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Isolation and Characterization of Glycosidic Tyrosinase Inhibitors from *Typhonium giganteum* Rhizomes

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Abstract: A new hydrocinnamoyl glucoside, 1-*O*-(4-hydroxyhydrocinnamoyl)-*β*-D-glucopyranose (**1**), together with fifteen known glycosides, including two phenylethanoid glycosides (**2**–**3**), two cinnamoyl glycosides (**4**–**5**), six phenolic glycosides (**6**–**11**), one lignan glycoside (**12**) and four megastigmane glycosides (**13**–**16**) were isolated from a 95% EtOH extract of the *Typhonium giganteum* rhizomes. The sixteen glycosides were structurally characterized by NMR, HRESIMS, enzymatic hydrolysis and comparison with literature. Upon evaluating inhibitory activities of compounds **1**–**16** against mushroom tyrosinase at 25 μM, compounds **10** and **11** exhibited obvious inhibitory activities, with %inhibition values of 20.94±0.59%, 23.28±1.09%, respectively, with arbutin used as the positive control (26.21±0.58%).

Keywords: *Typhonium giganteum*; tyrosinase inhibitor; glycoside; arbutin.

1. Introduction

Typhonium giganteum rhizomes, also known as *Typhonii Rhizoma*, are widely utilized in Traditional Chinese Medicines to treat tetanus, stroke and epilepsia [1]. Previous investigations have shown that crude extracts of *T. giganteum* rhizomes possess tyrosinase inhibitory activity [2–3], and many glycosides have been isolated from various parts of this plant [4–6]. In search for potential tyrosinase inhibitors from natural sources [7–9], our investigation on an EtOH extract of the *T. giganteum* rhizomes has led to the isolation of one new and fifteen known compounds. Two of them showed strong tyrosinase inhibitory activities [10]. In continuing our study on the constituents of the EtOH extract of *T. giganteum* rhizomes, we have isolated one new and fifteen known glycosidic compounds (Figure 1). During the subsequent antityrosinase assay, glycosides **10** and **11** showed strong inhibitory activities similar to that of arbutin. Here, we describe the characterization of these glycosides and the evaluation of their inhibitory effects against mushroom tyrosinase.

