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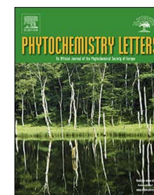

New aromatic compounds from the rhizomes of *Homalomena occulta*

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ABSTRACT

Three new aromatic compounds, identified as 1-(3′,4′-methylenedioxy-phenyl)-10-(3″-hydroxyphenyl)-decane (**1**), 1-(3′,4′-methylenedioxy-phenyl)-12-(3″-hydroxyphenyl)-dodecane (**2**), and 1-(3′,4′-methylenedioxy-phenyl)-12-(3″-hydroxyphenyl)-6*Z*-dodecylene (**3**), along with six known compounds (**4–9**) were isolated from the 95% EtOH extract of *Homalomena occulta*. Their structures were elucidated by chemical and spectral methods Compounds **4–9** were isolated for the first time from this plant. Compounds **1–3** exhibited inhibitory activity against BACE1, with IC_{50} values of 0.82–1.09 μmol/L.

1. Introduction

The genus *Homalomena* (Family Araceae) comprises about 140 species worldwide, distributed mainly in tropical and subtropical regions of Africa and America. Among them, six species are found in Southeastern and Southwestern China, especially in the Guangdong, Guangxi, and Yunnan provinces (Zhao et al., 2016). The rhizome of *Homalomena occulta* (Lour.) Schott is a traditional Chinese medicine, called "Qiannianjian", used as a folk remedy for the treatment of stomach disorders, rheumatoid arthritis, muscle soreness, and quadriplegia, as well as anti-inflammatory and tonic agent (Commission, 2015). Previous phytochemical studies on *H. occulta* have resulted in the isolation of a series of sesquiterpenoids, triterpenoids, triterpenoid saponins, flavonoids, lignans, and essential oils (Hu et al., 2008, 2009; Tian et al., 2010; Yang et al., 2016).

The deposition of β-amyloid peptide (Aβ) is considered to play a pivotal role in the pathogenesis of Alzheimer's disease (AD), an age-related neurodegenerative disease characterized clinically by severe memory loss and impairment of various cognitive functions (Jingqiu Dai et al., 2010). Aβ is generated by sequential proteolytic cleavages of the amyloid precursor protein (APP) by β-secretase (also called BACE1 for β-site APP-cleaving enzyme) and γ-secretase. In view of the involvement of BACE1 in the primary pathogenic event of AD and the obvious lack of severe side effects in BACE1 knockout mice, novel BACE1 inhibitors may provide the most effective and promising strategy for the treatment of AD (Dai et al., 2016; Tian et al., 2010; Videira et al., 2014).

A previous study suggested that *H. occulta* exhibits moderate-to-strong BACE1 inhibitory activity (Tian et al., 2010). In continuation of our research on the discovery of new bioactive compounds from traditional Chinese medicines, we have undertaken a further phytochemical investigation of *H. occulta* (Lour.) Schott in order to identify potential anti-AD components. In this study, three new aromatic compounds **1–3** along with six known compounds including five sesquiterpenoids, namely, aromadendrane-4α,10α-diol (**4**), alloaromadendrane-4*β*,10α-diol (**5**), caryolane-1,9*β*-diol (**6**), torreyol (**7**), and 5α,7α(H)-6,8-cycloeudesma-1*β*,4*β*-diol (**8**), and the furofuran lignan sesartemin (**9**) were isolated from this plant for the first time. Herein, we report the isolation and structure elucidation of compounds **1–3**, and their BACE1 inhibitory activity.

2. Experimental section

2.1. General experimental

Optical rotation data were recorded on a Perkin-Elmer 243 B digital polarimeter. HPLC separation was carried out on an Agilent 1260 series LC system equipped with a DAD detector, or on an Agilent 1100 series LC system using DAD and ELSD detectors. UV spectra were recorded on a Shimadzu UV-2450 spectrophotometer. IR spectra were recorded on a Nicolet NEXUS-470 FTIR spectrometer using KBr disks. NMR spectra were recorded on a Varian INOVA-500 spectrometer in $CDCl_3$ with TMS as an internal standard, operating at 500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR. ESI–MS spectra were measured on an Agilent series 1200 HPLC coupled to an Agilent 6320 ion trap MS. HR-ESI–MS spectra were measured on a Waters Xevo G2 QTOF mass spectrometer. GC–MS analysis was carried out on an Agilent 6890N/5973N GC–MS system. Column chromatography (CC) was performed on silica gel

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(SiO_2; 200–300 mesh, Qingdao Haiyang Chemical Company, Qingdao, China), RP C-18 silica gel (40–63 μm, Merck, Germany), or Sephadex LH-20 (18–110 μm, Pharmacia Co., Sweden). TLC analyses were carried out on glass plates pre-coated with silica gel, and the spots were visualized by spraying with 10% H_2SO_4 in EtOH (v/v) followed by heating. All solvents used were of analytical grade.

