A novel polyprenylated phloroglucinol, garcinialone, from the roots of *Garcinia multiflora*

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**Abstract**

A novel polyprenylated phloroglucinol garcinialone (1) along with a known compound isoxanthochymol (2) have been isolated from the roots of *Garcinia multiflora*. The structures of 1 and 2 were elucidated spectroscopically, by 1D and 2D NMR and mass spectrometry.

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**Garcinia multiflora** is an evergreen tree, belonging to the family Guttiferae. The genus *Garcinia* numbers over 200 species, though only three species occur in Taiwan, namely *G. subelliptica*, *G. multiflora*, and *G. lintii*. *G. multiflora* is a dioecious tree, about 3–10 m tall, distributed in southern mainland China, Hong Kong, and the southern part of Taiwan.1 It is used in furniture manufacture and as a dye.

Previous phytochemical studies by Konoshima et al.2 on the bark of *G. multiflora* led to the identification of 7 biflavonoids, and studies by Chen et al.3,4 on the heartwood of this plant identified 11 flavonoids and xanthones. Several new xanthone derivatives and new benzophenone derivatives were isolated from the stems of *G. multiflora* and exhibited cytotoxic and antioxidative activity.5 The twigs and leaves of this species were found to inhibit

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strongly the polymerase of HIV-1 RT.\textsuperscript{6} The roots of \textit{G. multiflora} have not yet been analyzed, and we therefore resolved to research the chemical principals of this part.

The methanol extract of roots of \textit{G. multiflora} exhibited good free radical scavenger activity, trapping superoxide, reducing power, and metal chelating activity (unpublished data). The MeOH extract was partitioned with EtOAc and H\textsubscript{2}O, and the organic layer afforded a black syrup. This black syrup was repeatedly chromatographed on SiO\textsubscript{2} columns and by HPLC to give a novel polypropylenated phloroglucinol garcinialone (1) along with the known compound isoxanthochymol (2).\textsuperscript{7,8} The structure of 2 had previously been determined from an X-ray crystallographic analysis of its di-p-bromobenzensulfonate,\textsuperscript{9} whereas the structure of 1 was deduced from that of 2 by a comparison of the physical and chemical data for 1 and 2.

Garcinialone (1),\textsuperscript{9} [\textit{x}]\textsubscript{D}\textsuperscript{25} +2.0 (c 0.02, MeOH), was obtained as a pale yellow plate. Its HRESIMS exhibited a molecular ion peak at m/z 618.3558, [M\textsuperscript{+}] (calc 618.3557) corresponding to C\textsubscript{31}H\textsubscript{36}O\textsubscript{7} with 14 degrees of unsaturation. IR absorption bands at 3410, 1726, 1627, 1587, and 1474 cm\textsuperscript{-1} implied the existence of hydroxyl, carbonyl, and phenyl groups. In the UV spectrum of 1, absorption maxima were observed at 221, 249, 282 nm revealing the presence of the conjugated system.\textsuperscript{10}

