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A New Monoterpene Rhamnoside from *Cercis glabra* Legumes

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Abstract: A new monoterpene rhamnoside, (+)-(*R*)-*α*-terpineol *α*-L-rhamnoside (**1**), along with ten known compounds (**2**–**11**) were obtained after purification of the ethanol extract of *Cercis glabra* legumes. Their structures were elucidated by spectroscopic evidence including NMR, optical rotatory dispersion (ORD), HR-ESI-MS and chemical hydrolysis. In the acetylcholinesterase inhibitory assay, compounds **3** and **8** showed high percentages of inhibition which were comparable to the activity of donepezil (a commercial drug, the positive control), and exhibited IC_{50} values of 0.488, 0.391 mg/mL. These bioactive components could be promising acetylcholinesterase inhibitors.

Keywords: *Cercis glabra;* monoterpene; acetylcholinesterase; acid hydrolysis.

1. Introduction

As a progressive neurodegenerative disorder, Alzheimer's disease (AD) affects about 10% of people over 65 years of age. It is estimated that by 2050, over 115 million people worldwide will be affected by this pathology [1]. Based on the cholinergic hypothesis, the inhibition of acetylcholinesterase (AChE) could increase the acetylcholine level in the brain, thus enhancing cholinergic functions in AD patients [2-4]. Therefore, AChE inhibitors (AChEi) have been developed as drugs to treat AD, such as galantamine, rivastigmine and donepezil, though most of them have limited effectiveness and unpleasant side effects [5]. It is still urgent to find new compounds with anti-AChE activity.

Cercis glabra is a plant belonging to Leguminosae family. It is endemic to China and mainly distributed in Henan, Hubei, Yunnan, Hunan, Shaanxi, Guizhou, Sichuan, Guangdong, Guangxi, Anhui and Zhejiang Provinces [6]. *Cercis glabra* is usually used as street trees because of its beautiful flowers. However, in the past decades little attention has been paid on its phytochemical constituents and medicinal values [7]. In the course of investigating novel AChEi from natural plants [8-9], the ethanolic extract of *C. glabra* legumes was tested to show potential AChE inhibitory activity. A further phytochemical research on the ethanolic extract resulted in the isolation and structure elucidation of a

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monoterpene rhamnoside (**1**), one lactone (**2**), three gallic acid derivatives (**3–5**), three flavones (**6–8**), two quinones (**9–10**), along with one lignin (**11**). Compounds **3** and **8** showed obvious AChE inhibitory activities.

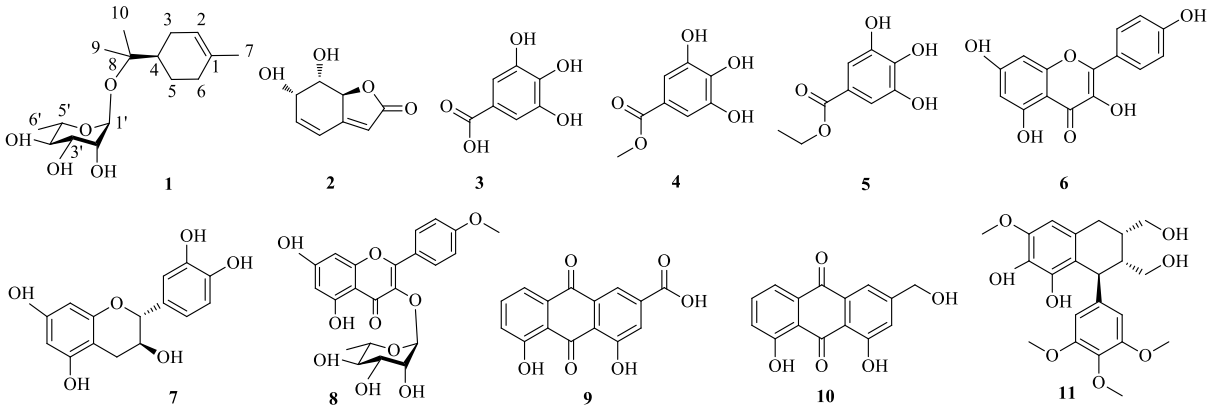

Figure 1. Structures of compounds **1**–**11** isolated from *C. glabra* legumes

2. Materials and Methods

2.1. General Experimental Procedures

NMR and HR-ESI-MS spectra were recorded on a Bruker AM-400 spectrometer, a Waters Xevo G2-XS QTof spectrometer, respectively. Column chromatography (CC) was performed on silica gel, ODS (50 μm, Fuji Silysia Chemical Ltd., Japan), Sephadex LH-20 (GE health care Bio-Sciences AB, Sweden) and high performance liquid chromatography (Agilent 1200).

