Chinese Herbal Medicines 15 (2023) 151–154

Contents lists available at ScienceDirect

Chinese Herbal Medicines

journal homepage: www.elsevier.com/locate/chmed

Original Article

Chemical constituents from aerial parts of *Scoparia dulcis*

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ARTICLE INFO

Article history:
Received 24 June 2022
Revised 9 August 2022
Accepted 23 September 2022
Available online 14 October 2022

Keywords:
alkaloids
chemical constituents
α-glucosidase inhibitory activity
Scoparia dulcis L.

ABSTRACT

Objective: To study the chemical constituents from the aerial parts of *Scoparia dulcis*.
Methods: Various chromatographic techniques were used to separate the constituents and their structures were elucidated using spectroscopic methods and by comparing their data to those reported in the literatures. The α-glucosidase inhibitory activity assay was used to identify potential α-glucosidase inhibitors.
Results: Nine compounds were isolated from the aerial parts of *S. dulcis*. Their structures were identified as Scoparic zolone (**1**), (2*S*)-2,7-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**2**), (2*R*)-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-D-glucopyranoside (**3**), (2*R*)-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-D-glucopyranoside (**4**), (2*S*)-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-D-glucopyranoside (**5**), 6-methoxy-benzoxazolin-2(3*H*)-one (**6**), 4-acetonyl-3,5-dimethoxy-*p*-quinol (**7**), zizyvoside I (**8**), and 3,4-dihydroxy benzeneacetic acid (**9**). Compound **2** showed the potent α-glucosidase inhibitory activity with an IC_{50} value of (132.8 ± 11.5) μmol/L, which is 28-fold higher than the positive control acarbose.
Conclusion: Compound **1** is a new natural product. Compounds **2** and **9** have not been reported in Scoparia before. Compounds **3**, **5**, **7**, **8** are isolated from Scrophulariaceae for the first time.

1. Introduction

The genus *Scoparia* contains 10 species, mainly distributed in Mexico and South America, one of which is widespread in the global tropics, and there is only one species in China (*Scoparia dulcis* L.) (Editorial Committee of Flora Reipublicae Popularis Sinicae). *S. dulcis* has commonly been used as Chinese folk medicines, had antidiabetic, antigastric ulcer, antiviral, analgesic, anti-inflammatory, sympathomimetic, and diuretic activities (Wu, Chen, Lu, Chen, & Chang, 2012). In previous chemical investigations, alkaloids, saponin, cardiac glycosides, steroids, flavonoids, and terpenoids, have been isolated from *S. dulcis*. In this study, we isolated and identified nine compounds from the aerial parts of *S. dulcis*, and examined their α-glucosidase inhibitory activity.

2. Materials and methods

2.1. Apparatus and reagents

Optical rotations were measured on a Krüss-P800-T polarimeter. UV spectra were recorded on a JASCO J-180 spectrometer (JASCO Co., Tokyo, Japan). IR spectra were obtained with a Nicolet-380 spectrometer (Thermo Electron Co., MA, USA). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 600 Spectrometer (Bruker Co., Karlsruhe, Germany) with tetramethylsilane as an internal standard. HRESIMS were obtained on a Waters UPLC Premior QTOF spectrometer (Waters Co., MA, USA), and UPLC-MS analysis was performed on an Acquity Waters Ultra-Performance liquid chromatographic system equipped with a Waters UPLC column (Acquity UPLC BEH C_{18} 1.7 μm, 2.1 mm × 50 mm) and a Micromass ZQ 2000 ESI mass spectrometer (Waters Co., MA, USA). Thin-layer chromatography was carried out on HSGF254 plates (Yantai Jiangyou Silica Gel Development Co., Ltd., Yantai, China). Column chromatography was performed with silica gel (300–400 mesh, Qingdao Makall Group Co., Ltd., Qingdao, China), MCI gel CHP 20P (70–150 μm, Mitsubishi Chemical Co., Tokyo, Japan), Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Uppsala, Sweden), and YMC gel ODS-A-HG (50 μm, YMC Co., Ltd., Kyoto, Japan). α-D-Glucosidase and acarbose were purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.2. Plant materials

The aerial parts of *S. dulcis* were collected and authenticated by Mr. Yilin Zhu from Guangxi University of Chinese Medicine in Nanning, Guangxi Zhuang Autonomous Region, China, in Septem-

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https://doi.org/10.1016/j.chmed.2021.12.007
1674-6384/

ber 2018. A voucher specimen (No. YGC-Nanning1210) was deposited in the herbarium of the Institute of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine.

