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•Special topic•

Novel carbohydrate-triazole derivatives as potential *α*-glucosidase inhibitors

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[ABSTRACT] A series of novel pyrano[2, 3-d]trizaole compounds were synthesized and their *α*-glucosidase inhibitory activities were evaluated by *in vitro* enzyme assay. The experimental data demonstrated that compound **10f** showed up to 10-fold higher inhibition (IC_{50} 74.0 ± 1.3 μmol·L^{-1}) than acarbose. The molecular docking revealed that compound **10f** could bind to *α*-glucosidase *via* the hydrophobic, *π*-*π* stacking, and hydrogen bonding interactions. The results may benefit further structural modifications to find new and potent *α*-glucosidase inhibitors.

[KEY WORDS] Pyrano[2, 3-d]trizaole; *α*-Glucosidase inhibitor; Enzyme assay; Molecular docking
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Introduction

Glucosidases are enzymes involved in hydrolysis of interglycosidic bonds, which play significant roles in metabolic pathways, closely relating to carbohydrate digestion in the intestinal tract [1]. A number of studies have proved that the inhibition of *α*-glucosidases can lower postprandial plasma glucose levels in human body [2]. Therefore, *α*-glucosidase has been recognized as an important target for the treatment of type II diabetes [3]. In addition, *α*-glucosidases have been also regarded as therapeutic targets for many other carbohydrate processing-related diseases such as cancers [4], hepatitis [5], and HIV [6]. Some related compounds are on the clinical trial. Nowadays, there are four *α*-glucosidase inhibitors [7, 8] (acarbose, voglibose, miglitol, and emiglitate) that have been introduced to the market for the treatment of type II diabetes mellitus. Meanwhile, plenty of unpleasant side-effects of these inhibitors have been widely acknowledged, including flatulence, abdominal pain, and diarrhea [9]. Hence, the research and development of new types of *α*-glucosidase inhibitors are still in great demand.

Azole-containing glycopyranosides with the half-chair conformation may mimic the oxocarbenium transition state in the hydrolyzing process of glycosidic bonds [10, 11]. Therefore, a number of glycoazoles (shown in Fig. 1) have been regarded as the potential inhibitors of glycosidases. The natural product, nagstatin (**1**) [12], is known as a potent *N*-acetyl-*β*-D-glucosaminidase (NAG) inhibitor. Glycoazoles bearing imidazole (**2**, **3**) [13, 14], triazole (**4**) [15], and tetrazole (**5**) [16] have been synthesized as different glycosidase inhibitors. Besides, it is noteworthy that the lack of hydroxymethyl group may impair the intensity of binding forces with glycosidases according to the previous reports [17, 18].

On the other hand, 1, 2, 3-triazoles have drawn much attention in the drug discovery field since the 'click' chemistry concept is introduced [19, 20], which have been widely applied to the medicinal chemistry. Fusing the scaffold of carbohydrates and 1, 2, 3-triazoles (shown in Fig. 1) to find new glycosidase inhibitors is a general attempt. Rossi *et al.* [21] designed and synthesized a series of 1-glycosyl-4-phenyl triazoles *via* the click reaction between glycosyl azides and phenylacetylene. The galactotriazole **6** dispalyed modest inhibition of *Escherichia coli β*-galactosidase. In another work, Perion *et al.* [22] synthesized carbohydrate-triazole derivatives that are structurally similar to acarbose, and it was found that compound **7** showed 2-fold higher inhibitory activity against yeast *α*-glucosidase than acarbose. Ferreira *et al.* [23] reported the synthesis of a series of 4-substituted 1, 2, 3-triazoles conjugated with carbohydrates. Among these synthetic com-

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These authors have no conflict of interest to declare.

