Guttiferones O and P, Prenylated Benzophenone MAPKAPK-2 Inhibitors from *Garcinia solomonensis*

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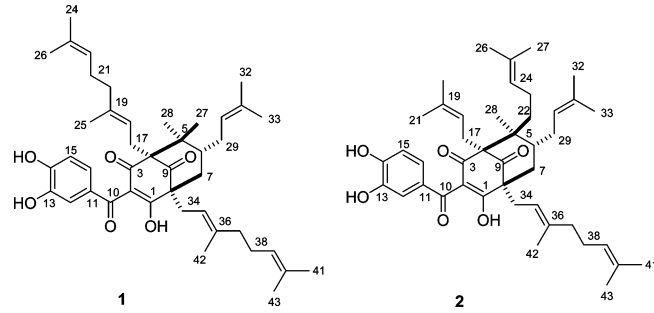
Received April 22, 2009

Two prenylated benzophenones, guttiferones O (**1**) and P (**2**), were isolated from the stem bark of the Papua New Guinean plant *Garcina solomonensis*. The structures of these compounds and their relative configurations were determined by spectroscopic methods. Both compounds inhibited the phosphorylation of the synthetic biotinylated peptide substrate KKLNRTLSVA by the serine/threonine protein kinase MAPKAPK-2 with IC_{50} values of 22.0 μM.

The cyclohexatrione moiety can be considered a privileged scaffold since it is associated with a wide range of biological activities including antibacterial,[1] cytotoxic,[2] antidepressant,[3] insecticidal,[4] anthelmintic,[5] TRH receptor binding,[6] and antioxidant activities.[7] This motif is found in species from a variety of higher plant families including the Clusiaceae, Myrtaceae, Fabaceae, and Annonaceae, from *Dryopteris* ferns, and from several fungal species.[8] The cyclohexatrione moiety found in compounds isolated from species of *Clusia*, *Symphonia*, *Alanblackia*, *Marila*, *Rheedia*, and *Garcinia* from the family Clusiaceae is generated by incorporation of several isoprenyl groups into C-2 and C-4 of a 1,3,5-trihydroxybenzophenone to form a bicyclo[3.3.1]nonane These compounds show a wide range of biological activities including liver X receptor binding affinity,[9] HIV inhibitory activity,[10] topoisomerase and microtubule disassembly inhibition,[11] cytotoxicity[12] trypanosomal activity,[13] and antibacterial activity.[14] Mitogen-activated protein kinase activated protein kinase 2 (MAPKAPK-2) is a protein serine/threonine kinase that is a member of the MAPK family of protein kinases and is phosphorylated and activated by p38 in response to cytokines, stress, and chemotactic factors. It is thought to play an important role in the regulation of cellular activities such as gene expression, mitosis, differentiation, and cell survival/apoptosis.[15] As a consequence, inhibitors of this enzyme could be important in treating inflammatory diseases and cancer.[16] We undertook a high-throughput screening campaign of 40 000 extracts from a diverse collection of plants, marine organisms, insects, and fungi collected in Queensland, Papua New Guinea (PNG), the GuangXi Province of China, and India to find MAPKAPK-2 inhibitors that could be used as potential lead compounds to treat inflammatory diseases. An extract from the stem bark of a PNG plant, *Garcinia solomonensis* A.C. Sm (Clusiaceae), was targeted for further investigation since it inhibited the phosphorylation of the synthetic biotinylated peptide substrate KKLNRTLSVA by human MAPKAPK-2 at a concentration of 0.2 mg/mL.[17] We report herein the assay-guided purification, structure determination, and biological activities of the two active constituents, guttiferones O (**1**) and P (**2**), isolated from *G. solomonensis*.

The dried ground stem bark of *G. solomonensis* was extracted with a continuous flow gradient of H_2O to MeOH (0.1% TFA in both solvents). The eluent from the extraction was immediately fractionated through two columns connected in series, the first column containing polyamide gel (PAG) and the second column containing C_{18} silica gel. The selection of fractions for further purification was determined using a MAPKAPK-2 bioassay. The active fractions were further purified by centrifugal partition chromatography (CPC) employing a solvent mix of heptane/CH_2Cl_2/CH_3CN (10:3:7) and the upper phase as mobile phase to yield two active fractions consisting of a mixture of guttiferones O (**1**) and P (**2**) and pure guttiferone O (**1**), respectively. The mixture was further separated by HPLC on PVA-coated silica gel eluting with CH_2Cl_2 to yield guttiferone P (**2**) followed by guttiferone O (**1**).