2.2. Plant material

The rhizomes of *H. occulta* (Lour.) Schott, produced in Guangxi in May 2014, were purchased from the medicinal herb market of Bozhou (Anhui province, China). The plant material was authenticated by Prof. Peng-Fei Tu from Peking University Health Science Center. A voucher specimen (No. 20150124) was deposited in the Herbarium of Huaqiao University.

2.3. Extraction and isolation

Dried rhizomes of *H. occulta* (20.0 kg) were powdered and extracted three times with boiling 95% EtOH (40 L, 3 h each). The combined EtOH extracts were concentrated in vacuo to give a dark brown residue (800 g), which was suspended in H2O (1:1), partitioned successively with petroleum ether (PE), CHCl3, AcOEt, and BuOH (each three times), and concentrated under reduced pressure. The solvent was recovered to yield a PE fraction (333 g), a CHCl3 fraction (110 g), an AcOEt fraction (85 g), and a BuOH fraction (200 g). The PE fraction (300 g) was dissolved in a small amount of mixed solvent, and 500 g (100–200 mesh) silica gel was added. The mixture was stirred until the solvent evaporated to give a uniform powder, which was loaded onto columns packed with 2000 g of silica gel (200–300 mesh) and eluted with CH_2Cl_2:acetone (80:1, 50:1, 30:1, 20:1, 10:1, 5:1, 2:1, 1:1, and 0:1, v/v) to give fractions P-1–P-7. P-1 was purified by silica gel CC with a gradient of CH_2Cl_2:acetone (20:1–0:1) followed by HPLC with ACN-H_2O (1:1, 2 mL/min) to give compound **7** (5.5 mg). Fraction P-2 was separated by silica gel CC with CH_2Cl_2:acetone (100:1) followed by HPLC with ACN-H_2O (90:10, 2 mL/min) to give compounds **1** (6.2 mg), **2** (7.5 mg), and **3** (4.6 mg). Fraction P-6 was separated by silica gel CC with a gradient of CH_2Cl_2:acetone (10:1–1:1) followed by HPLC with ACN-H_2O (75:25, 2 mL/min) to give **8** (6.8 mg). Fraction P-7 was separated by silica gel CC with a gradient of CH_2Cl_2:acetone (8;1–1:1) to give P-7-1–P-7-2. Fraction P-7-2 was purified by Sephadex LH-20 CC (CH_2Cl_2:MeOH 1:1) followed by HPLC with ACN-H_2O (1:1, 2 mL/min) to give compounds **4** (6.4 mg), **5** (5.5 mg), and **6** (5.0 mg). The AcOEt fraction (60 g) was dissolved in a small amount of solvent, and 110 g (100–200 mesh) of silica gel was added and homogeneously mixed. The solvent was evaporated to dryness, and the obtained powder was loaded onto columns packed with 600 g of silica gel (200–300 mesh) and eluted with $CHCl_3$:MeOH (35:1, 23:1, 20:1, 16:1, 12:1, 8:1, 4:1, and 0:1 v/v) to give fractions E-1–E-4. Fraction E-4 was repeatedly purified by silica gel CC with CH_2Cl_2:acetone (8:1) to give E-4-1–E-4-6. E-4-6 was separated by silica gel CC followed by HPLC with ACN−H_2O (45:55, 2 mL/min) to give compound **9** (6.6 mg).

2.3.1. 1-(3′,4′-methylenedioxy-phenyl)-10-(3″-hydroxyphenyl)-decane (1)

$C_{23}H_{30}O_3$; white solid, UV (MeOH) λ_{max} 210, 282 nm; IR (KBr) ν_{max} 3401, 1589, 1501 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; (−) HR-ESI–MS *m/z* 353.2119 [M − H]− (calcd for $C_{23}H_{29}O_3$, 353.2117).

2.3.2. 1-(3′,4′-methylenedioxy-phenyl)-12-(3″-hydroxyphenyl)-dodecane (2)

$C_{25}H_{34}O_3$; white solid, UV (MeOH) λ_{max} 222, 282 nm; IR (KBr) ν_{max} 3361, 1587, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; (−) HR-ESI–MS *m/z* 381.2430 [M − H]− (calcd for $C_{25}H_{33}O_3$, 381.2430).

