7 Hz, ArH), 6.26 (s, 1H, H-5), 5.24 (t, 1H, *J* = 9.36 Hz, CH), 4.97 (t, 1H, *J* = 9.8 Hz, CH), 4.87 (t, 1H, *J* = 9.5 Hz, CH), 4.18 (dd, 1H, J_1 = 5.6 Hz, J_2 = 12.3 Hz, H-6″a), 4.04 (dd, 1H, J_2 = 10.5 Hz, H-6″b), 3.91—3.87 (m, 4H, H-1″, OCH_3), 3.78–3.73 (m, 1H, H-5″), 2.88 (dd, 1H, J_1 = 2.9 Hz, J_2 = 14.7 Hz, C*Ha*H), 2.75 (dd, 1H, J_1 = 8.5 Hz, J_2 = 14.7 Hz, C*Hb*H), 2.04, 2.01, 1.98, 1.86 (each singlet 4 × $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.1, 174.8, 174.7, 174.5($OCOCH_3$), 167.2, 166.6, 164.7, 155.6, 135.1 (ArCH), 133.5 (ArCH), 122.0 (ArCH), 112.4 (CN), 101.2, 80.1 (CH), 78.8 (CH), 78.2 (CH), 77.3 (CH), 76.8 (CH), 67.5 (OCH_2), 60.7 (OCH_3), 40.4(OCH_2), 25.9 (CH_3), 25.8 (CH_3), 25.6 (CH_3); DART-HRMS: *m/z* calcd for $C_{28}H_{30}N_2O_{11}$ $(M+H)^+$ 571.1931; found: 571.1927; ESIMS: *m/z* 571 $(M+H)^+$; Anal. Calcd for $C_{28}H_{30}N_2O_{11}$: C, 58.94; H, 5.30; N, 4.91. Found: C, 58.90; H, 5.37; N, 4.97.

4.1.1.5. 3-Cyano-4-(3′,4′-dimethoxyphenyl)-6-[(2″,3″,4″,6″tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6e). Compound **6e** was obtained by the reaction of compound **5e** (0.65 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL) and Ac_2O (1.0 mL, 10.70 mmol) as a white solid (0.58 g, yield 54%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ +6.15 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3470 (NH stretching), 2225 (C≡N stretching), 1753 (O–C=O stretching), 1660 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 12.7 (s, 1H, NH), 7.31–7.24 (m, 2H, ArH), 7.00–6.97 (m, 1H, ArH), 6.38 (s, 1H, H-5), 5.29 (t, 1H, *J* = 9.36 Hz, CH), 5.11 (t, 1H, *J* = 9.8 Hz, CH), 5.03 (t, 1H, *J* = 9.6 Hz, CH), 4.19 (d, 2H, *J* = 3.4 Hz, H-6″), 4.05 (m, 1H, H-1″), 3.97 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.83–3.77 (m, 1H, H-5″), 3.03–2.87 (m, 2H, CH_2), 2.09, 2.03, 2.00, 1.97 (each singlet, 12H, 4 × $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.6, 170.1, 170.0, 169.4 ($OCOCH_3$), 163.7, 160.5, 151.4, 149.1, 148.6 (ArCH), 127.8, 121.6 (ArCH), 116.0 (CN), 111.2, 109.3, 75.7 (CH), 75.3 (CH), 73.9 (CH), 71.2 (CH), 68.2 (CH), 61.9 (OCH_2), 56.1 (OCH_3), 56.0 (OCH_3), 35.8 (CH_2), 20.8, 20.5 (CH_3); DART-HRMS: *m/z* calcd for $C_{29}H_{32}N_2O_{12}$ $(M+H)^+$ 601.2033; found: 601.2043; ESIMS: *m/z* 601 $(M+H)^+$; Anal. Calcd for $C_{29}H_{32}N_2O_{12}$: C, 58.00; H, 5.37; N, 4.66. Found: C, 58.05; H, 5.40; N, 4.66.

4.1.1.6. 4-(4′-Chlorophenyl)-3-cyano-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6f). Compound **6f** was obtained by the reaction of compound **5f** (0.61 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL) and Ac_2O (1.0 mL, 10.70 mmol) as a white solid (0.6 g, yield 58%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −11.3 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3472 (NH stretching), 2226 (C≡N stretching), 1752 (O–C=O stretching), 1661 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 12.4 (s, 1H, NH), 7.54 (d, 2H, *J* = 8.5 Hz, ArH), 7.44 (d, 2H, *J* = 8.5 Hz, ArH), 6.19 (s, 1H, H-5), 5.19 (t, 1H, *J* = 9.8 Hz, CH), 5.01 (t, 1H, *J* = 9.8 Hz, CH), 4.87 (t, 1H, *J* = 9.5 Hz, CH), 4.13–4.03 (m, 2H, H-6″), 3.84–3.77 (m, 1H, H-1″), 3.69–3.64 (m, 1H, H-5″), 2.88 (dd, 1H, J_1 = 3.2 Hz, J_2 = 14.7 Hz, C*Ha*H), 2.757 (dd, 1H, J_1 = 8.2 Hz, J_2 = 14.7 Hz, C*Hb*H), 2.01, 1.97, 1.94, 1.88 (each singlet, 4x$COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.3, 175.0, 174.7, 174.4 ($OCOCH_3$), 167.1, 164.0, 155.5, 141.6, 139.7, 134.7 (ArCH), 112.0 (ArCH), 121.1 (CN), 104.8, 80.5 (CH), 78.9 (CH), 78.9 (CH), 76.5 (CH), 73.5 (CH), 67.2 (OCH_2), 40.5 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 25.65 (CH_3); DART-HRMS: *m/z* calcd for $C_{27}H_{27}ClN_2O_{10}$ (M^+) 575.1450; found: 575.1432, ESIMS: *m/z* 575 $(M+H)^+$; Anal. Calcd for $C_{27}H_{27}ClN_2O_{10}$: C, 56.40; H, 4.73; N, 4.87. Found: C, 56.45; H, 4.77; N, 4.90.

4.1.1.7. 3-Cyano-4-phenyl-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6g). Compound **6g** was obtained by the reaction of compound **5g** (0.55 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL) and Ac_2O (1.0 mL, 10.70 mmol) as a white solid (0.52 g, yield 54%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −39.1 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3474 (NH stretching), 2227 (C≡N stretching), 1756 (O–C=O stretching), 1659 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 12.5 (s, 1H, NH), 7.60–7.55 (m, 5H, ArH), 6.37 (s, 1H, H-5), 5.27 (t, 1H, *J* = 9.3 Hz, CH), 4.90–4.73 (m, 2H, 2 × CH), 4.08–3.91 (m, 4H, H-6″, H-1″, H-5″), 2.92 (m, 2H, CH_2), 1.97, 1.92, 1.73 (12H, 4 × $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 170.5, 170.3, 170.2 ($OCOCH_3$), 162.1, 160.7, 152.3, 136.9, 131.3, 129.7, 128.8 (ArCH), 117.2 (CN), 107.7, 75.1 (CH), 74.0 (CH), 72.1 (CH), 69.2 (CH), 63.0 (CH), 63.0 (OCH_2), 35.5 (CH_2), 21.3, 21.2, 21.1, 20.9 (CH_3); DART-HRMS: *m/z* calcd for $C_{27}H_{29}N_2O_{10}$ (M^+) 541.1822; found: 541.1829; ESIMS: *m/z* 541 $(M+H)^+$; Anal. Calcd for $C_{27}H_{27}ClN_2O_{10}$: C, 60.00; H, 5.22; N, 5.18. Found: C, 60.04; H, 5.25; N, 5.15.