1 **2**

Accurate mass measurement of the pseudomolecular ion $[M - H]^-$ in the (−)-HRESIMS at *m/z* 669.5159 allowed a molecular formula of $C_{43}H_{58}O_6$ to be assigned to guttiferone O (**1**). The molecule contained hydroxyl and saturated and unsaturated ketone groups, determined from IR absorption bands observed at 3421, 1733, 1717, and 1684 cm^{-1}. The presence of a conjugated ketone was supported by a UV absorbance at 327 nm.

The ^1H NMR spectrum of **1** in d_5-pyridine exhibited signals for a trisubstituted aromatic ring (δ_H 7.18 d $J = 7.8$ Hz; 7.60 dd $J = 1.8$, 7.8 Hz; 7.86 d $J = 1.8$ Hz), five olefinic triplets at δ_H 5.12, 5.20, 5.25, 5.50, and 5.77, and 10 methyl singlets between δ_H 0.89 and 1.86. The remaining signals were aliphatic proton multiplets. All 43 carbons were visible in the ^{13}C NMR spectrum, and four ketone carbonyl resonances were observed at δ_C 188.5, 190.6, 195.8, and 209.0. Sixteen of 17 carbon resonances between δ_C 115 and 155 could be assigned to a dioxygenated aromatic ring and five double bonds. The remaining carbon resonances were upfield of δ_C 70. Correlations observed in a gHSQC spectrum determined the presence of 55 carbon-bound protons (10 methyls, eight methylenes, and nine methines). A gCOSY experiment established that **1** contained five trisubstituted double bonds that were associated with two geranyl and one isoprene unit. The isoprene group was attached to a $CHCH_2$ group since a COSY correlation was observed between the methylene protons H-29a (δ_H 1.80) and H-29b (δ_H 2.20) of the isoprene and the methine proton H-6 (δ_H 2.30) of the $CHCH_2$ unit. Correlations observed in a gHMBC spectrum indicated that the trisubstituted phenyl group could be assigned to a 3,4-dihydroxybenzoyl group since correlations were observed between

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10.1021/np900246t CCC: $40.75

H-12 (δ_H 7.86) and H-16 (δ_H 7.60) and an oxygenated aromatic carbon at δ_C 152.8 (C-14) and an unsaturated ketone carbon at δ_C 195.8 (C-10), while H-15 (δ_H 7.18) correlated to a second oxygenated aromatic carbon at δ_C 149.9 (C-13) and an aromatic quaternary carbon at δ_C 131.1 (C-11). Thirteen of the 15 elements of unsaturation were accounted for by this data, indicating that **1** must possess another two rings. Guttiferone O contained an isopropyl group attached to the methine carbon C-6 since HMBC correlations were observed between the methyl protons 27-CH_3 and 28-CH_3 and C-6. In addition these protons correlated to two quaternary aliphatic carbons at δ_C 46.8 (C-5) and 68.7 (C-4). One of the methylene protons (H-17a, δ_H 2.95) of one of the geranyl groups also correlated to C-4 as well as to two ketone carbons at δ_C 188.5 (C-3) and 209.0 (C-9). These data indicated that the isopropyl group and one of the geranyl groups were each attached to a carbon that was substituted by two ketones. The methylene proton H-7α (δ_H 1.75) and 34-CH_2 (δ_H 2.90) of the second geranyl group also correlated to one of these ketone carbons (C-9) as well as to a second more upfield ketone carbon at δ_C 190.6 (C-1). These data indicated that the molecule contained a cyclohexanone with geranyl and ketone groups attached to both carbons α to C-9. The chemical shifts of C-3 and C-1 were indicative of a β-diketone, leaving the unassigned carbon at δ_C 120.5 to be assigned to the carbon (C-2) α to the two ketones, thus forming the remaining ring.[9] Attachment of the benzoyl group to C-2 generated the planar structure of guttiferone O (**1**). The relative configurations the three stereogenic centers in **1** were assigned from interpretation of correlations observed in a ROESY spectrum. H-7α and 27-CH_3 were both axial since a strong ROESY correlation was observed between them. The axial configuration for 28-CH_3 was also consistent with the upfield ^{13}C chemical shift observed for C-28 (δ_C 16.3).[18] A large $^1H-^1H$ coupling observed between H-7α and H-6 indicated that H-6 was also axial. A ROESY correlation between H-6 and H-16 suggested that the bicyclo[3.3.1]nonane ring system adopted a chair conformation. This conformation was further supported by ROESY correlations between 28-CH_3 and 17-CH_2, and between H-7α and 34-CH_2, indicating that both geranyl groups were equatorial. Guttiferone O possesses the same relative configuration at C-4, C-6, and C-8 as aristophenone A but differs from that compound by the replacement of both isoprene groups attached to C-4 and C-8 with geranyl groups.[19]