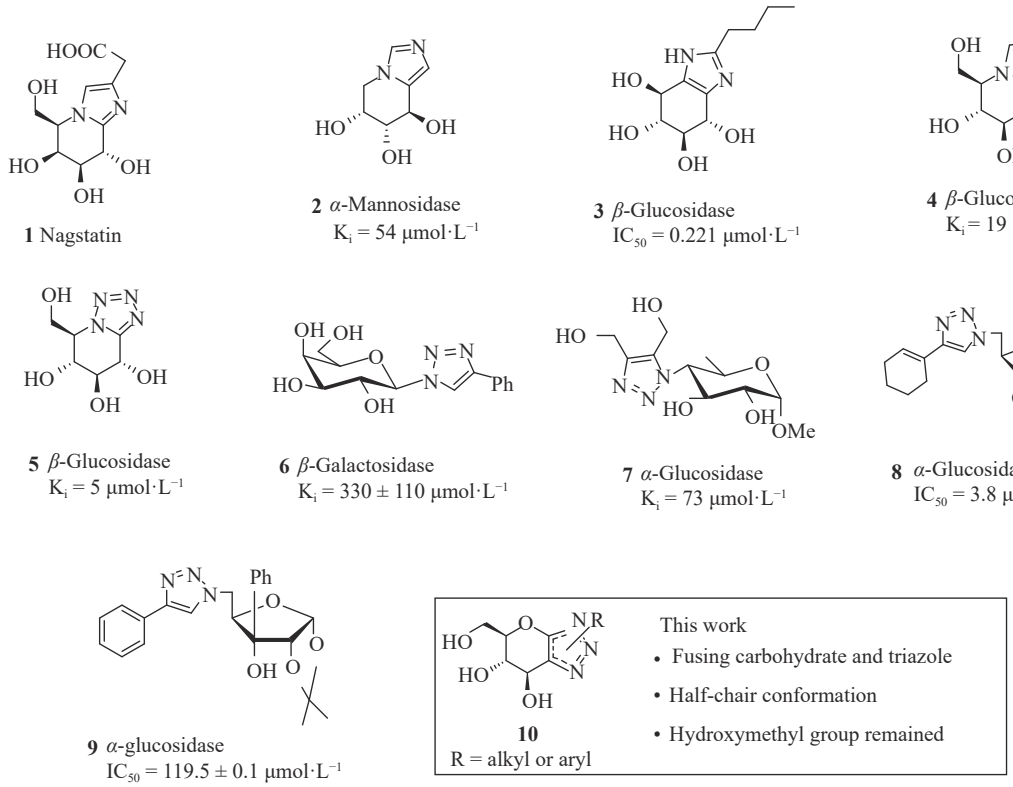


Fig. 1 Structures of glycoazole-type glycosidase inhibitors

pounds, the 4-phenyl-1, 2, 3-triazole derivative **8** showed up to 25-fold higher inhibitory potency than acarbose. In a following work [24], the isopropylidene moiety was moved to the C-1 and C-2 positions and a phenyl group was introduced at the C-3 position of the carbohydrate ring to afford compound **9** with a moderate *α*-glucosidase inhibition. Although glycoazole derivatives as glycosidase inhibitors are disclosed, the pyrano[2, 3-d]triazole type compounds (compound **10**) as glycosidase inhibitors have never been explored. Therefore, we design a series of carbohydrate-triazole ring-fused derivatives (compounds **10a**−**10l**, Fig. 2), in which the half-chair conformation and the hydroxymethyl functionality are kept. These compounds can be regarded as derivatives of the natural product nagstatin (**1**). After synthesizing these compounds, their inhibitory activities against *α*-glucosidases will be evaluated.

Results and Discussion

Chemistry

The synthetic route for the designed target compounds **10a**−**10l** is described in Scheme 1. Starting from the commercially available 3, 4, 6-tri-*O*-acetyl-D-glucal (**11a**), after deacetylation and benzylation, compound **12a** was obtained. The nitro group was smoothly introduced to the C-2 position of glucal **12a**, affording 2-nitro-glucal **13a**. Following the reported method [25, 26], compound **13a** was reacted with sodium azide to afford the key carbohydrate-triazole compound **14a**. Debenzylation of **14a** gave compound **10a**. The alkylation or arylation of **14a** under different conditions provided the benzyl-protected carbohydrate-triazole derivatives **15b**−**15g**. Finally, removal of the benzyl groups by hydrogenolysis using $Pd(OH)_2/C$ as catalyst afforded the target compounds **10b**−**10g**. Starting from the corresponding galactal derivative **11b** and following the same route, several galacto-triazole-type compounds **10h**−**10l** were obtained. All the compounds were isolated and fully characterized by their ^{1}H NMR, ^{13}C NMR, and HRMS. The position of alkyl substitution was verified through the 2D NMR analysis. We take compounds **15b** and **10h** as examples. In the HMBC spectra, there are no signals between the hydrogen atoms of the methylene directly linked to the nitrogen and the 1′ or 2′ carbon atom of the pyranose ring. Based on these observations, the alkyl groups are linked at the 2-N position of triazole ring. As for the position of phenyl substitution, we take compound **15f** as an example. The NOESY data of **15f** showed that the 2′ and 6′ hydrogen atoms of the phenyl substituent are correlated with the 5′ and 6′ hydrogen atoms of the pyranose ring, and are also correlated with the hydrogen of methylene in the benzyl group linked to the hydroxymethyl group. Therefore, it was proved that the phenyl group is connected to the 3-N position of triazole ring.

α-Glucosidase inhibitory activities

The synthetic carbohydrate-triazole derivatives **10a**−**10l** were initially evaluated at 200 μmol·L^{-1} concentration for their *α*-glucosidase inhibitory activities by *in vitro* enzyme assay. The commercially available *α*-glucosidase (G5003-

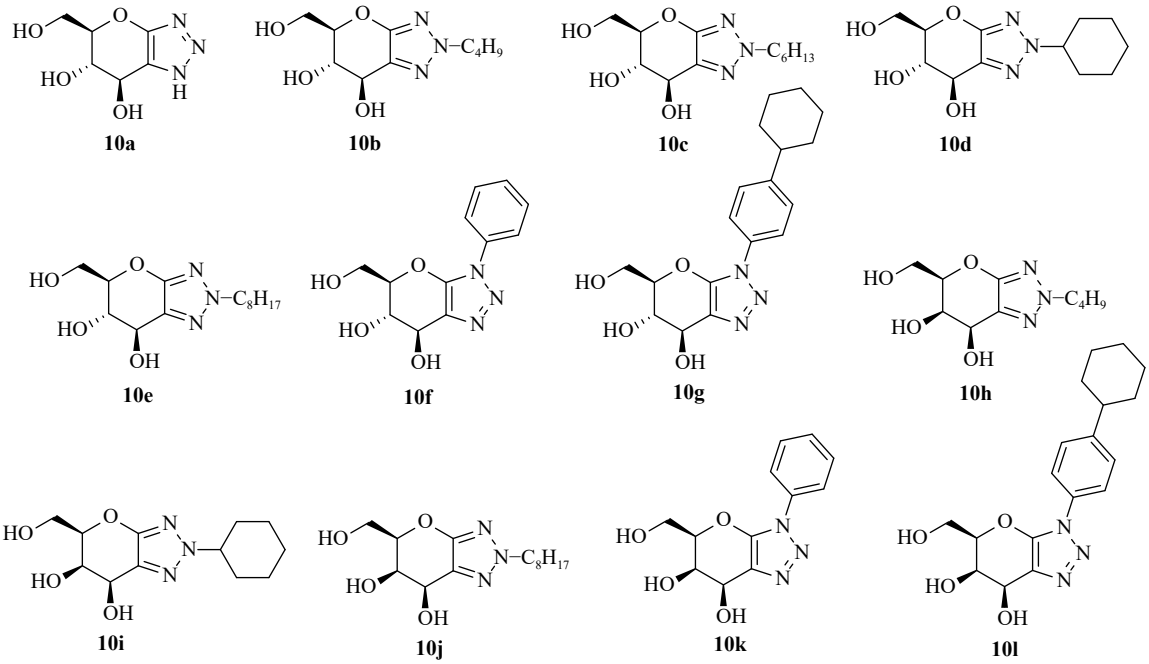
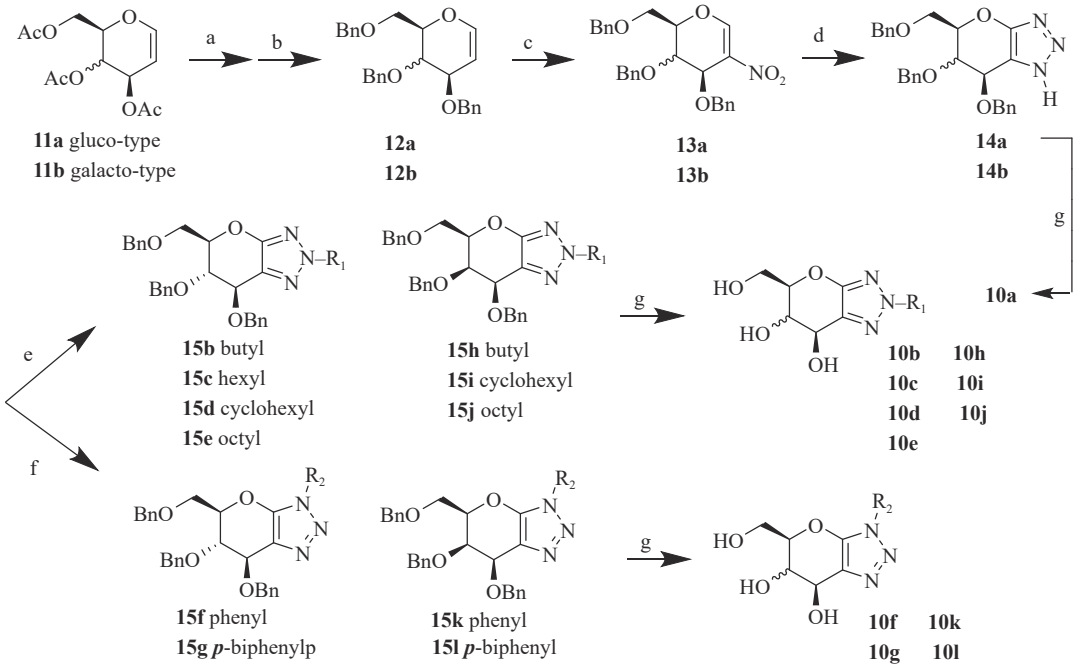


