SHORT REPORT

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Structures and Biological Evaluation of 8,4′-oxyneolignans from the Roots of *Platycodon grandifloras*

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Abstract: Chemical investigations of *Platycodon grandiflorus* have resulted in the isolation and identification of seven 8,4'-oxyneolignans, including four undescribed compounds (**1**-**4**). The structures of these novel compounds were determined using HR-ESI-MS and NMR (1D and 2D) spectroscopic analyses, combined with ECD calculations. The inhibitory activity of these terpenoids against *α*-glucosidase was also evaluated, and the results revealed that none of the compounds exhibited significant *α*-glucosidase inhibitory activity at a concentration of 50 μM. Compared with the positive control, all the compounds displayed weak inhibitory activity, with inhibition rates ranging from 1.06% to 7.31%.

Keywords: *Platycodon*; *Platycodon grandiflorus*; α-glucosidase; chemical constituents; 8,4'-oxyneolignan.

1. Plant Source

P. grandiflorus roots were collected from Taihe, Anhui Province, China, in July 2021. Professor Qing-shan Yang from Anhui University of Chinese Medicine identified the plant. The Herbarium specimen was preserved in the Herbarium of Anhui University of Chinese Medicine (ACM), with Herbarium number of No. 20210701.

2. Previous Studies

The Campanulaceae family is rich in species and widely distributed worldwide, with a major distribution in southwestern China. The genus *Platycodon* includes *Platycodon grandiflorus*; the genus *Codonopsis* includes *Codonopsis pilosula*, *Cyclocodon lancifolius*, and *Codonopsis nervosa*; the genus *Lobelia* includes *Lobelia chinensis* Lour.; the genus *Campanumoea* includes *Campanumoea javanica* and *Campanumoea javanica* var. major; the genus *Adenophora* includes *Adenophora stricta* Miq.; the genus *Wahlenbergia* includes *Wahlenbergia marginata* (Thunb.) A. DC; the genus *Cyananthus* includes *Cyananthus lobatus* Wall.ex Benth. and, others [1]. Among these, *Platycodon grandiflorus*, the sole species in the genus *Platycodon*, is distributed mainly in Northeast Asia [2,3]. The rhizome of

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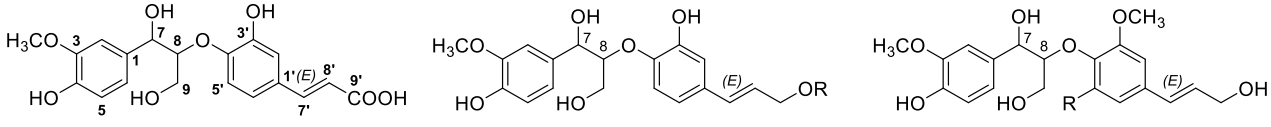
Structures and biological activity of 8,4′-oxyneolignans

Platycodon grandiflorus has a long history of use as a traditional herbal medicine for the treatment of cough, excessive phlegm, sore throat, lung abscess, and other ailments [4]. Rhizomes are frequently used as an ingredient in health foods and vegetable dishes, both as an approved medicine and dietary supplement dishes [5,6]. *Platycodon grandiflorus* is known for producing diverse compounds, including steroidal saponins; flavonoids; phenolic acids; polyacetylenes; sterols and phenolic groups, which exhibit apophlegmatic, immunostimulatory, anti-inflammatory, and antidiabetic properties [7-10]. In our ongoing phytochemical investigation of *P. grandiflorus* [11-13], we obtained four undescribed (**1**-**4**) and three known 8,4'-oxyneolignans (**5**-**7**) from the roots of *P. grandiflorus*. The inhibitory activities of these 8,4'-oxyneolignans against *α*-glucosidase were also evaluated to gain deeper insight into the biological activities of the secondary constituents. This study presents the isolation, structural elucidation, and *α*-glucosidase-inhibitory activity of these 8,4'-oxyneolignans.

