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Abstract

The phytochemical investigation of the leaf extracts of *Uvaria hamiltonii* (Annonaceae) led to the isolation and identification of ten compounds including a new *seco*-cyclohexene (**1**) together with nine known compounds (**2**–**10**). Their structures were elucidated by intensive analysis by spectroscopic methods and comparisons of their spectroscopic data with those of compounds reported in the literature. Compounds **2**, **8**, and **9** showed potent *α*-glucosidase inhibitory activity with the IC_{50} values ranging from 2.6–7.1 μM.

Keywords: *Uvaria hamiltonii*; Annonaceae; seco-cyclohexene; *α*-glucosidase inhibitory activity.

1. Introduction

Uvaria genus belongs to the Annonaceae family which is distributed throughout tropical and subtropical countries and 26 species have been found in Thailand (Auranwiwat et al. 2017; Chuan-Rui et al. 2006). In previous studies, various types of secondary metabolites, including flavonoids (Auranwiwat et al. 2017; Hsu et al. 2016; Huang et al. 1998), alkaloids (Hasan et al. 2001; Nahar Asha et al. 2004), chalcones (Macabeo et al. 2017b), polyoxygenated cyclohexenes (Chuan-Rui et al. 2006; Jolad et al. 1981; Yong-Hong et al. 1997), polyoxygenated seco-cyclohexenes (Macabeo et al. 2017a; Zhang et al. 2010) and aurones (Huang et al. 1998) were reported. Many of these compounds displayed interesting biological activities, including cytotoxic (Asha et al. 2003; Auranwiwat et al. 2017; Huang et al. 1998; Macabeo et al. 2004), antibacterial (Asha et al. 2003; Nahar et al. 2004) and antitubercular (Macabeo et al. 2017a) activities. *Uvaria hamiltonii* Hook. f. & Thomson is a large woody scandent shrub which is used in traditional medicine for the treatment of minor infections. (Asha et al. 2003). A

preliminary screening of α-glucosidase inhibitory activity of this plant indicated that the EtOAc extract of the leaf displayed promising α-glucosidase inhibitory activities with an IC_{50} value of 78.4 µg/mL. This information led us to investigate the chemical constituents of this extract and their α-glucosidase inhibitory activity.

2. Results and discussion

The EtOAc extract of the leaf of *U. hamiltonii* was separated and purified by column chromatography using various stationary phases to yield ten compounds (Figure 1) including a new *seco*-cyclohexene, uvarahamiltone (**1**) and nine known compounds (**2**–**10**). The known compounds were identified as grandifloracin (**2**) (Yong-Hong et al. 1997), zeylenone (**3**) (Yong-Hong et al. 1997), (–)-1,6-desoxypipoxide (**4**) (Schulte et al. 1982), (–)-zeylenol (**5**) (Jolad et al. 1981), uvarinbonol A (**6**) (Matthew et al. 2012), uvarirufol A (**7**) (Chuan-Rui et al. 2006), kaempferol (**8**) (Yuh-Chwen et al. 2000), pinocembrin (**9**) (Kuroyanagi et al. 1983) and benzoic acid (**10**) by analysis of their spectroscopic data and by comparisons of this data with those reported.

Uvarahamiltone (**1**) was obtained as a viscous oil. This compound has a molecular formula of $C_{21}H_{20}O_5$ as deduced from the ion peak at *m/z* $[M + Na]^+$ 375.1206 (calcd for $C_{21}H_{20}O_5Na$, 375.1208) in the HRESIMS. The UV spectrum exhibited absorption maxima at 230 and 275 nm, indicating the presence of the benzoyl group (Macabeo et al. 2017a) while, the IR spectrum displayed bands for an aryl ester and/or ketone carbonyl and aromatic/olefinic moieties at 1719 and 1601 cm^{-1}, respectively (Macabeo et al. 2017b). The ^{13}C NMR and DEPT data revealed resonances for the presence of 21 carbon atoms, including five quaternary carbons, four methylene carbons and twelve methine carbons. The ^{1}H and ^{13}C NMR spectra of **1** displayed resonances for two monosubstituted aromatic rings at δ_H 8.08 (2H, m, H-3′, H-7′)/δ_C 129.9, 7.46 (2H, m, H-4′, H-6′)/δ_C 128.5, 7.57 (1H, m, H-5′)/δ_C 133.4, 8.04 (2H, m, H-3″, H-7″)/δ_C 129.6, 7.46 (2H, m, H-4″, H-6″)/δ_C 128.3 and 7.57 (2H, m, H-5′, H-5″)/δ_C 132.9, two methine protons at δ_H 5.85 (1H, dt, J = 6.6, 15.6 Hz, H-5)/δ_C 133.6 and 5.74 (1H, dt, J = 6.0, 15.6 Hz, H-6)/δ_C 125.4 and four methylene protons at δ_H 4.88 (2H, s, H-1)/δ_C 68.4, 2.64 (2H, t, J = 7.2 Hz, H-3)/δ_C 38.0, 2.43 (2H, dd, J = 6.6, 7.2 Hz, H-4)/δ_C 25.7 and 4.77 (2H, dd, J = 0.8, 6.0 Hz, H-7)/δ_C 65.2. The connections of C-3 to C-7 was suggested by the analysis of the following key COSY (Figure S13, Supporting material): H-3 (δ_H 2.64)/H-4 (δ_H 2.43)/H-5 (δ_H 5.85)/H-6 (δ_H 5.74)/H-7 (δ_H 4.77). The *E*-geometry of the double bond at C-5/C-6 was determined from the large J value of H-5/H-6 (15.6 Hz). Key HMBC correlations