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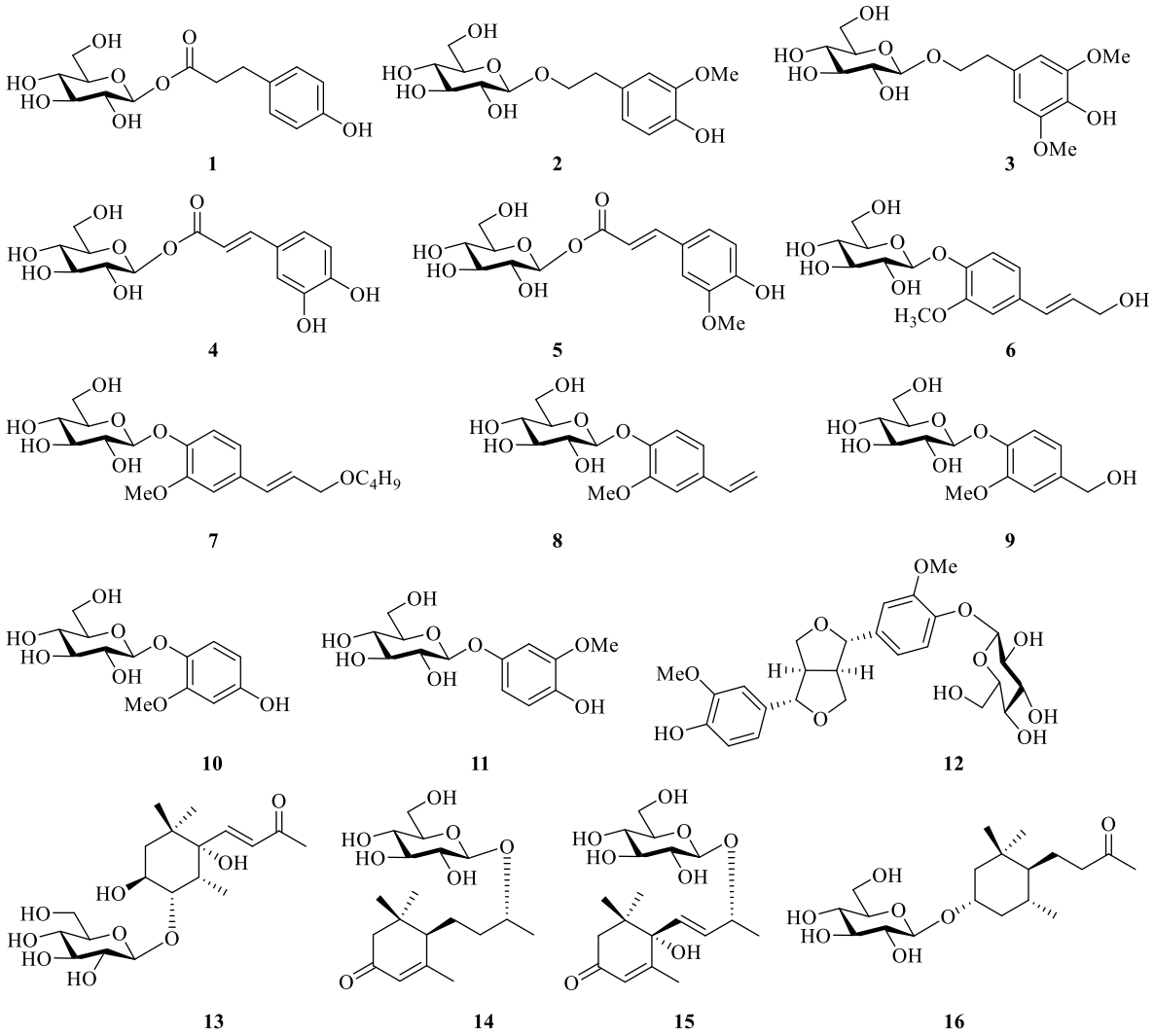

Figure 1. Chemical structures of compounds **1**–**16**

2. Materials and Methods

2.1. General Experimental Procedures

Column chromatography (CC) was performed using silica gel (Qingdao Marine Chemical Inc., China), Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden) and RP-C18 (50 μm, Fuji Silysia Chemical Ltd., Japan). TLC was performed with silica gel 60 F254 (Yantai Chemical Industry Research Institute). The spots on TLC were visualized by warming 10% H_2SO_4 (10% H_2SO_4 in ethanol) sprayed plates on a hot plate. NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz), and the ^1H and ^{13}C NMR chemical shifts were referenced to the solvent or solvent impurity peaks for CD_3OD at δ_H 3.31 and δ_C 49.15. HRESIMS spectra were carried out on a Bruker micrOTOF II spectrometer. Optical rotations were determined on a Rudolph Autopol IV polarimeter. UV and IR spectra were determined using Puxi TU-1950 and FTIR-650 instruments, respectively.

2.2. Plant Material

The rhizomes of *Typhonium giganteum* were collected in Yuzhou, P. R. China, in September 2020 and authenticated by Prof. Lin Yang at Lanzhou University of Technology. The specimen (SPH2020A) was stored in Food and Pharmacy College, Xuchang University.