4.1.1.8. 3-Cyano-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]-4-(3′,4′,5′-trimethoxyphenyl)-pyridone (6h). Compound **6h** was obtained by the reaction of compound **5h** (0.82 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL) and Ac_2O (1.0 mL, 10.70 mmol) as a

white solid (0.7 g, yield 62%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ +68.97 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3474 (NH stretching), 2223 (C≡N stretching), 1753 (O–C=O stretching), 1658 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 12.5 (s, 1H, NH), 6.91 (s, 2H, ArH), 6.36 (s, 1H, H-5), 5.29 (t, 1H, *J* = 9.36 Hz, CH), 5.11 (t, 1H, *J* = 9.8 Hz, CH), 5.02 (t, 1H, *J* = 9.6 Hz, CH), 4.23 (m, 2H, H-6″), 4.00 (m, 1H, H-1″), 3.98 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.81–3.78 (m, 1H, H-5″), 3.03–2.86 (m, 2H, CH_2), 2.18, 2.15, 2.10, 2.01 (each singlet, 12H, 4 × $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0, 170.6, 170.4, 169.9 ($OCOCH_3$), 163.9, 161.2, 153.8, 149.2, 140.6, 131.0, 116.2 (CN), 109.8, 106.1, 76.1 (CH), 75.6 (CH), 74.3 (CH), 71.4 (CH), 68.5 (CH), 62.2 (OCH_2), 61.4 (OCH_3), 56.8 (OCH_3), 56.0 (OCH_3), 36.1 (CH_2), 21.2, 21.0, 20.9 (CH_3); DART-HRMS: *m/z* calcd for $C_{30}H_{34}N_2O_{13}$ (M^+) 631.2139; found: 631.2146; ESIMS: *m/z* 631 $(M+H)^+$; Anal. Calcd for $C_{30}H_{34}N_2O_{13}$: C, 57.14; H, 5.43; N, 4.44. Found: C, 57.11; H, 5.38; N, 4.40.

4.1.1.9. 3-Cyano-4-(2′-napthyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6i). Compound **6i** was obtained by the reaction of compound **5i** (0.63 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL) and Ac_2O (1.0 mL, 10.7 mmol) as a white solid (0.61 g, yield 58%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −151 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3461 (NH stretching), 2228 (C≡N stretching), 1748 (O–C=O stretching), 1663 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 8.01–7.93 (m, 2H, ArH), 7.72–7.63 (m, 1H, ArH), 7.58–7.50 (m, 4H, ArH), 6.36 (s, 1H, H-5), 5.24 (t, 1H, *J* = 8.9 Hz, CH), 4.93 (t, 1H, *J* = 8.5 Hz, CH), 4.84 (t, 1H, *J* = 9.2 Hz, CH), 4.03–3.96 (m, 3H), 3.91–3.81 (m, 1H), 2.90–2.89 (m, 1H), 2.72–2.63 (m, 1H), 2.12, 2.04, 2.01, 1.96 (each singlet, 12H, 4 × $COCH_3$); DART-HRMS: *m/z* calcd for $C_{31}H_{31}N_2O_{10}$ (M^+) 591.1978; found: 591.1971; ESIMS: *m/z* 591 $(M+H)^+$; Anal. Calcd for $C_{31}H_{30}N_2O_{10}$: C, 63.05; H, 5.12; N, 4.74. Found: C, 63.00; H, 5.15; N, 4.80.

4.1.1.10. 4-(4′-*O*-Acetylphenyl)-3-cyano-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (6j). Compound **6j** was obtained by the reaction of compound **5j** (0.58 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), *t*-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL) and Ac_2O (1.0 mL, 10.7 mmol) as a white solid (0.6 g, yield 56%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ +18.5 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 3428 (NH stretching), 2215 (C≡N stretching), 1632 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 12.3 (s, 1H, NH), 7.70–7.68 (d, 2H, *J* = 8.3 Hz, ArH), 6.28–7-26 (d, 2H, *J* = 8.3 Hz, ArH), 6.35 (s, 1H, H-5), 5.28 (t, 1H, *J* = 7.2 Hz, CH), 5.12–4.94 (m, 2H, 2xCH), 4.19 (m, 2H, H-6″), 3.95 (m, 1H, H-1″), 3.80 (m, 1H, H-5″), 2.94–2.84 (m, 2H, CH_2), 2.37, 2.11, 2.06, 2.04, 2.01 (15H, 5 × $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.8, 136.5, 130.8, 129.5, 122.3, 116.3 (CN), 109.1, 75.8 (CH), 75.4 (CH), 73.8 (CH), 71.1 (CH), 68.2 (CH), 61.9 (OCH_2), 35.6 (CH_2), 21.1, 20.7, 20.5 (CH_3); DART-HRMS: *m/z* calcd for $C_{29}H_{31}N_2O_{12}$ $(M+H)^+$ 599.1877; found: 599.1895; ESIMS: *m/z* 599 $(M+H)^+$. Anal. Calcd for $C_{29}H_{30}N_2O_{12}$: C, 58.19; H, 5.05; N, 4.68. Found: C, 58.23; H, 5.00; N, 4.60.

4.1.2. General procedure for synthesis of compounds 7a–7j

To a stirring solution of 3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridones (**6a–6j**) (7.16 mmol) in MeOH at 25 °C, was added a solution of NaOMe (10 mL, 10 mol %). The reaction mixture was stirred until the disappearance of the starting material was confirmed (TLC). After completion of the reaction, the reaction mixture was neutralized by 2% aq HCl solution at 0 °C and filtered, and the filtrate was concentrated in vacuum to give a residual mass that was triturated with a mixture of $CHCl_3$ and MeOH and filtered. The filtrate was evaporated, and the residue so obtained was dissolved in MeOH and filtered through a short column of silica gel to afford the products (**7a–7j**). The compounds were crystallized with MeOH.