Fig. 2 Structures of target compounds 10a−10l



Scheme 1 Synthetic route of final compounds. Reagents and conditions: (a) NaOMe, MeOH/CH_2Cl_2 = 1/2, r.t., 0.5 h; (b) NaH, BnBr, DMF, 0 °C to r.t., 5 h, 65% over two steps; (c) HNO_3, Ac_2O, −50 °C to r.t.; then Et_3N, CH_2Cl_2, 0 °C to r.t., 0.5 h, 60%; (d) NaN_3, PTSA, DMF, 60 °C, 10 h, 47%; (e) NaH, alkyl iodide, 0 °C to r.t., 5 h, 53%−70%; (f) aryl iodide, CuO, $Fe(acac)_3$, Cs_2CO_3, DMF, 100 °C, 30 h, 36line-height-add:0.3pt−43%; (g) H_2, $Pd(OH)_2$/C, 10 h, 93%−97%

100UN, Sigma) was used, acarbose was used as a positive control and DMSO as the blank control for this assay. The results are shown in Table 1. Among all the screened compounds, compound **10f** with phenyl ring showed the best *α*-glucosidase inhi-bitory activity (IC_{50} 74.0 ± 1.3 μmol·L^{-1}). It is 10-fold more potent than the positive control acarbose (IC_{50} 787.3 ± 5.3 μmol·L^{-1}). Subsequently, we tested the inhibitory selectivity to other glycosidases of these compounds. As shown in Table 2, compounds **10a**, **10b**, **10c**, **10f** displayed nearly no inhibitory activities at 200 μmol·L^{-1} concen-

Table 1 IC_{50} values (μmol·L^{-1}) of the final compounds for the inhibition of *α*-glucosidase (mean ± SD, *n* = 3)

Compounds	IC_{50}/(μmol·L^{-1})	Compounds	IC_{50}/(μmol·L^{-1})
Acarbose	787.3 ± 5.3		
10a	NI[a]	**10g**	NI
10b	> 200[b]	**10h**	NI
10c	> 200[b]	**10i**	NI
10d	NI	**10j**	NI
10e	NI	**10k**	NI
10f	74.0 ± 1.3	**10l**	NI

[a] NI, less than 2% inhibitory activities at 200 μmol·L^{-1}; [b] **10b** and **10c** showed 10.6% and 9.9% inhibitory activities at 200 μmol·L^{-1}, respectively

Table 2 The selectivity of compounds to other glycosidases[a]

Compounds	*β*GAL	*α*GCB	*β*GAO
10a	3.84%	−0.26%	2.58%
10b	−11.48%	−0.57%	4.86%
10c	−4.36%	−2.01%	0.71%
10f	−4.58%	−0.41%	−0.38%

[a] Values are the mean of three experiments at 200 μmol·L^{-1}

tration against the almond *β*-glucosidase (*β*GAL) (49290-250MG, Sigma), *α*-galactosidase from green coffee beans (*α*GCB) (S10065-5U, Yuanye), or *β*-galactosidase from *Aspergillus oryzae* (*β*GAO) (S27128-25ku, Yuanye). Based on these results, the preliminary structure-activity relationships of this class of compounds could be summarized. It seemed that the glucose configuration and phenyl group are necessary for the inhibitory activity of this series of compounds. The flexibility of alkyl groups might hinder the binding of compounds to the active site of α-glucosidase.