2.2. Plant Material

The fresh *Cercis glabra* legumes were collected in Yanling county of Henan province, China, in May 2021. The original samples were identified by Prof. Lin Yang of Lanzhou University of Technology. The specimen (SPH2021J) was stored at Food and Pharmacy College, Xuchang University.

2.3. Extraction and Isolation

The air-dried *Cercis glabra* legumes (9.4 kg) were powdered and extracted with 95% ethanol (3d × 3 × 50 L) under room temperature. After removal of the solvent, 495.6 g crude extract was obtained, which was suspended in H_2O and sequentially extracted with petroleum ether, CH_2Cl_2 and EtOAc, respectively. The EtOAc extract (82.5 g) was graded on silica gel CC (CH_2Cl_2-MeOH, 100:0 to 2:1) to give nine fractions F1-F9. Fractions F1, F3, F5, F7 and F9 were further purified to afford compounds **1**–**11**.

Compound **7** (16.6 mg) was purified by Sephadex LH-20 CC (CH_2Cl_2) from subfraction F1. Fraction F3 (4.8 g) was then further separated with Sephadex LH-20 CC (CH_2Cl_2-MeOH 1:1) to obtain subfractions F3-1–F3-3. F3-2 (2.1 g) was passed on silica gel CC (CH_2Cl_2-MeOH, 60:1 to 50:1) to give compound **2** (27.6 mg). The subfraction F3-3 was isolated by Sephadex LH-20 CC (MeOH) to obtain **11** (10.7 mg). F5 (4.1 g) was divided to three subfractions (F5-1-F5-3) by a silica gel CC (CH_2Cl_2-MeOH, 80:1 to 20:1). The subfraction F5-1 was separated on Sephadex LH-20 CC (MeOH) to obtain **1** (12.7 mg) and **10** (26.9 mg). Compound **5** (8.4 mg) was purified from F5-3 by HPLC (MeOH-H_2O, 9:91). Fraction F7 (12.1 g) gave three subfractions (F7-1–F7-3) after polyamide CC eluted with ethanol-water (30:70 to 90:10). Subfraction F7-1 was further purified by ODS CC (MeOH-H_2O, 60:40 to 90:10) to provide **6** (2.7 mg) and **9** (44.1 mg). F7-2 was passed through Sephadex LH-20 CC (MeOH) to obtain

compound **8** (10.2mg). Compound **4** (8.5mg) was purified from subfraction F7-3 by HPLC RP-C_{18} CC (MeOH-H_2O 9:91). Fraction F9 (5.0 g) was eluted by ODS CC (MeOH-H_2O, 30:70 to 90:10) to obtain subfractions F9-1–F9-3. Compound **3** (32.6 mg) was obtained from subfraction F9-3 after purification by Sephadex LH-20 CC (MeOH).

*2.4. Acid hydrolysis of Compound **1***

Acid hydrolysis of the new monoterpene rhamnoside (**1**, 12.7 mg) was conducted according to the literature procedures [10]. After extraction and purification, the reaction residue gave (+)-(*R*)-*α*-terpineol and L-rhamnose.

*(+)-(R)-α-Terpineol (**1a**)*: Colorless oil. $[\alpha]_D^{20}$+56.7° (c 0.18, $CHCl_3$).^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.36 (1H, s, H-2), 2.07-1.92 (3H, m, H-3, H-6a), 1.86 (1H, ddt, *J* = 12.0, 5.2, 2.0 Hz, H-6b), 1.77 (1H, m, H-5b), 1.62 (3H, s, H-7), 1.47 (1H, dddd, *J* = 12.8, 12.4, 4.8, 2.4 Hz, H-4), 1.24 (1H, m, H-5a), 1.16 (3H, s, H-9), 1.14 (3H, s, H-10). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 134.2 (C-1), 120.7 (C-2), 72.9 (C-8), 45.2 (C-4), 31.2 (C-3), 27.6 (C-10), 27.1 (C-6), 26.5 (C-9), 24.2 (C-5), 23.5 (C-7) [11].