2.3. Extraction and Isolation

The air-dried rhizomes of *Typhonium giganteum* (6.4 kg) were extracted with 95% EtOH (3 × 35 L, room temperature) to yield a crude extract (347 g), which was suspended in warm H_2O and partitioned by CH_2Cl_2 and *n*-BuOH. The *n*-BuOH fraction (90.2 g) was subjected to silica gel CC eluted by CH_2Cl_2–MeOH (50:1 to 2:1) to give eleven fractions F1–F11. The fraction F5 (3.1 g, eluted by CH_2Cl_2–MeOH 25:1) was subsequently purified using RP-C_{18} CC (MeOH–H_2O, 65:35 to 100:0) to afford compounds **7** (5.4 mg) and **8** (6.7 mg). The fraction F6 (2.6 g, eluted by CH_2Cl_2–MeOH 20:1) was further separated using Sephadex LH-20 column (MeOH) to give compounds **12** (10.3 mg) and **1** (20.5 mg). The fraction F7 (17.5 g, eluted by CH_2Cl_2–MeOH 15:1) was passed through a RP-C_{18} CC using MeOH-H_2O (20:80 to 100:0) as eluents to give six subfractions (F7-1 to F7-6). The subfraction F7-1 was purified on the silica gel CC to give compounds **13** (3.8 mg) and **15** (5.6 mg). The subfraction F7-3 was chromatographed by RP-C_{18} CC (MeOH–H_2O, 35:65) to obtain compounds **4** (5.7 mg) and **14** (4.9 mg). The subfraction F7-5 was purified by Sephadex LH-20 column (MeOH) to afford compound **3** (5.5 mg) and **6** (7.8 mg). The fraction F8 (17.6 g, eluted by CH_2Cl_2–MeOH 10:1) was further separated using RP-C_{18} CC (MeOH-H_2O, 20:80 to 50:50) to give eight subfractions F8-1–F8-8. After further purification with Sephadex LH-20 column (MeOH), the subfraction F8-1 gave compounds **2** (3.1 mg) and **11** (6.2 mg), and the subfractions F8-2, F8-4, F8-5 gave compounds **5** (3.1 mg), **6** (4.8 mg), **16** (5.4 mg), respectively. The subfraction F8-8 was chromatographed through a RP-C_{18} CC eluted with MeOH-H_2O (25:75) to afford compounds **9** (6.4 mg) and **10** (4.9 mg).

*Compound **1***: Colorless syrup. $[\alpha]_D^{20}$ +15° (c 0.4, MeOH). IR (KBr) ν_{max} 3316, 2921, 2852, 1737, 1513, 1444, 1367, 1243, 1074 cm^{-1}. UV λ_{max} (MeOH) nm (log ε): 224 (3.7), 278 (3.0). HRESIMS *m/z* 351.1064 $[M + Na]^+$ (calcd for $C_{15}H_{20}O_8Na$, 351.1056). ^{1}H-NMR (CD_3OD, 400MHz) δ: 7.03 (2H, d, *J* = 6.8 Hz, H-2′, H-6′), 6.68 (2H, d, *J* = 6.8 Hz, H-3′, H-5′), 5.45 (1H, d, *J* = 8.0 Hz, H-1), 4.47 (1H, dd, *J* = 12.0, 0.8 Hz, H-6a), 4.32 (1H, dd, *J* = 12.0, 5.2 Hz, H-6b), 3.59 (1H, ddd, *J* = 5.2, 0.8 Hz, H-5), 3.42 (1H, dd, *J* = 9.2, 9.2 Hz, H-3), 3.36 (1H, dd, *J* = 9.2, 9.2 Hz, H-4), 3.34 (1H, dd, *J* = 9.2, 8.0 Hz, H-2), 2.84 (2H, t, *J* = 8.0 Hz, H-7′), 2.65 (2H, t, *J* = 8.0 Hz, H-8′). ^{13}C-NMR (CD_3OD, 100MHz) δ: 173.5 (C-9′), 157.0 (C-4′), 132.7 (C-1′), 130.5 (C-2′, C-6′), 116.4 (C-3′, C-5′), 95.7 (C-1), 77.9 (C-3), 76.1 (C-5), 74.0 (C-2), 71.3 (C-4), 65.9 (C-6), 37.3 (C-8′), 30.9 (C-7′).

*2.4. Enzymatic Hydrolysis of Compound **1***

The enzymatic hydrolysis of compound **1** was achieved according to the literature procedures [11]. To a solution of compound **1** (10.2 mg) in 2 mL of H_2O was added β-glucosidase (40 mg, CAS: 9001-22-3), and the reaction mixture was stirred at room temperature overnight. After 14 h, the reaction mixture was extracted with EtOAc, washed with water, dried by Na_2SO_4, concentrated under vacuum, and purified to give 4-hydroxyphenyl propionic acid (**1a**) as the aglycone.