3. Present Study

The dried roots of *P. grandiflorus* (20 kg) were pulverized and reflux extracted with 80% ethanol for two-hours, with the extraction process repeated three times. A crude ethanol extract (1.2 kg) was obtained by evaporating the methanol using a rotary evaporator at low pressure. The crude extract was suspended in 1.5 L of distilled water, and subsequently partitioned three times each with 1.5 L of EtOAc and 1.5 L of *n*-BuOH. The EtOAc -soluble extract (397 g) was separated by silica gel CC elution with a step gradient of CH_2Cl_2/MeOH (40:1 to 1:1, v/v) to obtain nine fractions (G1-G9). G 6 (12.6 g) was applied to C_{18} MPLC utilizing MeOH-H_2O (20-100%, v/v) to produce ten subfractions (G6-1 to G6-10). G6-2 was further purified on an HPLC preparative column with CH_3CN-H_2O (25-40%, 8 ml/min) to afford **5** (5.1 mg, t_R=14.50 min). G 7 (14.2 g) was applied to C_{18} MPLC utilizing MeOH-H_2O (15-100%, v/v) to produce seven subfractions (G7-1 to G7-8). Subfraction G7-5 (0.88 g) was subjected to chromatography on Sephadex LH-20 (MeOH) to yield G7-5-1 to G7-5-4. G7-5-1 was further purified on an HPLC preparative column with CH_3CN-H_2O (25-40%, 8 ml/min) to afford **7** (48.8 mg, t_R=20.9 min). Subfraction G7-6 (0.98 g) was subjected to chromatography on Sephadex LH-20 (MeOH) to yield G7-6-2 to G7-6-6. G7-6-2 was further purified on an HPLC preparative column with CH_3CN-H_2O (30-45%, 8 ml/min) to afford **6** (2.3 mg, t_R=17.8 min). G7-6-3 was further purified on the HPLC preparative column with CH_3CN-H_2O (30-45%, 8 ml/min) to afford **3** (4.1 mg, t_R=26.0 min). Subfraction G7-7 (0.81 g) was subjected to chromatography on Sephadex LH-20 (MeOH) to yield G7-7-1 to G7-7-3. G7-7-2 was further purified on an HPLC preparative column with CH_3CN-H_2O (35-50%, 8 ml/min) to afford **4** (2.8 mg, t_R=25.4 min). G 8 (26.4 g) was applied to MPLC utilizing MeOH-H_2O (15-100%, v/v) to produce seven subfractions (G8-1 to G8-12). Subfraction G8-7 (1.2 g) was subjected to chromatography on Sephadex LH-20 (MeOH) to yield G8-7-1 to G8-7-7. G8-7-7 was further purified on an HPLC preparative column with CH_3CN-H_2O (40-60%,8 ml/min) to afford **1** (1.9 mg, t_R=19.4 min) and **2** (4.0 mg, t_R=20.3 min) (Figure 1).



1 7*S*,8*S*
2 7*R*,8*S*

	R
3 (7*R*,8*S*)	CH_3
4 (7*S*,8*R*)	Ac
7 (7*R*,8*S*)	H

	R
5 (7*S*,8*S*)	H
6 (7*R*,8*R*)	OCH_3

Figure 1. The chemical structures of compounds **1**-**7**

*Compound **1** (7S,8S,7'E-4,7,9,3'-tetrahydroxy-3-methoxy-1'-acrylic acid-8,4'-oxyneolignan)*: Pale yellow oil; $[\alpha]_D^{20}$=-101.13 (c 0.027, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 7.45 (1H, d, *J* = 15.8 Hz, H-7'), 7.05 (1H, s, H-2'), 7.01 (1H, s, H-2), 6.97 (1H, d, *J* = 8.1 Hz, H-5'), 6.92 (1H, d, *J* = 8.1 Hz, H-6'), 6.84 (1H, d, *J* = 8.1 Hz, H-6), 6.74 (1H, d, *J* = 8.1 Hz, H-5), 6.30 (1H, d, *J* = 15.8 Hz, H-8'), 4.92 (1H, d, *J* = 5.2 Hz, H-7), 4.30 (1H, m, H-8), 3.81 (3H, s, 3-OC$\underline{H}_3$), 3.78 (1H, dd, *J* = 11.5, 4.9 Hz,

H-9a), 3.56 (1H, dd, *J* = 11.5, 4.9 Hz, H-9b); ^{13}C NMR (150 MHz, CD_3OD): δ (ppm) = 54.9 ($\underline{C}H_3$, OMe), 60.8 (CH_2, C-9), 72.5 (CH, C-7), 85.2 (CH, C-8), 110.6 (CH, C-2), 114.2 (CH, C-2'), 114.5 (C, C-5), 116.4 (CH, C-5'), 118.2 (CH, C-8'), 119.2 (C, C-6), 120.2 (CH, C-6'), 129.5 (C, C-1'), 132.6 (C, C-1), 143.1 (CH, C-7'), 145.9 (C, C-4), 147.5 (C, C-3), 147.9 (C, C-3'), 148.3 (C, C-4'), 171.1 (C, C-9'); HR-ESI-MS *m/z*: 375.1089 $[M-H]^-$ ($C_{19}H_{19}O_8^-$, calcd. for 375.1085).