2.3. Extraction and isolation

Aerial parts of dried *S. dulcis* (3.7 kg) were soaked with 70% aqueous acetone solution at room temperature for three times at an in-terval of 7 d. After filtration and elimination of organic solvent, the extraction was extracted with petroleum ether, ethyl acetate in turn, to acquire 29 g of petroleum ether extracts, 108 g of ethyl acetate extracts, and 194 g of water solution portion, respectively. The ethyl acetate extract was eluted with MeOH-H_2O (0:1 to 1:0, volume percent), performed by MCI gel CHP 20P column chromatography, to obtain three fractions (Fr. A–C).

Fr. A was separated by column chromatography via Sephadex LH-20, eluted with MeOH-H2O, (2:8 to 6:4, volume percent) and the YMC-column, eluted with MeOH-H2O (1:9 to 6:4) sequentially to afford compounds 7 (17 mg), 8 (7 mg), 9 (6 mg). Column chromatography through Sephadex LH-20, eluted with MeOH-H_2O (0:1 to 8:2, volume percent) and YMC, eluted with MeOH-H_2O (1:9 to 6:4, volume percent), acquired **1** (3 mg), **2** (7 mg), **3** (43 mg), **4** (14 mg), **5** (8 mg) from Fr. B. Chromatography of Fr. C on MCI gel CHP 20P eluted with MeOH-H_2O (4:6 to 9:1, volume percent) and silica gel eluted with CH_2Cl_2-MeOH (20:1 to 1:1, volume percent) yielded **6** (67 mg) (Fig. 1).

Scoparic zolone (**1**), white amorphous powder; [α] – 42.0 (*c* 0.03, MeOH); UV (MeOH) λ^{max} (log ε) 208 (4.37), 262 (3.75) nm; IR (KBr) ν_{max} 3365, 2923, 2852, 1711, 1655, 1632, 1469, 1382, 1204, 1075, 620 cm^{-1}; ^{1}H NMR (600 MHz, MeOD): δ_H 6.30 (1H, d, *J* = 2.2 Hz, H-4), 6.68 (1H, dd, *J* = 8.3, 2.2 Hz, H-6), 6.72 (1H, d, *J* = 8.3 Hz, H-7), 3.30 (1H, d, *J* = 16.5 Hz, H-8a), 3.13 (1H, d, *J* = 16.5 Hz, H-8b), 2.10 (3H, s, H-10); ^{13}C NMR (125 MHz, MeOD): δ_C 181.1 (C-2), 75.3 (C-3), 133.4 (C-3a), 112.9 (C-4), 154.5 (C-5), 116.6 (C-6), 111.8 (C-7), 135.5 (C-7a), 51.1 (C-8), 207.4 (C-9), 30.8 (C-10); HRESIMS 220.0618 $[M-H]^{\pm}$ (calcd. for 220.0610).

(2*S*)-2,7-Dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**2**), white amorphous powder; ^{1}H NMR (400 MHz, MeOD): δ_H 5.50 (1H, s, H-2), 6.77 (1H, d, *J* = 8.5 Hz, H-5), 6.46 (1H, dd, *J* = 8.5, 2.4 Hz, H-6), 6.49 (1H, d, *J* = 2.4 Hz, H-8); ^{13}C NMR (100 MHz, MeOD): δ_C 92.2 (C-2), 164.7 (C-3), 119.8 (C-4a), 117.3 (C-5), 110.5 (C-6), 115.4 (C-7), 106.0 (C-8), 143.2 (C-8a).

