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Dihydrostilbene glycosides from *Camellia sasanqua* and their α-glucosidase and α-amylase inhibitory activities

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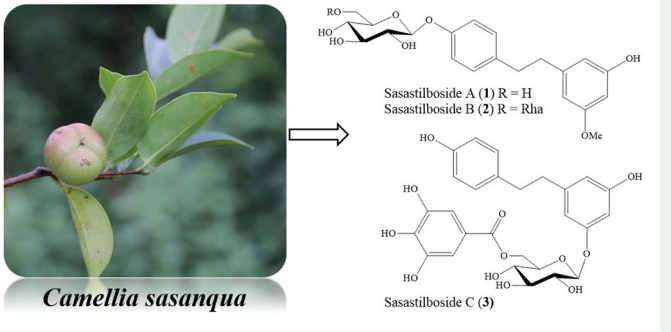
ABSTRACT

Using chromatographic methods, three new dihydrostilbene glycosides, sasastilbosides A-C (**1**-**3**) and four known compounds, catechin (**4**), rutin (**5**), nicotiflorin (**6**), and rehmaionoside A (**7**) have been isolated from *Camellia sasanqua* Thunb. Their chemical structures were elucidated by spectroscopic methods (1 D-, 2 D-NMR) and mass spectra. Compounds **1**-**7** were evaluated for α-glucosidase and α-amylase inhibitory effects. Compounds **3** and **4** showed α-glucosidase inhibitory activity with IC_{50} values of 77.6 ± 1.6 and 72.4 ± 1.3 μM, respectively. Compound **1** showed α-amylase inhibitory activity with IC_{50} value of 53.7 ± 1.6 μM.



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1. Introduction

The *Camellia* genus (Theaceae) comprises of about 300 species which are mainly distributed in tropical and subtropical regions (Stevens et al. 2004). Previous phytochemical investigations of *Camellia sasanqua* Thunb. led to the isolation of phenolics (Yoshida et al. 1990) and terpenoids (Matsuda et al. 2010). As a part of our continuing search for

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compounds with anti-diabetes activity from Vietnamese medicinal plants, the methanol extract of *C. sasanqua* was found to show significant inhibitory effects against α-glucosidase. Herein, we report the isolation and structural elucidation of three new dihydrostilbene glycosides along with four known compounds from *C. sasanqua* and evaluation of their α-glucosidase and α-amylase inhibitory effects.

2. Results and discussion

Compound **1** was obtained as a white amorphous powder. Its molecular formula was determined as $C_{21}H_{26}O_8$ by HR-ESI-MS at *m/z* 441.1312 $[M+Cl]^-$ (Calcd. for $[C_{21}H_{26}O_8Cl]^-$, 441.1316). The ^{1}H-NMR spectrum of **1** showed proton signals assignable of one *p*-substituted aromatic ring at δ_H 7.01 (2H, d, $J = 8.5$ Hz) and 7.08 (2H, d, $J = 8.5$ Hz), one 1,3,5-trisubstituted aromatic ring at δ_H 6.20 (1H, dd, $J = 1.5$, 2.0 Hz), 6.23 (1H, d, $J = 2.0$ Hz), and 6.24 (1H, d, $J = 1.5$ Hz), two methylene groups at δ_H 2.75 (2H, t, $J = 8.0$ Hz) and 2.83 (2H, t, $J = 8.0$ Hz), one methoxy group at δ_H 3.70 (3H, s), and one anomeric proton at δ_H 4.88 (1H, d, $J = 7.5$ Hz). The ^{13}C-NMR and HSQC spectra of **1** showed the signals of 21 carbons, including 5 non-protonateds (δ_C 137.1, 145.3, 157.3, 159.3, and 162.1), 12 methines (δ_C 71.4, 74.9, 77.9, 78.0, 99.9, 102.5, 106.7, 109.1, 117.6 × 2, and 130.4 × 2), 3 methylenes (δ_C 37.8, 39.3, and 62.5), and one methoxy carbon (δ_C 55.5). Analysis of the ^{1}H- and ^{13}C-NMR data suggested the structure of **1** was similar to 3,5-dihydroxydihydrostilbene 4′-*O*-β-D-glucopyranoside, a compound previously reported from *Camellia oleifera* Abel (Chen et al. 2011) except for the addition of a methoxy group at C-3. The positions of methoxy group at C-3 and hydroxy group at C-5 were confirmed by the HMBC correlations (Figure S1) from H-2 (δ_H 6.23) to C-3 (δ_C 162.1)/C-4 (δ_C 99.9)/C-6 (δ_C 109.1), from H-6 (δ_H 6.24) to C-2 (δ_C 106.7)/C-4 (δ_C 99.9)/C-5 (δ_C 159.3), from the methoxy group (δ_H 3.70) to C-3 (δ_C 162.1). The monosaccharide was identified as D-glucose after acid hydrolysis, as a trimethylsilyl by GC (Nhiem et al. 2011). The large coupling constant between glc H-1″ and glc H-2″, $J = 7.5$ Hz confirmed the configuration of anomeric proton as *axial* orientation and thus sugar moiety as β-D-glucopyranosyl. The HMBC correlation between glc H-1″ (δ_H 4.88) and C-4′ (δ_C 157.3) confirmed the position of β-D-glucopyranosyl at C-4′. Based on the above evidence, the structure of **1** was determined as 3-methoxy-5-hydroxydihydrostilbene 4′-*O*-β-D-glucopyranoside and named sasastilboside A.