2.5. Acetylcholinesterase Inhibitory Assay

The acetylcholinesterase inhibition activities of compounds **1**–**11** were evaluated by the reported procedure with slight modification. [12] 120 μL of 0.1 M phosphate buffer (pH 8.0), 20 μL of 3 mM DTNB solution, 20 μL of sample solution and 20 μL of AChE (0.2 U/mL) were sequentially added to the 96-well microplate, and the solution was reacted for 10 min at 37 ºC. The reaction was started by adding 20 μL of 3 mM ATCI and the mixture was incubated at 37 ºC for 20 min. The absorbance at 412 nm was tested on a Multiskan FC microplate reader (Thermo Fisher Scientific, Inc.). Donepezil was used as the positive control. The % inhibition was calculated by [1 - (As-Aj)/Ac] × 100, where As, Aj and Ac represented the absorbance of tested compound, blanks and untreated control respectively.

3. Results and Discussion

3.1. Isolation and Structure Elucidation

Compounds **1**–**11** were identified as (+)-(*R*)-*α*-terpineol *α*-L-rhamnoside (**1**), griffonilide (**2**) [13], gallic acid (**3**) [14], methyl gallate (**4**) [15], ethyl gallate (**5**) [16], kaempferol (**6**) [17], (+)-catechin (**7**) [18], kaempferide-3-O-*α*-L-rhamnopyranoside (**8**) [19], rhein (**9**) [20], aloe-emodin (**10**) [21], lingueresinol (**11**) [22], respectively, by comparison of spectral data in the literatures. Compounds **1**–**2** and **8**–**11** were for the first time isolated from genus *Cercis*, which would enrich our knowledge about phytochemical constituents of *Cercis glabra*.

Compound **1** was isolated as a colorless syrup. Its molecular formula $C_{16}H_{28}O_5$, with three degrees of unsaturation, was established by the HR-ESI-MS data (*m/z* 301.2010 $[M + H]^+$, calcd. for 301.2015). The IR absorption bands at 3374 cm^{-1} and 1644 cm^{-1} indicated the presence of hydroxyl group and olefinic group respectively. The ^{1}H NMR spectrum revealed the signals of one olefinic proton [δ_H 5.33 (1H, br s, H-2)], one methine [δ_H 1.55 (1H, dddd, *J* = 12.8, 12.4, 4.8, 2.4 Hz, H-4)], three methylenes [δ_H 2.03-1.85 (3H, m, H-3, H-6a), 1.84-1.70 (2H, m, H-6b, H-5b), 1.21 (1H, m, H-5a)], three methyl groups [δ_H 1.61 (3H, s, H-7), 1.15 (3H, s, H-9), 1.13 (3H, s, H-10)] and a rhamnose moiety [δ_H 4.85 (1H, d, *J* = 1.6 Hz, H-1´), 3.79 (1H, dd, *J* = 3.2, 1.2 Hz, H-2´), 3.76 (1H, dq, *J* = 9.2, 6.0 Hz, H-5´), 3.74 (1H, m, H-3´), 3.43 (1H, t, *J* = 9.2 Hz, H-4´), 1.24 (3H, d, *J* = 6.0 Hz, H-6´)]. Correspondingly, its ^{13}C NMR and DEPT spectra showed two olefinic carbons [δ_C 134.2 (C-1), 120.8 (C-2)], one oxygenated methine [δ_C 79.5 (C-8)], one methine [δ_C 44.0 (C-4)], three methylenes [δ_C 31.3 (C-3), 26.9 (C-6), 24.3 (C-5)], three methyl groups [δ_C 24.2 (C-10), 23.5 (C-7), 22.9 (C-9)], and a rhamnose moiety [δ_C 94.2 (C-1´), 73.4 (C-4´), 72.8 (C-3´), 72.2 (C-2´), 68.1 (C-5´), 17.7 (C-6´)]. The key ^{1}H-^{1}H COSY, HSQC and HMBC correlations (Figure 2 and supplemental data) demonstrated the above speculations. Upon acid hydrolysis, compound **1** gave (+)-(*R*)-*α*-terpineol (**1a**) { $[\alpha]_D^{20}$ +56.7° (c 0.18, $CHCl_3$) [reported:

