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# Synthesis and α-glucosidase inhibitory activity evaluation of N-substituted aminomethyl-β-D-glucopyranosides ☆

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ABSTRACT

A series of N-substituted 1-aminomethyl-β-D-glucopyranoside derivatives was prepared. These novel synthetic compounds were assessed in vitro for inhibitory activity against yeast α-glucosidase and both rat intestinal α-glucosidases maltase and sucrase. Most of the compounds displayed α-glucosidase inhibitory activity, with $IC_{50}$ values covering the wide range from 2.3 μM to 2.0 mM. Compounds **19a** ($IC_{50}$ = 2.3 μM) and **19b** ($IC_{50}$ = 5.6 μM) were identified as the most potent inhibitors for yeast α-glucosidase, while compounds **16** ($IC_{50}$ = 7.7 and 15.6 μM) and **19e** ($IC_{50}$ = 5.1 and 10.4 μM) were the strongest inhibitors of rat intestinal maltase and sucrase. Analysis of the kinetics of enzyme inhibition indicated that **19e** inhibited maltase and sucrase in a competitive manner. The results suggest that the aminomethyl-β-D-glucopyranoside moiety can mimic the substrates of α-glucosidase in the enzyme catalytic site, leading to competitive enzyme inhibition. Moreover, the nature of the N-substituent has considerable influence on inhibitory potency.



## 1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) throughout the world is increasing at an alarming rate. T2DM affects about 173 million people worldwide and is associated with vascular complications that result in excess morbidity and mortality.[1,2] Such complications include cardiovascular disease, stroke, nephropathy, retinopathy, renal failure, and amputations.[1,2] It is now generally accepted that diabetes is a cardiovascular disease (CVD) and that these cardiovascular complications are related to prevailing hyperglycemia, particularly postprandial hyperglycemia (PPHG). It is now established that PPHG per se is a strong risk factor for the development of CVD.[3,4] PPHG has also been identified as one of the earliest detectable abnormalities expressed in diabetes. It is thus a better predictor for the progression of diabetes and has been implicated in inducing the oxidative stress that is recognized as a major pathophysiological link between CVD and diabetes.[5,6]

Pharmacological agents that specifically decrease PPHG, such as α-glucosidase inhibitors (AGIs), may become therapeutics of colossal importance. Food starches contribute to major postprandial blood glucose, an issue that is of particular relevance to those of Asian descent because of their specific dietary habits. Slowing digestion and absorption of dietary starches has shown promise in reducing PPHG, the burden of oxidative stress, and CVD.[7–9] These results can be achieved through dietary manipulation with low glycemic-index food or by inhibition of the starch-digesting enzyme α-glucosidase, which is present at the intestinal brush borders. Such α-glucosidase inhibitors (AGIs) retard carbohydrate digestion and prolong overall carbohydrate digestion, slowing the rate of glucose absorption and consequently blunting the postprandial plasma glucose increase.[10,11] Several AGIs, including acarbose, voglibose, and miglitol (Fig. 1), have been used effectively in the clinic to treat T2DM and to prevent CVD.[12,13] But only a few AGIs are available commercially, and some side-effects, such as flatulence, occur due to treatment with α-glucosidase inhibitors.[14] Therefore, investigators have developed considerable interest in the design and synthesis of specific glycosidase inhibitors of high affinity.[15,16]

The structure of enzyme inhibitors usually resembles that of a substrate, transition state, or product of an enzyme-catalyzed reaction.[17] Marketed AGIs all have structures similar to those of sugars. For instance, acarbose and voglibose are amino sugars, and miglitol is an azasugar. Docking simulations of α-glucosidase inhibitors revealed that the ammonium cation moieties of these amino sugar and azasugar inhibitors exhibit strong electrostatic interactions with amino acid residues, such as Asp, in the binding pocket. The hydroxyl groups of these sugar analogs interact with amino acid residues through hydrogen bonding. These interactions appear to be very important for specific molecular recognition and affinity. In recent years, various azasugars, amino sugars, and



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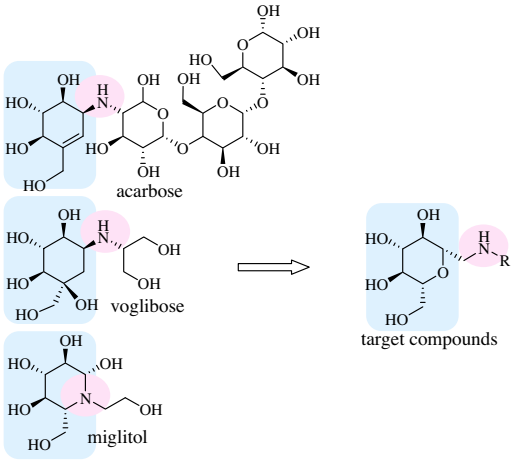



**Figure 1.** Structures of acarbose, voglibose, miglitol and target compounds.

polyhydroxylated five- and six-membered cyclic compounds have been studied intensively as structural analogs to monosaccharides. These compounds have been investigated as potential inhibitors of glycosidases.[18–21] It was suggested that the introduction of certain non-sugar moieties to the sugar structures can enhance inhibitory activity owing to additional interactions with a hydrophobic pocket of the enzyme.[21] In the search for simple, readily accessible compounds that would still be efficient glycosidase inhibitors, we prepared and assessed a series of N-substituted 1-aminomethyl-β-D-glucopyranoside derivatives (Fig. 1). These sugar mimetics were found to be α-glycosidase inhibitors, and the structure–activity relationships of these compounds are also discussed.

## 2. Result and discussion

### 2.1. Chemistry

The target compounds comprised two series according to the structure of N-substituted moieties: the amino sugar analogues and the amide sugar analogues. Both series were prepared from 1-aminomethyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**5**) through reductive amination or acylation, respectively (Fig. 2). Compound **5**, the key intermediate for the preparation of target compounds, was prepared according to procedures described in the literature.[22] The synthetic route is outlined in Scheme 1. Anhydrous D-glucose **1** was treated with benzaldehyde dimethyl acetal **2** and then reacted with nitromethane in the presence of DBU to form 1-nitromethyl-4,6-*O*-benzylidene-β-D-glucopyranoside **4**. This compound was then reduced with ammonium formate and Pd/C to give intermediate **5**.

A generalized synthetic approach to the amino sugar analogues (**8a–8n**) is shown in Scheme 2 and Scheme 3. Intermediate **5** reacted with different aromatic aldehydes at reflux under $N_2$ and

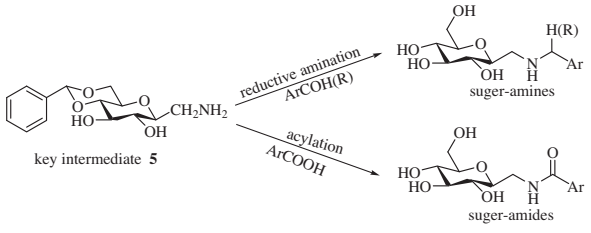
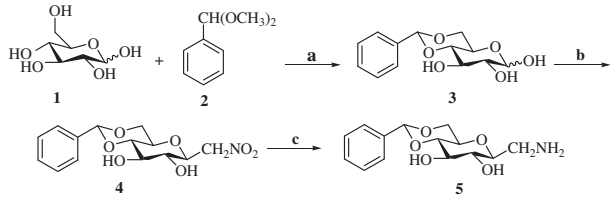
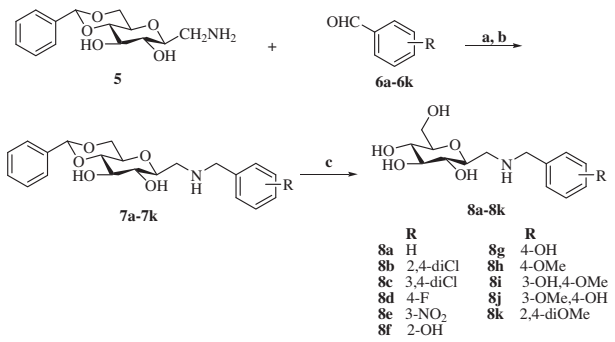


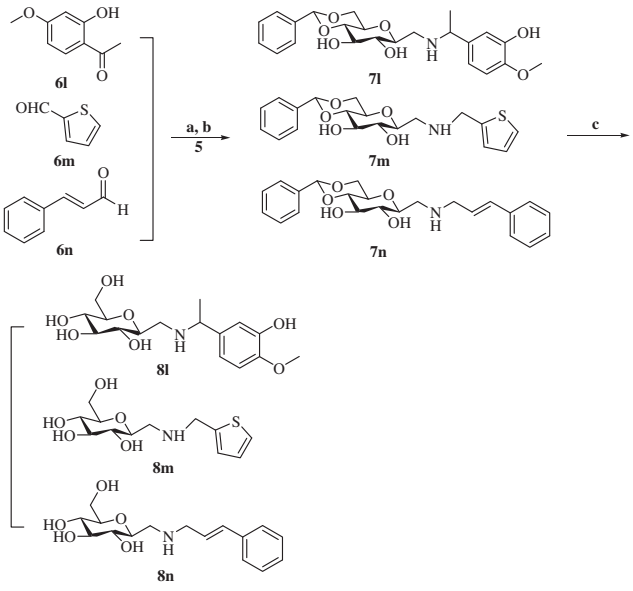

**Figure 2.** The general structure of the target compounds and key intermediate **5**.




**Scheme 1.** Synthesis of 1-aminomethyl-4,6-*O*-benzylidene-β-D-glucopyranoside **5**. Reagents and conditions: (a) *p*-TsOH, DMF, 60 °C, 5 h, 43.3%; (b) $CH_3NO_2$, DBU, THF, $N_2$, rt, 48 h, 83.3%; (c) $HCOONH_4$, 10% Pd/C, MeOH, 65 °C, 3 h, 97.8%.



