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α-Glucosidase Inhibitory Hydrolyzable Tannins from *Eugenia jambolana* Seeds

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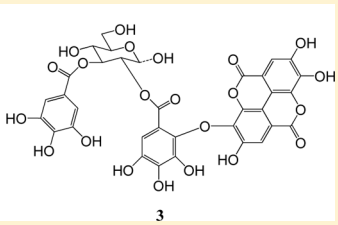
Supporting Information

ABSTRACT: Three new hydrolyzable tannins including two gallotannins, jamutannins A (**1**) and B (**2**), and an ellagitannin, iso-oenothein C (**3**), along with eight known phenolic compounds were isolated from the seeds of *Eugenia jambolana* fruit. The structures were elucidated on the basis of spectroscopic data analysis. All compounds isolated were evaluated for α-glucosidase inhibitory effects compared to the clinical drug acarbose.



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The edible fruit of the native Indian medicinal plant *Eugenia jambolana* Lam. (syn. *Syzygium cuminii* Skeels; *Eugenia cuminii* Druce) is commonly known as Jamun.[1] The seeds of the Jamun fruit is widely regarded in the Indian traditional system of medicine, Ayurveda, for regulating blood glucose levels and treating diabetes.[2] Laboratory studies have revealed that Jamun seed extracts inhibit the activities of the carbohydrate hydrolyzing enzymes α-amylase and α-glucosidase.[3−5] Animal and human clinical studies also support the antidiabetic effects of Jamun seeds.[6−9] Furthermore, botanical dietary supplements containing Jamun seed extracts are commercially available to consumers as natural approaches for lowering blood glucose (for example, Madeglucyl from Indena; http://www.indena.com/index.php/madeglucyl-the-natural-way-to-maintain-healthy-blood-sugar-levels.html). Despite all of the aforementioned facts, there is limited knowledge on the chemical constituents of Jamun seeds, prompting the initiation of this research project. Herein, the isolation and structure elucidation of three new hydrolyzable tannins (**1**−**3**) along with the purification of eight known phenolic compounds from Jamun seeds are reported. The isolates were evaluated for their α-glucosidase inhibitory effects compared to the clinical drug acarbose.

Compound **1**, a colorless, viscous liquid, was assigned the molecular formula $C_{25}H_{32}O_{13}$ based on HRESIMS data at *m*/*z* 539.1769 $[M - H]^-$ (calcd for $C_{25}H_{31}O_{13}$, 539.1765). The IR absorptions revealed the presence of hydroxy (3500−3020 cm^{-1}), ester carbonyl (1722 cm^{-1}), ketocarbonyl (1714 cm^{-1}), COOH (1700 cm^{-1}), and aromatic (1618 and 1516 cm^{-1}) functionalities. The ^1H NMR spectrum (Table 1) showed a two-proton singlet at δ_H 7.06 (H-2″, 6″), suggesting the presence of a galloyl group, which was confirmed by the ^{13}C NMR data (Table 1) and HMBC correlations. Two olefinic protons at δ_H 5.28 (1H, dd, *J* = 12.6, 10.3 Hz, H-3) and 5.52 (1H, ddd, *J* = 10.3, 8.6, 6.5 Hz, H-4) revealed the presence of a *cis* double bond. The ^{13}C NMR data of **1** (Table 1) showed 25 carbons, including one methyl, six methylenes, and 12 methines along with six quaternary carbons [including one ester carbonyl at δ_C 166.6 (C-7″), one ketocarbonyl at δ_C 219.4 (C-2′), and one carboxylic group at δ_C 174.8 (C-7′)]. The NMR data suggested the presence of a β-glucopyranose moiety for which the anomeric proton resonated at δ_H 4.27 (1H, d, *J* = 8.0 Hz, H-1‴). Detailed analysis of the 1D and 2D NMR ($^1H-^1H$ COSY, HSQC, HMBC) data allowed for the construction of the structure of compound **1**. All of the proton signals were assigned to the corresponding carbons through direct ^1H and ^{13}C correlations in the HSQC spectrum. From the $^1H-^1H$ COSY analysis, two substructures (drawn with bold bonds in Figure 2) were established. In the HMBC spectrum, the correlations from H-1′, H-3′, H-4′a (δ_H 2.15) and H-5′ to the ketocarbonyl (C-2′) indicated the presence of a cyclopentanone structure. Furthermore, the correlation from H-6′ to C-7′, C-5′, and C-4′ suggested that a carboxymethyl group was attached to the cyclopentanone moiety at C-5′. The aforementioned NMR data allowed for the determination of the aglycone of **1** as 5-(5-carboxymethyl-2-oxocyclopentyl)-3*Z*-2-pentenol. The HMBC correlations from H_2-6‴ to C-7″ and from H-1‴ to C-2 revealed that the galloyl group was attached to the glucopyranose moiety at C-6‴ and that the 2-pentenol moiety was attached to C-1‴. The relative configuration of C-1′ and C-5′ was identified as *trans* based on comparison of the chemical shifts of H-1′ and H-5′ (δ_H 1.50 and 2.22, respectively) to those of the corresponding protons of the previously reported compound (1′*R*,5′*R*)-5-(5-carboxymethyl-2-oxocyclopentyl)-3*Z*-pentenyl-β-D-(6-*O*-galloyl)-glucopyranoside.[10]