Table 1
^1H NMR and ^{13}C NMR data for compounds **1–3** (δ in ppm, *J* in Hz).

Position	**1** δ_H (*J* in Hz)	δ_C	**2** δ_H (*J* in Hz)	δ_C	**3** δ_H (*J* in Hz)	δ_C
1′		137.0		137.0		136.5
2′	6.69, brs	112.6	6.69, brs	112.6	6.68, brs	108.9
3′		147.5		147.5		147.4
4′		145.4		145.4		145.4
5′	6.74, dd (8.1, 2.1)	108.2	6.76, d (7.8)	108.1	6.73, d (7.8)	108.1
6′	6.64, brd (8.1)	121.2	6.66, brd (8.0)	121.2	6.64, brd (8.1)	121.1
7′	5.92, s	100.8	5.93, s	100.7	5.91, s	100.7
1	2.54, dd (7.5, 15.4)	36.0	2.57, dd (7.8, 15.4)	35.9	2.56, dd (6.6, 13.8)	35.2
2	1.58, m	31.9	1.61, m	31.9	1.62, m	31.3
3	1.22-1.37, m	29.4	1.23-1.41, m	29.4	1.23-1.37, m	29.7
4	1.22-1.37, m	29.6	1.23-1.41, m	29.6	1.23-1.37, m	29.3
5	1.22-1.37, m	29.7	1.23-1.41, m	29.7	1.95-2.10, m	27.2
6	1.22-1.37, m	29.7	1.23-1.41, m	29.8	5.33-5.43, m	129.3
7	1.22-1.37, m	29.6	1.23-1.41, m	29.8	5.33-5.43, m	129.4
8	1.22-1.37, m	29.3	1.23-1.41, m	29.7	1.95-2.10, m	26.9
9	1.58,m	31.4	1.23-1.41, m	29.6	1.23-1.37, m	29.2
10	2.54, dd (7.5, 15.4)	35.8	1.23-1.41, m	29.3	1.23-1.37, m	29.4
11			1.61, m	31.4	1.62, m	31.7
12			2.57, dd (7.8, 15.4)	35.8	2.56, dd (6.6, 13.8)	35.8
1″		145.1		145.0		144.9
2″	6.67, brs	115.4	6.69, brs	115.4	6.65, brs	115.3
3″		155.6		155.5		155.5
4″	6.66, d (7.6)	109.0	6.68, d (7.7)	109.0	6.64, d (7.8)	112.5
5″	7.15, t (7.6)	129.5	7.16, t (7.7)	129.5	7.14, t (7.8)	130.5
6″	6.76, d (7.6)	121.0	6.79, d (7.7)	121.0	6.75, d (7.8)	121.1

2.3.3. 1-(3′,4′-methylenedioxy-phenyl)-12-(3″-hydroxyphenyl)-6Z-dodecylene (3)

$C_{25}H_{32}O_3$; white solid, UV (MeOH) λ_{max} 210, 282 nm; IR (KBr) ν_{max} 3396, 1589, 1501 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; (−) HR-ESI–MS *m/z* 379.2271 [M − H]− (calcd for $C_{25}H_{31}O_3$, 379.2273).

2.4. Ozonolysis

The double bond position in compound **3** was determined by the following ozonolysis procedure. The compound was dissolved in 0.5 mL of CH_2Cl_2, and ozone, generated with an ozone generator, was bubbled through the solution at −78 °C until a blue color persisted indicating ozone saturation. The reaction mixture was stirred for 4 h and then quenched by the addition of DMSO (200 μL). The solution was allowed to warm to room temperature before GC–MS analysis(Dawid et al., 2012).

2.5. Assay for inhibitory activity against BACE1

β-Secretase-mediated cleavage of APP was determined as described by Dai (Jingqiu Dai et al., 2010). Compounds with a purity > 98% were dissolved in DMSO at the desired concentration and incubated with the enzyme for 16 h in 96-well plates. A control (DMSO) and a standard inhibitor (β-secretase inhibitor IV, Calbiochem) were also tested. All compounds were tested in triplicate. The chemiluminescence signals were determined using a Fluostar Optima spectrophotometer.

3. Results and discussion

The EtOH extract of the rhizomes of *H. occulta* was fractionated by silica gel and Sephadex LH-20 CC. As a result, three new aromatic compounds (**1–3**), five known sesquiterpenoids (**4–8**), and one furofuran lignan (**9**) were isolated, and their structures are shown in Fig. 1.

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