Compound ***2*** *(7R,8S,7'E-4,7,9,3'-tetrahydroxy-3-methoxy-1'-acrylic acid-8,4'-oxyneolignan)*: Pale yellow oil; $[\alpha]_D^{20}$=+66.67 (c 0.042, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 7.48 (1H, d, *J* = 15.8 Hz, H-7'), 7.02 (1H, s, H-2'), 7.01 (1H, s, H-2), 6.90 (1H, d, *J* = 8.1 Hz, H-6'), 6.83 (1H, d, *J* = 8.1 Hz, H-6), 6.82 (1H, d, *J* = 8.1 Hz, H-5'), 6.74 (1H, d, *J* = 8.1 Hz, H-5), 6.27 (1H, d, *J* = 15.8 Hz, H-8'), 4.87 (1H, overlapped, H-7), 4.34 (1H, m, H-8), 3.80 (3H, s, 3-OC$\underline{H}_3$), 3.78 (1H, dd, *J* = 11.5, 4.9 Hz, H-9a), 3.56 (1H, dd, *J* = 11.5, 4.9 Hz, H-9b); ^{13}C NMR (150 MHz, CD_3OD): δ (ppm) = 54.9 ($\underline{C}H_3$, OMe), 60.6(CH_2, C-9), 72.5 (CH, C-7), 85.0 (CH, C-8), 110.3 (CH, C-2), 114.3 (CH, C-2'), 114.4 (C, C-5), 116.9 (CH, C-5'), 117.2 (CH, C-8'), 119.3 (C, C-6), 120.3 (CH, C-6'), 129.2 (C, C-1'), 132.3 (C, C-1), 144.1 (CH, C-7'), 145.7 (C, C-4), 147.4 (C, C-3), 148.0 (C, C-3'), 148.2 (C, C-4'), 170.2 (C, C-9'); HR-ESI-MS *m/z* 375.1091 $[M-H]^-$ ($C_{19}H_{19}O_8^-$, calcd. for 375.1085).

Compound ***3*** *(7R,8S,7'E-4,7,9,3'-tetrahydroxy-3,9'-dimethoxy-8,4'-oxyneolignan):* Light yellow oil; $[\alpha]_D^{20}$ =+13.47 (c 0.049, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 6.99 (1H, d, *J* = 1.8 Hz, H-2), 6.87 (1H, d, *J* = 1.8 Hz, H-2'), 6.73 (1H, overlapped, H-6'), 6.73 (1H, overlapped, H-5'), 6.83 (1H, dd, *J* = 8.0, 1.8 Hz, H-6), 6.74 (1H, overlapped, H-5), 6.47 (1H, dd, *J* = 15.9, 6.1 Hz, H-7'), 6.11 (1H, m, H-8'), 4.84 (1H, overlapped, H-7), 4.21 (1H, m, H-8), 4.03 (1H, dt, *J* = 6.1, 1.7 Hz, H-9'), 3.85 (1H, m, H-9a), 3.80 (3H, s, 3-OC$\underline{H}_3$), 3.75 (1H, m, H-9b), 3.34 (3H, s, H-1"); ^{13}C NMR (150 MHz, CD_3OD): δ (ppm) = 56.3 (CH_3, 3-OMe), 58.2 (CH_3, C-1"), 62.0 (CH_2, C-9), 73.9 (CH, C-7),74.2 (CH, C-9'), 87.2 (CH, C-8), 111.6 (CH, C-2), 114.7 (CH, C-2'), 115.8 (CH, C-5), 119.4 (CH, C-5'), 119.4 (CH, C-6'), 120.7 (CH, C-6), 125.0 (CH, C-8'), 133.3 (C, C-1'), 133.7 (C, C-1), 133.8 (C, C-7'), 147.1 (C, C-4), 147.5 (C, C-4'), 148.8 (C, C-3), 149.5 (C, C-3'); HR-ESI-MS *m/z* 399.1415 $[M+Na]^+$ ($C_{20}H_{24}O_7Na^+$, calcd. for 399.1414).