Compound **2**, a colorless liquid, was identified as an epimer of compound **1** with an identical molecular formula of $C_{25}H_{32}O_{13}$ as determined by HRESIMS at *m*/*z* 539.1786 $[M - H]^-$ (calcd for $C_{25}H_{31}O_{13}$, 539.1765). The NMR data of

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Table 1. ^{1}H NMR and ^{13}C NMR Data of Compounds 1 and 2[a]

	1		2	
no.	δ_C	δ_H, mult. (J in Hz)	δ_C	δ_H, mult. (J in Hz)
1	20.3	1.20, d (6.3)	19.5	1.22, d (6.3)
2	67.3	4.87, dq (12.6, 6.3)	70.6	4.68, dq (9.1, 6.3)
3	132.0	5.28, dd (12.6,10.3)	133.2	5.47, t (9.1)
4	129.8	5.52, ddd (10.3, 8.6, 6.5)	127.6	5.21, q (9.1)
5	24.0	2.02, ddd (13.8, 10.8, 5.6)	25.2	2.28, m
		2.39, ddd (13.8, 8.3, 4.0)		
1′	53.5	1.50, m	53.4	1.80, m
2′	219.4		220.0	
3′	36.9	1.94, ddd (18.6, 11.7, 8.7)	36.9	1.97, m
		2.24, ddd (18.6, 11.5, 3.1)		2.15, m
4′	26.8	2.15, m	26.6	1.39, m
		2.40, m		2.14, m
5′	36.8	2.22, m	37.8	2.14, m
6′	38.0	2.16, m	38.0	2.22 (m)
		2.52, dd (15.2, 3.8)		2.62, dd (15.3, 3.4)
7′	174.8		174.7	
1″	120.0		120.1	
2″, 6″	108.7	7.06, s	108.7	7.08, s
3″	145.1		145.1	
4″	138.4		138.4	
5″	145.1		145.1	
7″	166.6		116.8	
1‴	98.6	4.27, d (8.0)	101.0	4.37, d (7.6)
2‴	73.5	3.20, m	73.7	3.20, m
3‴	76.4	3.37, m	76.6	3.40, t (8.7)
4‴	70.8	3.30, m	70.9	3.33, t (8.7)
5‴	74.2	3.51, m	74.0	3.56, m
6‴	63.7	4.30, d (11.8, 7.5)	63.7	4.40, dd (11.8, 7.1)
		4.71, dd (11.8, 1.8)		4.52, d (11.8)

[a]Data were measured in methanol-d_4 at 500 MHz (^{1}H) and 125 MHz (^{13}C).