(2*R*)-7-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-*D*-glucopyranoside (**3**), white amorphous powder; ^{1}H NMR (400 MHz, MeOD): δ_H 5.77 (1H, s, H-2), 6.95 (1H, m, H-5), 7.03 (1H, m, H-6), 7.03 (1H, m, H-7), 7.11 (1H, m, H-8), 4.70 (1H, d, *J* = 7.8 Hz, H-Glc-1), 3.21 (1H, t, *J* = 8.6 Hz, H-Glc-2), 3.30–3.40 (3H, m, H-Glc-3, 4, 5), 3.87 (1H, dd, *J* = 11.9, 1.7 Hz, H-Glc-6a), 3.70 (1H, dd, *J* = 11.9, 4.6 Hz, H-Glc-6b); ^{13}C NMR (100 MHz, MeOD): δ_C 96.5 (C-2), 163.2 (C-3), 127.1 (C-4a), 116.8 (C-5), 125.1 (C-6), 124.2 (C-7), 119.0 (C-8), 142.1 (C-8a), 103.9 (C-Glc-1), 74.9 (C-Glc-2), 78.5 (C-Glc-3), 71.1 (C-Glc-4), 77.9 (C-Glc-5), 62.6 (C-Glc-6).

(2*R*)-7-Methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-*D*-glucopyranoside (**4**), white amorphous powder; ^{1}H NMR (600 MHz, MeOD): δ_H 5.74 (1H, s, H-2), 6.86 (1H, d, *J* = 8.7 Hz, H-5), 6.62 (1H, dd, *J* = 8.7, 2.5 Hz, H-6), 6.75 (1H, d, *J* = 2.5 Hz, H-8), 4.70 (1H, d, *J* = 7.9 Hz, H-Glc-1), 3.21 (1H, t, *J* = 8.6 Hz, H-Glc-2), 3.30–3.40 (3H, m, H-Glc-3, 4, 5), 3.88 (1H, dd, *J* = 11.9, 1.9 Hz, H-Glc-6a), 3.70 (1H, dd, *J* = 11.9, 5.1 Hz, H-Glc-6b); ^{13}C NMR (150 MHz, MeOD): δ_C 96.7 (C-2), 162.7 (C-3), 120.4 (C-4a), 116.2 (C-5), 110.1 (C-6), 158.2 (C-7), 104.9 (C-8), 142.9 (C-8a), 103.1 (C-Glc-1), 74.8 (C-Glc-2), 78.5 (C-Glc-3), 71.1 (C-Glc-4), 77.9 (C-Glc-5), 62.6 (C-Glc-6).

(2*S*)-7-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-*D*-glucopyranoside (**5**), white amorphous powder; ^{1}H NMR (600 MHz, MeOD): δ_H 5.82 (1H, s, H-2), 6.77 (1H, d, *J* = 8.5 Hz, H-5), 6.48 (1H, dd, *J* = 8.5, 1.9 Hz, H-6), 6.56 (1H, d, *J* = 1.9 Hz, H-8), 4.74 (1H, d, *J* = 7.9 Hz, H-Glc-1), 3.15 (1H, t, *J* = 8.6 Hz, H-Glc-2), 3.30–3.39 (3H, m, H-Glc-3, 4, 5), 3.91 (1H, br d, *J* = 12.0 Hz, H-Glc-6a), 3.70 (1H, dd, *J* = 11.9, 6.0 Hz, H-Glc-6b); ^{13}C NMR (150 MHz, MeOD): δ_C 93.3 (C-2), 162.7 (C-3), 119.5 (C-4a), 117.4 (C-5), 111.0 (C-6), 155.7 (C-7), 106.2 (C-8), 142.6 (C-8a), 99.9 (C-Glc-1), 74.5 (C-Glc-2), 78.4 (C-Glc-3), 71.4 (C-Glc-4), 77.8 (C-Glc-5), 62.7 (C-Glc-6).

6-Methoxy-benzoxazolin-2(3*H*)-one (**6**), colorless needle crystal; ^{1}H NMR (600 MHz, Pyridine d_6): δ_H 7.01 (1H, d, *J* = 8.5 Hz, H-4), 6.78 (1H, d, *J* = 8.5, 2.4 Hz, H-5), 7.03 (1H, d, *J* = 2.4 Hz, H-7), 3.68 (3H, s, OMe), 12.97 (1H, brs, NH); ^{13}C NMR (125 MHz, Pyridine d_6): δ_C 156.1 (C-2), 125.0 (C-3a), 110.0 (C-4), 109.5 (C-5), 156.4 (C-6), 97.5(C-7), 145.4 (C-7a), 55.9 (OMe).