Compound ***4*** *(7S,8R,7'E-4,7,9-trihydroxy-3-methoxy-1'-allyl acetate-8,4'-oxyneolignan)*: Light yellow oil; $[\alpha]_D^{20}$=+4.76 (c 0.042, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 7.04 (1H, d, *J* = 1.8 Hz, H-2), 6.87 (1H, d, *J* = 1.8 Hz, H-2'), 6.74 (1H, overlapped, H-6'), 6.74 (1H, overlapped, H-5'), 6.83 (1H, dd, *J* = 8.0, 1.8 Hz, H-6), 6.73 (1H, overlapped, H-5), 6.52 (1H, dd, *J* = 15.9, 6.3 Hz, H-7'), 6.13 (1H, m, H-8'), 4.85 (1H, overlapped, H-7), 4.66 (1H, m, H-9'), 4.22 (1H, m, H-8), 3.86 (1H, dd, *J* = 11.8, 6.4 Hz, H-9a), 3.79 (3H, s, 3-OC$\underline{H}_3$), 3.76 (1H, dd, *J* = 11.8, 3.5 Hz,, H-9b), 2.05 (3H, s, 1"-CH_3); ^{13}C NMR (150 MHz, CD_3OD): δ (ppm) = 20.8 (CH_3, 1"-CH_3), 56.4 (CH_3, 3-OMe), 62.0 (CH_2, C-9), 66.3 (CH, C-9'), 74.0 (CH, C-7), 87.1 (CH, C-8), 111.7 (CH, C-2), 114.7 (CH, C-2'), 115.8 (CH, C-5), 119.2 (CH, C-5'), 119.5 (CH, C-6'), 120.7 (CH, C-6), 122.7 (CH, C-8'), 132.9 (C, C-1'), 133.7 (C, C-1), 135.0 (C, C-7'), 147.1 (C, C-4), 147.7 (C, C-4'), 148.8 (C, C-3), 149.5 (C, C-3'), 172.7 (C, C-1"); HR-ESI-MS *m/z* 465.3338 $[M+Na]^+$ ($C_{21}H_{24}O_8Na^+$, calcd. for 465.3339).

α-Glucosidase Assay: α-Glucosidase inhibitory activities were evaluated following the methodology described in our published study [14]. The α-glucosidase inhibition assay was performed using 0.1 M sodium phosphate buffer (SPB, pH 7.5). Solutions of α-glucosidase (2.0 U/mL) and *p*-NPG (10 mM) were prepared using this buffer. In each well, 10 μL of the DMSO stock solution of the samples (50 μM), 90 μL of SPB, and 80 μL of the α-glucosidase solution were added. The samples were shaken for 2 min and incubated at 37 °C for 15 min. Then, a 20 μL aliquot of the *p*-NPG solution was added to initiate the reaction. Enzyme inhibition was determined by measuring the OD values at 405 nm using a microplate reader. Acarbose (MedChemExpress, China) was used as a positive control.

Compound **1** was isolated as a pale yellow oil. It exhibited an $[M-H]^-$ ion at *m/z* 375.1089 ($C_{19}H_{19}O_8^-$, calculated for 375.1085). In conjunction with ^{13}C NMR data (Tab. S2-12), this corresponded to the molecular formula $C_{19}H_{20}O_8$, indicating ten degrees of unsaturation. The ^{1}H NMR data (Table 1) revealed the presence of one *trans*-double bond at δ_H 7.45 (1H, d, *J* = 15.8 Hz) and 6.30 (1H, d, *J* = 15.8 Hz); two 1,3,4-substituted aromatic rings at δ_H 7.01 (1H, d, *J* = 1.8 Hz), 6.74 (1H, d, *J* = 8.1 Hz), 6.84