The molecular docking results

The crystallographic structure for the *α*-glucosidase has not been settled, but a few homology models have been publishied [23, 27, 28]. Therefore, the homology model for the *α*-glucosidase was established by using the same method as reported by Taha *et al.* [28]. *Saccharomyces cerevisiae* isomaltase (PDB code 3AJ7) with 72.4% of sequence identity with the target enzyme was chosen as the template for homology modelling. The structure of *α*-glucosidase for *Saccharomyces cerevisiae* was built by the Prime module of Schrodinger Suites, and the docking simulation was performed by the Glide module. The results of the molecular docking showed that compound **10f** has stronger binding affinities to the *α*-glucosidase than compound **10b**. The phenyl ring of **10f** could form the *π*-*π* interaction and hydrophobic interaction with the residue Phe-158, whereas the *n*-butyl group of **10b** showed weak affinity with the residue Phe-157. In addition, the other two nitrogen atoms have hydrogen bonding interactions with the residue Gln-181, the 3′ and 4′ hydroxyl groups of **10f** could form two hydrogen bonds with Asp-214 and the hydroxymethyl group of **10f** could form hydrogen bond with the residue Asp-349 (Fig. 3).

Conclusions

In conclusion, we designed and synthesized a series of new pyrano[2, 3-d]trizaole derivatives. All of the compounds were screened for their *α*-glucosidase inhibitory activities. Among these synthetic compounds, **10f** showed the potent *α*-glucosidase inhibitory activity (IC_{50} 74.0 ± 1.3 μmol·L^{-1}), which is 10-fold more active than the positive control acarbose. Meanwhile, compound **10f** showed good inhibitory selectivity to other glycosidases. The inhibitory activity of **10f** was rationalized by the molecular docking simulation, showing the strong binding to *α*-glucosidase *via* the hydrophobic interaction, *π*-*π* stacking interaction, and hydrogen bonding interaction. This work may serve as a useful starting point in the discovery of new *α*-glucosidase inhibitors.

Experimental

General procedures

All reagents were purchased as reagent grade and used without further purification unless otherwise indicated. Organic solutions were removed by rotary evaporation with a

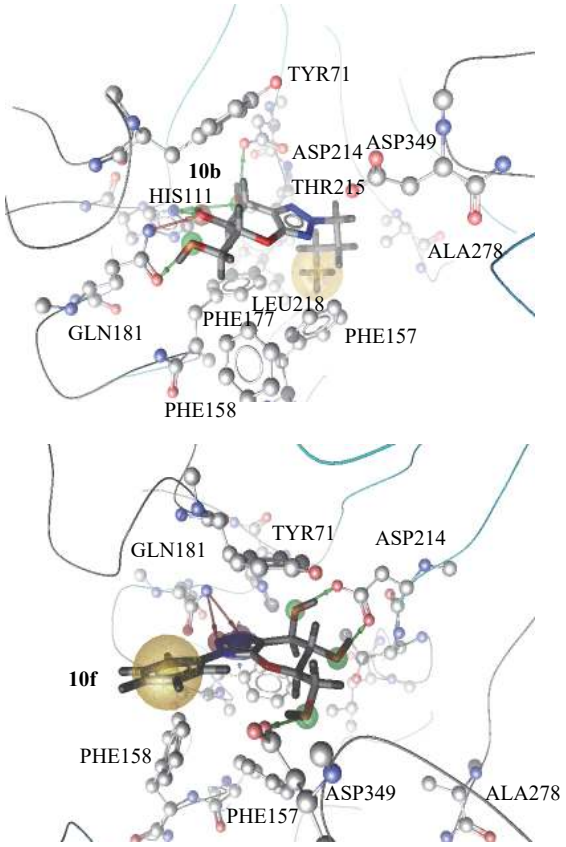


Fig. 3 Compounds 10b (upper) and 10f (down) were docked to the binding pocket of *Saccharomyces cerevisiae* *α*-glucosidase

water bath temperature below 50 °C. Reactions were monitored by thin-layer chromatography (TLC) analysis, and stained by the solution of potassium permanganate or acidic ceric ammonium molybdate. The product was purified by column chromatography on silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Bruke 400 MHz or 600 MHz spectrometer at 20 °C. The residual solvent of $CDCl_3$ (7.26 ppm for ^{1}H NMR), methanol-d_4 (3.31 ppm for ^{1}H NMR) or TMS (0 ppm for ^{1}H NMR) was used as an internal standard for ^{1}H NMR spectra, and the residual solvent of $CDCl_3$ (77.16 ppm for ^{13}C NMR) or methanol-d_4 (49.15 ppm for ^{13}C NMR) was used as an internal standard for ^{13}C NMR. Chemical shifts (δ) are recorded in ppm, coupling constants (*J*) are reported in Hz. High resolution mass spectra were obtained using a Fourier transform ion cyclotron resonance mass spectrometer.

*General procedure for the synthesis of compounds **14a** and **14b***

2-Nitroglycal (1.0 g, 2.17 mmol) and NaN_3 (0.21 g, 3.25 mmol) were stirred in DMF (5 mL), *p*-TsOH (0.21 g, 1.08 mmol) was then carefully added to the mixture. The mixture was stirred at 60 °C in nitrogen atmosphere for 10 h. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature, quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to afford the carbohydrate-trizaole **14a** or **14b** as light yellow oil.

*General procedure for the synthesis of compounds **15b**−**e** and **15h**−**j***

The carbohydrate-triazole **14a** (or **14b**) (0.65 mmol) was dissolved in 3 mL of DMF. NaH (0.98 mmol) and alkyl iodide (0.98 mmol) were added into the mixture at 0 °C. The mixture was stirred at room temperature for 3 h. After completion of the reaction (detected by TLC), the reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford the product as light yellow oil.

*General procedure for the synthesis of compounds **15f**, **15g**, **15k** and **15l***

The carbohydrate-triazole **14a** (or **14b**) (0.65 mmol) was dissolved in 3 mL of DMF. Aryl iodide (1.30 mmol), CuO (0.33 mmol), $Fe(acac)_3$ (0.98 mmol) and Cs_2CO_3 (1.3 mmol) were added into the mixture under nitrogen atmosphere. The mixture was stirred at 100 °C under reflux. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature, quenched with H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford the product as light oil.

General procedure for removal of the benzyl group

To a solution of the benzyl-protected compound (100 mg) in MeOH/dichloromethane (2 mL/2 mL) were added 10% $Pd(OH)_2$/C (30 mg) and two drops of 2mol·L^{-1} HCl. The mixture was stirred under H_2 atmosphere (4 atm.) overnight. The solution was filtered through Celite, and the filtrate was removed under rotary evaporation, and the residue was purified by flash column chromatography on silica gel (MeOH/dichloromethane = 1/10), and further purified by C-18 reversed phase column chromatography (H_2O) to afford the final product.