$[\alpha]_D^{23}$+93.3° (c 2.2, $CHCl_3$)] [23]} and L-rhamnose {$[\alpha]_D^{20}$+5.5° (c 0.18, H_2O) [reported: $[\alpha]_D^{20}$+2.4° (c 1, H_2O)] [24]}, confirmed by optical rotation and NMR. In the HMBC spectrum, the cross-peak from H-1′ to C-8 indicated the glycosylation occurred at C-8. The ^{13}C NMR data of the rhamnose moiety in compound **1** indicated that the relative configuration of the glycosidic bond was *α*-orientation [25]. Finally, the new compound was identified as (+)-(*R*)-*α*-terpineol *α*-L-rhamnoside.

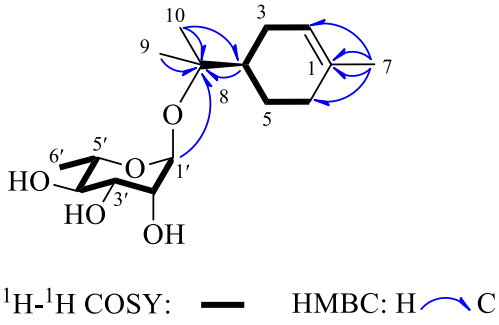

Figure 2. Key ^{1}H-^{1}H COSY and HMBC correlations for compound **1**

*(+)-(R)-α-Terpineol α-L-rhamnoside (**1**)*: Colorless syrup. $[\alpha]_D^{20}$+15.1° (c 0.42, $CHCl_3$). IR (KBr) ν_{max} 3374, 2971, 2921, 1446, 1384, 1251, 1228, 1047, 981, 912, 838, 800 cm^{-1}. UV λ_{max} ($CHCl_3$) nm (log ε): 239 (4.6). HR-ESI-MS *m/z* 301.2010 [M + H] $^+$ (calcd for $C_{16}H_{29}O_5$, 301.2015). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.33 (1H, br s, H-2), 4.85 (1H, d, *J* = 1.6 Hz, H-1′), 4.62-4.07 (3H, m, 2′-OH, 3′-OH, 4′-OH), 3.79 (1H, dd, *J* = 3.2, 1.2 Hz, H-2′), 3.76 (1H, dq, *J* = 9.2, 6.0 Hz, H-5′), 3.74 (1H, m, H-3′), 3.43 (1H, t, *J* = 9.2 Hz, H-4′), 2.03-1.85 (3H, m, H-3, H-6a), 1.84-1.70 (2H, m, H-6b, H-5b), 1.61 (3H, s, H-7), 1.55 (1H, dddd, *J* = 12.8, 12.4, 4.8, 2.4 Hz, H-4), 1.24 (3H, d, *J* = 6.0 Hz, H-6′), 1.21 (1H, m, H-5a), 1.15 (3H, s, H-9), 1.13 (3H, s, H-10). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*c 134.2 (C-1), 120.8 (C-2), 94.2 (C-1′), 79.5 (C-8), 73.4 (C-4′), 72.8 (C-3′), 72.2 (C-2′), 68.1 (C-5′), 44.0 (C-4), 31.3 (C-3), 26.9 (C-6), 24.3 (C-5), 24.2 (C-10), 23.5 (C-7), 22.9 (C-9), 17.7 (C-6′).

*Griffonilide (**2**)*: Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.62 (1H, dd, *J* = 9.6, 2.4 Hz, H-2), 6.27 (1H, dd, *J* = 9.6, 2.0 Hz, H-3), 5.89 (1H, d, *J* = 1.2 Hz, H-7), 4.90 (1H, dd, *J* = 10.4, 1.6 Hz, H-3), 4.33 (1H, m, H-4), 3.53 (1H, dd, *J* = 10.8, 7.2 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*c 176.0 (C-8), 165.0 (C-1), 144.4 (C-3), 120.8 (C-2), 112.7 (C-7), 85.4 (C-6), 80.2 (C-5), 73.7 (C-4) [13].