(Figure S13, Supporting material) between H-1 at δ_H 4.88 (2H, s, H-1) and C-1′ at δ_C 165.8, and between H-7 at δ_H 4.77 (2H, dd, J = 0.8, 6.0 Hz, H-7) and C-1″ at δ_C 166.3 suggested the presence of two benzoyloxy groups at C-1 and C-7, respectively. The ketone carbonyl group resonance at δ_C 203.1 was assigned to C-2 from the HMBC correlations between H-1 (δ_H 4.88), H-3 (δ_H 2.64), H-4 (δ_H 2.43) and H-5 (δ_H 5.85) with C-2 (δ_C 203.1). Putative biosynthetic pathways toward the formation of uvarahamiltone (**1**) is shown in Figure S14 (Supporting material). Uvarahamiltone could obtain from the common precursor A (not isolated from this study) *via* multiteps including ring cleavage at C-1/C-2 (Wang et al. 2003), selective benzylation of primary alcohol and oxidation.

The EtOAc extract and compounds **1**–**3**, **5** and **8**–**10** were evaluated for their α-glucosidase inhibitory activities . The EtOAc extract showed good inhibition of α-glucosidase activity with an IC_{50} value of 78.4 μg/mL. Compounds **2**, **8** and **9** displayed potent α-glucosidase inhibitory activity with IC_{50} values of 7.1, 2.6 and 4.2 μM, respectively (Table S2). Compounds **1**, **3** and **5** showed moderate α-glucosidase inhibitory activities with IC_{50} values of 37.9, 71.1 and 35.6 μM, respectively which were better than that of the positive control, acarbose, (IC_{50} = 170.7 μM).

3. Experimental

For the details of all experimental parts see the Supplementary material.

3.3.1 Uvarahamiltone

Viscous oil; UV)MeOH (λ_{max}) log ε (282 (1.18), 275 (1.24), 230 (3.57) nm; IR (neat) ν_{max} 2927, 2853, 1719, 1601, 1584, 1491, 1272, and 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 8.08 (2H, m, H-3′, H-7′), 8.04 (2H, m, H-3″, H-7″), 7.57 (2H, m, H-5′, H-5″), 7.46 (4H, m, H-4′, H-6′, H-4″, H-6″), 5.85 (1H, m, H-5), 5.74 (1H, m, H-6), 4.88 (2H, s, H-1), 4.77 (2H, dd, J = 0.8, 6.0 Hz, H-7), 2.64 (2H, t, J = 7.2 Hz, H-3), 2.43 (2H, dd, J = 6.6, 14.0 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 203.1 (C-2), 166.3 (C-1″), 165.8 (C-1′), 133.6 (C-5), 133.4 (C-5′), 132.9 (C-5″), 130.2 (C-2″), 129.9 (C-3′, C-7′), 129.6 (C-3″, C-7″), 129.1 (C-2′), 128.5 (C-4′, C-6′), 128.3 (C-4″, C-6″), 125.4 (C-6), 68.4 (C-1), 65.2 (C-7), 38.0 (C-3), 25.7 (C-4); HRESIMS m/z 375.1206 $[M+Na]^+$ (calcd for $C_{21}H_{20}O_5Na$, 378.1208).

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Supplementary material

The NMR and HRESIMS spectra of compound **1** are available in supporting information.

Disclosure statement

The authors declare no conflicts of interest.

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