4-Acetonyl-3,5-dimethoxy-*p*-quinol (**7**), white amorphous powder; ^{1}H NMR (400 MHz, DMSO): δ_H 5.32 (2H, s, H-2,6), 3.06 (2H, s, H-7), 2.02 (3H, s, H-9), 3.66 (6H, s, OCH3-2, 6), 6.16 (1H, s, OH-4); ^{13}C NMR (100 MHz, MeOD): δ_C 186.6 (C-1), 100.1 (C-2,6), 171.5 (C-3,5), 69.4 (C-4), 49.4 (C-7), 204.7 (C-8), 30.8 (C-9), 56.2 (3,5-OMe)。.

Zizyvoside I (**8**), white amorphous powder; ^{1}H NMR (400 MHz, MeOD): δ_H 5.90 (1H, s, H-2), 2.54 (1H, d, *J* = 16.9 Hz, H-6a), 2.16 (1H, d, *J* = 16.9 Hz, H-6b), 5.87 (1H, d, *J* = 3.0 Hz, H-7), 5.89 (1H, d, *J* = 3.0 Hz, H-8), 3.40 (1H, m, H-9), 1.31 (3H, d, *J* = 6.3 Hz, H-10), 1.94 (3H, s, H-11), 1.06 (3H, s, H-12), 1.06 (3H, s, H-13), 4.43 (1H, d, *J* = 7.5 Hz, H-1′), 5.26 (1H, d, *J* = 1.3 Hz, H-1″); ^{13}C NMR (100 MHz, MeOD): δ_C 201.2 (C-1), 127.7 (C-2), 167.2 (C-3), 78.0 (C-4), 42.5 (C-5), 50.7 (C-6), 131.6 (C-7), 135.4 (C-8), 77.2 (C-9), 21.2 (C-10), 19.6 (C-11), 24.7 (C-12), 23.4 (C-13), 101.2 (C-1′), 79.5 (C-2′), 77.9 (C-3′), 72.2 (C-4′), 78.7 (C-5′), 62.8 (C-6′), 102.0 (C-1″), 71.8 (C-2″), 72.3 (C-3″), 73.9 (C-4″), 69.7 (C-5″), 18.1 (C-6″).

3,4-Dihydroxy benzeneacetic acid (**9**), white amorphous powder; ^{1}H NMR (400 MHz, MeOD): δ_H 7.05 (1H, d, *J* = 2.1 Hz, H-2), 6.80 (1H, d, *J* = 8.2 Hz, H-5), 6.95 (1H, dd, *J* = 8.2, 2.1 Hz, H-6), 7.55 (1H, d, *J* = 15.9 Hz, H-β), 6.24 (1H, d, *J* = 15.9 Hz, H-α).

2.4. α-Glucosidase inhibitory activity assay

The assay was carried out according to a reported method (Yang, et al. 2015). α-Glucosidase (from *Saccharomyces cerevisiae*) was dissolved in potassium phosphate buffer (pH 6.8) with a concentration of 0.25 U/mL. Test samples and the positive control, acarbose, were also dissolved in potassium phosphate buffer (pH 6.8).

3. Results and discussion

Compound **1** was obtained as a white amorphous powder, with the molecular formula $C_{11}H_{11}NO_4$ deduced by HR-ESI-MS at *m*/*z* 220.0618 ($[M-H]^-$, calcd for 220.0610), ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectroscopic characteristics demonstrated that the structure of this compound contains a set of aromatic protons attributed to a 1,3,4-trisubstituted benzene ring [δ_H 6.30 (1H, d, *J* = 2.2 Hz, H-4), 6.72 (1H, d, *J* = 8.3 Hz, H-7), 6.68 (1H, dd, *J* = 8.3, 2.2 Hz, H-6)] and one methyl [δ_H 2.10 (3H, s, H-10)]. Removed the signals of benzene ring from ^{13}C NMR data, other carbon signal were observed, including two carbonyl groups [δ_C 207.4 (C-9), 181.1 (C-2)], one oxygenated carbon [δ_C 75.3 (C-3)], and two saturated alkane carbons [δ_C 51.1 (C-8), 30.8 (C-10)]. Conjectured from the degrees of unsaturation, compound **1** should contain an extra ring structure apart from a benzene ring. Compared with literature (Luppi, et al. 2005), the above spectral characteristics are very similar to 3-(2-oxopropyl)-3-hydroxyindolin-2-one, except for an additional hydroxyl group in compound **1**. HMBC correlations of H-4 (δ_H 6.30) with C-3 (δ_C 75.3), H-8 (δ_H 3.30, 3.13) with C-2 (δ_C 181.1),