*Gallic acid (**3**)*: White powder. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 7.14 (2H, s, H-2, H-6). ^{13}C NMR (CD_3OD, 100 MHz): *δ*c 170.7 (C-7), 146.1 (C-3, C-5), 139.5 (C-4), 121.8 (C-1), 110.5 (C-2, C-6) [14].

*Methyl gallate (**4**)*: Brown amorphous powder. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 7.14 (2H, s, H-2, H-6), 3.81 (3H, s, 7-OC*H*$_3$). ^{13}C NMR (CD_3OD, 100 MHz): *δ*c 169.2 (C-7), 146.6 (C-3, C-5), 139.9 (C-4), 121.6 (C-1), 110.2 (C-2, C-6), 52.4 (7-O*C*H$_3$) [15].

*Ethyl gallate (**5**)*: White powder. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 7.05 (2H, s, H-2, H-6), 4.27 (1H, q, *J* = 6.8 Hz, H-1′), 1.34 (1H, t, *J* = 6.8 Hz, H-2′). ^{13}C NMR (CD_3OD, 100 MHz): *δ*c 168.7 (C-7), 146.6 (C-3, C-5), 139.8 (C-4), 121.9 (C-1), 110.2 (C-2, C-6), 61.8 (C-2′), 14.8 (C-1′) [16].

*Kaempferol (**6**)*: Yellow powder. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ_H 8.14 (2H, dd, *J* = 6.8, 2.0 Hz, H-2′, H-6′), 7.00 (2H, dd, *J* = 6.8, 2.0 Hz, H-3′, H-5′), 6.52 (1H, d, *J* = 2.0 Hz, H-8), 6.23 (1H, d, *J* = 2.0 Hz, H-6). ^{13}C NMR (CD_3COCD_3, 100 MHz): *δ*c 177.6 (C-4), 166.0 (C-7), 163.3 (C-5), 161.2 (C-4′), 158.8 (C-9), 148.1 (C-2), 137.7 (C-3), 131.5 (C-2′, C-6′), 124.4 (C-1′), 117.4 (C-3′, C-5′), 105.2 (C-10), 100.2 (C-6), 95.6 (C-8) [17].

*(+)-Catechin (**7**)*: Red powder. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 6.84 (1H, d, *J* = 1.6 Hz, H-2′), 6.75 (1H, d, *J* = 8.0 Hz, H-5′), 6.71 (1H, dd, *J* = 8.0, 1.6 Hz, H-6′), 5.92 (1H, d, *J* = 2.0 Hz, H-8), 5.85 (1H, d, *J* = 2.4 Hz, H-6), 4.56 (1H, d, *J* = 7.6 Hz, H-2), 3.97 (1H, m, H-3), 2.84 (1H, dd, *J* = 16.4, 5.6 Hz, H-4a), 2.50 (1H, dd, *J* = 16.4, 8.0 Hz, H-4b). ^{13}C NMR (CD_3OD, 100 MHz): *δ*c 158.0 (C-9), 157.7 (C-5),

157.0 (C-7), 146.4 (C-3′, C-4′), 132.4 (C-1′), 120.2 (C-6′), 116.2 (C-5′), 115.4 (C-2′), 101.0 (C-10), 96.4 (C-8), 95.7 (C-6), 83.0 (C-2), 69.0 (C-3), 28.7 (C-4) [18].

*Kaempferide-3-O-α-L-rhamnopyranoside (**8**)*: Colorless syrup. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 7.23 (2H, d, *J* = 8.4 Hz, H-2′, H-6′), 6.91 (2H, dd, *J* = 6.8, 2.0 Hz, H-3′, H-5′), 6.32 (1H, d, *J* = 1.6 Hz, H-8), 6.16 (1H, d, *J* = 2.0 Hz, H-6), 5.47 (1H, br s, OH), 5.37 (1H, d, *J* = 1.2 Hz, H-1′′), 4.24 (1H, m, H-5′′), 3.73 (1H, m, H-2′′), 3.34 (3H, 4′-OC*H*$_3$), 3.33 (2H, m, H-3′′, H-4′′), 0.92 (3H, d, *J* = 5.2 Hz, H-6′′). ^{13}C NMR (CD_3OD, 100 MHz): *δ*c 179.6 (C-4), 165.8 (C-7), 163.2 (C-5), 161.6 (C-4′), 159.3 (C-9), 158.5 (C-2), 136.3 (C-3), 132.0 (C-2′, C-6′), 122.7 (C-1′), 116.6 (C-3′, C-5′), 106.0 (C-10), 103.6 (C-1′′), 99.9 (C-6), 94.9 (C-8), 73.3 (C-4′′), 72.2 (C-3′′), 72.1 (C-2′′), 72.0 (C-5′′), 54.9 (4′-O*C*H$_3$), 17. 8(C-6′′) [19].