(1H, d, J = 8.1 Hz) and 7.05 (1H, s), 6.97 (1H, d, J = 8.1 Hz), 6.92 (1H, d, J = 8.1 Hz); two oxygenated methines at δ_H 4.92 (1H, d, J = 8.1 Hz), 4.30 (1H, m), two oxygenated methylenes at δ_H 3.78 (1H, dd, J = 11.7, 4.9 Hz) and 3.56 (1H, dd, J = 11.7, 4.9 Hz) and one methoxy group at δ_H 3.81 (s). The ^{13}C NMR and DEPT spectra of Compound **1** revealed 19 carbon resonances, which were classified into 12 aromatic carbons from two benzene rings, three aliphatic carbons (δ_C 85.2, 72.5, 60.8), two olefinic carbons (δ_C 143.1, 118.2) and one carboxyl carbon (δ_C 171.1). These data indicated that Compound **1** was an 8,4'-oxyneolignan [15,16]. The ^{1}H-^{1}H COSY spectrum of Compound **1** revealed the following correlations: H-5/H-6, H-7/H-8/H-9, H-5'/H-6', and H-7'/H-8'. HSQC and HMBC spectra were used to analyze the planar structure of Compound **1** (Figure 2).

Compound **2** has the same molecular formula ($C_{19}H_{20}O_8$) as **1**, as established from the HR-ESI-MS ion peak at m/z 375.1091 [M-H]$^-$ (calcd. for $C_{19}H_{19}O_8^-$, 375.1085). A comparison of the NMR data (^{1}H NMR, ^{13}C NMR, HSQC, HMBC, ^{1}H-^{1}H COSY, and DEPT) between **2** and **1** revealed that both had the same gross structure. However, **1** and **2** were fractionated by semipreparative HPLC (CH_3CN-H_2O, 40-60%, v/v) with retention times of 19.4 and 20.3 min, respectively, indicating that Compound **2** (Figure S1-10) was an isomer of **1**.

According to the literature [17,18], the relative configuration at the 7,8-position can be determined by the difference in chemical shifts between H-9a and H-9b ($\Delta\delta_{H9a-H9b}$) in two deuterated solvents: CD_3OD or DMSO-d_6. As shown in Table 3, a comparison of the chemical shift differences between H-9a and H-9b revealed that the larger $\Delta\delta$ (0.22 ppm) value of **2** was assigned to the *threo*-configuration, and the smaller $\Delta\delta$ (0.07 ppm) value of **1** was assigned to the *erythro*-configuration. The absolute configurations of Compounds **1** and **2** were identified as 7*S*, 8*S* and 7*R*, 8*S* by comparing their calculated ECD and experimental ECD (Fig. s3). Consequently, **1** and **2** were identified as 7*S*,8*S*,7′*E*-4,7,9,3′-tetrahydroxy-3-methoxy-1′-acrylic acid-8,4′-oxyneolignan and 7*R*,8*S*,7′*E*-4,7,9,3′-tetrahydroxy-3-methoxy-1′-acrylic acid-8,4′-oxyneolignan, respectively.

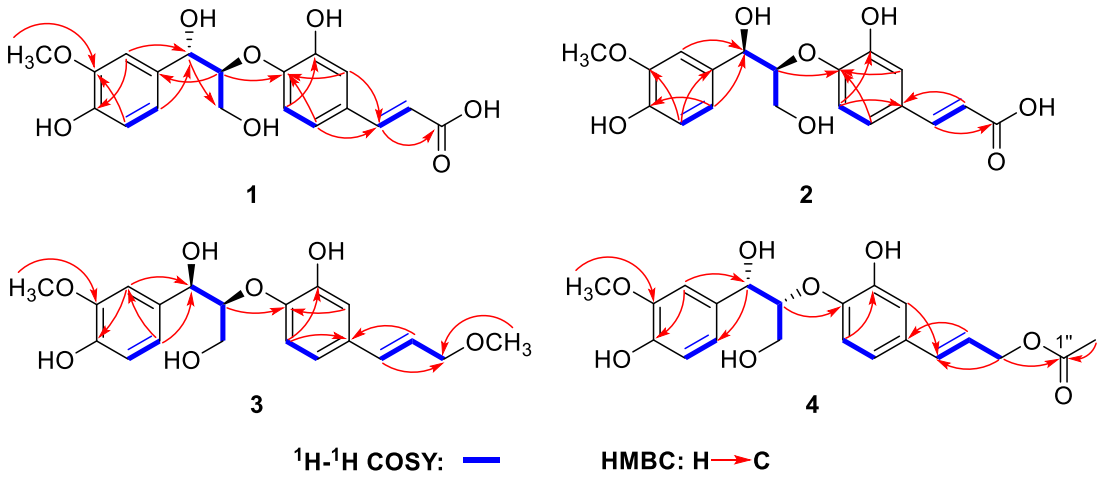


Figure 2. Key HMBC and ^{1}H-^{1}H COSY correlations for compound **1**.