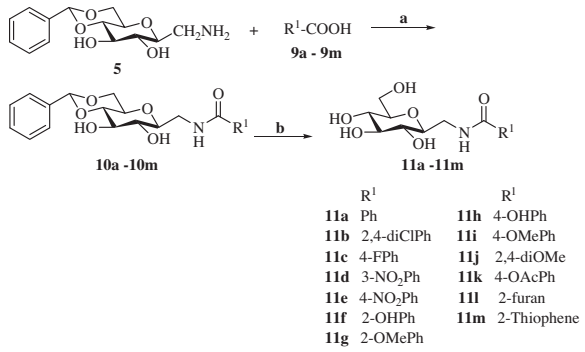

**Scheme 2.** Synthesis of sugar–amines **8a–8k**. Reagents and conditions: (a) EtOH, reflux under $N_2$, 3–10 h; (b) $NaBH_4$, MeOH, rt, 30 min, 60–80%; (b) AcOH/$H_2O$, 90 °C, 1 h, 28–40%.



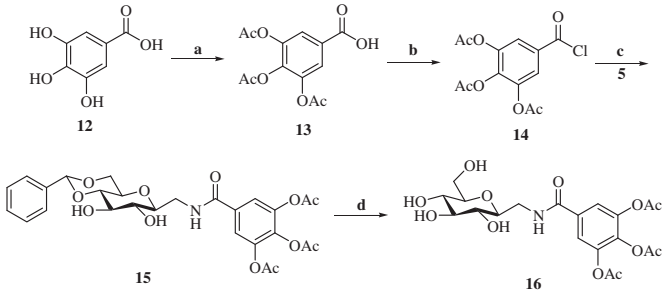

**Scheme 3.** Synthesis of sugar–amines **81–8n**. Reagents and conditions: (a) intermediate **5**, EtOH, reflux under $N_2$, 3–10 h; (b) $NaBH_4$, MeOH, rt, 30 min, 60–80%; (c) AcOH/$H_2O$, 33–43%.

then reduced with $NaBH_4$ to give **7a–7n**. These intermediates were deprotected cleanly with AcOH/$H_2O$ to afford compounds **8a–8n**.

The amido sugar analogues **11a–11m** and **19a–19e** were prepared via the synthetic route shown in Schemes 4–6. Intermediate **5** was coupled with various substituted aromatic acids **9a–9m** under HOBt/EDCI/DIPEA conditions to form **10a** to **10m**. These intermediates were deprotected with AcOH/$H_2O$ to give compounds **11a–11m** (Scheme 4). The synthesis of the title compound **16** was completed as depicted in Scheme 5. The reaction of compound **5** with 3,4,5-triacetoxybenzoyl chloride **14** gave amide **15**, which




**Scheme 4.** Synthesis of sugar–amides **11a–11m**. Reagents and conditions: (a) HOBt, EDCI, DIPEA, DMF, rt, 2 h; (d) AcOH/$H_2O$, 90 °C, 1 h, 35–56%.



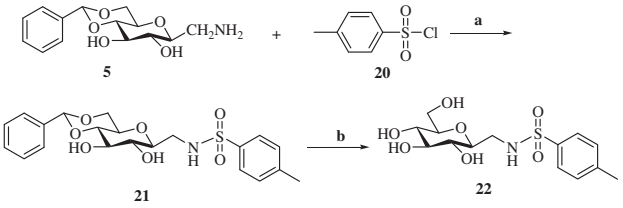

**Scheme 5.** Synthesis of sugar–amide **16**. Reagents and conditions: (a) Py., $Ac_2O$, rt, overnight, 78%; (b) $SOCl_2$, DMF, DCM, reflux, 3 h, 94%; (c) TEA, DMF–DCM, rt, 75%; (d) AcOH/$H_2O$, 90 °C, 1 h, 54.7%.

underwent deprotection to give **16**. The treatment of compound **5** with cinnamic acid or substituted cinnamic acids in presence of HOBt/EDCI gave intermediates **18a–18e**. Subsequent deprotection afforded compounds **19a–19e** (Scheme 6). A similar procedure employing *para*-toluenesulfonyl chloride was used to prepare sulfonamide **22** (Scheme 7).

## 2.2. Biological activity

### 2.2.1. α-Glucosidase inhibitory activity

The activity of the synthesized compounds was evaluated in vitro against yeast α-glucosidase from *Saccharomyces cerevisiae* and rat intestinal α-glucosidase (maltase and sucrase). The α-glucosidase inhibitory activity was determined using methods described in the literature.[23–25] The results are expressed as the inhibitor concentration required to achieve 50% inhibition of α-glucosidase activity ($IC_{50}$) and are reported in Table 1. The $IC_{50}$ data demonstrate that most of the synthesized compounds inhibited α-glucosidase with $IC_{50}$ values ranging from 2.3 μM to



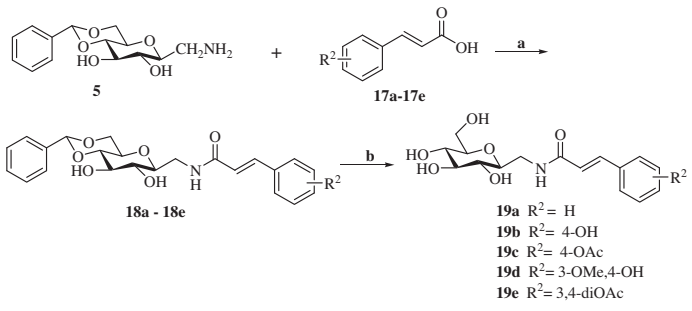

**Scheme 7.** Synthesis of target compound **22**. Reagents and conditions: (a) TEA, DMF–DCM, rt, 70%; (b) AcOH/$H_2O$, 90 °C, 1 h, 54.7%.

2.0 mM, suggesting that the nature of the N-substituents had significant effects on the inhibitory potencies.

In the amino sugar series, **8a** exhibited strong inhibitory activity against yeast α-glucosidase ($IC_{50}$ = 39.2 μM). The introduction of substituents on the aromatic ring (**8b–8l**) noticeably decreased potency, with the exception of **8e** ($IC_{50}$ = 44.3 μM), which bears a nitro group at the C3 position of the phenyl ring. The presence of 3,4-dichloro (**8c**, $IC_{50}$ = 613.3 μM) or 2,4-dimethoxy substituents (**8k**, $IC_{50}$ = 622.1 μM) decreased potency by about 16-fold. This result may indicate that bulky groups on the aromatic ring are disadvantageous for yeast α-glucosidase inhibitory activity. Replacement of the phenyl ring with thiophene (**8m**) or cinnamoyl (**8n**) also attenuated potency as compared with **8a**.

The sugar–amine compounds showed different inhibition profiles against rat intestinal α-glucosidase from what were observed for yeast α-glucosidase. Compounds **8a** and **8e**, good inhibitors of yeast α-glucosidase, displayed weaker activity on maltase than did other sugar–amine analogues. Compound **8e** was also the least potent of the sugar-amine analogues against sucrase. Substitution of the aromatic ring gave compounds (**8b–8l**), with clearly enhanced potency against maltase over that of **8a**; however, the $IC_{50}$ values were greater than 100 μM. It is interesting that the introduction of bulky groups to aromatic ring led to enhanced activity, as evidenced by the $IC_{50}$ values of **8b**, **8c**, **8j** and **8k**. These compounds were found to be between 6–11-fold more potent than **8a**. It is worth noting that the *N*-cinnamyl derivative **8n** appeared to be a dual inhibitor of both maltase and sucrase, with $IC_{50}$ values of 121.3 and 97.4 μM, respectively.

The synthesized amido sugar series mainly comprises benzamide (**11a–11m**, **16**) and cinnamide derivatives (**19a–11e**). The cinnamic amide derivatives **19a** and **19b** were most potent against yeast α-glucosidase, with $IC_{50}$ values of 2.3 and 5.6 μM, respectively. Altering the substitution pattern of the aromatic ring on the cinnamide unit led to sharply decreased activity, giving compounds 2 orders of magnitude less potent than **19a** and **19b**. Benzamides **11e** and **11k** showed strong inhibition of yeast α-glucosidase with $IC_{50}$ values of 36.2 and 96.5 μM, respectively. In comparing the effects of different aromatic ring substituents, it seems that groups introduced at the 4-position have considerable influence over activity. For instance, **11e** and **11k** were 14- and




**Scheme 6.** Synthesis of sugar–amides **19a-19e**. Reagents and conditions: (a) HOBt, EDCI, DMF, rt, 2 h; (b) AcOH/$H_2O$, 90 °C, 1 h, 30–50%.