*4-Hydroxyphenyl propionic acid (**1a**)* [12]: Amorphous powder. ^{1}H-NMR (CD_3OD, 400MHz) δ: 7.01 (2H, d, 8.0, H-2, H-6), 6.68 (2H, d, 8.0, H-3, H-5), 2.80 (2H, t, 8.0, H-7), 2.53 (2H, t, 8.0, H-8); ^{13}C-NMR (CD_3OD, 100MHz) δ: 177.1 (C-9), 156.9 (C-4), 133.1 (C-1), 130.4 (C-2, C-6), 116.3 (C-3, C-6), 37.3 (C-8), 31.4 (C-7).

2.5. Mushroom Tyrosinase Inhibition Assay

Mushroom tyrosinase inhibition assay was conducted according to the literature procedures [8]. Arbutin (25 μM) was used as the positive control. All experiments were performed three times. The %inhibition was calculated by [1 − (As/Ac)] × 100, where As is the absorbance of tested compound and Ac the non-treated control. The results were analyzed by program GraphPad Prism 5.0. Data are expressed as means ± SEMs of triplicate.

3. Results and Discussion

3.1. Isolation and Structure Elucidation

The air-dried *T. giganteum* rhizomes were extracted with 95% EtOH to afford the EtOH extract, which was sequentially fractionated into CH_2Cl_2-, *n*-BuOH- and H_2O-soluble fractions. The mushroom tyrosinase inhibition assay was employed to evaluate the bioactivities of all crude extracts at a derivative concentration of 100 μg/mL. As summarized in Table 1, the *n*-BuOH-soluble fraction showed the best inhibitory activity against mushroom tyrosinase. Therefore, the *n*-BuOH-soluble fraction was chosen for further investigation of its chemical constituents in this study.

Table 1. Inhibitory effects of various fractions obtained from the extract of *T. giganteum* rhizomes and arbutin on mushroom tyrosinase activity [a]

Fraction	Tyrosinase inhibition (%)
Control (100% DMSO)	NI [b]
95% EtOH extract	5.12±0.77
CH_2Cl_2-Soluble fraction	8.34±0.38
n-BuOH-Soluble fraction	13.62±0.72
H_2O-Soluble fraction	NI [b]
arbutin (positive control)	38.07±0.95

[a] Measured at 100 μg/mL, using L-tyrosine as the substrate. Results were shown as means ± SEMs. [b] NI: no inhibition.

After repeated column chromatography over silica gel, RP-C18 and Sephadex LH-20, the *n*-BuOH-soluble fraction gave sixteen glycosides (**1**–**16**), one of which was a new compound. The fifteen known glycosides (**2**–**16**) were identified as 2-(4-hydroxy-3-methoxyphenyl)ethyl-*β*-D-glucopyranoside (**2**) [13], *β*-(4-hydroxy-3,5-dimethoxyphenyl)ethyl-*β*-D-glucopyranoside (**3**) [14], 1-*O*-caffeoyl-*β*-D-glucopyranose (**4**) [15], 1-*O*-feruloyl-*β*-D-glucopyranose (**5**) [15], coniferin (**6**) [16], butylconiferin (**7**) [17], 2-methoxy-4-vinylphenol glycoside (**8**) [18], vanilloloside (**9**) [19], isotachioside (**10**) [20], tachioside (**11**) [21], pinoresinol-4-*O*-glucopyranoside (**12**) [22], lasianthionosides A (**13**) [23], byzantionoside B (**14**) [24], (6*S*,9*R*)-roseoside (**15**) [25], 3*β*-*O*-(*β*-D-glucopyranosyloxyl)-megastigma-9-one (**16**) [26], respectively, by spectral comparison with literature. All compounds were reported from *T. giganteum* for the first time. The structure of the new compound (**1**) was elucidated on the basis of spectroscopic analysis, enzymatic hydrolysis and comparison with literature as described below.