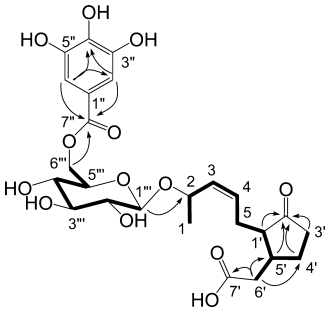

Figure 2. Key ^{1}H–^{1}H COSY (–) and selected HMBC correlations (H→C) of compound **1**.

compound **2** (Table 1) were similar to that of compound **1** except for marked differences in the carbon chemical shifts of C-2 (compound **1**, δ_C = 67.3; compound **2**, δ_C = 70.6), suggesting that they differed only in configuration at C-2. The absolute configurations of C-2 in compounds **1** and **2** were assigned as *S* and *R*, respectively, based on comparison with the ^{13}C NMR data of roseoside, which contains a similar structural moiety.[11] On the basis of the previous report, the chemical shift of the corresponding carbon in roseoside bearing an *R* configuration is further downfield than the isomer with an *S* configuration.[11] Thus, the structures of compounds **1** and **2** were identified as 5-(5-carboxymethyl-2-oxocyclopentyl)-3*Z*-2*S*-pentenyl-*β*-(6-*O*-galloyl)glucopyranoside and 5-(5-carboxymethyl-2-oxocyclopentyl)-3*Z*-2*R*-pentenyl-*β*-(6-*O*-galloyl)-glucopyranoside, assigned the trivial names jamutannins A and B, respectively.

Compound **3**, a brown, amorphous powder, displayed a molecular formula of $C_{34}H_{24}O_{22}$ based on HRESIMS m/z 783.0694 $[M - H]^-$ (calcd for $C_{34}H_{23}O_{22}$, 783.0681). The IR absorptions revealed the presence of hydroxy (3500–3020 cm^{-1}), ester carbonyls (1722, 1685 cm^{-1}), and aromatic (1620, 1513 cm^{-1}) functionalities. The ^{1}H NMR data (Table 2) of compound **3** revealed two distinct patterns of proton