**Table 1**
In vitro inhibitory activity of target compounds against α-glucosidases ($IC_{50}$ μM)[a]

| Compd | Yeast | Rat intestine | |
|---|---|---|---|
| | | Maltase | Sucrase |
| **8a** | 39.2 ± 1.2 | 1326.4 ± 13.4 | 270.5 ± 6.4 |
| **8b** | 317.6 ± 8.5 | 115.7 ± 2.8 | 154.3 ± 3.1 |
| **8c** | 613.3 ± 12.2 | 221.4 ± 6.2 | 144.3 ± 2.5 |
| **8d** | 115.4 ± 4.6 | 202.5 ± 5.2 | 301.1 ± 5.2 |
| **8e** | 44.3 ± 1.5 | 714.2 ± 12.8 | 627.2 ± 9.6 |
| **8f** | 155.6 ± 4.3 | 383.5 ± 7.8 | 181.5 ± 4.3 |
| **8g** | 149.3 ± 3.6 | 171.7 ± 4.7 | 124.4 ± 3.1 |
| **8h** | 457.2 ± 9.4 | 306.3 ± 7.1 | 179.5 ± 3.4 |
| **8i** | 465.4 ± 8.9 | 407.4 ± 7.9 | 185.8 ± 4.5 |
| **8j** | 377.3 ± 14.1 | 222.7 ± 4.5 | 186.3 ± 5.1 |
| **8k** | 622.1 ± 13.5 | 160.1 ± 2.8 | 105.2 ± 1.9 |
| **8l** | 184.4 ± 5.5 | 393.2 ± 9.9 | 106.8 ± 1.7 |
| **8m** | 373.5 ± 13.8 | 324.2 ± 7.6 | 172.6 ± 3.1 |
| **8n** | 116.2 ± 3.6 | 121.3 ± 2.3 | 97.4 ± 2.3 |
| **11a** | 499.2 ± 14.2 | 842.2 ± 12.4 | >2000 |
| **11b** | 466.3 ± 13.0 | 585.4 ± 14.1 | 991.4 ± 14.6 |
| **11c** | 1517.6 ± 24.4 | 463.8 ± 8.33 | 403.5 ± 7.9 |
| **11d** | 283.3 ± 5.3 | 261.5 ± 4.9 | 381.2 ± 7.7 |
| **11e** | 36.2 ± 0.6 | 846.4 ± 15.2 | 1003.4 ± 14.5 |
| **11f** | 470.5 ± 6.7 | 1014.7 ± 17.8 | >2000 |
| **11g** | 471.4 ± 7.2 | 719.2 ± 14.2 | 1087.3 ± 14.1 |
| **11h** | 1912.5 ± 21.4 | 757.8 ± 13.1 | 1640.8 ± 20.6 |
| **11i** | 231.3 ± 4.1 | 831.4 ± 13.5 | 795.3 ± 15.2 |
| **11j** | 1860.2 ± 25.6 | 160.1 ± 3.1 | >2000 |
| **11k** | 96.5 ± 1.8 | 165.2 ± 2.6 | 160.4 ± 4.4 |
| **11l** | 534.4 ± 8.6 | 926.5 ± 11.9 | 770.3 ± 9.6 |
| **11m** | 324.6 ± 8.7 | 445.3 ± 10.1 | >2000 |
| **16** | 225.2 ± 3.3 | 7.7 ± 0.1 | 15.6 ± 0.3 |
| **19a** | 2.3 ± 0.04 | 167.8 ± 3.5 | 314.3 ± 7.7 |
| **19b** | 5.6 ± 0.12 | 368.6 ± 6.8 | 405.5 ± 12.1 |
| **19c** | 142.2 ± 4.1 | 165.6 ± 3.8 | 154.8 ± 3.8 |
| **19d** | 101.8 ± 1.9 | 382.2 ± 6.8 | 253.4 ± 7.1 |
| **19e** | 355.4 ± 6.9 | 5.1 ± 0.1 | 10.4 ± 0.2 |
| **22** | 101.2 ± 12.2.1 | 476.2 ± 5.8 | 1416.7 ± 24.8 |
| Acarbose | 235.1 ± 3.89 | 3.3 ± 0.8 | 0.4 ± 0.005 |

[a] The results summarized are the mean values of $n = 3$ for $IC_{50}$ values.

5-fold more potent, respectively, than **11a**. Alternatively, **11h** was only 0.3 times as active as **11a** against yeast α-glucosidase. In evaluating inhibition of rat intestinal α-glucosidase, it was initially noted that the gallamide derivative **16** and the caffeoyl amide derivative **19e** were the most potent inhibitors, with maltase $IC_{50}$ values of 7.7 μM and 5.1 μM, respectively, and sucrase $IC_{50}$ values of 15.9 and 10.4 μM. These compounds were 2 orders of magnitude more active than other compounds. Substitution of the aromatic ring had a significant influence on inhibitory potency. In comparing compounds **11a** and **11k**, it was noted that the presence of an acetoxy group at the C4 position of the aromatic ring led to a remarkable increase in activity. The 3,4,5-triacetoxy motif (**16**) increased activity more than 120-fold, suggesting that the acetoxy groups play an important role. This conclusion can also be drawn from a comparison of **19a** with **19e**. The favorable role of acetoxy groups may be attributable to their H-bond accepting capabilities. The sulfonamide derivative **22** did not exhibit conspicuous inhibitory activity, demonstrating that the replacement of carbonyl with sulfonyl did not enhance activity.

When comparing the amino sugar and amido sugar compounds displaying equivalent N-substituents (e.g., **8a** vs **11a**, **8b** vs **11b**, **8n** vs **19a**, etc.), the sugar–amine compounds were generally more potent than the corresponding sugar–amide compounds. It is presumed that amino sugar compounds have greater binding affinities for the enzyme than do amido sugars, as has been observed for each of the clinical α-glucosidase inhibitors possessing amine structures. Additional data and further research are needed to confirm this hypothesis.[17–21]

The $IC_{50}$ data (Table 1) demonstrate that the target compounds exhibit different inhibition profiles against α-glucosidase from rat intestine compared with α-glucosidase from yeast. Some compounds, such as **19a**, **19b**, **11e**, **8a** and **8e**, were good inhibitors of yeast α-glucosidase but were not highly active against rat intestinal α-glucosidase. Alternatively, compounds **16** and **19e** were more effective against rat intestinal α-glucosidase. They were one to two orders of magnitude more potent against this enzyme than against yeast α-glucosidase. These results are not readily explained. However, a hypothesis may be based on the structural classification of α-glucosidases and the different amino acid sequences in the target binding sites. Chiba[25] suggested that α-glucosidases can be classified into two families, I and II, according to their primary structures. Yeast α-glucosidase shows similarities in its amino acid sequence to family I, whereas the amino acid sequence of rat intestinal α-glucosidase is highly conserved with that of the α-glucosidase family II. These differences in structure might explain the differences in the relative binding of different inhibitors. This would suggest that certain effective inhibitors of yeast α-glucosidase may be inactive against rat intestinal α-glucosidase. Alternatively, some compounds that might be inactive and ignored in screens against yeast α-glucosidase could be good inhibitors of rat intestinal α-glucosidase. The use of yeast α-glucosidase inhibition assays to evaluate α-glucosidase inhibitors may give false positive or false negative results. The results of our present study support this viewpoint. Therefore, assessment of α-glucosidases from mammalian intestines may be more rational and judicious for the evaluation of α-glucosidase inhibitors.

### 2.2.2. Kinetics of enzyme inhibition

Compound **19e** was selected for further investigation on the kinetics of enzyme inhibition against rat intestinal maltase and sucrase. The enzymatic reaction was performed according to the reaction conditions described in the literature.[25] The Dixon plot for maltase and sucrase in the presence of compound **19e** is shown in Figure 3. The kinetics show that **19e** is a competitive inhibitor of

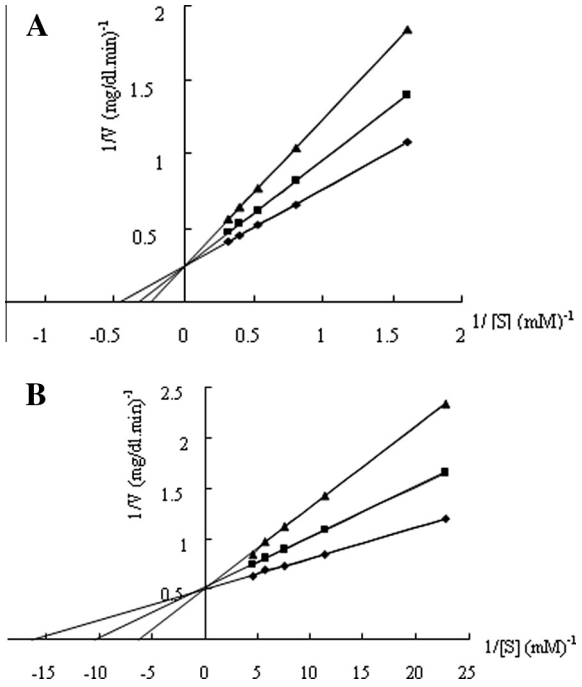



**Figure 3.** Lineweaver–Burk plot analysis of kinetics of α-glucosidase inhibition by compound **19e**. (A) maltase; (B) sucrase. Inhibitor concentration: ♦ control; ■10.0 μM; ▲ 20.0 μM.

maltase and sucrase, with *K*i values of 4.8 and 17.1 μM, respectively. This competitive inhibition indicates that **19e** may bind to the catalytic sites of these enzymes and compete with their primary substrates. Based on these results, we speculate that the competitive interactions of the tested compounds may be attributed to the 1-aminomethyl-β-D-glucopyranoside unit. This moiety may imitate the substrates of the enzymes and bind to the catalytic site, thus leading to inhibitory activity. However, differences in potency among the target compounds suggests that this competitive interaction may be highly sensitive to the nature of the N-substituent, resulting in a range of potencies.

## 3. Conclusion

In conclusion, several N-substituted 1-aminomethyl-β-D-glucopyranoside derivatives were conveniently prepared. Most of these novel compounds inhibited α-glucosidases from yeast and rat intestine (maltase and sucrase) with $IC_{50}$ values covering a wide range from 2.3 μM to 2.0 mM in our assay. Compounds **19a** and **19b** were identified as the most potent inhibitors for yeast α-glucosidase, and compounds **16** and **19e** were the strongest inhibitors of maltase and sucrase. These compounds are one to two orders of magnitude more potent than any other compound. Studies on the enzyme inhibition kinetics of **19e** indicated that target compound inhibits rat intestinal maltase and sucrase in a competitive fashion. The collective results strongly suggest that the aminomethyl-β-D-glucopyranoside moiety is an important skeleton for α-glucosidase inhibition. This core structure exerts its activity through competitive interactions with the enzyme catalytic site. Alteration of the N-substituent has a significant influence on activity, indicating that potency also depends on the structural features of the N-substituents. This suggests that additional interactions with appropriate N-substituents with enzyme contribute considerably to inhibitory potency. Further studies directed toward the enhancement of inhibitory activity will focus on the variation of the N-substituents through replacement of the aromatic moiety with different chain structures. The effects of compounds **16** and **19e** on postprandial blood glucose are being tested in mammalian animal models.