Guffiferone P (**2**) was very similar in structure to **1**. Accurate mass measurement of the pseudomolecular ion peak in the (−)-HRESIMS determined a molecular formula of **2** to be $C_{43}H_{58}O_6$. Inspection of the ^1H NMR spectrum of **2** in d_5-pyridine suggested that **2** was substituted at the equatorial methyl carbon C-28 since the methyl proton singlet 28-CH_3 was missing while the rest of the spectrum was very similar to that of **1**. Analysis of COSY and HSQC spectroscopic data indicated that **2** was also substituted at C-6 by an isoprene group, but one of the isolated geranyl groups was replaced by an isoprenyl group. A 4-methylpent-3-enyl group and an axial quaternary methyl group were also present in the molecule. The points of attachment of the substituents around the cyclo[3.3.1]nonane were determined from interpretation of correlations observed in a HMBC spectrum. The geranyl group was attached to C-8 since HMBC correlations were observed between 34-CH_2 and C-1, C-7, C-8, and C-9. Correlations from 28-CH_3 to C-22 indicated that the 4-methylpent-3-enyl group was attached to C-5. The isoprenyl group was attached to C-4 since HMBC correlations were observed between 17-CH_2, 28-CH_3, 22-CH_2, and C-4. The relative configuration of the four stereogenic centers in **2** was determined by interpretation of ROESY correlations, $^1H-^1H$ coupling constants, and ^{13}C chemical shifts. ROESY correlations between 28-CH_3 and H-7α in combination with the ^{13}C chemical shift of C-28 (δ_C 16.3) indicated that H-7α and 28-CH_3 were 1,3-diaxial. A large vicinal coupling (J = 13.8 Hz) between H-7α and H-6 indicated that H-6 was also axial. ROESY correlations between 28-CH_3 and H-17 and between H-7α and 34-CH_2 indicated that the isoprene attached to C-4 and the geranyl group attached to C-8 were both equatorial. Guttiferone P possessed the same relative configuration as guttiferone I but differed from it by swapping the geranyl and isoprenyl substituents attached at C-6 and C-8.[9]

Guttiferones O (**1**) and P (**2**) inhibited phosphorylation of the synthetic biotinylated peptide substrate KKLNRTLSVA by the serine/threonine protein kinase MAPKAPK-2, both with IC_{50} values of 22.0 μM. The reference compound staurosporine exhibited an IC_{50} value of 0.15 μM. Guttiferones O and P are only weak inhibitors of MAPKAPK2 and therefore unlikely to be of therapeutic value. However these compounds could be considered to be leads from which more potent analogues could be designed. MAPKAPK-2 is located in the cell nucleus and is therefore associated with the late stages of the signal transduction pathway. The weak antiproliferative activity observed for analogues[20] of guttiferones O and P may thus be associated with the inhibition of MAPKAPK-2 or related kinases within the cell nucleus.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO P-1020 polarimeter (10 cm cell). UV spectra were recorded on a CAMSPEC M501 UV/vis spectrophotometer, and IR spectra were recorded on a Bruker Tensor 27 spectrometer. NMR spectra were recorded on Varian Inova 600 and 500 MHz NMR spectrometers. Samples were dissolved in d_5-pyridine, and chemical shifts were calculated relative to the d_5-pyridine solvent peak (δ_H 8.71 and δ_C 149.9). 2D NMR spectra were recorded at 30 °C using standard Varian pulse sequences gCOSY, gHMQC, gHSQC, gHMBC, and ROESY. HRESIMS were recorded on a Bruker Daltonics Apex III 4.7e Fourier-transform mass spectrometer. HPLC separations were achieved using a YMC PVA-coated silica gel semipreparative column (5 μm, 10 mm × 150 mm). CPC separations were performed on a SANKI LLB-M high-performance CPC system. DAVISIL bonded C_{18} (30−40 μm) silica gel was used during purification. All solvents used were Omnisolv HPLC grade. Steptavidin-coated (scintillation proximity assay (SPA)) beads were obtained from Amersham. The peptide was obtained from Neosystem Groupe SNPE, and recombinant MAPKAPK-2 was obtained from AstraZeneca.

Plant Material. Stem bark of *G. solomonensis* was collected by T.R. on October 26, 1998, from the Edevu mountain range in the Central Province of Papua New Guinea. A voucher specimen, 668, is deposited at Biodiversity Ltd., at the University of Papua New Guinea, Port Moresby.