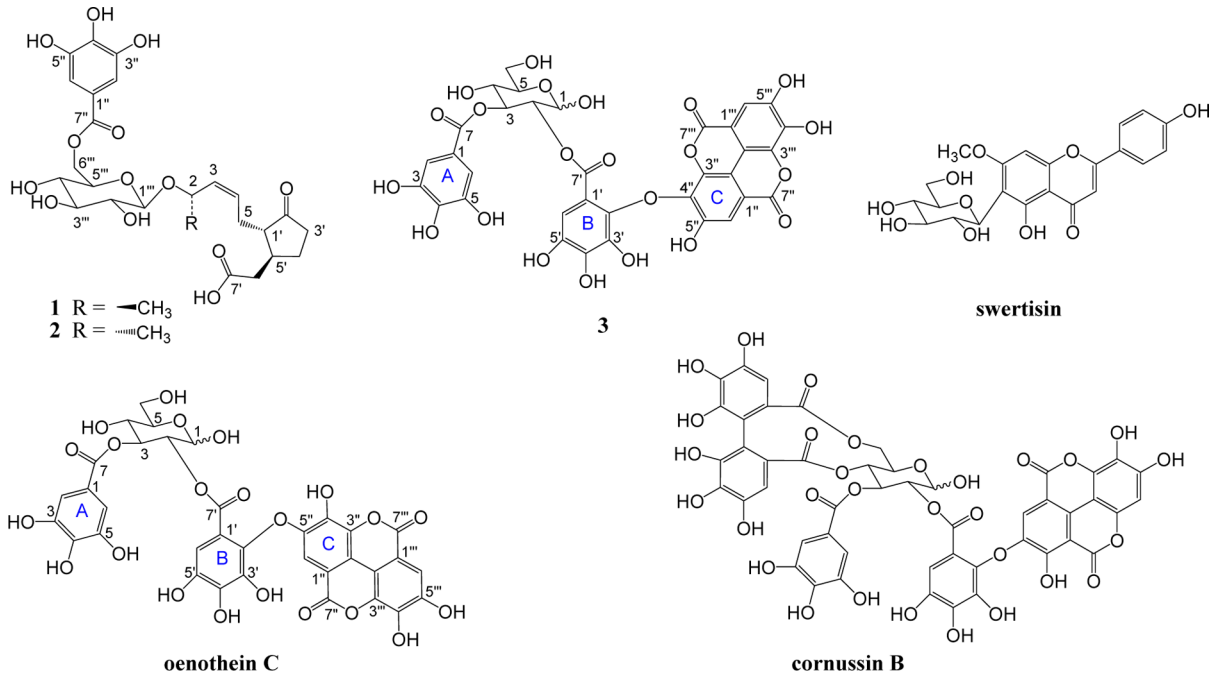

Figure 1. Structures of the compounds **1**–**3**, oenothein C, cornussin B, and swertisin.

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Table 2. ^{1}H NMR and ^{13}C NMR Data of the α- and β-D-Glucose Residues of Compound 3 and Oenothein C[a]

	3		oenothein C	
no.	δ_C	δ_H, mult. (J in Hz)	δ_C	δ_H, mult. (J in Hz)
1_α	89.9	5.45, d (3.5)	89.3	5.30, d (3.5)
2_α	72.1	5.05, dd (10.5, 3.5)	71.9	5.00, dd (9.5, 3.5)
3_α	72.4	5.63, t (10.5)	73.0	5.54, t (9.5)
4_α	69.1	3.61, t (10.5)	69.0	3.60, t (9.5)
5_α	71.5	3.93, m	71.5	3.92, m
6_α	60.8	3.74, dd (12.0, 4.5)	60.8	3.71, dd (12.0, 4.5)
		3.79, d (12.0)		3.77, dd (12.0, 2.0)
1_β	94.9	4.79, overlapped with solvent	94.8	4.74, d (7.0)
2_β	72.9	5.07, m	72.9	5.02, dd (9.5, 7.0)
3_β	75.7	5.12, t (9.0)	75.8	4.99, t (9.5)
4_β	69.1	3.61, t (10.5)	68.9	3.54, t (9.5)
5_β	76.6	3.41, m	76.6	3.39, m
6_β	61.0	3.69, dd (12.0, 4.5)	60.9	3.65, dd (11.5, 5.5)
		3.87, d (12.0)		3.84, dd (11.5, 2.0)

[a]Data were measured in methanol-d_4 at 500 MHz (^{1}H) and 125 MHz (^{13}C).

resonances (1.6:1) for the sugar and phenolic moieties, suggesting that the anomeric position of the sugar moiety was not acylated. The ^{13}C NMR data (Table 3) also showed 12 characteristic sugar moiety carbons including two anomeric carbons at δ_C 89.9 (C-1α) and 94.9 (C-1β), suggesting that compound **3** exists as an equilibrium mixture of α and β forms

Table 3. ^{1}H NMR and ^{13}C NMR Data of the Aromatic Regions of Compound 3 and Oenothein C[a]