Compound **2** possessed a molecular formula of $C_{27}H_{36}O_{12}$ as deduced from HR-ESI-MS at *m/z* 587.1901 $[M+Cl]^-$ (Calcd. for $[C_{27}H_{36}O_{12}Cl]^-$, 587.1895). The ^{1}H- and ^{13}C-NMR data of **2** were similar to sasastilboside A (**1**) except for the addition of a rhamnopyranosyl moiety at glc C-6″. Furthermore, the structure of **2** was also found to be similar to 3,5-dimethoxydihydrostilbene 4′-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, a compound was also isolated from *Camellia oleifera* Abel (Chen et al. 2011). The presence of sugar components in **2**, D-glucose and L-rhamnose were confirmed using acid hydrolysis and identifying as trimethylsilyl derivatives. The HMBC cross peaks from rha H-1‴ (δ_H 4.74) to glc C-6″ (δ_C 67.9) and from glc H-1″ (δ_H 4.82) to C-4′ (δ_C 157.3) confirmed the sugar linkages as α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl and at C-4′. Thus, the structure of **2** was determined as 3-methoxy-

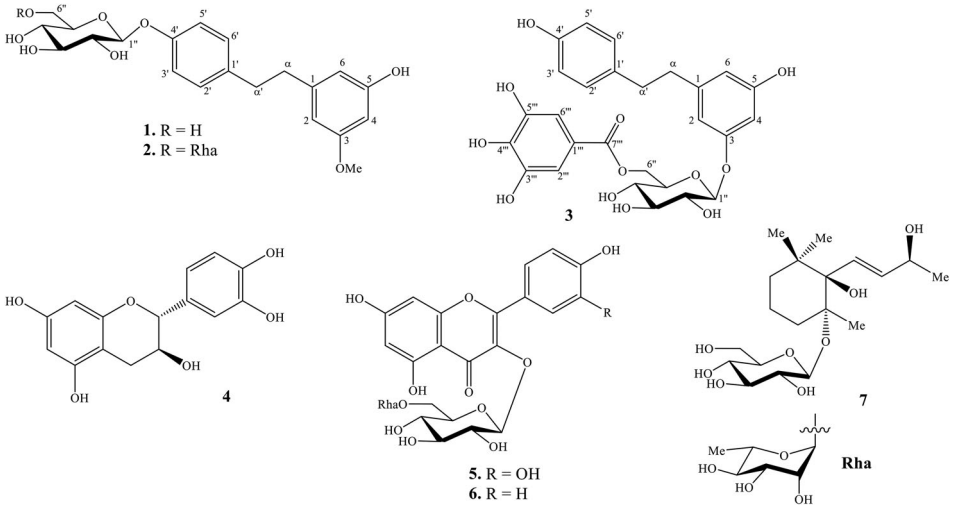

Figure 1. The chemical structures of compounds **1-7.**

5-hydroxydihydrostilbene 4′-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside and named sasastilboside B.