Data for compounds

*(5R, 6S, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-1, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole (**14a**)*: Yield: 47%. $[\alpha]_D^{25}$ 16.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.69 (s, 1H), 7.35−7.25 (m, 15H), 4.92 (d, *J* = 11.6 Hz, 1H), 4.77−4.75 (m, 2H), 4.72 (d, *J* = 3.7 Hz, 1H), 4.67−4.62 (m, 2H), 4.54 (d, *J* = 1.8 Hz, 2H), 4.13 (t, *J* = 4.9 Hz, 1H), 3.85 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.78 (dd, *J* = 11.0, 4.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.29, 137.81, 137.63, 137.45, 128.52, 128.46, 128.41, 128.00, 127.96, 127.93, 127.84, 127.78, 127.73, 79.41, 77.26, 74.45, 73.54, 73.06, 71.55, 70.85, 68.28; HR-MS (ESI) Calcd. for $C_{27}H_{28}N_3O_4$ $[M + H]^+$: 458.2074, found: 458.2074.

*(5R, 6R, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-1, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole (**14b**)*: Yield: 38%. $[\alpha]_D^{25}$ 25.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.07 (s, 1H), 7.45–7.28 (m, 15H), 5.00 (d, *J* = 12.1 Hz, 1H), 4.92–4.82 (m, 3H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.18 (t, *J* = 3.1 Hz, 1H), 3.94 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.88 (dd, *J* = 10.6, 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.37, 137.82, 137.78, 137.69, 128.73, 128.46, 128.43, 128.42, 128.09, 127.90, 127.87, 127.79, 79.23, 73.50, 73.34, 72.54, 71.75, 68.02; HR-MS (ESI) Calcd. for $C_{27}H_{28}N_3O_4$ $[M + H]^+$: 458.2074, found: 458.2073.

*(5R, 6S, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-butyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole (**15b**)*: Yield: 68%. $[\alpha]_D^{25}$ 14.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.19 (m, 15H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.70–4.61 (m, 3H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.53–4.45 (m, 3H), 4.21 (t, *J* = 7.2 Hz, 2H), 3.76 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.70 (dd, *J* = 10.9, 4.2 Hz, 1H), 1.88–1.81 (m, 2H), 1.32–1.26 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.07, 138.06, 137.94, 137.69, 128.50, 128.43, 128.40, 127.94, 127.75, 127.71, 127.65, 127.00, 79.26, 74.71, 73.52, 73.03, 71.44, 71.30, 68.43, 55.11, 31.64, 19.80, 13.57. HR-MS (ESI) Calcd. for $C_{31}H_{36}N_3O_4$ $[M + H]^+$: 514.2700, found: 514.2706.

*(5R, 6S, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-hexyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole (**15c**)*: Yield: 73%. $[\alpha]_D^{25}$ 20.9 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400

MHz, $CDCl_3$) δ: 7.32–7.26 (m, 15H), 4.91 (d, *J* = 11.6 Hz, 1H), 4.77–4.68 (m, 3H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.58–4.53 (m, 3H), 4.26 (t, *J* = 7.1 Hz, 2H), 4.10 (t, *J* = 4.6 Hz, 1H), 3.83 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.77 (dd, *J* = 10.8, 3.8 Hz, 1H), 1.97–1.87 (m, 2H), 1.36–1.26 (m, 6H), 0.87 (t, *J* = 5.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.99, 137.99, 137.87, 137.62, 128.44, 128.37, 128.34, 127.87, 127.70, 127.66, 127.60, 126.92, 79.18, 74.61, 73.45, 72.95, 71.35, 71.19, 68.35, 55.35, 31.22, 29.54, 26.18, 22.45, 13.97. HR-MS (ESI) Calcd. for $C_{33}H_{40}N_3O_4$ $[M + H]^+$: 542.3013, found: 542.3028.

(5R, 6S, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-cyclohexyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15d)***: Yield: 55%. $[\alpha]_D^{25}$ 25.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.28 (m, 15H), 4.96 (d, *J* = 11.6 Hz, 1H), 4.82–4.72 (m, 3H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.61–4.57 (m, 3H), 4.37–4.27 (m, 1H), 4.13 (dd, *J* = 5.6, 4.4 Hz, 1H), 3.87 (dd, *J* = 10.9, 5.6 Hz, 1H), 3.81 (dd, *J* = 10.9, 4.2 Hz, 1H), 2.24–2.14 (m, 2H), 1.98–1.82 (m, 4H), 1.78–1.68 (m, 1H), 1.50–1.37 (m, 2H), 1.37–1.27 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.66, 138.03, 137.93, 137.64, 128.46, 128.38, 128.34, 127.93, 127.91, 127.69, 127.66, 127.59, 126.39, 79.19, 74.70, 73.46, 73.06, 71.44, 71.41, 68.39, 64.41, 53.42, 32.56, 32.50, 25.26, 25.09. HR-MS (ESI) Calcd. for $C_{33}H_{38}N_3O_4$ $[M + H]^+$: 540.2857, found: 540.2870.

(5R, 6S, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-octyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15e)***: Yield: 61%. $[\alpha]_D^{25}$ 25.9 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.26 (m, 15H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.77–4.65 (m, 4H), 4.56 (d, *J* = 11.3 Hz, 2H), 4.28 (t, *J* = 7.0 Hz, 2H), 4.11 (brs, 1H), 3.84–3.79 (m, 2H), 2.05–1.90 (m, 2H), 1.40–1.25 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.03, 138.02, 137.91, 137.65, 128.50, 128.43, 128.39, 127.93, 127.74, 127.71, 127.66, 126.94, 79.23, 74.65, 73.50, 73.02, 71.41, 71.25, 68.40, 55.42, 31.80, 29.65, 29.15, 29.08, 26.58, 22.66, 14.12. HR-MS (ESI) Calcd. for $C_{35}H_{44}N_3O_4$ $[M + H]^+$: 570.3326, found: 570.3341.