Compound **1** was obtained as a colorless syrup. The molecular formula $C_{15}H_{20}O_8$, with six degrees of unsaturations, was established based on its quasi-molecular ion peak at *m/z* 351.1064 $[M + Na]^+$ (calcd for $C_{15}H_{20}O_8Na$, 351.1056) in the HRESIMS spectrum. The IR absorption bands at 1737 and 3316 cm^{-1} suggested the presence of a carbonyl group and hydroxyl groups. The ^{1}H-NMR spectrum of **1** revealed the signals of an AA´BB´ spin system at δ 7.03 (2H, d, J = 6.8 Hz, H-2´, H-6´), 6.68 (2H, d, J = 6.8 Hz, H-3´, H-5´), suggesting the presence of one *para*-disubstituted benzene ring. Its ^{13}C NMR and DEPT spectra showed the signals of six aromatic carbons (two signals at δ 130.5 and 116.4 appearing as double intensity), one quaternary carbon (δ 173.5), two methylene carbons (δ 37.3, 30.9), which suggested the presence of 4-hydroxyhydrocinnamoyl group. The proton signals at δ_H 5.45 (1H, d, J = 8.0 Hz, H-1), 4.47 (1H, dd, J = 12.0, 0.8 Hz, H-6a), 4.32 (1H, dd, J = 12.0, 5.2 Hz, H-6b),

3.59 (1H, ddd, *J* = 5.2, 0.8 Hz, H-5), 3.42 (1H, dd, *J* = 9.2, 9.2 Hz, H-3), 3.36 (1H, dd, *J* = 9.2, 9.2 Hz, H-4), 3.34 (1H, dd, *J* = 9.2, 8.0 Hz, H-2), and ^{13}C-NMR signals at δ_C 95.7 (C-1), 77.9 (C-3), 76.1 (C-5), 74.0 (C-2), 71.3 (C-4), 65.9 (C-6) demonstrated the presence of a glucose. The speculations above were confirmed by the key ^{1}H-^{1}H COSY and HMBC correlations shown in Figure 2. The sugar moiety was decided as *β*-glucose ($J_{1,2}$ = 8.0 Hz) and elucidated as D-sugar by subsequent enzymatic hydrolysis. The HMBC correlations from H-1 to C-9′ suggested that the 4-hydroxyphenyl propionic acid was attached to C-1 position of the sugar moiety. Therefore, the structure of compound **1** was identified as 1-*O*-(4-hydroxyhydrocinnamoyl)-*β*-D-glucopyranose. Although searching the structure of **1** in Scifinder database gave a similar structure (CAS: 2569469-61-8) and one literature [27], further investigation of the original reference could not find the target compound. Therefore, compound **1** is still determinated as a new compound.