4.1.2.1. 3-Cyano-4-(4′-fluorophenyl)-6-[(β-D-glucopyranosyl)methyl]pyridone (7a). Compound **7a** was obtained by reaction of 3-cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (**6a**) (0.4 g, 7.16 mmol) and MeOH/NaOMe (10 mL, 10 mol %). White solid (0.26 g, yield 71%); mp >240 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −49.4 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3467–3412 (OH and NH stretching), 2223 (C≡N stretching), 1690 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 12.3 (br s, 1H, NH), 7.74–7.70 (m, 2H, ArH), 7.39–7.33 (m, 2H, ArH), 6.44 (s, 1H, H-5), 4.91–4.60 (m, 4H, 4 × OH), 3.47–3.36 (m, 2H), 3.23–3.17 (m, 2H), 3.11–3.01 (m, 3H), 2.97–2.91 (m, 1H, –CHaH–), 2.70 (dd, 1H, J_1 = 8.22 Hz, J_2 = 15.2 Hz, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 166.5, 162.1, 159.5, 154.1, 133.4, 133.3, 131.2 (ArCH), 131.5 (ArCH), 117.5, 116.8, 116.4 (CN), 107.7, 81.4, 78.7, 77.8, 74.1, 71.1, 62.1 (OCH_2), 36.1 (CH_2); DART-HRMS: *m/z* calcd for $C_{19}H_{20}FN_2O_6$ (M^+) 391.1305; found: 391.1310; ESIMS: *m/z* 391 $(M+H)^+$; Anal. Calcd for $C_{19}H_{19}FN_2O_6$: C, 58.46; H, 4.91; N, 7.18. Found: C, 58.43; H, 4.94; N, 7.14.

4.1.2.2. 4-(4′-Bromophenyl)-3-cyano-6-[(β-D-glucopyranosyl)-methyl]pyridone (7b). Compound **7b** was obtained by the reaction of compound **6b** (0.50 g, 0.81 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.28 g, yield 77%); mp 225–227 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −117 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3503–3353 (OH and NH stretching), 2230 (C≡N stretching), 1682 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, D_2O): δ 7.72 (d, 1H, *J* = 8.5 Hz, ArH), 7.63–7.51 (m, 3H, ArH), 6.42 (s, 1H, H-5), 3.62–3.59 (m, 2H), 3.20–3.01 (m, 4H), 2.95–2.92 (m, 1H), 2.72–2.70 (m, 1H, CHbH); DART-HRMS: *m/z* calcd for $C_{19}H_{20}BrN_2O_6$ (M^+) 451.0504; found: 451.0508; ESIMS: *m/z* 451 $(M+H)^+$; Anal. Calcd for $C_{19}H_{19}BrN_2O_6$: C, 50.57; H, 4.24; N, 6.21. Found: C, 50.52; H, 4.20; N, 6.15.

4.1.2.3. 4-(4′-Benzyloxyphenyl)-3-cyano-6-(β-D-glucopyranosyl)methyl]pyridone (7c). Compound **7c** was obtained by the reaction of compound **6c** (0.40 g, 0.62 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 67%); mp >218–220 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −45.9 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3346–3279 (OH and NH stretching), 2224 (C≡N stretching), 1690 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 12.2 (br s, 1H, NH), 7.67–7.64 (d, 2H, ArH), 7.49–7.34 (m, 5H, ArH), 7.17 (d, 2H, *J* = 8.8 Hz), 6.44 (s, 1H, H-5), 5.27 (d, 1H, *J* = 5.3 Hz, OH), 5.19 (s, 2H, OCH_2), 5.05 (d, 1H, *J* = 4.3 Hz, OH), 5.00 (d, 1H, *J* = 4.9 Hz, OH), 4.52 (t, 1H, *J* = 5.7 Hz, OH), 3.65 (dd, J_1 = 6.2 Hz, J_2 = 10.5 Hz, 1H, H6a″), 3.45–3.39 (m, 1H), 3.17–3.01 (m, 6H), 2.95 (dd, 1H, J_1 = 5.37 Hz, J_2 = 8.91 Hz, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.4, 160.9, 160.0, 153.5, 137.5, 130.8 (ArCH), 129.3 (ArCH), 129.1, 128.8 (ArCH), 128.6 (ArCH), 117.8, 115.8 (CN), 107.5, 81.3 (CH), 78.7 (CH), 77.8 (CH), 74.0 (CH), 71.1 (CH), 70.3 (OCH_2), 62.1 (OCH_2), 36.0 (CH_2); DART-HRMS: *m/z* calcd for $C_{26}H_{27}N_2O_7$ (M^+) 479.1818; found: 479.1830; ESIMS: *m/z* 479 $(M+H)^+$; Anal. Calcd for $C_{26}H_{26}N_2O_7$: C, 65.26; H, 5.48; N, 5.85. Found: C, 65.22; H, 5.50; N, 5.80.

4.1.2.4. 3-Cyano-4-(4′-methoxyphenyl)-6-[(β-D-glucopyranosyl)methyl]pyridone (7d). Compound **7d** was obtained by the reaction of compound **6d** (0.40 g, 0.70 mmol), MeOH/NaOMe (10 mL, 10 mol %) as a white solid (0.2 g, yield 71%); mp >240 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −142 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3380–3272 (OH and NH stretching), 2219 (C≡N stretching), 1653 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, DMSO-d_6): δ

12.2 (br s, 1H, NH), 7.67 (d, 2H, J = 8.8 Hz, ArH), 7.10 (d, 2H, J = 8.8 Hz, ArH), 5.30 (d, 1H, J = 5.2 Hz, OH), 5.10 (d, 1H, J = 4.4 Hz, OH), 5.04 (d, 1H, J = 4.8 Hz, OH), 4.54 (t, 1H, J = 5.8 Hz, OH), 3.83 (s, 3H, OCH_3), 3.60 (dd, 1H, J = 6.3 Hz, H-6a″), 3.43–3.38 (m, 2H), 3.18–2.91(m, 5H), 2.70 (dd, 1H, J_1 = 8.22 Hz, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 167.1, 166.6, 164.8, 158.2, 135.5, 133.6 (ArCH), 122.6, 119.8 (ArCH), 112.2 (CN), 86.1 (CH), 83.5 (CH), 82.6 (CH), 78.8 (CH), 75.9 (CH), 66.8 (OCH_2), 61.0 (OCH_3), 40.8 (CH_2); DART-HRMS: m/z calcd for $C_{20}H_{22}N_2O_7$ (M^+) 403.1505; found: 403.1515; ESIMS: m/z 403 $(M+H)^+$; Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.70; H, 5.51; N, 6.96. Found: C, 59.73; H, 5.48; N, 6.90.

4.1.2.5. 3-Cyano-4-(3′,4′-dimethoxyphenyl)-6-[(β-D-glucopyranosyl)methyl]pyridone (7e). Compound **7e** was obtained by the reaction of compound **6e** (0.40 g, 0.67 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 64%); mp >240 °C; R_f 0.5 (2.5:7.5, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −124 (c 0.1c, MeOH); IR (KBr): ν_{max} 3631–3356 (OH and NH stretching), 2229 (C≡N stretching), 1619 cm^{-1} (N–C=O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (br s, 1H, NH), 7.29–7.24 (m, 2H, ArH), 7.11–7.08 (m, 2H, ArH), 6.48 (s, 1H, H-5), 5.23 (d, 1H, J = 5.3 Hz, OH), 4.99 (d, 1H, J = 4.2 Hz, OH), 4.95 (d, 1H, J = 4.9 Hz, OH), 4.49 (t, 1H, J = 5.6 Hz, OH), 4.12–4.11 (m, 1H, H-1″), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.60 (dd, 1H, J_1 = 5.6 Hz, J_2 = 11.0 Hz, H-6a″), 3.46 (dd, 1H, J_1 = 8.7 Hz, H-6b″), 3.17–2.91 (m, 5H), 2.70 (dd, 1H, J_1 = 8.28 Hz, J_2 = 15.21 Hz, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.4, 160.3, 153.3, 151.5, 149.4, 129.0, 122.2, (ArCH), 122.6, 112.5, 112.4 (ArCH), 117.9 (CN), 81.3(CH), 78.7 (CH), 77.8 (CH), 74.1 (CH), 71.2 (CH), 62.1 (OCH_2), 56.5 (OCH_3), 36.0 (CH_2); DART-HRMS: m/z calcd for $C_{21}H_{25}N_2O_8$ $(M+H)^+$ 433.1610; found: 433.1618; ESIMS: m/z 433 $(M+H)^+$; Anal. Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.59; N, 6.48. Found: C, 58.30; H, 5.53; N, 6.44.