(5R, 6S, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-3-phenyl-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15f)***: Yield: 43%. $[\alpha]_D^{25}$ 20.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.42–7.38 (m, 1H), 7.37–7.26 (m, 13H), 7.22 (dd, *J* = 6.7, 2.8 Hz, 2H), 4.95 (d, *J* = 11.7 Hz, 1H), 4.91 (dt, *J* = 7.3, 3.2 Hz, 1H), 4.83 (d, *J* = 1.9 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.07 (t, *J* = 3.1 Hz, 1H), 3.83 (dd, *J* = 11.2, 7.5 Hz, 1H), 3.72 (dd, *J* = 11.2, 4.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 145.80, 137.90, 137.67, 137.18, 135.66, 129.40, 128.62, 128.46, 128.45, 128.16, 128.12, 127.99, 127.95, 127.87, 127.76, 127.69, 124.46, 121.03, 81.82, 73.72, 73.35, 72.38, 71.02, 69.06, 68.07. HR-MS (ESI) Calcd. for $C_{33}H_{32}N_3O_4$ $[M + H]^+$: 534.2387, found: 534.2390.

(5R, 6S, 7R)-3-([1, 1'-Biphenyl]-4-yl)-6, 7-bis(benzyloxy)-5-((benzyloxy)methyl)-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15g)***: Yield: 36%. $[\alpha]_D^{25}$ 18.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.69–7.62 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.47–7.29 (m, 16H), 5.06 (d, *J* = 11.6 Hz, 1H), 4.90–4.77 (m, 3H), 4.77–4.67 (m, 2H), 4.66–4.55 (m, 2H), 4.22–4.17 (m, 1H), 3.94 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.88 (dd, *J* = 11.0, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.30, 140.14, 139.69, 139.18, 137.88, 137.64, 137.46, 130.04, 128.89, 128.53, 128.49, 128.42, 128.09, 128.02, 127.95, 127.90, 127.83, 127.76, 127.73, 127.53, 126.99, 118.44, 79.49, 74.49, 73.58, 73.12, 71.67, 70.93, 68.37; HR-MS (ESI) Calcd. for $C_{39}H_{36}N_3O_4$ $[M + H]^+$: 610.2700, found: 610.2701.

(5R, 6R, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-butyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15h)***: Yield: 70%. $[\alpha]_D^{25}$ 19.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34–7.15 (m, 15H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.75–4.67 (m, 2H), 4.68 (d, *J* = 3.8 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.48–4.40 (m, 2H), 4.37 (d, *J* = 11.9 Hz, 1H), 4.17 (t, *J* = 7.2 Hz, 2H), 4.03 (t, *J* = 3.4 Hz, 1H), 3.83 (dd, *J* = 10.8, 4.5 Hz, 1H), 3.75 (dd, *J* = 10.8, 7.4 Hz, 1H), 1.85–1.78 (m, 2H), 1.30–1.24 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 156.13, 138.06, 138.03, 137.81, 128.39, 128.01, 127.85, 127.79, 127.67, 127.65, 79.04, 73.40, 72.98, 71.54, 68.09, 55.04, 31.60, 19.77, 13.57. HR-MS (ESI) Calcd. for $C_{31}H_{36}N_3O_4$ $[M + H]^+$: 514.2700, found: 514.2704.

(5R, 6R, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-cyclohexyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15i)***: Yield: 45%. $[\alpha]_D^{25}$ 26.4 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.26 (m, 15H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.84–4,75 (m, 3H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.56–4.47 (m, 2H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.31–4.23 (m, 1H), 4.10 (t, *J* = 3.4 Hz, 1H), 3.91 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.83 (dd, *J* = 10.8, 7.4 Hz, 1H), 2.15–2.13 (m, 2H), 1.94–1.76 (m, 4H), 1.72–1.68 (m, 1H), 1.47–1.33 (m, 2H), 1.31–1.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.93, 138.23, 137.94, 128.52, 128.50, 128.17, 127.98, 127.96, 127.91, 127.77, 126.97, 79.15, 73.50, 73.08, 71.65, 68.26, 64.52, 32.73, 32.56, 25.39, 25.23. HR-MS (ESI) Calcd. for $C_{33}H_{38}N_3O_4$ $[M + H]^+$: 540.2857, found: 540.2866.

(5R, 6R, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-octyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15j)***: Yield: 54%. $[\alpha]_D^{25}$ 26.7 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45–7.23 (m, 15H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.90–4.71 (m, 3H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.55–4.49 (m, 2H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.24 (t, *J* = 7.2 Hz, 2H), 4.11 (t, *J* = 3.4 Hz, 1H), 3.91 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.83 (dd, *J* = 10.9, 7.3 Hz, 1H), 1.93–1.87 (m, 2H), 1.31–1.25 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.99, 137.99, 137.87, 137.61, 128.46, 128.39, 128.35,

127.90, 127.71, 127.67, 127.62, 126.91, 79.20, 74.62, 73.48, 72.99, 71.38, 71.22, 68.37, 55.40, 31.77, 29.63, 29.13, 29.05, 26.57, 22.64, 14.10. HR-MS (ESI) Calcd. for $C_{35}H_{44}N_3O_4$ $[M + H]^+$: 570.3326, found: 570.3340.

(5R, 6R, 7R)-6, 7-Bis(benzyloxy)-5-((benzyloxy)methyl)-3-phenyl-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15k)***: Yield: 45%. $[\alpha]_D^{25}$ 22.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.46 (dd, *J* = 8.9, 7.5 Hz, 3H), 7.44–7.27 (m, 15H), 5.11 (d, *J* = 12.1 Hz, 1H), 4.93–4.86 (m, 3H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.56–4.53 (m, 2H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.19 (dd, *J* = 3.7, 2.7 Hz, 1H), 3.92 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.86 (dd, *J* = 10.6, 7.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.52, 140.05, 137.96, 137.88, 137.79, 130.84, 129.16, 128.50, 128.45, 128.44, 128.13, 127.99, 127.92, 127.87, 127.78, 126.70, 118.04, 79.34, 73.55, 73.47, 72.74, 71.91, 68.15. HR-MS (ESI) Calcd. for $C_{33}H_{32}N_3O_4$ $[M + H]^+$: 534.2387, found: 534.2390.