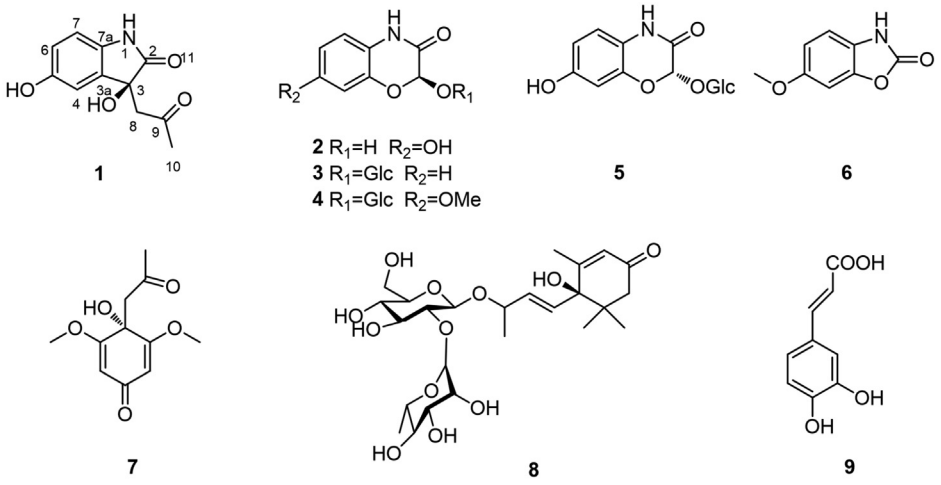

Fig. 1. Structures of compounds **1**–**9** isolated from *S. dulcis*.

C-3 (δ_C 75.3), C-3a (δ_C 133.4) and C-9 (δ_C 207.4) further confirmed the above inference, assigning that the hydroxyl at the C-5 position. In addition, the CD spectrum of this compound displayed a positive Cotton effect between 220 and 260 nm, indicating that the configuration of C-3 was determined to be *S*, by comparison with the CD spectrum of 3-(2-oxopropyl)-3-hydroxyindolin-2-on e (Luppi, et al. 2005). Thus, the structure of compound **1** was established, named Scoparic zolone.

Compound **2** was isolated as a white amorphous powder. Analysis of its ^{1}H NMR spectrum, there displayed a 1,3,4-trisubstituted benzene ring signal [δ_H 6.77 (1H, d, *J* = 8.5 Hz, H-5), 6.49 (1H, d, *J* = 2.4 Hz, H-8), 6.46 (1H, dd, *J* = 8.5, 2.4 Hz, H-6)] and a dioxymethine proton [δ_H 5.50 (1H, s H-2)]. Also, ^{13}C NMR spectrum exhibited eight carbon signals totally. The above spectroscopic data was identical to those of (2*S*)-2,7-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (Kluge, Hartenstein, Hantschmann, & Sicker, 1995). Accordingly, the structure of compound **2** was elucidated as (2*S*)-2,7-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one.

Compound **3** was isolated as a white amorphous powder. ^{1}H NMR data displayed one disubstituted benzene ring signal [δ_H 7.11 (1H, m, H-8), δ_H 7.03 (2H, m, H-6, 7), δ_H 6.95 (1H, m, H-5)] and one *β*-glucosyl anomeric proton signal [δ_H 4.70 (1H, d, *J* = 7.8 Hz, Glc-1)]. After comparing with the spectral data of the literature (Yin, Zhang, Luo, & Liu, 2008), the structure of this compound was established as (2*R*)-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-D-glucopyranoside.

Compound **4** was isolated as a white amorphous powder. Similar to compound **3**, compound **4** has a benzene ring signal and a group of *β*-glucosyl signals in the ^{1}H NMR spectrum. The only difference between compound **3** and compound **4** was an extra methoxy signal (δH 3.78, 3H, s) in compound **4**. The spectral data of compound **4** were consistent with those reported in the literature (Baumeler, Hesse, & Werner, 2000) for (2*R*)-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-D-glucopyranoside.