4.1.2.6. 4-(4′-Chlorophenyl)-3-cyano-6-[(β-D-glucopyranosyl)-methyl]pyridone (7f). Compound **7f** was obtained by the reaction of compound **6f** (0.40 g, 1.78 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 71%); mp >240 °C; R_f 0.5 (2.5:7.5, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −59.3 (c 0.1, MeOH); IR (KBr): ν_{max} 3667–3374 (OH and NH stretching), 2223 (C≡N stretching), 1649 cm^{-1} (N–C=O stretching); ^{1}H NMR (300 MHz, D_2O): δ = 7.65–7.54 (m, 4H, ArH), 6.42 (s, 1H, H-5), 3.62–3.56 (m, 1H), 3.39–3.20 (m, 2H), 3.16–2.86 (m, 5H), 2.73 (m, 1H, J_1 = 8.4 Hz, J_2 = 15.3 Hz, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.1, 159.3, 154.3, 136.0, 135.7, 130.9, 129.7, 117.3 (CN), 107.5, 81.4 (CH), 78.7 (CH), 77.8 (CH), 74.1 (CH), 71.1 (CH), 62.0 (OCH_2), 36.1 (CH_2); DART-HRMS: m/z calcd for $C_{19}H_{19}ClN_2O_6$ $(M+H)^+$ 407.1009; found: 407.1020; ESIMS: m/z 407 $(M+H)^+$; Anal. Calcd for $C_{19}H_{19}ClN_2O_6$: C, 56.09; H, 4.71; N, 6.89. Found: C, 56.00; H, 4.65; N, 6.83.

4.1.2.7. 3-Cyano-4-phenyl-6-[(β-D-glucopyranosyl)methyl]pyridone (7g). Compound **7g** was obtained by the reaction of compound **6g** (0.40 g, 0.74 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.21 g, yield 76%); mp >240 °C; R_f 0.5 (2.5:7.5, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −141 (c 0.1, MeOH); IR (KBr): ν_{max} 3667–3268 (OH and NH stretching), 2225 (C≡N stretching), 1617 cm^{-1} (N–C=O stretching); ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.3 (br s, 1H, NH), 7.63–7.53 (m, 5H, ArH), 6.43 (s, 1H, H-5), 3.62–3.4 (m, 4H, 4 × OH), 3.20–3.04 (m, 6H), 2.95 (m, 2H), 2.73 (m, 1H, J_1 = 7.8 Hz, J_2 = 14.9 Hz, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 161.8, 136.5, 130.8, 129.2, 128.5, 116.3 (CN), 107.2, 80.9 (CH), 78.3 (CH), 77.4 (CH), 73.6 (CH), 73.6 (CH), 621.6 (OCH_2), 36.8 (CH_2); DART-HRMS: m/z calcd for $C_{19}H_{21}N_2O_6$ $(M+H)^+$ 373.1399; found: 373.1394; ESIMS: m/z 373 $(M+H)^+$; Anal. Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.25; H, 5.37; N, 7.49.

4.1.2.8. 3-Cyano-6-[(β-D-glucopyranosyl)methyl]-4-(3′,4′,5′-trimethoxyphenyl)-pyridone (7h). Compound **7h** was obtained by the reaction of compound **6h** (0.40 g, 0.63 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 68%); mp >240 °C; R_f 0.5 (2.5:7.5, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −138 (c 0.1c, MeOH); IR (KBr): ν_{max} 3633–3356 (OH and NH stretching), 2225 (C≡N stretching), 1621 cm^{-1} (N–C=O stretching); ^{1}H NMR (300 MHz, DMSO): δ 12.2 (br s, 1H, NH), 6.96 (s, 2H, ArH), 6.51 (s, 1H, H-5), 5.28 (d, 1H, J = 5.1 Hz, OH), 5.05 (d, 1H, J = 3.4 Hz, OH), 4.99 (d, 1H, J = 5.6 Hz, OH), 4.49 (t, 1H, J = 5.6 Hz, OH), 3.84 (m, 6H, 2 × OCH_3), 3.73 (s, 3H, OCH_3), 3.64–3.59 (m, 2H, H-1″, H-6a″), 3.47–3.35 (m, 2H, J_1), 3.17–2.99 (m, 4H), 2.96 (m, 1H, –CHbH–); ^{13}C NMR (50 MHz, DMSO) δ 162.2, 160.5, 153.6, 132.0, 117.8 (CN), 106.7, 81.3 (CH), 78.7 (CH), 77.7 (CH), 74.1 (CH), 71.0 (CH), 62.1 (OCH_2), 61.02 (OCH_3), 56.9 (OCH_3), 39.9 (CH_2); DART-HRMS: m/z calcd for $C_{22}H_{27}N_2O_9$ $(M+H)^+$ 463.1716; found: 463.1713; ESIMS: m/z 463 $(M+H)^+$; Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14; H, 5.67; N, 6.06. Found: C, 57.10; H, 5.64; N, 6.00.

4.1.2.9. 3-Cyano-4-(2′-napthyl)-6-[(β-D-glucopyranosyl)methyl]-pyridone (7i). Compound **7i** was obtained by the reaction of compound **6i** (0.40 g, 0.67 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 70%); mp >240 °C; R_f 0.5 (2.5:7.5, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −156 (c 0.1, MeOH); IR (KBr): ν_{max} 3633–3319 (OH and NH stretching), 2230 (C≡N stretching), 1621 cm^{-1} (N–C=O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.20–8.03 (m, 2H, ArH), 7.74–7.71 (m, 1H, ArH), 7.65–7.52 (m, 4H, ArH), 6.39 (s, 1H, H-5), 5.11–4.47 (m, 4H, 4 × OH), 3.61–3.57 (m, 2H), 3.39 (m, 1H), 3.15–3.05 (m, 4H), 2.96–2.90 (m, 2H), 2.76 (m, 1H, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.4, 160.4, 154.4, 135.0, 133.9, 130.5, 129.3, 128.0, 127.3, 126.2, 125.6, 117.8 (CN), 109.2, 81.3 (CH), 78.7 (CH), 78.0 (CH), 77.7 (CH), 74.4 (CH), 62.0 (OCH_2), 36.3 (CH_2); DART-HRMS: m/z calcd for $C_{23}H_{22}N_2O_6$ $(M+H)^+$ 423.1556; found: 423.1561; ESIMS: m/z 423 $(M+H)^+$; Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.35; H, 5.28; N, 6.60.