## 4. Experimental

### 4.1. Chemistry

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. The progress of the reactions was monitored by TLC using Qingdao Haiyang Chemical Co. Ltd, HG/T2354-92 Silica Gel GF254. Purifications of compounds were made by flash column chromatography using Qingdao Haiyang Chemical Co. Ltd, silica gel (100–200 mesh). $^1$H (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded with a Bruker AV400 spectrometer,—chemical shifts were recorded in ppm, tetra-methylsilane was used as the internal standard and coupling constants (*J*) were given in Hertz. Melting points were recorded using Tech. Instrument Co. Ltd, XT-4 melting point apparatus and were uncorrected. The percentates of halogen and sulphur in some target compounds were obtained by the oxygen flask combustion method.

#### 4.1.1. 4,6-*O*-Benzylidene-glucose (3)[22]

Compound **3** was prepared according to the literature procedure (mp 176–178 °C as reported).

#### 4.1.2. 1-Nitromethyl-4,6-*O*-benzylidene-β-D-glucopyranoside (4)[22]

Compound **4** was prepared according to the literature procedure (mp 213–214 °C as reported).

#### 4.1.3. 1-Aminomethy-4,6-*O*-benzylidene-β-D-glucopyranoside (5)[22]

Compound **5** was prepared according to the literature procedure (mp 233–235 °C as reported).

#### 4.1.4. General procedure for synthesis of 8a–n

The appropriate aldehydes (1.78 mmol) was added to a solution of **5** (500 mg, 1.78 mmol) in dry EtOH (15 ml) and refluxed at $N_2$ for 3–10 h until the start material was consumed. Following the solvent was evaporated, the residue was dissolved in MeOH (10 ml), then $NaBH_4$ (1.78 mmol) was added and the mixture was stirred at rt for 30 min. After the solvent was evaporated, $H_2O$ (15 ml) was added and the mixture was extracted with EtOAc (20 ml ×2). The organic phase was dried over anhydrous $Na_2SO_4$ and the solvent was evaporated to give the crude products of intermediates **7a–n** which were used directly for the next step without further purification.

The **7a–n** were dissolved in AcOH/$H_2O$ (15/10 ml) and stirred at 90 °C for 1 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica-gel and eluted with increasing polarity gradient mixture of chloroform and methanol to afford the corresponding target product **8a–n**.

**4.1.4.1. *N*-(β-D-Glucopyranosylmethyl)benzylamine (8a).** Yield 38% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.21–7.35 (m, 5H, Ph′), 3.68–3.77 (m, 2H, $CH_2$-Ph′), 3.65 (t, 1H, *J* = 11.6 Hz, H-6b), 3.33–3.37 (m, 1H, H-6a), 3.09–3.18 (m, 3H, H-3, H-4, H-5), 3.04 (t, 1H, *J* = 9.2 Hz, Glu-CH), 2.91–2.97 (m, 2H, H-1, H-2), 2.81 (d, 1H, *J* = 10.4 Hz, Glu-CH). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.32; H, 7.49; N, 4.96.

**4.1.4.2. *N*-(β-D-Glucopyranosylmethyl)-2,4-dichloro benzylamine (8b).** Yield 28% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.41–7.57 (m, 3H, Ph′), 3.71–3.81 (m, 2H, –$CH_2$Ph′), 3.64 (d, 1H, *J* = 11.2 Hz, H-6b), 3.34–3.39 (m, 2H, H-6a, H-5), 3.10–3.16 (m, 2H, H-3, H-4), 3.05 (t, 1H, *J* = 8.0 Hz, Glu-CH), 2.94–2.98 (m, 2H, H-1, H-2), 2.82 (d, 1H, *J* = 11.6 Hz, Glu-CH). Anal. Calcd for $C_{14}H_{19}Cl_2NO_5$: C, 47.74; H, 5.44; Cl, 20.13; N, 3.98. Found: C, 47.72; H, 5.47; Cl, 20.09; N, 4.01.

**4.1.4.3. *N*-(β-D-Glucopyranosylmethyl)-3,4-dichloro benzylamine (8c).** Yield 32% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.40–7.58 (m, 3H, Ph′), 3.71–3.81 (m, 2H, –$CH_2$Ph′), 3.64 (d, 1H, *J* = 11.6 Hz, H-6b), 3.35–3.39 (m, 2H, H-6a, H-5), 3.12–3.18 (m, 2H, H-3, H-4), 3.05 (t, 1H, *J* = 8.8 Hz, Glu-CH), 2.94–2.99 (m, 2H, H-1, H-2), 2.82(d, 1H, *J* = 10.8 Hz, Glu-CH). Anal. Calcd for $C_{14}H_{19}Cl_2NO_5$: C, 47.74; H, 5.44; Cl, 20.13; N, 3.98. Found: C, 47.75; H, 5.47; Cl, 20.11; N, 3.97.

**4.1.4.4. *N*-(β-D-Glucopyranosylmethyl)-4-fluoro benzylamine (8d).** Yield 30% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.10–7.38 (m, 4H, Ph′), 3.62–3.74 (m, 4H, $CH_2$-Ph′, H-6a, H-6b), 3.33–3.38 (m, 1H, H-5), 3.09–3.15 (m, 2H, H-3, H-4), 3.04 (t, 1H, *J* = 6.8 Hz, Glu-CH), 2.92–2.97 (m, 2H, H-1, H-2), 2.78 (d, 1H, *J* = 11.2 Hz, Glu-CH). Anal. Calcd for $C_{14}H_{20}FNO_5$: C, 55.81; H, 6.69; F, 6.31; N, 4.65. Found: C, C, 55.83; H, 6.70; F, 6.33; N, 4.67.

**4.1.4.5. *N*-(β-D-Glucopyranosylmethyl)-3-nitro benzylamine (8e).** Yield 35% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.21 (s, 1H, 4-Ph′), 8.09 (d, 1H, $J$ = 8.4 Hz, 2-Ph′), 7.80 (d, 1H, $J$ = 7.2 Hz, 6-Ph′), 7.61 (t, 1H, $J$ = 8.0 Hz, 5-Ph′), 3.79–3.89 (m, 2H, $CH_2$-Ph′), 3.64 (d, 1H, $J$ = 11.2 Hz, H-6b), 3.34–3.39 (m, 2H, H-6a, H-5), 3.07–3.18 (m, 2H, H-3, H-4), 3.05 (t, 1H, $J$ = 8.8 Hz, Glu-CH), 2.92–2.97 (m, 2H, H-1, H-2), 2.80 (d, 1H, $J$ = 11.6 Hz, Glu-CH). Anal. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.22; H, 6.14; N, 8.53. Found: C, 51.22; H, 6.11; N, 8.55.

**4.1.4.6. *N*-(β-D-Glucopyranosylmethyl)-2-hydroxy benzylamine (8f).** Yield 31% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.05–7.07 (m, 2H, 4-Ph′, 6-Ph′), 6.67–6.73 (m, 1H, 3-Ph′, 5-Ph′), 3.63–3.92 (m, 4H, $CH_2$-Ph′, H-6a, H-6b), 3.36 (dd, 1H, $J_1$ = 6.4 Hz, $J_2$ = 11.2 Hz, H-5), 3.05–3.19 (m, 3H, Glu-CH, H-3, H-4), 2.92–2.98 (m, 2H, H-1, H-2), 2.85–2.90 (m, 1H, Glu-CH). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 6.07; N, 4.68. Found: C, 56.20; H, 6.05; N, 4.67.

**4.1.4.7. *N*-(β-D-Glucopyranosylmethyl)-4-hydroxy benzylamine (8g).** Yield 35% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.20 (s, 1H, -Ph′-OH), 7.09 (d, 2H, $J$ = 10.8 Hz, 2-Ph′, 6-Ph′), 6.68 (d, 2H, $J$ = 10.8 Hz, 3-Ph′, 5-Ph′), 3.52–3.65 (m, 3H, H-6b, $-CH_2$Ph′), 3.34 (dd, 1H, $J_1$ = 8.4 Hz, $J_2$ = 15.2 Hz, H-6a), 3.01–3.17 (m, 4H, H-5, H-4, H-3, Glu-CH), 2.92–2.98 (m, 2H, H-1, H-2), 2.76–2.80 (m, 1H, Glu-CH). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 155.6, 131.0, 129.7, 115.3 (C-Ph′), 82.1 (C-1), 78.6 (C-5), 78.5 (C-3), 73.1 (C-2), 71.0 (C-4), 62.2 (C-6), 53.1 ($CH_2$Ph′), 51.0 (Glu-CH). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 6.07; N, 4.68. Found: C, 56.15; H, 6.09; N, 4.64.

**4.1.4.8. *N*-(β-D-Glucopyranosylmethyl)-4-methoxy benzylamine (8h).** The reaction produced **8e** in a 34% yield (two steps) as amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.25 (d, 2H, 2-Ph′, 6-Ph′), 6.86 (d, 2H, 3-Ph′, 5-Ph′), 3.73 (s, 3H, -$CH_3$), 3.62–3.69 (m, 4H, $CH_2$Ph′, H-6a, H-6b), 3.33–3.39 (m, 1H, H-5), 3.02–3.17 (m, 3H, H-3, H-4, Glu-CH), 2.91–2.98 (m, 2H, H-1, H-2), 2.81 (d, 1H, $J$ = 16.0 Hz, Glu-CH). Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.51; H, 7.38; N, 4.45.