*Rhein (**9**)*: Orange-brown powder. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 8.16 (1H, s, H-4), 7.89 (1H, t, *J* = 8.0 Hz, H-6), 7.80 (1H, s, H-2), 7.78 (1H, br d, *J* = 8.0 Hz, H-5), 7.46 (1H, d, *J* = 8.0 Hz, H-7). ^{13}C NMR (DMSO-d_6, 100 MHz): *δ*c 192.3 (C-9), 181.9 (C-10), 166.4 (3-*C*OOH), 162.4 (C-1), 162.1 (C-8), 139.2 (C-3), 138.6 (C-6), 134.8 (C-10a), 134.2 (C-4a), 125.6 (C-4), 125.2 (C-5), 120.4 (C-2), 119.8 (C-7), 119.6 (C-8a), 117.2 (C-9a) [20].

*Aloe-emodin (**10**)*: Yellow amorphous solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 11.94 (2H, br s, 8-OH, 1-OH), 7.80 (1H, t, *J* = 8.0 Hz, H-6), 7.70 (1H, dd, *J* = 7.2, 1.6 Hz, H-5), 7.68 (1H, d, *J* = 1.6 Hz, H-4), 7.38 (1H, d, *J* = 8.4 Hz, H-7), 7.28 (1H, br s, H-2), 5.61 (1H, br s, 3-CH$_2$O*H*), 4.62 (2H, d, *J* = 4.4 Hz, 3-C*H*$_2$OH). ^{13}C NMR (DMSO-d_6, 100 MHz): *δ*c 191.6 (C-9), 181.4 (C-10), 161.6 (C-1), 161.3 (C-8), 153.7 (C-3), 137.3 (C-6), 133.3 (C-11), 133.1 (C-14), 124.4 (C-7), 120.6 (C-2), 119.3 (C-5), 117.1 (C-4), 115.9 (C-12), 114.4 (C-13), 62.0 (3-*C*H$_2$OH) [21].

*Lingueresinol (**11**)*: White powder. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 6.58 (1H, s, H-5), 6.38 (2H, s, H-2′, H-6′), 4.30 (1H, d, *J* = 5.6 Hz, H-1), 3.85 (3H, s, 6-OC*H*$_3$), 3.73 (6H, s, 3′-OC*H*$_3$, 5′-OC*H*$_3$), 3.59 - 3.46 (4H, m, H-2a, H-3a), 3.37 (3H, s, 4′-OC*H*$_3$), 2.71 (1H, dd, *J* = 15.2, 4.8 Hz, H-4a), 2.56 (1H, dd, *J* = 15.2, 12.0 Hz, H-4b), 1.97 (1H, m, H-2), 1.61 (1H, m, H-3). ^{13}C NMR (CD_3OD, 100 MHz): *δ*c 149.1 (C-3′, C-5′), 148.8 (C-6), 147.8 (C-4′), 139.4 (C-8), 139.0 (C-7), 134.7 (C-1′), 130.3 (C-8a), 126.4 (C-4a), 107.9 (C-5), 107.0 (C-2′, C-6′), 66.9 (C-2a), 64.3 (C-3a), 60.3 (4′-O*C*H$_3$), 56.9 (3′-O*C*H$_3$, 5′-O*C*H$_3$), 56.8 (6-O*C*H$_3$), 42.4 (C-2), 41.0 (C-1), 33.7 (C-3) [22].

3.2. Acetylcholinesterase Activities

At a concentration of 1 mg/mL, compounds **3** and **8** were singled out as the most potent inhibitors of the AChE with high percentages of inhibition (>68%, Figure 3) which were comparable to the activity of donepezil (a commercial drug).