4.1.2.10. 3-Cyano-4-(4′-hydroxyphenyl)-6-[(β-D-glucopyranosyl)methyl]pyridone (7j). Compound **7j** was obtained by the reaction of compound **6j** (0.40 g, 0.67 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.20 g, yield 77%); mp >240 °C; R_f 0.5 (2.5:7.5, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −134 (c 0.1, MeOH); IR (KBr): ν_{max} 3667–3363 (OH and NH stretching), 2225 (C≡N stretching), 1648 cm^{-1} (N–C=O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55 (d, 2H, J = 8.6 Hz, ArH), 6.94 (d, 2H, J = 8.6 Hz, ArH), 6.40 (s, 1H, H-5), 5.06–5.00 (m, 3H, 3 × OH), 4.49 (br s, 1H, OH), 3.63–3.59 (m, 1H), 3.20–3.02 (m, 8H), 2.95–2.89 (m, 1H), 2.69–2.61 (dd, 1H, J_1 = 8.1 Hz, J_2 = 15.2 Hz, –CHbH–); DART-HRMS: m/z calcd for $C_{19}H_{20}N_2O_7$ $(M+H)^+$ 389.1348; found: 389.1335; ESIMS: m/z 389 $(M+H)^+$; Anal. Calcd for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.19; N, 7.21. Found: C, 58.73; H, 5.15; N, 7.18.

4.1.2.11. 3-Cyano-6-[(2″,3″,6″,2‴,3‴,4‴,6‴-hepta-O-acetyl-β-cellobiosyl)methyl]-4-(2′-napthyl)-pyridone (9). Compound **9** was obtained by the reaction of compound **8** (0.87 g, 1.79 mmol), cyanoacetamide (0.15 g, 1.79 mmol), t-BuOK (0.80 g, 7.14 mmol), pyridine (10 mL), and Ac_2O (1.0 mL, 10.70 mmol) as a white solid (0.6 g, yield 54%); mp 155–157 °C; R_f 0.5 (4:96, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −138.12 (c 0.1, $CHCl_3$); IR (KBr): ν_{max} 3414 (NH stretching), 2245 (C≡N stretching), 1747 (O–C=O stretching), 1644 cm^{-1} (N–C=O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.7 (s, 1H, NH), 8.18 (s, 1H, ArH), 7.94–7.89 (m, 4H, ArH), 7.73–7.56 (m, 2H, ArH), 6.43 (s, 1H, H-5), 5.20–5.04 (5H), 4.61–4.52 (2H), 4.38–4.35 (1H), 4.17–3.87 (3H), 3.78–3.66 (3H), 3.01–2.89 (m, 2H), 2.08–1.78(21H, 7 × $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0, 169.8, 169.5, 168.9, 168.7 ($OCOCH_3$), 163.4, 160.7, 134.0, 132.8, 128.8,

127.7, 126.9, 124.7, 109.4 (CN), 100.6 (C-1‴), 76.3, 75.2, 73.6, 72.9, 71.9, 71.5, 67.7 (CH), 61.7 (OCH_2), 35.8 (CH_2), 20.7, 20.5, 20.4; ESIMS: *m/z* 879 $(M+H)^+$; Anal. Calcd for $C_{43}H_{46}N_2O_{18}$: C, 58.77; H, 5.28; N, 3.19. Found: C, 58.70; H, 5.25; N, 3.24.

4.1.2.12. 6-[(β-Cellobiosyl)methyl]-3-cyano-4-(2′-napthyl)pyridone (10). Compound **10** was obtained by the reaction of compound **9** (0.50 g, 0.56 mmol), NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 60%); mp >240 °C; R_f 0.5 (3:7, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ +8.03 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3667–3380 (OH and NH stretching), 2225 (C≡N stretching), 1649 cm^{-1} (N–C=O stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 12.3 (br s, 1H, NH), 8.36 (s, 1H, ArH), 7.77–7.61 (m, 2H, ArH), 7.63–7.53 (m, 5H, ArH), 6.58 (s, 1H, H-5), 5.50–5.48 (m, 1H, OH), 5.29–5.27 (m, 1H, OH), 5.14–5.10 (m, 2H, OH), 4.80 (s, 1H, H-1‴), 4.68–4.63 (m, 3H, OH), 4.27–4.24 (1H, m, H-1″), 3.70–3.66 (m, 3H), 3.56–3.54 (m, 3H), 3.29–3.18 (m, 4H), 3.09–3.00 (m, 3H), 2.98 (m, 1H); ESIMS: *m/z* 585 $(M+H)^+$; Anal. Calcd for $C_{29}H_{32}N_2O_{11}$: C, 59.58; H, 5.52; N, 4.79. Found: C, 59.55; H, 5.48; N, 4.70.

4.1.3. General procedure for synthesis of compounds 11a–11e

To a stirring solution of 1:1 $POCl_3$–toluene, was added 3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]-pyridone (**6a–6e**) (0.896 mmol) at room temperature. The reaction mixture was then heated to 90–100 °C for 3 h with continuous stirring. After completion of the reaction, the mixture was cooled, poured into ice containing K_2CO_3, and the whole mixture was neutralized (pH 7.0) with aq ammonia. The reaction mixture was extracted with EtOAc, and the organic layer was evaporated under reduced pressure to give 2-chloro-3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridines (**11a–11e**) as white solids.

4.1.3.1. 2-Chloro-3-cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)methyl]pyridine (11a). Compound **11a** was obtained by the reaction of compound **6a** (0.50 g, 0.896 mmol), $POCl_3$ (10 mL), and toluene (10 mL), as a white solid (0.3 g, yield 58%); mp 119–120 °C; R_f 0.5 (3:97, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −120 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 2232 (C≡N stretching), 1754 cm^{-1} (O–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.61 (m, 2H, ArH), 7.28–7.22 (m, 3H, ArH), 5.20 (t, 1H, *J* = 9.33 Hz, CH), 5.04 (t, 1H, *J* = 9.81 Hz, CH), 4.95 (t, 1H, *J* = 9.63 Hz, CH), 4.13 (dd, 1H, *J* = 4.98 Hz, H-6″a), 4.06–4.00 (m, 2H, H-1″, H-6″b), 3.52–3.64 (m, 1H, H-5″), 3.05–2.99 (m, 2H, –CH_2–), 2.05, 2.04, 2.03, 1.91 (each singlet, 12H, 4 × $OCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.3, 170.2, 169.8, 169.5 ($OCOCH_3$), 161.9, 155.0, 154.1, 131.3, 131.1 (ArCH), 130.9 (ArCH), 123.8, 117.1 (ArCH), 116.6 (ArCH), 114.8 (CN), 76.7, 76.3, 74.4, 72.1, 68.8, 62.1 (OCH_2), 40.8 (CH_2), 21.0, 20.9, 20.8 (CH_3); DART-HRMS: *m/z* calcd for $C_{27}H_{27}ClFN_2O_9$ (M^+) 577.1389; found: 577.1395; ESIMS: *m/z* 577 $(M+H)^+$; Anal. Calcd for $C_{27}H_{27}ClFN_2O_9$: C, 56.21; H, 4.54; N, 4.86. Found: C, 56.18; H, 4.50; N, 4.90.