**4.1.4.9. *N*-(β-D-Glucopyranosylmethyl)-3-hydroxy-4-methoxy benzylamine (8i).** Yield 40% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): 6.68–6.83 (m, 3H, Ph′), 3.72 (s, 3H, $-OCH_3$), 3.55–3.69 (m, 4H, $CH_2$-Ph′, H-6a, H-6b), 3.35–3.39 (m, 1H, H-5), 3.01–3.14 (m, 3H, H-3, H-4, Glu-CH), 2.92–2.98 (m, 2H, H-1, H-2), 2.78 (d, 1H, $J$ = 9.6 Hz, Glu-CH). Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.71; H, 7.02; N, 4.26.

**4.1.4.10. *N*-(β-D-Glucopyranosylmethyl)-3-methoxy-4-hydroxy benzylamine (8j).** Yield 42% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$):$\delta$ 6.69–6.89 (m, 3H, Ph′), 3.75 (s, 3H, $-OCH_3$), 3.60–3.66 (m, 3H, $CH_2$-Ph′, H-6b), 3.35–3.39 (m, 1H, H-6b), 3.02–3.17 (m, 4H, H-5, H-4, H-3, Glu-CH), 2.92–2.96 (m, 2H, H-1, H-2), 2.80 (d, 1H, $J$ = 11.1 Hz, Glu-CH). Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.68; H, 7.06; N, 4.26.

**4.1.4.11. *N*-(β-D-Glucopyranosylmethyl)-2, 4-dimethoxy benzylamine (8k).** The reaction produced **8c** in a 25% yield (two steps) as amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.19–6.47 (m, 3H, Ph′), 3.74–3.76 (m, 6H, 2× $OCH_3$), 3.64 (m, 4H, H-6a, H-6b), 3.35–3.39 (m, 1H, H-5), 3.12–3.17 (m, 2H, H-3, H-4), 3.04 (t, 1H, $J$ = 10.6 Hz, Glu-CH), 2.94–2.97 (m, 2H, H-1, H-2), 2.82 (m, 1H, Glu-CH). Anal. Calcd for $C_{16}H_{25}NO_7$: C, 55.97; H, 7.34; N, 4.08. Found: C, 56.01; H, 7.32; N, 4.06.

**4.1.4.12. *N*-(β-D-Glucopyranosylmethyl)-3-hydroxy-4-methoxy benzylamine (8l).** Yield 43% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.89–6.93 (m, 1H, 6-Ph′), 6.22–6.30 (m, 2H, 2-Ph′, 5-Ph′), 3.80–3.90 (m, 1H, CH-Ph′), 3.66 (s, 3H, -$OCH_3$), 3.64 (m, 1H, H-6b), 3.37 (m, 1H, H-6a), 3.05–3.20 (m, 3H, H-3, H-4, H-5), 2.78–2.97 (m, 3H, Glu-CH, H-1, H-2), 2.41 (t, 1H, $J$ = 9.2 Hz, Glu-CH), 1.27–1.31 (m, 3H, $-CH_3$). Anal. Calcd for $C_{16}H_{25}NO_7$: C, 55.97; H, 7.34; N, 4.08. Found: C, 55.99; H, 7.36; N, 4.06.

**4.1.4.13. *N*-(β-D-Glucopyranosylmethyl)-thiophen-2-methylamine (8m).** Yield 38% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.37 (s, 1H, thiophene), 6.95 (s, 2H, thiophene), 3.63–3.94 (m, 4H, $CH_2$-Ph′, H-6a, H-6b), 3.33–3.38 (m, 1H, H-5), 3.09–3.17 (m, 2H, Glu-CH, H-4), 3.05 (t, 1H, $J$ = 6.8 Hz, H-3), 2.90–2.97 (m, 2H, H-1, H-2), 2.85 (d, 1H, $J$ = 12.0 Hz, Glu-CH). Anal. Calcd for $C_{12}H_{19}NO_5S$: C, 49.81; H, 6.62; N, 4.84; S, 11.08. Found: C, 49.83; H, 6.67; N, 4.86; S, 11.09.

**4.1.4.14. *N*-(β-D-Glucopyranosylmethyl)-cinnamyl amine (8n).** Yield 33% from **5**, a white amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.42 (d, 2H, $J$ = 7.6 Hz, 2-Ph′, 6-Ph′), 7.32 (d, 2H, $J$ = 7.6 Hz, 3-Ph′, 5-Ph′), 7.22 (t, 1H, $J$ = 7.6 Hz, 4-Ph′), 6.52 (d, 1H, $J$ = 16.0 Hz, C=C*H*–Ph′), 6.29–6.35 (m, 1H, *H*C=C–Ph′), 4.89 (t, 2H, C$H_2$–C=C–Ph′), 4.48 (t, 1H, $J$ = 6.0 Hz, H-6b), 3.65 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 11.6 Hz, H-6a), 3.32 (m, 1H, H-5), 3.13–3.18 (m, 2H, H-3, H-4), 3.05 (t, 1H, $J$ = 9.2 Hz, Glu-CH), 2.95–2.99 (m, 2H, H-1, H-2), 2.86 (d, 1H, $J$ = 11.6 Hz, Glu-CH). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.15; H, 7.51; N, 4.51.

### 4.1.5. General procedure for synthesis of 11a–m and 19a–e

To a solution of the appropriate substituted carboxylic acids (**9a**–**m**) (1.78 mmol) in DMF (15 ml), following reagents were added: HOBt (2.67 mmol), EDCI (2.67 mmol) and *N*,*N*-diisopropylethylamine (5.34 mmol). The mixture was stirred at rt. for 2 h, then **5** (500 mg, 1.78 mmol) was added and continued to stir until the reaction completed. $H_2O$ (15 ml) was added and the mixture was extracted with EtOAc (2 × 30 ml). The organic phase was washed with saturated brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated. The crude products of **10a**–**m** were obtained and they were applied directly to the next step without further purification.

The intermediates **10a**–**m** underwent the same deprotection procedure as described in Section 4.1.4 to afford the corresponding target compounds **11a**–**m**. From **5** and cinnmic acid or substituted cinnmic acids **12a**–**e**, the compounds **19a**–**e** were prepared through the similar procedure described above.

**4.1.5.1. *N*-(β-D-Glucopyranosylmethyl)benzamide (11a).** Yield 42% from **5**, a white solid. mp 222–224 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.32 (s, 1H, –NH–), 7.83 (t, 2H, $J$ = 7.6 Hz, 2-Ph′, 6-Ph′), 7.53 (t, 1H, $J$ = 7.2 Hz, 4-Ph′), 7.47 (t, 2H, $J$ = 7.6 Hz, 3-Ph′, 5-Ph′), 4.95–5.12(m, 3H, 2-OH, 3-OH, 4-OH), 4.44 (s, 1H, 6-OH), 3.85 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 11.2 Hz, H-6b), 3.67 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 11.2 Hz, H-6a), 3.39–3.42 (m, 1H, H-5), 3.16–3.23 (m, 3H, Glu-CH, H-3, H-4), 3.08 (t, 1H, $J$ = 9.2 Hz, H-2), 3.02 (t, 1H, $J$ = 9.2 Hz, H-1), 2.92–2.98 (m, 1H, Glu-CH). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.55; H, 6.41; N, 4.73.

**4.1.5.2. *N*-(β-D-Glucopyranosylmethyl)-2,4-dichloro benzamide (11b).** Yield 45% from **5**, a white solid. mp 85–88 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.39 (s, 1H, –NH–), 7.69 (s, 1H, 6-Ph′), 7.45–7.50 (m, 2H, 3-Ph′, 5-Ph′), 5.08 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.97 (d, 1H, $J$ = 3.6 Hz, 3-OH), 4.92 (d, 1H, $J$ = 4.8 Hz, 4-OH), 4.34 (t, 1H, $J$ = 7.2 Hz, 6-OH), 3.87 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 13.2 Hz,

H-6b), 3.64 (dd, 1H, $J_1$ = 10.4 Hz, $J_2$ = 19.6 Hz, H-6a), 3.37–3.39 (m, 1H, H-5), 3.13–3.17 (m, 2H, H-3, H-4), 3.05–3.09 (m, 2H, Glu-CH, H-2), 2.97–3.02 (m, 2H, Glu-CH, H-1). Anal. Calcd for $C_{14}H_{17}Cl_2NO_6$: C, 45.92; H, 4.68; N, 3.82. Found: C, 45.94; H, 4.67; N, 3.80.

**4.1.5.3. *N*-(β-D-Glucopyranosylmethyl)-4-fluoro benzamide (11c).** Yield 38% from **5**, a white solid. mp 247–249 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.34 (s, 1H, –NH–), 7.91 (t, 2H, $J$ = 5.6 Hz, 2-Ph′, 6-Ph′), 7.29 (t, 2H, $J$ = 8.4 Hz, 3-Ph′, 5-Ph′), 5.08 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.94 (d, 1H, $J$ = 4.4 Hz, 3-OH), 4.91 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.41 (t, 1H, $J$ = 5.6 Hz, 6-OH), 3.84 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 12.0 Hz, H-6b), 3.66 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 11.2 Hz, H-6a), 3.41–3.39 (m, 1H, H-5), 3.16–3.23 (m, 3H, Glu-CH, H-3, H-4), 3.08 (t, 1H, $J$ = 9.2 Hz, H-2), 3.02 (t, 1H, $J$ = 5.2 Hz, H-1), 2.92–2.98 (m, 1H, Glu-CH). Anal. Calcd for $C_{14}H_{18}FNO_6$: C, 53.33; H, 5.75; N, 4.44. Found: C, 53.37; H, 5.73; N, 4.41.