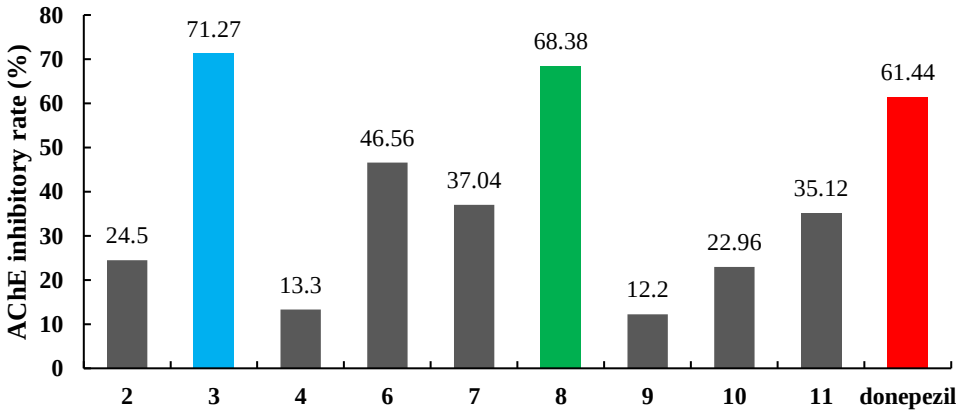

Figure 3. AChE inhibitory activities of **2–4**, **6–11** and donepezil at 1 mg/mL

Compound **3**, a natural organic acid which distributed widely in natural organisms, was also found to be an efficient AChEi in the previous reports [26-27]. Interestingly, as analogues of **3**, compounds **4** and **5** showed weak inhibitory activity, indicating that the free carboxyl group on the benzene ring is

crucial for AChE inhibitory activity. Compound **8** has been isolated from many plants, such as *Fortunella japonica* [28], *Cassia biflora* [29], and *Excoecaria agallocha* [30], to the best of our knowledge, this is the first screening of AChE inhibitory activity of it. The IC_{50} values of compounds **3** and **8** were further calculated based on the dose response curve as shown in Figure 4, exhibited to be 0.488, 0.391 mg/mL, respectively, while the IC_{50} of donepezil was tested to be 0.096 mg/mL. Till now little attention has been paid on the AChE inhibitory activities of extracts from *C. glabra* legumes and the exact active constituents behind are still uncertain. Thus, these results discussed in this research would be very instructive to the further utilization of medicinal value of *C. glabra*, as well as the development of new agents against various diseases induced by AChE overexpression.

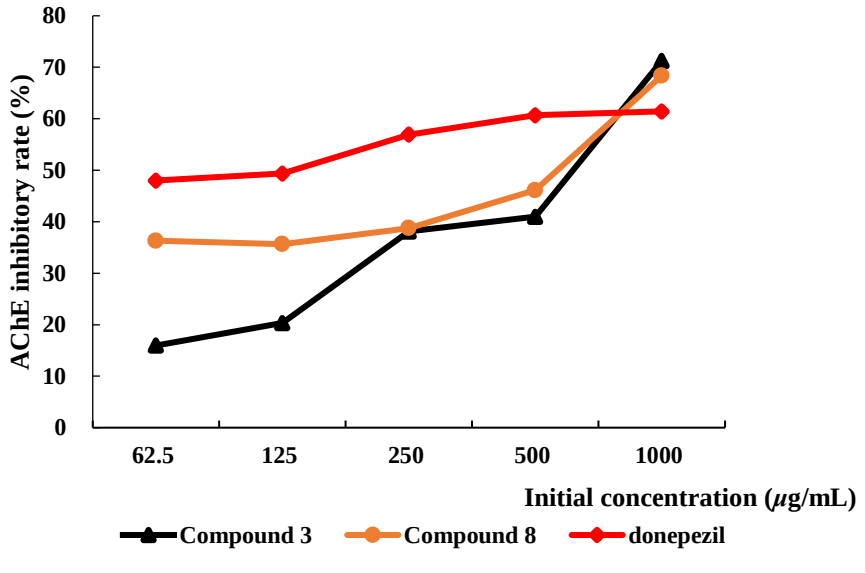

Figure 4. Dose response curve of AChE inhibitory rates by **3**, **8** and donepezil

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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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