Extraction and Isolation. The air-dried stem bark of *G. solomonensis* (10.0 g) was ground and extracted using an in-line chromatography system whereby the column containing plant material was connected to a MPLC column containing PAG (100 g), which was, in turn, connected to a column containing C_{18} silica gel (100 g). A gradient of H_2O to MeOH (0.1%TFA in both solvents) over 120 min followed by 40 min of isocratic elution with 99.9% MeOH/0.1% TFA at 10 mL/min was passed through the linked columns and the eluent collected into 160 test tubes. MAPKAPK-2 bioactivity was localized in fractions 70−80. These fractions were combined (165 mg) and separated by CPC in ascending mode using heptane/CH_2Cl_2/CH_3CN (10:3:7) and the upper phase as mobile phase and the lower phase as stationary phase at a flow rate of 3 mL/min. A total of 120, 1 min, fractions were collected. Bioactivity was concentrated in fractions 40−55. Fractions 50−55 were pure guttiferone O (**1**) (15 mg, 0.15%). Fractions 40−50 (90 mg) were still impure and were combined and further separated by HPLC on PVA-coated silica gel, eluting with CH_2Cl_2. Pure guttiferone P (**2**) (35 mg, 0.35%) and guttiferone O (**1**) (45 mg, 0.45%) eluted respectively.

Guttiferone O (1): yellow gum; $[\alpha]^{27}_D$ +30.7 (*c* 0.66, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 213 (4.46), 239 (4.42), 258 (4.39), 327 (4.00) nm; IR (KBr) ν_{max} 3421, 2973, 2923, 2853, 1733, 1717, 1684, 1654, 1618, 1386, 1296 cm^{-1}; ^1H NMR (600 MHz, d_5-pyridine) δ 0.89 (3H, s, H-28), 1.34 (3H, s, H-27), 1.50 (3H, s, H-43), 1.54 (9H, s, H-26, H-32, H-33), 1.58 (3H, s, H-41), 1.62 (3H, s, H-24), 1.75 (1H, dd, J = 14.0, 14.0 Hz, H-7α), 1.80 (3H, s, H-42), 1.80 (2H, m, H-29α), 1.86 (3H, s, H-25), 2.05 (4H, m, H-20, H-37), 2.15 (4H, m, H-21, H-38), 2.20 (1H, m, H-29β), 2.30 (1H, m, H-6), 2.37 (1H, dd, J = 3.9, 14.0 Hz, H-7β), 2.90 (2H, d, J = 7.3 Hz, H-34), 2.95 (1H, dd, J = 7.2, 13.5 Hz, H-17α), 3.05 (1H, dd, J = 5.4, 13.5 Hz, H-17β), 5.12 (1H, br t, J

= 7.2 Hz, H-30), 5.20 (1H, br t, J = 7.2 Hz, H-22), 5.25 (1H, br t, J = 7.2 Hz, H-39), 5.50 (1H, br t, J = 7.2 Hz, H-18), 5.77 (1H, br t, J = 7.3 Hz, H-35), 7.18 (1H, d, J = 7.8 Hz, H-15), 7.60 (1H, dd, J = 1.8, 7.8 Hz, H-16), 7.86 (1H, d, J = 1.8 Hz, H-12); ^{13}C NMR (125 MHz, d_5-pyridine) δ 16.3 (C-28), 16.6 (C-25), 16.7 (C-42), 17.6 (C-26, C-43), 17.8 (C-33), 23.5 (C-27), 25.6 (C-17, C-24, C-32, C-41), 27.09 (C-38), 27.13 (C-21), 28.7 (C-29), 30.7 (C-34), 40.2 (C-20), 40.3 (C-7), 41.7 (C-37), 42.9 (C-6), 46.8 (C-5), 62.6 (C-8), 68.7 (C-4), 115.2 (C-15), 117.0 (C-12), 120.5 (C-2), 121.6 (C-18, C-35), 123.7 (C-30), 124.7 (C-22, C-39) 131.1 (C-11), 132.7 (C-23, C-40), 135.5 (C-31), 136.9 (C-19), 137.3 (C-36), 149.9 (C-13), 152.8 (C-14), 188.5 (C-3), 190.6 (C-1), 195.8 (C-11), 209.0 (C-9); (−)-HRESIMS m/z 669.4159 $[M - H]^-$ (calcd for $C_{43}H_{55}O_6$, 669.4160).