**4.1.5.4. *N*-(β-D-Glucopyranosylmethyl)-3-nitro benzamide (11d).** Yield 35% from **5**, a white solid. mp 190–192 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.74 (s, 1H, –NH–), 8.67 (s, 1H, 2-Ph′), 8.38 (d, 1H, $J$ = 8.0 Hz, 4-Ph′), 8.28 (d, 1H, $J$ = 7.6 Hz, 6-Ph′), 7.79 (t, 1H, $J$ = 8.0 Hz, 5-Ph′), 5.10 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.96 (d, 1H, $J$ = 4.0 Hz, 3-OH), 4.92 (d, 1H, $J$ = 5.6 Hz, 4-OH), 4.40 (t, 1H, $J$ = 6.0 Hz, 6-OH), 3.88 (dd, 1H, $J_1$ = 6.0 Hz, $J_2$ = 12.8 Hz, H-6b), 3.67 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 10.8 Hz, H-6a), 3.42 (m, 1H, H-5), 3.15–3.28 (m, 3H, Glu-CH, H-3, H-4), 3.10 (t, 1H, $J$ = 6.8 Hz, H-2), 2.94–3.05 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.15; H, 5.29; N, 8.16.

**4.1.5.5. *N*-(β-D-Glucopyranosylmethyl)-4-nitro benzamide (11e).** Yield 48% from **5**, a white solid. mp 224–226 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.67 (s, 1H, –NH–), 8.32 (d, 2H, $J$ = 8.0 Hz, 3-Ph′, 5-Ph′), 8.06 (d, 2H, $J$ = 8.4 Hz, 2-Ph′, 6-Ph′), 5.11 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.98 (d, 1H, $J$ = 4.4 Hz, 3-OH), 4.93 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.41 (t, 1H, $J$ = 5.6 Hz, 6-OH), 3.88 (dd, 1H, $J_1$ = 6.0 Hz, $J_2$ = 13.2 Hz, H-6b), 3.66 (dd, 1H, $J_1$ = 7.6 Hz, $J_2$ = 10.8 Hz, H-6a), 3.39–3.44 (m, 1H, H-5), 3.14–3.26 (m, 3H, Glu-CH, H-3, H-4), 3.09 (t, 1H, $J$ = 9.2 Hz, H-2), 3.02 (t, 1H, $J$ = 8.8 Hz, H-1), 2.93–2.99 (m, 1H, Glu-CH). Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.15; H, 5.31; N, 8.15.

**4.1.5.6. *N*-(β-D-Glucopyranosylmethyl)-2-hydroxy benzamide (11f).** Yield 47% from **5**, a white solid. mp 215–217 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.25 (s, 1H, Ph′-OH), 8.66 (s, 1H, –NH–), 7.88 (d, 1H, $J$ = 8.0 Hz, 6-Ph′), 7.39 (t, 1H, $J$ = 8.0 Hz, 4-Ph′), 6.88–6.92 (m, 2H, 3-Ph′, 5-Ph′), 5.09 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.95 (d, 1H, $J$ = 4.4 Hz, 3-OH), 4.91 (d, 1H, $J$ = 4.8 Hz, 4-OH), 4.40 (t, 1H, $J$ = 5.6 Hz, 6-OH), 3.86 (dd, 1H, $J_1$ = 5.6 Hz, $J_2$ = 11.2 Hz, H-6b), 3.68 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 11.2 Hz, H-6a), 3.40–3.46 (m, 1H, H-5), 3.16–3.27 (m, 3H, Glu-CH, H-3, H-4), 3.10 (t, 1H, $J$ = 7.6 Hz, H-2), 2.95–3.05 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.69; H, 6.10; N, 4.45.

**4.1.5.7. *N*-(β-D-Glucopyranosylmethyl)-2-methoxy benzamide (11g).** Yield 45% from **5**, a white solid. mp 154–156 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.31 (s, 1H, –NH–), 7.85 (d, 1H, $J$ = 7.6 Hz, 6-Ph′), 7.49 (t, 1H, $J$ = 7.2 Hz, 5-Ph′), 7.15 (d, 1H, $J$ = 8.4 Hz, 3-Ph′), 7.05 (t, 1H, $J$ = 7.6 Hz, 4-Ph′), 5.16 (d, 1H, $J$ = 5.6 Hz, 2-OH), 4.99 (d, 1H, $J$ = 4.4 Hz, 3-OH), 4.95 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.54 (m, 1H, $J$ = 5.6 Hz, 6-OH), 3.91 (s, 3H, –$OCH_3$), 3.79 (dd, 1H, $J_1$ = 5.2 Hz, $J_2$ = 13.2 Hz, H-6b), 3.71(dd, 1H, $J_1$ = 5.2 Hz, $J_2$ = 11.6 Hz, H-6a), 3.42 (m, 1H, H-5), 3.27 (m, 1H, H-2), 3.12–3.19 (m, 3H, Glu-CH, H-3, H-4), 2.98–3.07 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{15}H_{21}NO_7$: C, 53.04; H, 6.47; N, 4.28. Found: C, 53.07; H, 6.45; N, 4.25.

**4.1.5.8. *N*-(β-D-Glucopyranosylmethyl)-4-hydroxy benzamide (11h).** Yield 38% from **5**, a white solid. mp 123–125 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.99 (s, 1H, Ph′-OH), 8.07 (s, 1H, –NH–), 7.71 (d, 2H, $J$ = 8.8 Hz, 2-Ph′, 6-Ph′), 6.78 (d, 2H, $J$ = 8.4 Hz, 3-Ph′, 5-Ph′), 5.11 (d, 1H, $J$ = 4.8 Hz, 2-OH), 4.94 (d, 1H, $J$ = 4.4 Hz, 3-OH), 4.92 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.44 (t, 1H, $J$ = 6.0 Hz, 6-OH), 3.77 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 10.8 Hz, H-6b), 3.66 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 10.8 Hz, H-6a), 3.40–3.43 (m, 1H, H-5), 3.16–3.18 (m, 3H, Glu-CH, H-3, H-4), 3.08 (t, 1H, $J$ = 6.4 Hz, H-2), 2.89–3.00 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.65; H, 6.09; N, 4.49.

**4.1.5.9. *N*-(β-D-Glucopyranosylmethyl)-4-methoxy benzamide (11i).** Yield 40% from **5**, a white solid. mp 242–244 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.18 (s, 1H, –NH–), 7.83 (d, 2H, $J$ = 8.4 Hz, 2-Ph′, 6-Ph′), 6.99 (d, 2H, $J$ = 8.8 Hz, 3-Ph′, 5-Ph′), 5.11 (d, 1H, $J$ = 4.8 Hz, 2-OH), 4.95 (d, 1H, $J$ = 4.8 Hz, 3-OH), 4.92 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.44 (t, 1H, $J$ = 6.0 Hz, 6-OH), 3.83 (dd, 1H, $J_1$ = 6.0 Hz, $J_2$ = 11.2 Hz, H-6b), 3.81 (s, 3H, –$OCH_3$), 3.66 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 11.2 Hz, H-6a), 3.40–3.46 (m, 1H, H-5), 3.13–3.21 (m, 3H, Glu-CH, H-3, H-4), 3.08 (t, 1H, $J$ = 8.4 Hz, H-2), 3.01 (t, 1H, $J$ = 8.8 Hz, H-1), 2.90–2.94 (m, 1H, Glu-CH). Anal. Calcd for $C_{15}H_{21}NO_7$: C, 53.04; H, 6.47; N, 4.28. Found: C, 53.07; H, 6.45; N, 4.30.

**4.1.5.10. *N*-(β-D-Glucopyranosylmethyl)-2,4-dimethoxy benzamide (11j).** Yield 47% from **5**, a white solid. mp 133–135 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.28 (s, 1H, –NH–), 7.88 (d, 1H, $J$ = 8.8 Hz, 6-Ph′), 6.65 (d, 1H, $J$ = 9.2 Hz, 5-Ph′), 6.63 (s, 1H, 3-Ph′), 5.16 (d, 1H, $J$ = 5.6 Hz, 2-OH), 4.99 (d, 1H, $J$ = 2.8 Hz, 3-OH), 4.96 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.57 (t, 1H, $J$ = 5.6 Hz, 6-OH), 3.93 (s, 3H, $OCH_3$-2′), 3.82 (s, 3H, $OCH_3$-4′), 3.77 (dd, 1H, $J_1$ = 5.2 Hz, $J_2$ = 8.8 Hz, H-6b), 3.72 (dd, 1H, $J_1$ = 5.2 Hz, $J_2$ = 12.8 Hz, H-6a), 3.44 (m, 1H, H-5), 3.27 (m, 1H, H-2), 3.12–3.19 (m, 3H, Glu-CH, H-3, H-4), 2.99–3.07 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 3.92. Found: C, 53.80; H, 6.47; N, 3.91.

**4.1.5.11. *N*-(β-D-Glucopyranosylmethyl)-4-acetoxy benzamide (11k).** Yield 56% from **5**, a white solid. mp 172–174 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.34 (s, 1H, –NH–), 7.88 (d, 2H, $J$ = 8.0 Hz, 2-Ph′, 6-Ph′), 7.23 (d, 2H, $J$ = 8.0 Hz, 3-Ph′, 5-Ph′), 5.10 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.95 (d, 1H, $J$ = 3.6 Hz, 3-OH), 4.92 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.43 (t, 1H, $J$ = 5.6 Hz, 6-OH), 3.85 (dd, 1H, $J_1$ = 5.2 Hz, $J_2$ = 11.6 Hz, H-6b), 3.66 (dd, 1H, $J_1$ = 4.8 Hz, $J_2$ = 12.8 Hz, H-6a), 3.37–3.42 (m, 1H, H-5), 3.17–3.24 (m, 3H, Glu-CH, H-3, H-4), 3.08 (t, 1H, $J$ = 8.8 Hz, H-2), 2.92–3.03 (m, 2H, H-1, Glu-CH), 2.29 (s, 3H, –OAc). Anal. Calcd for $C_{16}H_{21}NO_8$: C, 54.08; H, 5.96; N, 3.94. Found: C, 54.11; H, 5.98; N, 3.92.