However, initial observation of the \textsuperscript{13}C NMR and DEPT spectra of 1 only found 38 signals, assigned as two carbonyl groups (one isolated and one conjugated), six phenyl carbons, eight olefinic carbons, nine CH\textsubscript{3} groups, six sp\textsuperscript{3} CH\textsubscript{2}, two oxygenated sp\textsuperscript{3} C, three sp\textsuperscript{2} C, and two sp\textsuperscript{3} CH. Characteristic \textsuperscript{13}C NMR resonances, including those for three tertiary oxygenated aromatic carbon signals appeared at \textit{\delta} 142.7, 151.6, and 150.8, together with one sp\textsuperscript{3} C (\textit{\delta} 115.8) and two sp\textsuperscript{3} CH signals (\textit{\delta} 102.2, \textit{\delta}\textsubscript{H} 6.82, \textit{\delta} 107.4, \textit{\delta}\textsubscript{H} 7.52, s) indicated the presence of a 1,2,4-tri oxygenated benzene ring. Two of them link to hydroxyl groups disclosing from two phenolic signals at \textit{\delta}\textsubscript{H} 7.50 and 9.10 (exchangeable with D\textsubscript{2}O). The lower shift of the aromatic proton at \textit{\delta} 7.52 disclosed that it was ortho to a carbonyl group, which was assigned as a \gamma-pyrone functionality due to its IR absorption (\textit{\nu}_{max} 1627 cm\textsuperscript{-1}) and \textsuperscript{13}C data (\textit{\delta} 177.5). Resonances for a six-membered ring consisting of an isolated ketone (\textit{\delta} 209.2, \textit{\nu}_{max} 1726 cm\textsuperscript{-1}) flanked by two quaternary carbons (\textit{\delta} 61.2, 54.4) and an enolized 1,3-dioxygenated carbon (\textit{\delta} 76.2, 122.0, 164.0) were also observed. Support for this assignment was provided by \textsuperscript{13}C NMR signals (signals are similar to compound 2) for quaternary (\textit{\delta} 49.6, C-5), methine (\textit{\delta} 44.0, C-6), and methylene (\textit{\delta} 38.8, C-7) carbons which are part of the bicyclo[3.3.1]nonane ring system. The \textsuperscript{1}H NMR spectrum indicated three trisubstituted olefinic protons (\textit{\delta}H 5.32 (1H, m), 4.91 (1H, br s), and 4.37 (1H, br s)), and nine quaternary methyl groups including six methyl groups attached to olefins (\textit{\delta}\textsubscript{H} 1.73, 1.65 \times 2, 1.51, 1.48, 1.12), one methyl group attached to a carbon bearing a hydroxyl group (\textit{\delta} 1.46), and two geminal methyl groups (\textit{\delta}\textsubscript{H} 0.97) attached to a sp\textsuperscript{3} carbon. H-18 (\textit{\delta}\textsubscript{H} 4.37) and H-20 (\textit{\delta}\textsubscript{H} 1.12) were shifted to higher field by shielding from the \textit{ax} double bond and an oxygen atom. On account of seven oxygen atoms in compound 1, the remaining two oxygens are present as two hydroxyl groups which are revealed from the \textsuperscript{13}C NMR data (two oxygenated sp\textsuperscript{3} C: \textit{\delta}C 76.2, C-1; \textit{\delta}C 74.0, C-31).

This partial structure was further refined by HMBC (see Fig. 1) and NOESY spectra (see Fig. 2). In analysis of the HMBC spectrum of 1, the correlations H\textsubscript{3}-33 (\textit{\delta}\textsubscript{H} 1.46)/C-30, C-31, C-32; H-32 (\textit{\delta}\textsubscript{H} 1.17)/C-31 were observed. Several further correlations H-29 (\textit{\delta}\textsubscript{H} 1.28)/C-7, C-8, C-9, and C-31; H-34 (\textit{\delta}\textsubscript{H} 1.83)/C-30, C-35, C-36 suggested that compound 1 has a cyclpentaxel ring and an isoprenyl group attached to the C-30, which led to the establishment of partial structure 1a (Fig. 1). In addition, the HMBC spectrum of 1 also shows correlations from CH\textsubscript{2}-22 (\textit{\delta}\textsubscript{H} 1.01, s) to C-4, C-5, and C-6, from CH\textsubscript{2}-23 (\textit{\delta}\textsubscript{H} 0.97, s) to C-4, C-5, and C-6, from H-17 (\textit{\delta}\textsubscript{H} 2.57, m) to C-9, C-18, and C-19, and from H-24 (\textit{\delta}\textsubscript{H} 1.54, m) to C-6 and C-25. These observed HMBC correlations showed that 1 has a bicyclo[3.3.1]nonane ring system, and two isoprenyl groups attached to the C-4 and C-6, respectively, and gave rise to another partial structure 1b (Fig. 1). A further HMBC correlation of H-7 (\textit{\delta}\textsubscript{H} 2.34, m) to C-1, C-6, C-8, and C-9 permitted fragment 1a and 1b to be joined together as shown in fragment 1c (Fig. 1).