4.1.3.2. 2-Chloro-4-(4′-bromophenyl)-3-cyano-6-[(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)methyl]pyridine (11b). Compound **11b** was obtained by the reaction of compound **6b** (0.50 g, 0.81 mmol), $POCl_3$ (10 mL), and toluene (10 mL) as a white solid (0.28 g, yield 77%); mp 140–142 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −25.1 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 2231 (C≡N stretching), 1751 cm^{-1} (O–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, 1H, *J* = 8.4 Hz, ArH), 7.61–7.49 (m, 3H, ArH), 7.30–7.27 (m, 1H, ArH), 5.20 (t, 1H, *J* = 9.63 Hz, CH), 5.04 (t, 1H, *J* = 9.71 Hz, CH), 4.95 (t, 1H, *J* = 9.63 Hz, CH), 4.13 (dd, 1H, *J* = 4.77 Hz, H-6″a), 4.06–3.99 (m, 2H, H-1″, H-6″b), 3.50–3.61 (m, 1H, H-5″), 3.04–3.00 (m, 2H, CH_2), 2.06, 2.05, 2.03, 2.01 (each singlet, 12H, 4 × $OCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.3, 170.2, 169.8, 169.5 ($OCOCH_3$), 162.0, 154.9, 135.4, 132.9 (ArCH), 131.0, 130.4 (ArCH), 129.6 (ArCH), 128.8(ArCH), 125.9, 123.7, 114.7 (CN), 76.3, 74.4, 72.0, 68.8, 62.3 (OCH_2), 40.7 (CH_2), 21.0, 20.9, 20.8, 20.7; DART-HRMS: *m/z* calcd for $C_{27}H_{27}BrClN_2O_9$ $(M+H)^+$ 637.0588; found: 637.0608; ESIMS: *m/z* 638 $(M+H)^+$; Anal. Calcd for $C_{27}H_{26}BrClN_2O_9$: C, 50.84; H, 4.11; N, 4.39. Found: C, 50.80; H, 4.09; N, 4.33.

4.1.3.3. 4-(4′-Benzyloxyphenyl)-2-chloro-3-cyano-6-[(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)methyl]pyridine (11c). Compound **11c** was obtained by the reaction of compound **6c** (0.50 g, 0.77 mmol), $POCl_3$ (10 mL), and toluene (10 mL) as a white solid (0.4 g, yield 77%); mp >240 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −48.4 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 2231 cm^{-1} (C≡N stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 2H, *J* = 8.7 Hz, ArH), 7.44–7.36 (m, 5H, ArH), 7.29 (s, 1H, ArH), 7.15–7.12 (d, *J* = 8.7 Hz, 2H, ArH), 5.15 (s, 2H, OCH_2), 5.22 (t, 1H, *J* = 9.36 Hz, CH), 5.09 (t, 1H, *J* = 9.66 Hz, CH), 4.94 (t, 1H, *J* = 9.57 Hz, CH), 4.21 (dd, 1H, *J* = 7.11 Hz, *J* = 12.2 Hz, H-6″a), 4.06–4.02 (m, 2H, H-1″, H-6″b), 3.66–3.62 (m, 1H, H-5″), 3.05–3.00 (m, 2H, CH_2), 2.06, 2.05, 2.03, 1.90 (each singlet, 12H, 4 × $OCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 170.2, 169.8, 169.5 ($OCOCH_3$), 161.4, 155.7, 154.1, 136.6, 130.5 (ArCH), 129.0 (ArCH), 128.6 (ArCH), 127.8 (ArCH), 127.7, 123.5 (ArCH), 115.9 (ArCH), 115.3 (CN), 107.0, 76.7, 74.4, 72.1, 70.5 (OCH_2), 68.8, 62.2 (OCH_2), 40.8 (CH_2), 23.1, 21.0, 20.9, 20.8; DART-HRMS: *m/z* calcd for $C_{34}H_{34}ClN_2O_{10}$ (M^+) 665.1902; found: 665.1897; ESIMS: *m/z* 665 $(M+H)^+$; Anal. Calcd for $C_{34}H_{33}ClN_2O_{10}$: C, 61.40; H, 5.00; N, 4.21. Found: C, 61.38; H, 5.09; N, 4.26.

4.1.3.4. 2-Chloro-3-cyano-4-(4′-methoxyphenyl)-6-[(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)methyl]pyridine (11d). Compound **11d** was obtained by the reaction of compound **6d** (0.40 g, 0.70 mmol), $POCl_3$ (10 mL), and toluene (10 mL) as a white solid (0.3 g, yield 73%); mp >240 °C; R_f 0.5 (2:98, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −24.0 (*c* 0.1, MeOH); IR (KBr): ν_{max} 2228 (C≡N stretching), 1749 cm^{-1} (O–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, 1H, *J* = 8.3 Hz, ArH), 7.25 (s, 1H, ArH), 7.05 (d, 1H, *J* = 8.3 Hz, ArH), 5.19 (t, 1H, *J* = 9.12 Hz, CH), 5.03 (t, 1H, *J* = 7.5 Hz, CH), 4.90 (t, 1H, *J* = 9.63 Hz, CH), 4.19 (m, 1H, H-6a″), 4.03–3.97 (m, 2H, H-1″, H-6b″), 3.88 (s, 3H, OCH_3), 3.63–3.59 (m, 1H, H-5″), 3.01–2.97 (m, 2H, CH_2), 2.02–1.53 (12H, 4xOCOCH$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.9, 169.8, 169.4, 169.1 ($OCOCH_3$), 161.6, 155.4, 153.7, 130.0 (ArCH), 127.0, 123.1 (ArCH), 114.9 (ArCH), 114.6 (CN), 106.6, 76.4 (CH), 75.9 (CH), 74.0 (CH), 71.7 (CH), 68.4 (CH), 61.8 (OCH_2), 55.3 (OCH_3), 40.3 (CH_2), 20.6, 20.5, 20.4, 20.3; DART-HRMS: *m/z* calcd for $C_{28}H_{30}N_2ClO_{10}$ $(M+H)^+$ 589.1589; found: 589.1582; ESIMS: *m/z* 589 $(M+H)^+$; Anal. Calcd for $C_{28}H_{29}ClN_2O_{10}$: C, 57.10; H, 4.96; N, 4.76. Found: C, 57.10; H, 4.96; N, 4.76.