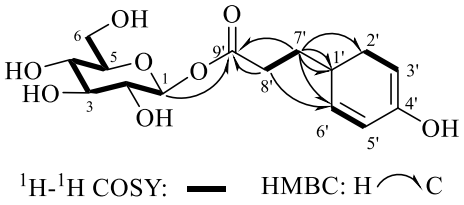

Figure 2. Key ^{1}H-^{1}H COSY and HMBC correlations for compound **1**

3.2. Tyrosinase Inhibitory Activity

All isolated compounds **1**–**16** were evaluated for their tyrosinase inhibitory activities at a concentration of 25 *μ*M, using arbutin as the positive control. The results were summarized in Table 2. Compounds **10** and **11** showed obvious inhibitory activities, with %inhibition values of 20.94±0.59%, 23.28±1.09%, respectively, close to the known melanogenesis inhibitor, arbutin (4-hydroxyphenyl *β*-D-glucopyranoside; 26.21±0.58%), which has been used as an effective skin-whitening agent in the cosmetic industry [28]. However, their analogues **6**–**9** showed weaker inhibitory activities. Other compounds showed weak or no inhibitory activities (%inhibition < 5%). Among the compounds tested, the structures of **6**–**11** possess a high similarity to arbutin. Therefore, a simple structure activity relationship of arbutin and its analogues **6**–**11** was discussed in Figure 3. The results indicate that groups at C-2, C-4, and C-5 in arbutin are important factors for inhibitory activity against tyrosinase. The electron-donating substituents at C-2 (**10**) or C-5 (**11**) lead to increased inhibitory activities, and replacing the hydroxyl group at C-4 in arbutin with electron-donating groups such as vinyl (**8**) or others (**6**, **7**, **9**) lead to a sharp decrease of inhibitory activities. Among these, isotachioside (**10**) and tachioside (**11**) have been demonstrated to be the most relevant principles of the tyrosinase inhibitory activity of the extract, and these glycosidic analogues of arbutin **6**–**11** isolated from *Typhonium giganteum* rhizomes in this study may be valuable as potential skin-whitening agents.

Table 2. Inhibitory effects of compounds **4**, **6–11** and of arbutin on mushroom tyrosinase[a]

Compound	Tyrosinase inhibition (%)
4	5.27±0.74
6	10.54±0.81
7	7.17±0.85
8	14.20±0.84
9	12.44±1.11
10	20.94±0.59
11	23.28±1.09
arbutin (positive control)	26.21±0.58

[a] Measured at 25 *μ*M, using L-tyrosine as the substrate. Results were expressed as means ± SEMs.

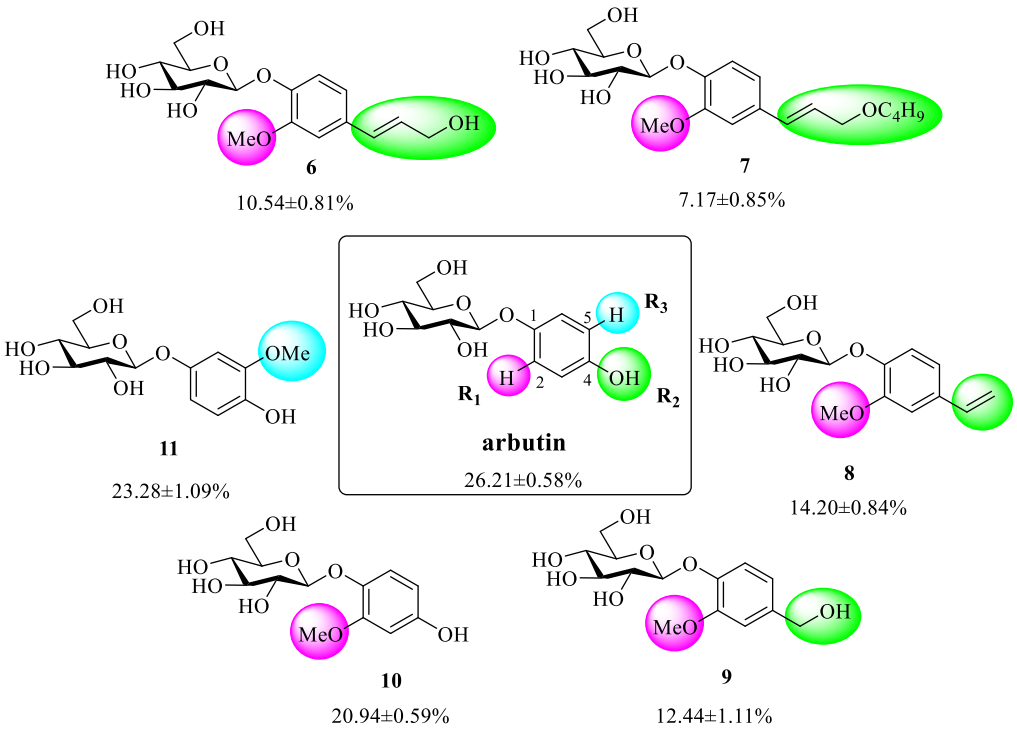

Figure 3. Structure activity relationship of arbutin analogues as tyrosinase inhibitors

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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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