Compound **3** was isolated as a light yellow oil, and its molecular formula was determined to be $C_{20}H_{24}O_7$, as established from its HR-ESI-MS (m/z 399.1415 [M+Na]$^+$; calculated for $C_{20}H_{24}O_7Na^+$, 399.1414) and ^{13}C-NMR spectra (Tab. S4-12), indicating nine degrees of unsaturation. Spectroscopic characteristics indicated that the architecture of Compound **3** resembled that of Compounds **1** and **2**. A comparison of the ^{1}H and ^{13}C NMR spectroscopic data of **3** and **1** revealed that the only difference was that Compound **3** has one oxygenated methylene group at C-9', instead of the carboxyl carbon at that position **1**. The HMBC spectrum revealed a correlation between δ_H 3.34 and C-9' (δ_C 58.2), confirming the presence of one methoxy group attached to C-9' (Figure 2). The relative stereochemistry was also determined by the difference in chemical shifts between H-9a and H-9b ($\Delta\delta_{H9a-H9b}$). Furthermore, the planar structure of Compound **3** was determined (Figure 1).

The absolute configuration of Compound **3** was subsequently verified using ECD calculations. As depicted in Fig. S4, the experimental ECD curve of Compound **3** closely matched the calculated ECD

spectrum, enabling explicit assignment of the absolute configuration as 7*R* and 8*S*. Therefore, Compound **3** was elucidated as 7*R*,8*S*,7′*E*-4,7,9,3′-tetrahydroxy-3,9′-dimethoxy-8,4′-oxyneolignan.

The HR-ESI-MS data of **4** indicated a molecular formula of $C_{21}H_{24}O_8$, owing to the quasimolecular ion peak at *m/z* 427.1364 ([M+Na]$^+$, calcd 427.1363). The ^{1}H and ^{13}C NMR data of **4** were found to be structurally similar to those of **3**. The molecular formula of **4** was 28 mass units greater than that of **1**, except for the presence of one carbonyl moiety (δ_C 172.7). This could be attributed to the marked lower field shift of C-1″ (δ_C 172.7) and the HMBC correlations from H-9′ to C-1″. The relative configurations and absolute configurations of C-7 and C-8 were determined in the same way as those of **1**, **2** and **3**. Finally, Compound **4** was determined to be 7*S*,8*R*,7′*E*-4,7,9-trihydroxy-3-methoxy-1′-allyl acetate-8,4′-oxyneolignan.

In addition, known compounds were identified by comparing their spectroscopic data with those reported in the literature. Known compounds were identified as 7*S*,8*S*,7′*E*-4,7,9-trihydroxy-3,3′-dimethoxy-1′-allyl alcohol-8,4′-oxyneolignan (**5**) [19], 7*R*,8*R*,7′*E*-4,7,9-trihydroxy-3,3′,5′-trimethoxy-1′-allyl alcohol-8,4′-oxyneolignan (**6**) [20], and 7*R*,8*S*,7′*E*-4,7,9-trihydroxy-3-methoxy-1′-allyl alcohol-8,4′-oxyneolignan (**7**) [21].

Table 3. *α*-Glucosidase inhibitory activity of compounds **1**-**7**

NO.	Inhibition rate (%, 50 μM)
1	1.84±1.96
2	1.06±1.98
3	3.18±2.12
4	6.27±1.71
5	7.31±2.00
6	5.77±2.76
7	6.11±2.02
Acarbose	78.7±0.20

Furthermore, the *α*-glucosidase inhibitory activities of Compounds **1**-**7** were assessed *in vitro*. Unfortunately, the results indicated that none of these compounds had significant *α*-glucosidase inhibitory activity at a concentration of 50 μM (Table 3). Compared with the positive control, all the compounds displayed weak inhibitory activity, with inhibition rates ranging from 1.06 to 7.31 %.

Acknowledgments

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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