4.1.3.5. 2-Chloro-3-cyano-4-(3′,4′-dimethoxyphenyl)-6-[(2″,3″,-4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)methyl]pyridine (11e). Compound **11e** was obtained by the reaction of compound **6e** (0.50 g, 0.83 mmol), $POCl_3$ (10 mL), and toluene (10 mL) as a white solid (0.35 g, yield 68%); mp 130–132 °C; R_f 0.5 (2.5:97.5, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ +153 (*c* 0.1, $CHCl_3$); IR (KBr): ν_{max} 2228 (C≡N stretching), 1750 cm^{-1} (O–C=O stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (s, 1H, ArH), 7.24–7.20 (m, 2H, ArH), 7.01 (d, 1H, *J* = 8.2 Hz, ArH), 5.24 (t, 1H, *J* = 9.36 Hz, CH), 5.07 (t, 1H, *J* = 9.72 Hz, CH), 4.99 (t, 1H, *J* = 9.63 Hz, CH), 4.22 (dd, 1H, J_1 = 5.16 Hz, J_2 = 12.33 Hz, H-6a″), 4.04–4.02 (m, 2H, H-1″, H-6b″), 3.97 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.65–3.59 (m, 1H, H-5″), 3.04–2.99 (m, 2H, CH_2), 2.04, 2.03, 2.0, 1.89 (12H, 4 × $OCOCH_3$); DART-HRMS: *m/z* calcd for $C_{29}H_{32}ClN_2O_{11}$ $(M+H)^+$

619.1694; found: 619.1686; ESIMS: *m/z* 619 $(M+H)^+$ Anal. Calcd for $C_{29}H_{31}ClN_2O_{11}$: C, 56.27; H, 5.05; N, 4.53. Found: C, 56.23; H, 5.10; N, 4.50.

4.1.4. General procedure for synthesis of compounds 12a–12e

To a stirring solution of 3-cyano-4-(aryl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridines **11a–11e** (0.3 g, 0.52 mmol) in MeOH was added a solution of NaOMe (10 mL, 10 mol %) at 25 °C. The reaction mixture was stirred until the disappearance of the starting material was confirmed (TLC). The reaction mixture was neutralized by 2% aq HCl and concentrated in vacuum to afford the corresponding desired products **12a–12e** as colorless solids.

4.1.4.1. 2-Chloro-3-cyano-4-(4′-fluorophenyl)-6-[(β-D-glucopyranosyl)methyl] pyridine (12a). To a stirring solution of 3-cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridine **11a** (0.3 g, 0.52 mmol) in MeOH was added a solution of NaOMe (10 mL, 10 mol %) at 25 °C. The reaction mixture was stirred until the disappearance of the starting material (TLC). The reaction mixture was neutralized by 2% aq HCl and concentrated in vacuum to afford the desired product **12a** as a colorless solid (0.18 g, yield 88%); mp 125–127 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −55.50 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3467–3412 (OH stretching), 2231 cm^{-1} (C≡N stretching); ^1H NMR (300 MHz, D_2O): δ 7.38–7.27 (m, 2H, ArH), 7.18 (s, 1H, ArH), 6.97–6.90 (m, 2H, ArH), 3.42–3.30 (m, 2H), 3.15–3.03 (m, 3H), 2.98–2.89 (m, 3H), 2.68 (dd, 1H, *J* = 9.15 Hz, –CHbH–); ^{13}C NMR (50 MHz, DMSO-d_6): δ 169.6, 167.7, 159.4, 157.8, 136.7, 136.1 (ArCH), 136.0 (ArCH), 135.7, 128.8, 121.1, 120.2, 111.2 (CN), 85.2, 79.1, 76.1, 67.2 (OCH_2), 45.9 (CH_2); ESIMS: *m/z* 409 $(M+H)^+$; Anal. Calcd for $C_{19}H_{18}ClFN_2O_5$: C, 55.82; H, 4.44; N, 6.85. Found: C, 55.79; H, 4.40; N, 6.80.

4.1.4.2. 4-(4′-Bromophenyl)-2-chloro-3-cyano-6-[(β-D-glucopyranosyl)methyl]pyridine (12b). Compound **12b** was obtained by the reaction of compound **11b** (0.50 g, 0.81 mmol) and NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.28 g, yield 77%); mp = 225–227 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −92.09 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3467 (OH stretching), 2233 cm^{-1} (C≡N stretching); ^1H NMR (300 MHz, D_2O): δ 7.67–7.44 (m, 2H, ArH), 7.34–7.28 (m, 1H, ArH), 3.77–3.60 (m, 5H), 3.36–3.28 (m, 3H), 3.02–2.99 (m, 1H); DART-HRMS: *m/z* calcd for $C_{19}H_{20}BrClN_2O_5$ $(M+2H)^+$ 470.0244; found: 470.0247; ESIMS: *m/z* 469 $(M+H)^+$; Anal. Calcd for $C_{19}H_{18}BrClN_2O_5$: C, 48.58; H, 3.86; N, 5.96. Found: C, 48.54; H, 3.82; N, 5.91.

4.1.4.3. 4-(4′-Benzyloxyphenyl)-2-chloro-3-cyano-6-[(β-D-glucopyranosyl)methyl]pyridine (12c). Compound **12c** was obtained by the reaction of compound **11c** (0.40 g, 0.6 mmol) and NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 84%); mp >240 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −18.7 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3445 (OH stretching), 2230 cm^{-1} (C≡N stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 7.74–7.71 (d, 2H, *J* = 8.76 Hz, ArH), 7.65 (s, 1H, ArH), 7.52–7.37 (m, 5H, ArH), 7.24 (d, 2H, *J* = 8.76 Hz, ArH), 5.23–5.21 (m, 3H, OCH_2, OH), 5.06 (d, 1H, *J* = 4.05 Hz, OH), 4.98 (d, 1H, *J* = 3.99 Hz, OH), 4.43 (t, 1H, *J* = 5.76 Hz, OH), 3.59–3.49 (m, 3H), 3.23–3.19 (m, 2H), 3.10–3.01 (m, 3H), 2.90 (dd, 1H, J_1 = 9.39 Hz, J_2 = 14.79 Hz, –CHbH–); DART-HRMS: *m/z* calcd for $C_{26}H_{26}ClN_2O_6$ $(M+H)^+$ 497.1479; found: 497.1469; ESIMS: *m/z* 497 $(M+H)^+$. Anal. Calcd for $C_{26}H_{25}ClN_2O_6$: C, 62.84; H, 5.07; N, 5.64. Found: C, 62.80; H, 5.00; N, 5.68.

4.1.4.4. 2-Chloro-3-cyano-6-[(β-D-glucopyranosyl)methyl]-4-(4′-methoxyphenyl)pyridine (12d). Compound **12d** was obtained by the reaction of compound **11d** (0.40 g, 0.68 mmol) and NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.2 g, yield 69%); mp = 159–160 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −121 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3446 (OH stretching), 2227 cm^{-1} (C≡N stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 7.71–7.61 (m, 2H, ArH), 7.19–7.07 (m, 3H, ArH), 5.12 (br s, 1H, OH), 4.88 (br s, 1H, OH), 4.30 (br s, 1H, OH), 4.00 (br s, 1H, OH), 3.83 (s, 3H, OCH_3), 3.75–3.74 (m, 1H), 3.65–3.49 (m, 2H), 3.27–3.01 (m, 4H), 2.99–2.78 (m, 2H); DART-HRMS: *m/z* calcd for $C_{20}H_{22}ClN_2O_6$ $(M+H)^+$ 421.1166; found: 421.1162; ESIMS: *m/z* 421 $(M+H)^+$; Anal. Calcd for $C_{20}H_{21}ClN_2O_6$: C, 62.84; H, 5.07; N, 5.64. Found: C, 62.80; H, 5.09; N, 5.62.

