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Polycyclic polyprenylated acylphloroglucinols and biphenyl derivatives from the roots of *Garcinia nuntasaenii* Ngerns. & Suddee

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ABSTRACT

Seven previously undescribed compounds, including three polycyclic polyprenylated acylphloroglucinols (garcinuntins A–C), three biphenyl derivatives (garcinuntabiphenyls A–C) and a lanostane triterpene (garcinuntine), along with thirteen known compounds were isolated from the root of *Garcinia nuntasaenii* Ngerns. & Suddee. Their structures were elucidated on the basis of spectroscopic techniques. For garcinuntins A–C, the absolute configurations were confirmed by the combination of single X-ray crystallography and ECD calculations. Anti-HIV activity using anti-HIV-1 reverse transcriptase and syncytium inhibition assays, and cytotoxic activity against a panel of cultured mammalian cancer cell lines of isolated compounds were investigated.

1. Introduction

Garcinia genus belongs to the large family Clusiaceae (Guttiferae). A number of plants in this genus have been regarded as medicinal plants and they are used in folk medicine and food. Reports on *Garcinia* plants indicated that they produce a large number of biologically active substances such as flavonoids, polycyclic polyprenylated acylphloroglucinols (PPAPs), xanthones and terpenoids (Ciochina and Grossman, 2006; Hongthong et al., 2016; Reutrakul et al., 2007, 2010), and some of which display remarkable biological activities.

Garcinia nuntasaenii Ngerns. & Suddee (Clusiaceae) was recently identified as a previously unclassified species in the *Garcinia* genus (Ngernsaengsaruay and Suddee, 2016). It is a shrub growing up to 1–2-m in height with white flowers and green fruits and commonly called “Chang-nga-ek” in Thai. It was sporadically found in the open-dry evergreen forest of the northeastern part of Thailand and its root is used in Thai folk medicine for treatment of muscle pain. Preliminary screening of the crude *n*-hexane, ethyl acetate and methanol extracts of the roots of *G. nuntasaenii* showed

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significant anti-inflammatory and anti-HIV activities. In the course of our continuing efforts to search for biologically active substances from plants in the *Garcinia* genus, we report the isolation and structural identification of previously undescribed compounds including three polycyclic polyprenylated acylphloroglucinols **1**–**3**, three biphenyl derivatives **4**–**6**, and a triterpene **7** (Fig. 1), along with thirteen known compounds **8**–**20** (Scheme S1) from the roots of *G. nuntasaenii*. The structures of these compounds were established via spectroscopic data or by comparison with the literature data. The biological activities of the isolated compounds were evaluated in a cytotoxicity assay against a panel of cultured mammalian cancer cell lines and in an anti-HIV-1 *in vitro* system. This work represents the first phytochemical investigation of the plant species.

2. Results and discussion

Garcinuntin A (**1**) was obtained as colorless needles and its molecular formula $C_{38}H_{50}O_4$ was determined on the basis of the HRESIMS peak at *m/z* 593.3600 $[M + Na]^+$ (calcd for $C_{38}H_{50}O_4Na$, 593.3601). The major peaks at 1716, 1694 and 1640 cm^{-1} in its FT-IR spectrum indicated the presence of three carbonyl groups in the molecule. The UV spectrum showed the absorption bands at λ_{max} 197, 247 and 277 nm in MeCN. The ^1H NMR spectroscopic data (Table 1) revealed the presence of monosubstituted phenyl group [δ_H 7.55 (2H, dd, $J = 8.3, 1.3$ Hz), 7.40 (1H, tt, $J = 7.5, 1.3$ Hz), 7.27 (2H, dd, $J = 8.3, 7.5$ Hz)] corresponding to the carbon resonances at δ_C 128.5 × 2, 132.0, and 127.9 × 2, respectively. Two vinylic protons [δ_H 4.97 (1H, br t, $J = 6.6$ Hz, H-33), 5.08 (1H, s, H-25)], and nine methyl groups [δ_H 0.91, 0.96, 1.12, 1.22, 1.39, 1.53, 1.56, and 1.66 × 2 (each 3H, s)] suggested the presence of isoprenyl groups. The ^{13}C NMR spectrum (Table 1) showed a non-conjugated ketone (δ_C 208.0), a conjugated carbonyl (δ_C 193.1), an enone moiety (δ_C 191.9, 113.0 and 170.1), three quaternary carbons (δ_C 79.7, 56.3, and 49.0), a methine carbon (δ_C 43.8) and a methylene carbon (δ_C 43.3). These data suggested a dimethyl substituted bicyclo[3.3.1]nonane ring system bonded to a benzoyl moiety, a known common feature in PPAPs.