Compound **5** was a white amorphous powder. Its ^{1}H spectrum was very similar to that of compound **4** (Baumeler, Hesse, & Werner, 2000), except for the lack of one methoxyl group singal. However, ^{13}C NMR showed that the chemical shift value of C-2 position (δ_C 93.3) was 3.4 × 10^{-6} lower than compound **4**, suggesting that C-2 configuration should be *S*. Further comparison of the two spectral data, compound **5** was identified as (2*S*)-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one-2-*O*-*β*-D-glucopyranoside.

Compound **6** was isolated as a colorless needle crystal ($CHCl_2$-MeOH 1:1). ^{13}C NMR spectroscopic data exhibited seven carbon resonances totally, representing the feature of benzoxazolone alkaloids. With reference to the spectra data which displayed in literature (Nagao, Otsuka, Kohda, Sato, & Yamasaki, 1985), the structure of compound **6** was established as 6-methoxy-benzoxazolin-2(3*H*)-one, accordingly.

Compound **7** was obtained as a white amorphous powder. The ^{1}H NMR spectroscopic data exhibited two methoxy signals [δ_H 3.66 (6H, s)] and two alkene hydrogen signals overlapped, respectively [δ_H 5.32 (2H, s)], suggesting that compound **7** beared symmetrical groups. Besides, the ^{13}C and DEPT NMR spectra revealed total eleven carbon signals, classified as three methyls, one methylenes, two methines, and five quaternary carbons. These spectral data match those of 4-acetonyl-3,5-dimethoxy-*p*-quinol reported in the literature completely (Wu, Yang, Wu, & Liu, 1995). Therefore, its structure was confirmed as 4-acetonyl-3,5-dimethoxy-*p*-quinol.

Compound **8** was obtained as a white amorphous powder. The ^{1}H NMR spectrum displayed two anomeric protons at δ_H 4.43 (1H, d, *J* = 7.5 Hz, Glc-1) and δ_H 5.26 (1H, d, *J* = 1.3 Hz, Rha-1). Apart from two group of sugar signals, the remaining signals in ^{13}C NMR data could be sorted into four methyls, a pair of olefinic carbons, one ketone group, one methylene group and one oxylated quaternary carbon. Based on ^{1}H NMR, 13C NMR and DEPT spectra data, the above spectroscopic characteristics closely resembled those of zizyvoside I (Yagi, et al., 1981), moreover, HMBC spectra also verified the identity of these two compounds. Thus, compound **8** was identified as zizyvoside I.

Compound **9** was isolated as a white amorphous powder. The ^{1}H NMR spectrum indicated an isolated methylene signal [δ_H 3.48 (2H, s, H-7)] and a group of 1,3,4-trisubstituted benzene ring signals. Combined with the literature (Ma, Yang, Zhang, Wang, & Wang, 2008), it was identified as 3,4-dihydroxy benzeneacetic acid.

All isolated compounds were evaluated for their inhibitory effect against α-glucosidase. Compound **2** was found to exhibit a strong inhibitory effect against α-glucosidase with an IC_{50} value of (132.8 ± 11.5) μmol/L, 28-fold higher than the positive control, acarbose, for which the IC_{50} value was (3760 ± 157.2) μmol/L. Other compounds failed to enhance the inhibitory activity relative to acarbose. Therefore, compound **2** is expected to be a promising lead compound for the treatment of diabetes.

4. Conclusion

The present study reports led to the isolation and identification of nine compounds from the aerial parts of S. dulcis, including six alkaloids (compounds **1**–**6**), 4-acetonyl-3,5-dimethoxy-*p*-quinol

(compound **7**), zizyvoside I (compound **8**) and 3,4-dihydroxy benzeneacetic acid (compound **9**). By comparison of the existing literature, compounds **2** and **9** have not been reported in Scoparia. Compounds **3**, **5**, **7**, **8** are isolated from Scrophulariaceae for the first time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are thankful for financial supports from the National Natural Science Foundation of China (32170402, 81703682, 81874335).

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