Guttiferone P (2): yellow gum; $[\alpha]^{27}_D$ +18.2 (c 0.33, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 214 (4.62), 238 (4.57), 261 (4.53), 328 (4.13) nm; IR (KBr) ν_{max} 3422, 2964, 2926, 2856, 1733, 1716, 1684, 1655, 1617, 1386, 1294 cm^{-1}; ^{1}H NMR (600 MHz, d_5-pyridine) δ 1.00 (3H, s, H-28), 1.57 (3H, s, H-43), 1.58 (3H, s, H-32), 1.62 (3H, s, H-33), 1.63 (3H, s, H-41), 1.65 (9H, s, H-20, H-26, H-27), 1.79 (1H, dd, J = 13.8, 13.8 Hz, H-7α), 1.80 (3H, s, H-21), 1.82 (3H, s, H-42), 1.92 (1H, ddd, J = 9.6, 9.6, 14.1 Hz, H-29α), 1.98 (2H, t, J = 8.3 Hz, H-22), 2.10 (1H, m, H-37α), 2.19 (1H, m, H-37β), 2.20 (2H, m, H-38), 2.23 (2H, m, H-23), 2.28 (1H, m, H-29β), 2.47 (1H, dd, J = 4.8, 13.8 Hz, H-7β), 2.56 (2H, m, H-6), 2.93 (2H, d, J = 7.1 Hz, H-34), 3.02 (1H, dd, J = 5.1, 14.1 Hz, H-17α), 3.10 (1H, dd, J = 7.1, 14.1 Hz, H-17β), 5.20 (2H, br t, J = 7.2 Hz, H-30, H-39), 5.23 (1H, br t, J = 7.2 Hz, H-24), 5.49 (1H, br t, J = 7.2 Hz, H-18), 5.76 (br t, J = 7.1 Hz, H-35), 7.18 (1H, d, J = 7.8 Hz, H-15), 7.61 (1H, dd, J = 1.8, 7.8 Hz, H-16), 7.86 (1H, d, J = 1.8 Hz, H-12); ^{13}C NMR (125 MHz, d_5-pyridine) δ 16.3 (C-28), 16.9 (C-42), 17.8 (C-43), 18.0 (C-27), 18.2 (C-33), 18.5 (C-21), 24.8 (C-23), 25.8 (C-26, C-41), 25.9 (C-20), 26.2 (C-32), 26.5 (C-17), 27.3 (C-38), 29.8 (C-29), 31.1 (C-34), 36.9 (C-22), 40.8 (C-6, C-37), 41.6 (C-7), 49.5 (C-5), 62.7 (C-8), 69.1 (C-4), 115.5 (C-15), 117.1 (C-12), 121.5 (C-35), 121.6 (C-2), 123.0 (C-18), 123.9 (C-30), 124.3 (C-16), 125.1 (C-39), 125.8 (C-24), 131.1 (C-11), 131.3 (C-40), 131.4 (C-25), 132.4 (C-19), 133.2 (C-31), 137.4 (C-36), 147.1 (C-13), 152.9 (C-14), 187.1 (C-3), 190.6 (C-1), 196.2 (C-10), 209.7 (C-9); (−)-HRESIMS m/z 669.4161 $[M - H]^-$ (calcd for $C_{43}H_{55}O_6$, 669.4160).

MAPKAPK-2 Enzyme Inhibition Assay. MAPKAPK-2 activity was determined using a SPA, which measures ^{33}P incorporation into a synthetic biotinylated peptide substrate (KKLNRTLSVA). The 25 μL assay was performed in 50 mM MOPS (pH 7.0), containing 1 μL of extract, fraction, or compound dissolved in DMSO, 12.5 mM magnesium acetate, 0.25 mM EDTA, 0.0025% Brij 35, 0.05% bovine serum albumin (BSA), 0.125% β-mercaptoethanol, 50 μM ATP (1.0 μCi, ^{33}P), 3.75 μM peptide substrate, and 25 mU of MAPKAPK-2 (activated GST-MAPKAPK-2, specific activity 1590 U/mg) at rt for 40 min. To stop the reaction, 175 μL of stop solution was added. The stop solution was prepared in Ca^{2+}- and Mg^{2+}-free PBS (pH 7.4) that contained 6.67 mM EDTA, 66.7 μM ATP, 0.13% Triton X-100, and 2.7 mg/mL SPA beads. The sample plates were counted using a Wallac Trilus after allowing time for the beads to settle (typically 6 h).

Acknowledgment. We thank AstraZeneca for financial support and Mr. R. Willis (Australia Institute of Marine Science) for obtaining accurate mass measurements.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for guttiferones O and P. This material is available free of charge via the Internet at http://pubs.acs.org.

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NP900246T