The molecular formula of **3**, $C_{27}H_{28}O_{12}$ was determined by HR-ESI-MS at *m/z* 579.1261 $[M+Cl]^-$ (Calcd. for $[C_{27}H_{28}O_{12}Cl]^-$, 579.1269). The ^{1}H-NMR spectrum of **3** showed the signals of one dihydrostilbene, one galloyl group, and one sugar unit. The ^{13}C-NMR and HSQC spectra of **3** showed the signals of 27 carbons, of which 14 were assigned to a dihydrostilbene, seven to a galloyl, and six to a β-D-glucopyranosyl unit. The ^{1}H- and ^{13}C-NMR data suggested the structure of **3** was similar to those of 5,4′-dihydroxydihydrostilbene 3-*O*-β-D-glucopyranoside (isolated from *Dryopteris sublaeta* Ching & Y.P. Hsu) (Feng et al. 2005) except for the addition of a galloyl group at glc C-6″. The HMBC correlations from H-4 (δ_H 6.37) to C-2 (δ_C 109.4)/C-3 (δ_C 159.9)/C-5 (δ_C 158.9)/C-6 (δ_C 111.1); from H-3′ (δ_H 6.66) to C-1′ (δ_C 133.8)/C-2′ (δ_C 130.6)/C-4′ (δ_C 156.3)/C-5′ (δ_C 116.0) confirmed the positions of hydroxy groups at C-5 and C-4′. The presence of D-glucose moiety in **3** was also confirmed by acid hydrolysis. The HMBC correlation between glc H-1″ (δ_H 4.70) and C-3 (δ_C 159.9) confirmed the position of β-D-glucopyranosyl at C-3. The *O*-galloyl group at glc C-6″ was confirmed by the HMBC correlations from glc H-6″ (δ_H 4.38/4.65) to C-7‴ (δ_C 168.3). Conseqently, the structure of **3** was established as 5,4′-dihydroxydihydrostilbene 3-*O*-(6‴-*O*-galloyl)-β-D-glucopyranoside, a new compound named sasastilboside C.

The structures of known compounds were identified as catechin (**4**) (Shen et al. 1993), rutin (**5**) (Beck and Haberlein 1999), nicotiflorin (**6**) (Park et al. 2008), and rehmaionoside A (**7**) (Wang et al. 2010) (Figure 1) by analyzing the NMR and MS methods and in comparison with the reported values in the literature.

All compounds from *C. sasanqua* were evaluated for their α-glucosidase and α-amylase inhibitory effects (Yen et al. 2020). Acarbose, an antidiabetic drug was used as a positive control. Compounds **3** and **4** exhibited significant α-glucosidase inhibitory activity with inhibitory percentages of 78.4 ± 1.6% and 67.7 ± 1.4 at the concentration of 200 μM, respectively (Figure S2). Thus, these compounds were further evaluated for α-glucosidase inhibitory activity at the concentration of 1.0, 10, 50, 100, and 200 μM to

get IC_{50} values. As the results, compounds **3** and **4** showed α-glucosidase inhibitory activity with the IC_{50} values of 77.6 ± 1.6 and 72.4 ± 1.3 μM, respectively, compared to the acarbose with the IC_{50} value of 57.6 ± 2.0 μM. Regarding α-amylase activity, compound **1** was found to inhibit α-amylase activity with IC_{50} value of 53.7 ± 1.6 μM (IC_{50} of acarbose, 23.4 ± 0.5 μM) (Figure S3). This is the first report of α-glucosidase and α-amylase inhibitory activities of compounds from *C. sasanqua*.

3. Experimental

3.1. General

see Supporting information.

3.2. Plant materials

The leaves of *Camellia sasanqua* Thunb. were collected in Nguyen Binh, Cao Bang, Viet Nam (N22^{0}34′09,6″ E:105^{0}52′29,9″) in April 2019, and identified by Dr. Nguyen The Cuong, Institute of Ecology and Biological Resources. A voucher specimen (NCCT-P85) was deposited at Herbarium of Vietnam Academy of Science and Technology (HN) and Institute of Marine Biochemistry, VAST.

3.3. Extraction and isolation

The dried powder leaves of *C. sasanqua* (6.0 kg) were sonicated with methanol (3 times, each 15 L MeOH). After removal of solvent, the MeOH extract (650 g) was suspended with water and then partitioned with *n*-hexane, dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) to give corresponding *n*-hexane (CS1A, 9.2 g), dichloromethane (CS1B, 95.0 g), ethyl acetate (CS1C, 54.0 g) residues and water layer (CS1D). The water layer (CS1D) was chromatographed on a Diaion HP-20 column, first eluting with water to remove sugar components, then increasing concentration of MeOH in water (25, 50, 75, and 100%) to obtain four fractions, CS1D1-CS1D4.