4.1.4.5. 2-Chloro-3-cyano-4-(3′,4′-dimethoxyphenyl)-6-[(β-D-glucopyranosyl)methyl]pyridine (12e). Compound **12e** was obtained by the reaction of compound **11e** (0.40 g, 0.64 mmol) and NaOMe/MeOH (10 mL, 10 mol %) as a white solid (0.25 g, yield 86%); mp >240 °C; R_f 0.5 (2:8, MeOH–$CHCl_3$); $[\alpha]_D^{25}$ −167 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3450 (OH stretching), 2108 cm^{-1} (C≡N stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.37 (m, 1H, ArH), 7.27–7.14 (m, 2H, ArH), 7.01–6.95 (m, 2H, ArH), 4.05–4.404 (m, 2H), 3.93–3.91 (m, 7H, 2 × OCH_3, OH), 3.72–3.63 (m, 3H), 3.48–3.38 (m, 3H), 3.30–3.21 (m, 2H), 2.92–2.89 (m, 1H); DART-HRMS: *m/z* calcd for $C_{21}H_{23}ClN_2O_7$ $(M+H)^+$ 451.1272; found: 451.1269; ESIMS: *m/z* 451 $(M+H)^+$; Anal. Calcd for $C_{21}H_{23}ClN_2O_7$: C, 55.94; H, 5.14; N, 6.21. Found: C, 55.90; H, 5.20; N, 6.25.

4.2. Biological assays

4.2.1. Assay of α-glucosidase[33]

Purified α-glucosidase (Sigma–Aldrich) was used as source for the enzyme for studying the effect of test compounds on α-glucosidase inhibition. All the compounds were analyzed for enzyme inhibitory activity using *p* nitrophenyl α-D-glucopyranoside (pNPG, Sigma) as the substrate. The assay system used consisted of 100 μL of phosphate buffer (0.67 mM, pH 6.8), 100 μL of glutathione, 50 μL of the substrate pNPG, along with 100 μL of the enzyme in 1.0 mL of reaction mixture containing 10.0 μL of the test compound. The control tube contained all but 10 μL of DMSO instead of compound. The change in OD, based on the rate of formation of product using a spectrophotometer, was observed for 3 min at intervals of 30 s.

4.2.2. Assay of glucose-6-phosphatase[34,35]

The liver of an overnight-fasted Wistar rat was excised, and a 10% homogenate was prepared in 150 mM KCl (w/v) using a Potter Elvejhem glass homogenizer fitted with a Teflon pestle. The homogenate was centrifuged at 1000×*g* for 15 min at 4 °C. The supernatant was decanted and used as the enzyme source.

The effect of the test compound was studied by pre-incubating 100 μM of the compound in a 1.0-mL reaction system for 10 min and then determining the residual glucose-6-phosphatase activity according to the method of Hubscher and West.[34] The assay system contained 0.3 M citrate buffer (pH 6.0), 28 mM EDTA, 14 mM NaF, 200 mM glucose-6-phosphate, and an appropriate amount of enzyme protein. The mixture was incubated at 37 °C for 30 min after which time the reaction was stopped by addition of 1.0 mL of 10% TCA. Estimation of inorganic phosphate (Pi) in the protein-free supernatant was done according to the method of Taussky and Shorr.[35] Glucose-6-phosphatase activity was defined as μM of Pi release per min per mg protein.

4.2.3. Assay of glycogen phosphorylase[35,36]

A rat of Wistar strain was put on 16 h fasting and its liver was excised. A 10% homogenate was prepared in 150 mM KCl (w/v) using a Potter–Elvejhem glass homogenizer fitted with a Teflon pestle. The homogenate was centrifuged at 1000×*g* for 15 min at 4 °C, supernatant was decanted and used as the enzyme source.

The effect of the test compound was studied by pre-incubating a 100 μM solution of the test compound in 1.0 mL of the reaction system for 10 min, and then determining the residual glycogen phosphorylase activity according to the method of Rall et al.[36] The assay mixture contained 0.2 mL of mixture A [glycogen 0.057 g, glucose-1-phosphate 0.188 g, NaF 0.042 g and 5′ AMP (4 mM) in 10 mL of distilled water] and 0.1 mL of mixture B, the enzyme protein. It was incubated at 37 °C for 30 min, after which time the reaction was stopped by addition of 0.1 mL of 10% TCA, and then 0.4 mL of NaOAc (100 mM) was added to prevent the spontaneous hydrolysis of G-1-P present in the reaction mixture. The estimation of inorganic phosphate in the protein-free supernatant was done according to the method of Taussky and Shorr.[35] Glycogen phosphorylase activity was defined as μM of Pi release per min per mg of protein.

4.2.4. Assessment of test compounds for antihyperglycemic activity in sucrose-challenged, streptozotocin-induced diabetic rats[29]

4.2.4.1. Preparation of test compounds and the standard antidiabetic drug. The test compounds and standard antidiabetic drug metformin were prepared in 1.0% freshly prepared gum acacia.

4.2.4.2. Induction of diabetes in rats. Overnight-starved male albino rats of the Sprague Dawley strain were used and diabetes was induced in the animals by a single intraperitoneal injection of streptozotocin with a 60 mg/kg body weight dose prepared in 0.1 M citrate buffer (pH 4.5). Fasting blood glucose level was measured by using a glucometer (ACCU-CHEK II, Roche Diagnostics, USA), after 48 h, and animals showing blood glucose levels between 140 and 270 mg/dL were considered as diabetic.

4.2.4.3. Grouping and treatment. The diabetic animals were divided into groups with five animals in each group and were administered a suspension of the desired test sample prepared in 1% gum acacia at desired dose levels (100 mg/kg) in the case of synthetic compounds and 100 mg/kg in case of the standard drug metformin). Animals of the control group were given an equal amount of 1% gum acacia and termed as sham controls. A sucrose load of 2.5 g/kg was given to each animal orally exactly after 30 min post administration of the test sample/vehicle. Blood glucose profile of animals of all groups was again checked at 30, 60, 90, 120, 180, 240, 300, and1440 min post administration of sucrose. Food but not water was withheld from the cages during the course of experimentation.

4.2.4.4. Statistical analysis. Quantitative glucose tolerance of each animal was calculated by the area under the curve (AUC) method using Prism Software. The area under the curve of the control group and the experimental group was compared to determine the percent antihyperglycemic activity. Statistical comparisons were performed by one-way analysis of variance (ANOVA), followed by Dunnett's multiple range test (DMRT). The results were considered statistically significant if the 'p' values were 0.05 or less. Results were expressed as mean ± SEM. Samples showing significant inhibition (p <0.05, p <0.01, and p <0.001) on postprandial hyperglycemia (AUC) were considered as active samples.

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Supplementary data

Supplementary data (ESMS, HRMS, ^{1}H, ^{13}C NMR, HSQC and HMBC spectra of prototype compounds) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.03.006.

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