**4.1.5.12. *N*-(β-D-Glucopyranosylmethyl) furoylamide (11l).** Yield 42% from **5**, a white solid. mp 198–200 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.12 (s, 1H, –NH–), 7.84 (s, 1H, 5-furan′), 7.13 (d, 1H, $J$ = 3.2 Hz, 3-furan′), 6.63 (t, 1H, $J$ = 1.6 Hz, 4-furan′), 5.11 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.96 (d, 1H, $J$ = 5.6 Hz, 3-OH), 4.93 (d, 1H, $J$ = 5.6 Hz, 4-OH), 4.48 (t, 1H, $J$ = 5.6 Hz, 6-OH), 3.79 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 11.6 Hz, H-6b), 3.66 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 10.8 Hz, H-6a), 3.39–3.42 (m, 1H, H-5), 3.13–3.20 (m, 3H, Glu-CH, H-3, H-4), 3.08 (t, 1H, $J$ = 9.2 Hz, H-2), 2.90–3.03 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{12}H_{17}NO_7$: C, 50.17; H, 5.96; N, 4.88. Found: C, 50.15; H, 5.97; N, 4.90.

**4.1.5.13. *N*-(β-D-Glucopyranosylmethyl)thienylamide (11m).** Yield 50% from **5**, a white solid. mp 224–225 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.37 (s, 1H, –NH–), 7.81 (d, 1H, $J$ = 3.2 Hz, 2-thiophene′), 7.76 (d, 1H, $J$ = 5.2 Hz, 4-thiophene′), 7.15 (t, 1H, $J$ = 8.4 Hz, 3-thiophene′), 5.07 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.95 (d, 1H, $J$ = 4.8 Hz, 3-OH), 4.91 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.41 (t, 1H, $J$ = 6.0 Hz, 6-OH), 3.81 (dd, 1H, $J_1$ = 5.6 Hz, $J_2$ = 11.6 Hz, H-6b), 3.68 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 10.8 Hz, H-6a), 3.45 (m, 1H, H-5), 3.14–3.22 (m, 3H, Glu-CH, H-3, H-4), 3.11 (t, 1H, $J$ = 8.4 Hz, H-2), 3.04–3.29 (m, 2H, H1, Glu-CH). Anal. Calcd for $C_{12}H_{17}NO_6S$: C, 47.52; H, 5.65; N, 4.62; S, 10.57. Found: C, 47.56; H, 5.63; N, 4.60; S, 10.55.

**4.1.5.14. *N*-(β-D-Glucopyranosylmethyl) cinnamide (19a).** Yield 55% from **5**, a white solid. mp 212–214 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.09 (s, 1H, –NH–), 7.57 (d, 2H, $J$ = 7.6 Hz, 2-Ph′, 6-Ph′), 7.44 (d, 1H, $J$ = 15.6 Hz, C=C*H*–Ph′), 7.32–7.42(m, 3H, 3-Ph′, 4-Ph′, 5-Ph′), 6.73 (d, 1H, $J$ = 15.6 Hz, *H*C=CH–Ph′), 5.08 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.96 (d, 1H, $J$ = 4.8 Hz, 3-OH), 4.94 (d, 1H, $J$ = 5.6 Hz, 4-OH), 4.41 (t, 1H, $J$ = 4.8 Hz, 6-OH), 3.79 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 12.8 Hz, H-6b), 3.69 (dd, 1H, $J_1$ = 7.6 Hz, $J_2$ = 11.2 Hz, H-6a), 3.39–3.46 (m, 1H, H-5), 3.07–3.18 (m, 4H, Glu-CH, H-2, H-3, H-4), 3.02 (t, 1H, H-1, $J$ = 9.2 Hz), 2.91–2.97 (m, 1H, Glu-CH). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 59.43; H, 6.65; N, 4.33. Found: C, 59.43; H, 6.66; N, 4.34.

**4.1.5.15. *N*-(β-D-Glucopyranosylmethyl)-4-hydroxy cinnamide (19b).** Yield 45% from **5**, a white solid. mp 236–238 °C. $^1$H NMR 400 MHz, DMSO-$d_6$): $\delta$ 9.89 (s, 1H, –OH–Ph′), 7.98 (s, 1H, –NH–), 7.39 (d, 2H, $J$ = 8.0 Hz, 2-Ph′, 6-Ph′), 7.34 (d, 1H, $J$ = 15.6 Hz, C=C*H*–Ph′), 6.79 (d, 2H, $J$ = 8.0 Hz, 3-Ph′, 5-Ph′), 6.51 (d, 1H, $J$ = 15.6 Hz, *H*C=CH-Ph′), 5.09 (d, 1H, $J$ = 4.8 Hz, 2-OH), 4.94–4.96 (m, 2H, 3-OH, 4-OH), 4.44 (t, 1H, $J$ = 6.0 Hz, 6-OH), 3.76 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 11.6 Hz, H-6b), 3.67 (dd, 1H, $J_1$ = 7.6 Hz, $J_2$ = 10.8 Hz, H-6a), 3.40–3.45 (m, 1H, H-5), 3.15–3.18 (m, 1H, H-4), 3.12–3.08 (m, 3H, Glu-CH, H-2, H-3), 2.89–3.01 (m, 1H, Glu-CH, H-1). Anal. Calcd for $C_{126}H_{21}NO_7$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.60; H, 6.22; N, 4.14.

**4.1.5.16. *N*-(β-D-Glucopyranosylmethyl)-4-acetoxy cinnamide (19c).** Yield 48% from **5**, a white solid. mp 165–168 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.10 (s, 1H, –NH–), 7.62 (d, 2H, $J$ = 8.0 Hz, 2-Ph′, 6-Ph′), 7.45 (d, 1H, $J$ = 15.2 Hz, C=C*H*–Ph′), 7.18 (d, 2H, $J$ = 8.0 Hz, 3-Ph′, 5-Ph′), 6.70 (d, 1H, $J$ = 15.6 Hz, *H*C=CH–Ph′), 5.09 (d, 1H, $J$ = 4.8 Hz, 2-OH), 4.97 (d, 1H, $J$ = 4.0 Hz, 3-OH), 4.94 (d, 1H, $J$ = 5.2 Hz, 4-OH), 4.44 (t, 1H, $J$ = 10.0 Hz, 6-OH), 3.80 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 12.8 Hz, H-6b), 3.69 (dd, 1H, $J_1$ = 8.4 Hz, $J_2$ = 10.4 Hz, H-6a), 3.41–3.44 (m, 1H, H-5), 3.10–3.18 (m, 4H, H-4, H-2, H-3, Glu-CH), 3.02 (t, 1H, $J$ = 8.4 Hz, H-1), 2.91–2.96 (m, 1H, Glu-CH), 2.28 (s, 3H, –OAc). Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.71; H, 6.07; N, 3.69.

**4.1.5.17. *N*-(β-D-Glucopyranosylmethyl)-3-methoxy-4-hydroxy cinnamide (19d).** Yield 54% from **5**, a white solid. mp 198–201 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.45 (s, 1H, –OH–Ph′), 7.92 (s, 1H, –NH–), 7.35 (d, 1H, $J$ = 15.2 Hz, C=C<u>H</u>–Ph′), 7.14 (d, 1H, $J$ = 2.4 Hz, 6-Ph′), 6.99 (dd, 1H, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 2-Ph′), 6.79 (d, 1H, 8.0 Hz, 5-Ph′), 6.53 (d, 1H, $J$ = 15.6 Hz, *H*C=CH–Ph′), 5.07 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.91–4.95 (m, 2H, 3-OH, 4-OH), 3.67–3.72 (m, 1H, 6-OH), 4.42 (dd, 1H, $J_1$ = 4.8 Hz, $J_2$ = 7.6 Hz, H-6b), 3.77(dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 12.4 Hz, H-6a), 3.40–3.46 (m, 1H, H-5), 3.06–3.18 (m, 4H, H-4, H-2, H-3, Glu-CH), 2.90–3.04 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{17}H_{23}NO_8$: C, 55.28; H, 6.28; N, 3.79. Found: C, 55.31; H, 6.26; N, 3.80.

**4.1.5.18. *N*-(β-D-Glucopyranosylmethyl)-3,4-diacetoxy cinnamide (19e).** Yield 52% from **5**, a white solid. mp 160–162 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.10 (s, 1H, –NH–), 7.49–753 (m, 2H, 2-Ph′, 6-Ph′), 7.43 (d, 1H, $J$ = 15.6 Hz, C=C*H*–Ph′), 7.31 (d, 1H, $J$ = 8.0 Hz, 5-Ph′), 6.71 (d, 1H, $J$ = 15.6 Hz, *H*C=CH–Ph′), 5.10 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.94–4.97 (m, 2H, 3-OH, 4-OH), 4.44 (m, 1H, 6-OH), 3.80 (dd, 1H, $J_1$ = 6.4 Hz, $J_2$ = 12.0 Hz, H-6b), 3.69 (dd, 1H, $J_1$ = 6.0 Hz, $J_2$ = 16.0 Hz, H-6a), 3.36 (m, 1H, H-5), 3.15–3.10 (m, 4H, H-4, H-2, H-3, Glu-CH), 2.94–3.03 (m, 2H, H-1, Glu-CH). Anal. Calcd for $C_{20}H_{25}NO_{10}$: C, 54.67; H, 5.73; N, 3.19. Found: C, 54.69; H, 5.71; N, 3.20.