(5R, 6R, 7R)-3-([1, 1'-Biphenyl]-4-yl)-6, 7-bis(benzyloxy)-5-((benzyloxy)methyl)-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole ***(15l)***: Yield: 41%. $[\alpha]_D^{25}$ 20.4 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08–8.02 (m, 2H), 7.70–7.65 (m, 2H), 7.65–7.60 (m, 2H), 7.51–7.27 (m, 18H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.96–4.85 (m, 3H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.59–4.50 (m, 2H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.20 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.93 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.87 (dd, *J* = 10.5, 7.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.60, 140.23, 139.57, 139.24, 137.94, 137.86, 137.79, 130.99, 128.90, 128.51, 128.46, 128.44, 128.13, 128.00, 127.93, 127.88, 127.81, 127.79, 127.51, 127.00, 118.36, 79.37, 73.56, 72.73, 71.96, 68.15. HR-MS (ESI) Calcd. for $C_{39}H_{36}N_3O_4$ $[M + H]^+$: 610.2700, found: 610.2701.

(5R, 6S, 7R)-5-(Hydroxymethyl)-1, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10a)***: Yield: 95%. $[\alpha]_D^{25}$ 65.1 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 4.75 (d, *J* = 5.7 Hz, 1H), 4.38–4.27 (m, 1H), 3.94 (d, *J* = 4.1 Hz, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 155.65, 127.54, 84.78, 71.13, 67.20, 61.87. HR-MS (ESI) Calcd. for $C_6H_{10}N_3O_4$ $[M + H]^+$: 188.0671, found: 188.0670.

(5R, 6S, 7R)-2-Butyl-5-(hydroxymethyl)-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10b)***: Yield: 96%. $[\alpha]_D^{25}$ 85.3 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 4.67 (d, *J* = 5.9 Hz, 1H), 4.23 (t, *J* = 6.9 Hz, 2H), 4.21–4.15 (m, 1H), 3.97–3.83 (m, 3H), 1.87–1.80 (m, 2H), 1.36–1.27 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 157.61, 130.57, 83.67, 71.57, 67.90, 62.13, 55.73, 32.70, 20.61, 13.77. HR-MS (ESI) Calcd. for $C_{10}H_{18}N_3O_4$ $[M + H]^+$: 244.1297, found: 244.1300.

(5R, 6S, 7R)-2-Hexyl-5-(hydroxymethyl)-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10c)***: Yield: 90%. $[\alpha]_D^{25}$ 74.6 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 4.67 (d, *J* = 6.0 Hz, 1H), 4.27–4.14 (m, 3H), 3.98–3.83 (m, 3H), 1.86 (t, *J* = 7.0 Hz, 2H), 1.34–1.22 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 157.60, 130.57, 83.65, 71.55, 67.90, 62.13, 56.04, 32.34, 30.61, 27.16, 23.49, 14.28. HR-MS (ESI) Calcd. for $C_{12}H_{22}N_3O_4$ $[M + H]^+$: 272.1610, found: 272.1609.

(5R, 6S, 7R)-2-Cyclohexyl-5-(hydroxymethyl)-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10d)***: Yield: 93%. $[\alpha]_D^{25}$ 87.4 (*c* 0.1, MeOH); 1H NMR (400 MHz, methanol-d_4) δ: 4.93 (d, *J* = 4.2 Hz, 1H), 4.31–4.23 (m, 1H), 4.23–4.19 (m, 1H), 4.13 (dd, *J* = 4.2, 1.4 Hz, 1H), 3.97 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.91 (dd, *J* = 11.7, 5.4 Hz, 1H), 2.15–2.05 (m, 2H), 1.95–1.68 (m, 5H), 1.53–1.39 (m, 2H), 1.37–1.23 (m, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 155.84, 128.58, 80.24, 66.02, 63.53, 63.35, 60.27, 31.81, 24.48, 24.21. HR-MS (ESI) Calcd. for $C_{12}H_{20}N_3O_4$ $[M + H]^+$: 270.1454, found: 270.1450.

(5R, 6S, 7R)-5-(Hydroxymethyl)-2-octyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10e)***: Yield: 93%. $[\alpha]_D^{25}$ 65.4 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 4.69 (d, *J* = 6.1 Hz, 1H), 4.27–4.20 (m, 3H), 3.94–3.88 (m, 3H), 2.01–1.77 (m, 2H), 1.32–1.25 (m, 10H), 0.91 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 157.79, 130.75, 83.81, 71.71, 68.08, 62.29, 56.19, 33.03, 30.79, 30.35, 30.24, 27.63, 23.78, 14.54. HR-MS (ESI) Calcd. for $C_{14}H_{26}N_3O_4$ $[M + H]^+$: 300.1923, found: 300.1924.

(5R, 6S, 7R)-5-(Hydroxymethyl)-3-phenyl-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10f)***: Yield: 95%. $[\alpha]_D^{25}$ 73.3 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 7.9 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 5.03 (d, *J* = 4.1 Hz, 1H), 4.32 (t, *J* = 5.8 Hz, 1H), 4.19 (d, *J* = 4.1 Hz, 1H), 4.01 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.95 (dd, *J* = 11.7, 5.4 Hz, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 157.52, 139.43, 132.39, 128.31, 125.62, 116.68, 80.37, 65.94, 63.51, 60.22. HR-MS (ESI) Calcd. for $C_{12}H_{12}N_3O_4$ $[M - H]^-$: 262.0828, found: 262.0824.