	3		oenothein c	
no.	$\delta_{C\ \alpha/\beta}$	$\delta_{H\ \alpha/\beta}$, mult.	$\delta_{C\ \alpha/\beta}$	$\delta_{H\ \alpha/\beta}$, mult.
1	119.4/119.2		119.6/119.3	
2,6	108.2/108.5	6.60/6.63, s	108.5/108.6	6.72/6.69, s
3,5	144.2/144.3		144.6/144.6	
4	137.6/137.8		138.0/138.2	
7	166.1/166.3		166.7/166.5	
1′	113.4/113.4		112.8/113.1	
2′	139.5/139.1		136.0/135.5	
3′	139.1/139.2		139.2/139.0	
4′	140.0/140.0		140.3/140.1	
5′	141.4/141.7		142.8/142.9	
6′	108.2/107.8	7.04/6.96, s	109.1/109.2	7.14/7.10, s
7′	165.9/165.4		164.5/164.3	
1″	111.9/112.1		107.4/107.7	
2″	112.7/112.5		114.4/114.5	
3″	137.8/138.0		136.5/136.5	
4″	139.2/139.2		140.6/140.2	
5″	147.8/147.7		148.9/149.0	
6″	110.5/110.3	7.34/7.34, s	108.4/108.2	6.96/6.92, s
7″	158.9/158.7		159.9/159.9	
1‴	112.5/112.5		108.6/108.6	
2‴	112.1/111.9		112.5/112.5	
3‴	136.0/136.1		136.4/136.3	
4‴	138.4/138.3		139.5/139.5	
5‴	150.7/150.1		148.3/148.3	
6‴	111.2/111.1	7.52/7.55, s	110.5/110.5	7.56/7.57, s
7‴	160.1/160.2		160.3/160.3	

[a]Data were measured in methanol-d_4 at 500 MHz (^{1}H) and 125 MHz (^{13}C).

in solution (methanol-d_4). This was corroborated by the ^{1}H NMR data with aromatic proton signals at $\delta_{H\ \alpha/\beta}$ 6.60/6.63 (2H, s), $\delta_{H\ \alpha/\beta}$ 7.34/7.34 (1H, s), 7.52/7.55 (1H, s), and $\delta_{H\ \alpha/\beta}$ 7.04/6.96 (1H, s). The ^{13}C NMR data showed ester carbonyls at $\delta_{C\ \alpha/\beta}$ 166.1/166.3 and 165.9/165.4. On the basis of consideration of the NMR data, compound **3** contained two galloyl groups, an ellagic acid moiety, and a glucopyranose core. The two galloyl groups were attached to C-2 and C-3 of the glucose moiety via ester bonds on the basis of the HMBC data (Figure 3). This was confirmed by the shifts of H-2 and H-3

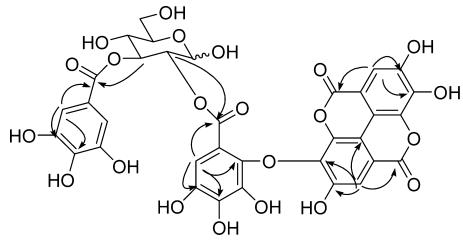

Figure 3. Key HMBC correlations (H→C) of compound **3**.

($\delta_{H\ \alpha/\beta}$ 5.05/5.07 and $\delta_{H\ \alpha/\beta}$ 5.63/5.12, respectively) in the glucose moiety. The NMR data of compound **3** were similar to those of the known compound oenothein C (Tables 2 and 3), implying that they were isomers.[12] However, compared with oenothein C, the H-6″ of compound **3** was further downfield ($\delta_{H\ \alpha/\beta}$ 7.34/7.34 vs $\delta_{H\ \alpha/\beta}$ 6.96/6.92), which suggested that its C-2′ (ring B) was attached to C-4″ of the ellagic acid unit via an ether bond. This was also supported by changes in the carbon chemical shifts of ring C and that of C-2″ in ring B of compound **3** compared with oenothein C (Table 3; Figure 1). Therefore, compound **3** was identified as a mixture of α- and β-anomers and assigned the common name iso-oenothein C.

Eight known compounds were identified as oenothein C,[12] cornusiin B,[12] valoneic acid dilactone,[13] phyllanthusiin E,[14] brevifolin carboxylic acid,[15] ellagic acid,[16] gallic acid,[17] and swertisin,[18] based on NMR and MS data.