The CS1D2 fraction was subjected on a silica gel CC eluting with gradient solvent of CH_2Cl_2/MeOH (20/1, 10/1, 5/1, v/v) to give three fractions, CS1D2A-CS1D2C. The CS1D2A was chromatographed on a RP-18 column eluting with acetone/water (1/3, v/v) to give three smaller sub-fractions, CS1D2A1-CS1D2A3. CS1D2A1 was subjected to HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 18% acetonitrile in water, a flow rate of 3 mL/min) to yield compound **4** (9.0 mg). The CS1D2B fraction was chromatographed on a RP-18 column eluting with MeOH/water (1/1.5, v/v) to give three fractions, CS1D2B1-CS1D2B3. Compound **3** (5.1 mg) was obtained from the CS1D2B2 fraction using HPLC column (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 22% acetonitrile in water, a flow rate of 3 mL/min). Compound **7** (170.0 mg) was chromatographed from the CS1D2B3 on a sephadex LH-20 column, eluting with MeOH/water (1/1, v/v). The CS1D2C fraction was loaded on a RP-18 column eluting with acetone/water (1/3, v/v) to give three fractions, CS1D2C1-CS1D2C3. CS1D2C1 was subjected to HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 22% acetonitrile in water, a flow rate of 3 mL/min) to yield compounds **5**

(18.0 mg) and **6** (10.0 mg). Compound **2** (69.0 mg) was obtained from the CS1D2C3 fraction using HPLC column (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 28% acetonitrile in water, a flow rate of 3 mL/min).

The CS1D4 fraction was applied to a silica gel column, eluting with a gradient of CH_2Cl_2/MeOH (20/1, 10/1, 5/1, 2.5/1, v/v) to give four fractions, CS1D4A-CS1D4D. The CS1D4B fraction was chromatographed on a RP-18 column, eluting with MeOH/water (1/1, v/v) to give three smaller sub-fractions, CS1D4B1-CS1D4B3. CS1D4B1 was subjected to HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 28% acetonitrile in water, a flow rate of 3 mL/min) to yield compound **1** (48.0 mg).

3.3.1. Sasastilboside A (1)

White amorphous powder; $[\alpha]_D^{25}$: −36.0 (*c* 0.1, MeOH); $C_{21}H_{26}O_8$; HR-ESI-MS *m/z*: 441.1312 $[M+Cl]^-$ (Calcd. for $[C_{21}H_{26}O_8Cl]^-$, 441.1316); ^{1}H-NMR (CD_3OD, 500 MHz) δ_H: 6.23 (d, $J=2.0$ Hz, H-2), 6.20 (dd, $J=1.5$, 2.0 Hz, H-4), 6.24 (d, $J=1.5$ Hz, H-6), 2.75 (t, $J=8.0$ Hz, H-α), 2.83 (t, $J=8.0$ Hz, H-α′), 7.08 (d, $J=8.5$ Hz, H-2′, 6′), 7.01 (d, $J=8.5$ Hz, H-3′, 5′), Glc: 4.88 (d, $J=7.5$ Hz, H-1″), 3.47 (m, H-2″), 3.43 (m, H-3″), 3.42 (m, H-4″), 3.48 (m, H-5″), 3.72 (dd, $J=5.0$, 12.0 Hz, H_a-6″), and 3.91 (dd, $J=1.5$, 12.0 Hz, H_b-6″); ^{13}C-NMR (CD_3OD, 125 MHz) δ_C: 145.3 (C-1), 106.7(C-2), 162.1 (C-3), 99.9 (C-4), 159.3 (C-5), 109.1 (C-6), 39.3 (C-α), 37.8 (C-α′), 137.1 (C-1′), 130.4 (C-2′, 6′), 117.6 (C-3′, 5′), 157.3 (C-4′), 55.5 (3-OMe), Glc: 102.5 (C-1″), 74.9 (C-2″), 78.0 (C-3″), 71.4 (C-4″), 77.9 (C-5″), and 62.5 (C-6″).