(5R, 6S, 7R)-3-(4-Cyclohexylphenyl)-5-(hydroxymethyl)-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10g)***: Yield: 90%. $[\alpha]_D^{25}$ 64.6 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 7.82 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 4.77 (d, *J* = 6.2 Hz, 1H), 4.33–4.24 (m, 1H), 4.02–3.90 (m, 3H), 2.61–2.51 (m, 1H), 1.94–1.72 (m, 5H), 1.55–1.28 (m, 5H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 145.31, 136.50, 130.45, 125.71, 115.93, 109.99, 81.00, 68.56, 65.01, 59.23, 42.57, 32.70, 25.03, 24.27. HR-MS (ESI) Calcd. for $C_{18}H_{24}N_3O_4$ $[M + H]^+$: 346.1767, found: 346.1761.

(5R, 6R, 7R)-2-Butyl-5-(hydroxymethyl)-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol ***(10h)***: Yield: 91%. $[\alpha]_D^{25}$ 117.5 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 4.92 (d, *J* = 4.1 Hz, 1H), 4.26–4.17 (m, 3H), 4.14 (d, *J* = 3.8, 1H), 3.98 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.92 (dd, *J* = 11.7, 5.3 Hz, 1H), 1.91–1.81 (m, 2H), 1.39–1.28 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, methanol-d_4) δ: 156.63, 129.59, 80.75, 66.47, 63.81, 60.79, 54.25, 31.37, 19.25, 12.42; HR-MS (ESI) Calcd. for $C_{10}H_{18}N_3O_4$ $[M + H]^+$:

244.1297, found: 244.1295.

*(5R, 6R, 7R)-2-Cyclohexyl-5-(hydroxymethyl)-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol (**10i**)*: Yield: 95%. $[\alpha]_D^{25}$ 120.3 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 4.93 (d, *J* = 4.2 Hz, 1H), 4.31–4.20 (m, 2H), 4.13 (dd, *J* = 4.2, 1.4 Hz, 1H), 3.97 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.91 (dd, *J* = 11.7, 5.4 Hz, 1H), 2.15–2.05 (m, 2H), 1.95–1.68 (m, 5H), 1.53–1.39 (m, 2H), 1.36–1.26 (m, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ: 156.33, 129.07, 80.73, 66.51, 64.02, 63.84, 60.76, 32.30, 32.24, 24.97, 24.70. HR-MS (ESI) Calcd. for $C_{12}H_{20}N_3O_4$ $[M + H]^+$: 270.1454, found: 270.1450.

*(5R, 6R, 7R)-5-(Hydroxymethyl)-2-octyl-2, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol (**10j**)*: Yield: 97%. $[\alpha]_D^{25}$ 129.8 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 4.91 (d, *J* = 4.2 Hz, 1H), 4.22(t, *J* = 6.8 Hz, 3H), 4.11 (d, *J* = 4.1 Hz, 1H), 3.96 (dd, *J* = 11.7, 6.5 Hz, 1H), 3.90 (dd, *J* = 11.7, 5.4 Hz, 1H), 1.92–1.79 (m, 2H), 1.39–1.20 (m, 10H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, methanol-d_4) δ: 158.03, 130.98, 82.15, 67.86, 65.20, 62.16, 55.95, 32.92, 30.71, 30.25, 30.13, 27.53, 23.67, 14.41. HR-MS (ESI) Calcd. for $C_{14}H_{26}N_3O_4$ $[M + H]^+$: 300.1923, found: 300.1920.

*(5R, 6R, 7R)-5-(Hydroxymethyl)-3-phenyl-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol (**10k**)*: Yield: 92%. $[\alpha]_D^{25}$ 158.8 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 7.96–7.90 (m, 2H), 7.52–7.43 (m, 2H), 7.35–7.27 (m, 1H), 5.05 (d, *J* = 4.1 Hz, 1H), 4.39–4.29 (m, 1H), 4.21 (dd, *J* = 4.2, 1.1 Hz, 1H), 4.03 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.97 (dd, *J* = 11.7, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, methanol-d_4) δ: 158.11, 140.02, 132.98, 128.90, 126.21, 117.27, 80.96, 66.53, 64.10, 60.81; HR-MS (ESI) Calcd. for $C_{12}H_{12}N_3O_4$ $[M - H]^-$: 262.0828, found: 262.0824.

*(5R, 6R, 7R)-3-(4-Cyclohexylphenyl)-5-(hydroxymethyl)-3, 5, 6, 7-tetrahydropyrano[2, 3-d][1, 2, 3]triazole-6, 7-diol (**10l**)*: Yield: 92%. $[\alpha]_D^{25}$ 135.4 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ: 7.81 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 5.02 (d, *J* = 4.1 Hz, 1H), 4.35–4.26 (m, 1H), 4.18 (d, *J* = 4.2 Hz, 1H), 4.01 (dd, *J* = 11.6, 6.7 Hz, 1H), 3.94 (dd, *J* = 11.6, 5.2 Hz, 1H), 1.89–1.84 (m, 2H), 1.78 (d, *J* = 14.9 Hz, 2H), 1.51–1.42 (m, 2H), 1.38–1.26 (m, 4H), 0.93–0.86 (m, 1H); ^{13}C NMR (101 MHz, methanol-d_4) δ: 159.04, 148.39, 139.58, 133.53, 128.79, 119.01, 113.06, 84.08, 71.63, 68.08, 62.31, 45.65, 35.77, 28.10, 27.35. HR-MS (ESI) Calcd. for $C_{18}H_{24}N_3O_4$ $[M + H]^+$: 346.1767, found: 346.1761.

In vitro assay of α-glucosidase inhibitory activity

α-Glucosidase inhibitory activity was assayed by using 0.1 mol·L^{-1} phosphate buffer (pH 6.8) at 37 °C. α-Glucosidase from *Saccharomyces cerevisiae* (G5003-100UN, SIGMA) was dissolved in phosphate buffer (0.1 U·mL^{-1}). In 96-well plates, 10 μL of final compounds dissolved in DMSO, 20 μL of enzyme and 140 μL of phosphate buffer were added and incubated at 37 °C in Waterproof culture box for 15 min. Then 1.25 mmol·L^{-1} *p*-nitrophenyl α-D-glucopyranoside was added to the mixture as a substrate (30 μL). After further incubation at 37 °C for 30 min. The absorbance was measured spectrophotometrically at 405 nm. The sample solution was replaced by DMSO as a black control. Acarbose was used as a positive control.

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