The α-glucosidase inhibitory effects of the compounds were evaluated along with the clinical α-glucosidase inhibitor acarbose. The α-glucosidase inhibitory effects of the compounds that were more active than acarbose are shown in Table 4. Among the isolates, compound **3** was the most active, with an IC_{50} value of 8.2 μM.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on an Auto Pol III automatic polarimeter (Rudolph Research, Flanders, NJ, USA) at room temperature. The IR spectra were recorded on a Nicolet 380 FT-IR spectrometer. NMR data were recorded on a Varian 500 MHz instrument with methanol-d_4 as

Table 4. α-Glucosidase Inhibitory Activities[a]

no.	IC_{50} (μM)[b]
3	8.2 ± 0.8
oenothein C	75.1 ± 5.9
cornussin B	12.2 ± 1.8
swertisin	146.5 ± 1.3
acarbose[c]	208.6 ± 3.4

[a]Only compounds with IC_{50} values < acarbose are shown. [b]IC_{50} values are shown as mean ± SD from two independent experiments. [c]Positive control.

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solvent and TMS as internal standard. HRESIMS data were acquired using an LTQ Orbitrap XL mass spectrometer (Thermo Scientific). Semipreparative HPLC separations were performed on a Hitachi Elite LaChrom system consisting of an L2130 pump, an L-2200 autosampler, and an L-2455 diode array detector, all operated by EZChrom Elite software, using a Waters Sunfire C_{18} column (250 × 10 mm, 5 μm). MPLC separations were carried out on a prepacked C_{18} column (37 × 5.5 cm; flow rate 4 mL/min) connected to a DLC-10/11 isocratic liquid chromatography pump (D-Star Instruments, Manassas, VA, USA) with a fixed-wavelength detector. All solvents were either ACS or HPLC grade and were obtained from Wilkem Scientific (Pawcatuck, RI, USA). Sephadex LH-20 gel (Amersham Biosciences) was packed in a glass column (3 × 70 cm) and used for chromatography. Acarbose was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Plant Material. The seeds of the *Eugenia jambolana* fruit were collected in Gujarat, India, in the summer of 2010 and kindly provided to our laboratory by Verdure Sciences (Noblesville, IN, USA). The plant was authenticated by Dr. Lal Hingorani (Pharmanza, Gujarat, India), and a voucher specimen (EJLH1) has been deposited at Pharmanza.

Extraction and Isolation. The air-dried ground Jamun seed powder (454.0 g) was extracted successively by cold percolation with hexanes (2.5 L, 2×), acetone (3 L, 2×), and MeOH (3 L, 2×) to afford 3.9, 15.0, and 95.0 g of dried extracts, respectively. The MeOH extract (90 g) was solubilized in MeOH/H_2O (1:4, v/v; 750 mL) and partitioned with EtOAc (1 L) followed by *n*-BuOH (1 L) to yield 6.7 and 16.6 g of dried extracts, respectively. The *n*-BuOH extract (16.6 g) was chromatographed by MPLC eluting with a gradient solvent system of MeOH/H_2O (from 20% to 100% MeOH) to afford five fractions (A–E). Fraction B (4.0 g) was further purified by MPLC with a gradient solvent system of MeOH/H_2O (from 30% to 100% MeOH) to provide four subfractions (B1–B4). Fraction B1 (858.7 mg) was chromatographed over a column of Sephadex LH-20 and eluted with MeOH to yield gallic acid (358.1 mg). Fraction B3 (275.4 mg) was subjected to semipreparative HPLC with an isocratic solvent system of MeOH/H_2O (24/76, v/v; 2 mL/min) to yield **3** (1.3 mg). Fraction B2 (1.2 g) was purified by Sephadex LH-20 column chromatography and eluted with MeOH to yield five subfractions (B2a–B2e). Fraction B2a (61.2 mg) was purified by semipreparative HPLC with an isocratic solvent system of MeOH/H_2O (24/76, v/v; 2 mL/min) to yield oenothein C (2.1 mg). Fraction C (1.7 g) was subjected to MPLC with a gradient solvent system of MeOH/H_2O (from 20% to 100% MeOH) to afford five subfractions (C1–C5). Fraction C2 was subjected to Sephadex LH-20 column chromatography eluted with MeOH to give four subfractions (C2a–C2d). Fraction C2a was further purified by semipreparative HPLC eluted with an isocratic solvent system of MeOH/H_2O (30/70, v/v; 2 mL/min) to yield **1** (2.0 mg) and **2** (2.1 mg). Fraction C2b (19.0 mg) was subjected to semipreparative HPLC with an isocratic solvent system of MeOH/H_2O (33/67, v/v; 2 mL/min) to yield swertisin (1.0 mg). Fraction C4 was purified by semipreparative HPLC with an isocratic solvent system of MeOH/H_2O (35/65, v/v; 2 mL/min) to yield valoneic acid dilactone (28.2 mg) and cornussin B (1.0 mg). Fraction C3 was purified by semipreparative HPLC with an isocratic solvent system of MeOH/H_2O (30/70, v/v; 2 mL/min) to yield brevifolin carboxylic acid (1.1 mg), ellagic acid (9.5 mg), and phyllanthusiin E (1.7 mg).