3.3.2. Sasastilboside B (2)

White amorphous powder; $[\alpha]_D^{25}$: −63.0 (*c* 0.1, MeOH); $C_{27}H_{36}O_{12}$; HR-ESI-MS *m/z*: 587.1901 $[M+Cl]^-$ (Calcd. for $[C_{27}H_{36}O_{12}Cl]^-$, 587.1895); ^{1}H-NMR (CD_3OD, 500 MHz) δ_H: 6.24 (dd, $J=1.5$, 2.0 Hz, H-2), 6.21 (dd, $J=2.0$, 2.0 Hz, H-4), 6.25 dd, $J=1.5$, 2.0 Hz, H-6), 2.77 (t, $J=8.0$ Hz, H-α), 2.83 (t, $J=8.0$ Hz, H-α′), 7.11 (d, $J=8.5$ Hz, H-2′, 6′), 7.00 (d, $J=8.5$ Hz, H-3′, 5′), 3.71 (s, 3-OMe), Glc: 4.82 (overlapped, H-1″), 3.47 (m, H-2″), 3.47 (m, H-3″), 3.39 (m, H-4″), 3.56 (m, H-5″), 3.62 (dd, $J=6.5$, 11.0 Hz, H_a-6″), 4.04 (dd, $J=1.5$, 11.0 Hz, H_b-6″), Rha**:** 4.74 (d, $J=2.0$ Hz, H-1‴), 3.88 (dd, $J=1.5$, 3.5 Hz, H-2‴), 3.74 (m, H-3‴), 3.39 (m, H-4‴), 3.68 (m, H-5‴), and 1.24 (d, $J=6.5$ Hz, H-6‴); ^{13}C-NMR (CD_3OD, 125 MHz) δ_C: 145.4 (C-1), 106.7 (C-2), 162.2 (C-3), 99.9 (C-4), 159.3 (C-5), 109.1 (C-6), 39.3 (C-α), 37.9 (C-α′), 137.2 (C-1′), 130.4 (C-2′, 6′), 117.7 (C-3′, 5′), 157.3 (C-4′), 55.6 3-OMe), Glc: 102.6 (C-1″), 74.9 (C-2″), 78.0 (C-3″), 71.6 (C-4″), 76.8 (C-5″), 67.9 (C-6″), Rha: 102.1 (C-1‴), 72.1 (C-2‴), 72.4 (C-3‴), 74.0 (C-4‴), 69.8 (C-5‴), and 17.9 (C-6‴).

3.3.3. Sasastilboside C (3)

White amorphous powder; $[\alpha]_D^{25}$: −42.0 (*c* 0.1, MeOH); $C_{27}H_{28}O_{12}$; HR-ESI-MS *m/z*: 579.1261 $[M+Cl]^-$ (Calcd. for $[C_{27}H_{28}O_{12}Cl]^-$, 579.1269); ^{1}H-NMR (CD_3OD, 500 MHz) δ_H: 6.22 (br s, H-2), 6.37 (br s, H-4), 6.29 (br s, H-6), 2.59 (m, H_a-α),2.65 (m, H_b-α), 2.63 (m, H_a-α′),/2.74 (m, H_b-α′), 6.83 (d, $J=8.5$ Hz, H-2′,6′), 6.66 (d, $J=8.5$ Hz, H-3′,5′), Glc: 4.70 (d, $J=8.0$ Hz, H-1″), 3.45 (m, H-2″), 3.49 (m, H-3″), 3.44 (m, H-4″), 3.68 (m, H-5″), 4.38 (dd, $J=6.5$, 12.0 Hz, H_a-6″), 4.65 (dd, $J=2.0$, 12.0 Hz, H_b-6″), and Gal: 7.13 (s, H-2‴, 6‴); ^{13}C-NMR (CD_3OD, 125 MHz) δ_C: 145.6 (C-1), 109.4 (C-2), 159.9 (C-3), 103.0 (C-4),

158.9 (C-5), 111.1 (C-6), 39.1 (C-α), 37.8 (C-α′), 133.8 (C-1′), 130.6 (C-2′, 6′), 116.0 (C-3′, 5′), 156.3 (C-4′), Glc: 102.5 (C-1″), 74.9 (C-2″), 77.8 (C-3″), 71.7 (C-4″), 75.6 (C-5″), 64.8 (C-6″), Gal**:** 121.4 (C-1‴), 110.3 (C-2‴, 6‴), 146.6 (C-3‴, 5‴), 139.9 (C-4‴), and 168.3 (C-7‴).

3.4. Sugar identification

see Supporting information.

3.5. α-Glucosidase assay

see Supporting information.

3.6. α-Amylase assays

see Supporting information.

Disclosure statement

No potential conflict of interest was reported by the authors.

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