**4.1.6. 3,4,5-Triacetoxybenzoic acid (13)**

Gallic acid (3.4 g, 20 mmol) was dissolved in acetic anhydride (11.1 ml, 120 mmol) at 0 °C, then pyridine (2 ml) was added, and the mixture was stirred at rt. overnight. The resulting mixture was poured into ice-water, and neutralized to pH 2 with HCl and extracted with EtOAc (30 ml ×2). The organic phase was washed with $H_2O$ and saturated brine, dried over $Na_2SO_4$, filtered and concentrated to get **13** as a white solid 4.6 g. Yield 78%. mp 170–172 °C.

**4.1.7. 3,4,5-Triacetoxybenzoyl chloride (14)**

To dissolve **13** (1.0 g, 3.38 mmol) in DCM (20 ml), $SOCl_2$ (0.73 ml, 10.13 mmol) was added dropwise and a little of DMF was added. The mixture was refluxed for 3 h. After the solvent was evaporated under reduced pressure, white solid was obtained which was recrystallized with carbon tetrachloride to afford compound **14** 1.0 g. Yield 94.2%. mp 106–107 °C.

**4.1.8. *N*-(β-D-Glucopyranosylmethyl)-3,4-diacetoxy cinnamide (15)**

To a solution of **5** (400 mg, 1.42 mmol) in DMF/DCM (5 ml/10 ml), triethylamine (0.4 ml, 2.84 mmol) was added. Then solution of **14** (447 mg, 1.42 mmol) in DMF was added at 0 °C slowly to above mixture, stirred at rt. until the reaction completed. Remove the solvent and $H_2O$ (20 ml) was added, then the mixture was extracted with EtOAc (30 ml ×2). The organic phase was dried and concentrated to give **15** as a white solid (600 mg, 75.5%), which were used directly for the next step without further purification.

**4.1.9. *N*-(β-D-Glucopyranosylmethyl)-3,4,5-triacetoxy benzamide (16)**

The mixture of **15** (300 mg, 0.54 mmol) in AcOH/$H_2O$ (20 ml/10 ml) was stirred at 90 °C for 1 h. Removed the solvent under reduced pressure and the crude product **16** was obtained which was purified by silica-gel chromatography column eluting with $CHCl_3$:MeOH = 8:1 to give **16** (100 mg, 54.7%) as white solid. mp143–145 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.46 (s, 1H, –NH–), 7.71 (s, 2H, 2-Ph′, 6-Ph′), 5.08 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.95 (d, 1H, $J$ = 4.0 Hz, 3-OH), 4.92 (d, 1H, $J$ = 4.8 Hz, 4-OH), 4.39 (t 1H, $J$ = 5.6 Hz, 6-OH), 3.84 (dd, 1H, $J_1$ = 5.6 Hz, $J_2$ = 12.8 Hz, H-6b), 3.66 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 11.6 Hz, H-6a), 3.39–3.44 (m, 1H, H-5), 3.13–3.24 (m, 3H, H-2, Glu-CH, H-3), 3.08 (t, 1H, $J$ = 9.2 Hz, H-4), 2.92–3.03 (m, 2H, H-1, Glu-CH), 2.33 (s, 3H, 4-OAc), 2.32 (s, 6H, 3-OAc, 5-OAc). Anal. Calcd for $C_{20}H_{25}NO_{12}$: C, 50.96; H, 5.35; N, 2.97. Found: C, 50.99; H, 5.32; N, 2.95.

**4.1.10. *N*-(β-D-Glucopyranosylmethyl)-*p*-toluenesulfonamide (22)**

To the solution of **5** (500 mg, 1.77 mmol) in DMF (10 ml), triethylamine (0.77 ml, 5.31 mmol) was added. Then the solution of **20** (339 mg, 1.77 mmol) in DMF was added at 0 °C slowly. The mixture was stirred at rt. until the reaction completed. Removed the solvent and $H_2O$ (20 ml) was added. The mixture was extracted with EtOAc (30 ml ×2). The organic phase was dried over $Na_2SO_4$, filtered and concentrated to get **21** (600 mg, 70.0%) as a white solid which was directly for the next step without further purification.

The **21** was dissolved in AcOH/$H_2O$ (10 ml/15 ml) and the mixture was stirred at 90 °C for 1 h. The solvent was evaporated under reduced pressure to give the crude product **22** (300 mg, 54.7%), which was purified by silica-gel chromatography column eluting with $CHCl_3$/MeOH = 5/1 as white solid. mp 84–86 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.68 (d, 2H, $J$ = 8.0 Hz, 2-Ph′, 6-Ph′), 7.49 (dd, 1H, $J_1$ = 3.2 Hz, $J_2$ = 8.0 Hz, –NH–), 7.40 (d, 2H, $J$ = 8.0 Hz, 3-Ph′, 5-Ph′), 5.02 (d, 1H, $J$ = 5.2 Hz, 2-OH), 4.90–4.93 (m, 2H, 3-OH, 4-OH), 4.43–4.46 (m, 1H, 6-OH), 3.64–3.59 (m, 1H, H-6b), 3.25–3.34 (m, 2H, H-5, H-6a), 2.94–3.06 (m, 3H, H-2, Glu-CH, H-3), 2.85–2.91 (m, 1H, H-4), 2.78–2.83 (m, 1H, H-1), 2.56–2.63 (m, 1H, Glu-CH), 2.39 (s, 3H, -$CH_3$). Anal. Calcd for $C_{14}H_{21}NO_7S$: C, 48.40; H, 6.09; N, 4.03; S, 9.23. Found: C, 48.43; H, 6.10; N, 4.01; S, 9.21.

### 4.2. Biological evaluation

#### 4.2.1. α-Glucosidase inhibitory activity

The α-glucosidase inhibitory activity of the newly synthesized compounds (Table 1) were evaluated towards yeast α-glucosidase (from *Saccharomyces cerevisiae*) and rat intestinal α-glucosidase (maltase and sucrase).

**4.2.1.1. Inhibitory activity towards yeast α-glucosidase.** The inhibitory activity of target compounds towards yeast α-glucosidase was determined as described in the literature[24,25] with a slight modification and was expressed as the concentration required for 50% inhibition of α-glucosidase activity ($IC_{50}$). Briefly, α-glucosidase from Saccharomyces cerevisiae (EC. 3.2.1.20, Sigma Aldrich Chemical Co. G0660) was dissolved in phosphate buffer (pH 6.86) at a final concentration of 10 U/ml. The enzyme solution (10 μl) preincubated with 50 μl of the target products at varying concentrations in phosphate buffer (pH 6.86) at 37 °C for 15 min. The reaction was started by the addition of 20 μl 4-nitrophenyl α-D-glucopyranoside (*p*-NPG, final concentration 5.3 mM) and stopped after 15 min with 50 μl of 0.5 M $Na_2CO_3$. The amount of released 4-nitrophenol from p-NPG was measured as the absorbance at 405 nm. The assay was performed with eight different concentrations around the $IC_{50}$ values, approximately estimated in previous experiments. In each set of experiments the assay was performed in triplicate and at least two times. The increased absorbance was compared with that of the control containing 50 μl of phosphate buffer in place of the test solution. $IC_{50}$ values were measured graphically by a plot of percent activity versus log of the test compound concentration.

**4.2.1.2. Inhibitory activity towards rat intestinal maltase and sucrose.** The α-glucosidase from rats intestinal brush border membranes were prepared according to literature method[24] that were used as the enzyme source of rat intestinal maltase and sucrose. For maltase activity determine, maltose was used as substrate. The D-glucose produced from hydrolysis of maltose was determined colorimetrically according to the designated method of Glucose Test Kit (Shanghai Rongsheng Biotech Co., Ltd). The enzyme solution 10 μl was preincubated with 50 μl of the target products at varying concentrations in phosphate buffer (pH 6.86) at 37 °C for 15 min. Then the substrate (50 mM of maltose, 20 μl) was added, and the reaction was continued to incubate for 60 min, and stopped in the boiling water bath. Then the above solution (10 μl) was added to the mixture of reagent A (500 μl, containing 10.6 mM of phenol) and reagent B (500 μl: containing of 70 mM phosphate buffer, 0.8 mM of 4-aminoantipyrine, >10 U/ml of glucose oxidase and > 10 U/ml of peroxidase, pH 7.0), and then reaction mixture was incubated at 37 °C for 15 min. The amount of D-glucose formed was measured as the absorbance at 505 nm. The assay was performed with five different concentrations around the $IC_{50}$ values and in each set of experiments the assay was performed in triplicate and at least 2 times.

Sucrase inhibitory activities were measured by the same procedure described above with using sucrose as substrate.

#### 4.2.2. Kinetic study of rat intestinal α-glucosidase inhibition

The inhibition kinetics of compound **19e** towards rat intestinal α-glucosidase was continuously measured.

The reaction was performed as described in Section 4.2.1.2 with inhibitors of various concentrations. Inhibition types for the inhibitors were determined by double-replot of slope versus the reciprocal of the substrate concentration. The $K_i$ value for **19e** was determined by measuring the releasing rate of glucose from substrate by α-glucosidase at varying inhibitor concentrations. Data was plotted in Lineweaver–Burk plots (1/rate vs 1/[substrate]) (Fig. 3). It revealed that compound **19e** was a competitive inhibitor with $K_i$ value of 4.85 μM for maltase, and 17.1 μM for sucrase.

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