α-Glucosidase Inhibitory Assay. The assay was performed as previously reported by our laboratory.[19] Briefly, a mixture of 50 μL of different concentrations (compound **3**, oenothein C, and cornussin B: 100, 50, 25, 12.5, 6.25 μg/mL; swertisin: 200, 100, 50, 25, 12.5 μg/mL) of the test samples and 100 μL of 0.1 M phosphate buffer (pH 6.9) containing yeast α-glucosidase solution (1.0 U/mL) was incubated in 96-well plates at 25 °C for 10 min. After preincubation, 50 μL of 5 mM *p*-nitrophenyl-α-D-glucopyranoside solution in 0.1 M phosphate buffer (pH 6.9) was added to each well at timed intervals. The reaction mixtures were incubated at 25 °C for 5 min. Before and after incubation, absorbance was recorded at 405 nm by a microplate reader (SpectraMax M2, Molecular Devices Corp., operated by SoftmaxPro v.4.6 software, Sunnyvale, CA, USA) and compared to that of the control, which had 50 μL buffer solutions instead of the test compounds. The α-glucosidase inhibitory activity was expressed as percent inhibition and was calculated as follows:

$$\%\text{inhibition} = \left(\frac{\Delta\text{Abs}_{\text{control}} - \Delta\text{Abs}_{\text{sample}}}{\Delta\text{Abs}_{\text{control}}}\right) \times 100$$

*Jamutannin A (**1**):* colorless, viscous liquid; $[\alpha]^{20}_{D}$ +94 (*c* 0.03, MeOH); IR (KBr) ν_{max} 3500–3020, 1722, 1714, 1700, 1618, 1516, 1317 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESIMS *m*/*z* 539.1769 $[M - H]^-$ (calcd for $C_{25}H_{31}O_{13}$, 539.1765).

*Jamutannin B (**2**):* colorless, viscous liquid; $[\alpha]^{20}_{D}$ +137 (*c* 0.02, MeOH); IR (KBr) ν_{max} 3500–3000, 1725, 1716, 1698, 1620, 1513, 1310 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESIMS *m*/*z* 539.1786 $[M - H]^-$ (calcd for $C_{25}H_{31}O_{13}$, 539.1765).

*Isooenothein C (**3**):* brown, amorphous powder; $[\alpha]^{20}_{D}$ +58 (*c* 0.01, MeOH); IR(KBr) ν_{max} 3500–3000, 1720, 1685, 1610, 1520, 1320 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; HRESIMS *m*/*z* 783.0694 $[M - H]^-$ (calcd for $C_{34}H_{23}O_{22}$, 783.0681).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The 1D and 2D NMR spectra for compounds **1**–**3** are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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