The relative stereochemistry of 1 was constructed from the combination of the NOESY spectrum (see Fig. 2) and 1D NMR of 1. The configuration of the hydroxyl group at C-31 was deduced to be the \alpha-equatorial orientation from the NOESY correlation of H-32 with H-29 (\textit{\delta}\textsubscript{H} 1.28, m), but the lack of NOESY correlation with H-30 suggested that H-32 was in the \beta-axial orientation. By further NOESY correlation of H-30 with H-35, H\textsubscript{2}-29 (\textit{\delta}\textsubscript{H} 2.05, dd, J = 13.2, 4.4 Hz), and H\textsubscript{2}-32 (\textit{\delta}\textsubscript{H} 1.17, d, J = 13.6 Hz), H-30 was deduced to be in the \alpha-axial orientation. The following NOESY correlation: H-6/H\textsubscript{2}-7, H-25, H-28/H\textsubscript{2}-24 disclosed H-6 and H-23 to be in \alpha-equatorial and \alpha-axial orientations, respectively. Furthermore, the H-33 (\textit{\delta}\textsubscript{H} 1.46, s) signal by the downfield shift indicated that the methyl group was in a 1,3-diaxial interaction with the hydroxyl group (attached to C-1). The H-18 and H\textsubscript{2}-20 observed at higher field [(\textit{\delta}\textsubscript{H} 4.37, br s) and (\textit{\delta}\textsubscript{H} 1.12, s)] indicated that both of the two must be shielded by the anisotropic effect from the oxygen atom and double bond.
The absolute configuration 1 must be like 2 because the two compounds were isolated from the same plant, the biotransformations of 1 were proposed from 2, and the pathway was sketched as in Figure 3. In acidic conditions, compound 2 was converted to the oxonium ion 3 which was subsequently hydrated to yield 4. After dehydration, compound 5 was produced, which then underwent acidic catalysis to form the tertiary cation 6. As the cyclization took place from the less hindered α-phase, the resulting β-axial hydroxyl group was formed. The hydration of cation 6 also occurred preferentially from the less hindered α-face to yield 7. Intramolecular oxidative coupling between the enol and aromatic ring of compound 7 produced garcinialone (1).

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References and notes

9. Garcinialone (1): Pale yellow plate, mp 252–253°C; [α]D20 = −2.0 (c 0.02, MeOH); UV (MeOH) λmax (log ε) 221 (3.90), 249 (4.06), 282 (3.85) nm; IR (KBr) mmax 3410, 1726, 1627, 1587, 1474, 1381, 1288, 1176, 1149 cm−1; positive ESIMS m/z (rel. int. %) 618 (M+, 8), 599 (54), 479 (92), 285 (100); HRESIMS m/z (calcd for C38H50O7, 618.3557).1H NMR (CDCl3): δ 0.97 (3H, s, H-23), 1.01 (3H, s, H-22), 1.07 (1H, m, H-6), 1.12 (3H, s, H-20), 1.17 (1H, d, J = 13.6 Hz, H-32), 1.42 (1H, overlap, H-7a), 1.46 (3H, s, H-33), 1.48 (3H, s, H-27), 1.51 (3H, s, H-21), 1.54 (1H, m, H-24), 1.65 (3H, s, H-37), 1.73 (1H, s, H-38), 1.83 (1H, dd, J = 14.8, 7.6 Hz, H-34), 2.05 (1H, dd, J = 13.2, 4.4 Hz, H-29), 2.23 (1H, overlap, H-34), 2.34 (1H, overlap, H-7b), 2.57 (1H, m, H-17), 2.59 (1H, d, J = 13.6 Hz, H-32), 2.76 (1H, br d, J = 13.6 Hz, H-17), 4.37 (1H, br s, H-18), 4.91 (1H, br s, H-25), 5.32 (1H, m, H-35), 5.70 (1H, br s, OH), 6.82 (1H, s, H-15), 7.52 (1H, s, H-12), 9.10 (1H, br s, OH); 13C NMR (CDCl3): δ C38H50O7, 618.3557).1H NMR (CDCl3): δ 18.3 (C-27), 18.5 (C-21), 18.6 (C-37), 20.5 (C-23), 24.3 (C-33), 25.4 (C-22), 25.8 (C-20), 26.2 (C-28), 26.3 (C-38), 27.6 (C-17), 29.0 (C-24), 29.6 (C-34), 33.7 (C-29), 38.8 (C-7), 43.9 (C-30), 44.0 (C-6), 49.6 (C-5), 50.7 (C-32), 54.4 (C-8), 61.2 (C-4), 74.0 (C-31), 76.2 (C-1), 102.2 (C-17), 107.4 (C-12), 115.8 (C-11), 118.4 (C-18), 122.0 (C-2), 122.6 (C-25), 123.3 (C-35), 132.4 (C-26), 132.4 (C-36), 134.1 (C-19), 142.7 (C-13), 150.8 (C-16), 151.6 (C-14), 164.0 (C-3), 177.5 (C-10), 209.2 (C-9).