In comparison of the NMR data with those of propolone A (Rubio et al., 1999), the prenyl side chain at C-5 (δ_C 56.3) found in propolone A was replaced by a (2,4,4-trimethylcyclohex-2-en-1-yl)methyl residue. The connectivity of the cyclohexenyl moiety was confirmed by the HMBC correlations from the vinylic proton H-25 [δ_H 5.08 (1H, s)] to three methyl carbons, C-29, C-30, C-31 (δ_C 22.0, 29.3, and 30.8, respectively), a methine carbon C-23 (δ_C 34.9) and a methylene carbon C-27 (δ_C 34.1) as well as from the *gem*-dimethyl protons H-30 and H-31 (δ_H 0.91 (3H, s) and 0.96 (3H, s), respectively) to the carbon C-27 (δ_C 34.1) and olefinic methine carbon C-25 (δ_C 133.1) (Fig. 2). The cross peaks between the methylene protons H-22 (δ_H 1.91, m) to quaternary olefinic carbon C-24 (δ_C 135.1), a methylene carbon C-6 (δ_C 43.3), isolated carbonyl carbon C-9 (δ_C 208.0), quaternary carbon C-5 (δ_C 56.3) and conjugated olefinic carbon C-4 (δ_C 170.1) supported the (2,4,4-trimethylcyclohex-2-en-1-yl)methyl residue to locate at C-5 (Fig. 2).

On the basis of the previously described core skeleton of PPAPs (type A) (Ciochina and Grossman, 2006), the up-field shift of C-7 carbon (δ_C 43.8), and a large coupling constant of diaxial protons H-6_{ax} and H-7 ($^3J = 13.0$ Hz) (Piccinelli et al., 2005), along with the cofacial relationship between H-6_{ax}, H-32 and H-37 in the NOESY spectrum (Fig. 2), suggested the isoprenyl side chain at C-7 to locate in an equatorial orientation.

Although the relative configuration at the chiral carbon C-23 could not be precisely assigned using NOESY data, the relative stereochemistry of **1** was later unambiguously assigned by means of single X-ray crystallographic technique using Mo Kα radiation (Fig. 3). Based on the spectroscopic data described above, compound **1** was possibly assigned as (1*R*,5*R*,7*S*,23*R*)-**1** or its enantiomers. Furthermore, the electronic circular dichroism (ECD) experiment and ECD calculation of **1** were conducted. The experimental ECD spectrum of **1** was in accordance with the calculated ECD spectrum for (1*R*,5*R*,7*S*,23*R*)-**1** (Fig. 4). Therefore, the absolute configurations of **1** were finally determined to be (1*R*,5*R*,7*S*,23*R*)-**1** and its chemical structure is depicted as shown (Fig. 1).

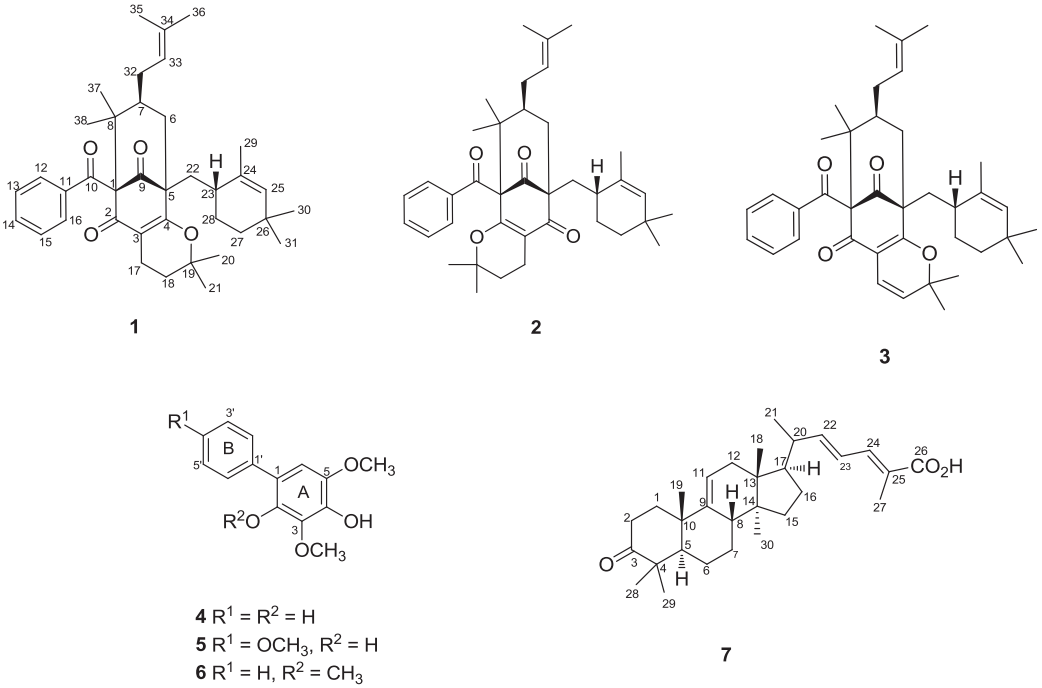

Fig. 1. Structures of compounds **1**–**7**.