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Complex Caged Polyisoprenylated Benzophenone Derivatives, Sampsoniones A and B, from *Hypericum sampsonii*

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Abstract: The aerial parts of the Chinese medicinal plant *Hypericum sampsonii* yielded two novel metabolites, sampsoniones A and B, which are characterised by their unique tetracyclo-polyketonic core with benzoyl, 3-methyl-2-butenyl and geranyl substituents. Their structures were determined by detailed spectral analysis. Sampsonione A exhibited moderate cytotoxicity to P388 cancer cell line.

Keywords: Sampsonione A; Sampsonione B; Polyisoprenylated Benzophenone; *Hypericum sampsonii*; Guttiferae

Hypericum sampsonii (Guttiferae) is a Chinese herbal medicine used in the treatment of numerous disorders such as backache, burns, diarrhoea, snakebites,swellings etc.[1] In the course of a search for biologically active compounds from medicinal plants, we have examined the dichloromethane extract of the aerial parts of this plant and succeeded in isolating two novel constituents named sampsoniones A and B. The UV, IR, MS, and NMR spectral data indicated that they are penta-isoprenylated benzophenone derivatives with a novel 5-oxatetracyclo$[7.3.1.0^{3,7}.0^{4,11}]$tridecane-2,12-dione skeleton.

Sampsonione A **1** (120 mg, 0.0024%) was isolated as an optically active colorless oil, $[\alpha]_D^{34.6}$ –49.10 (*c*, 0.37, $CHCl_3$), with the following spectral characteristics: IR (film) ν_{max} 3591(OH), 3409, 1724(unconjugated carbonyl), 1688(conjugated carbonyl) cm^{-1}; UV (MeOH) λ_{max} (log ε) 322 (2.90), 274 (3.42), 240 (4.06), 214 (3.82) nm; ^{1}H and ^{13}C NMR, Table 1.

The molecular formula, HRMS $[M]^+$ 586.36642, calcd. for $C_{38}H_{50}O_5$, 586.36584, and evidence from the IR, NMR (Table 1) and mass spectrum (m/z 77 $C_6H_5^+$, base peak at m/z 105 $C_6H_5CO^+$) for an unsubstituted phenyl ketone, indicated that sampsonione A is a benzophenone derivative incorporating five five-carbon units. It was also apparent that the tetra-oxygenated ring is non-aromatic, with two ketones and one hemiketal tetrasubstituted at all α positions. These conclusions are based on ^{13}C NMR signals for two nonconjugated carbonyls (δ 209.1 and 207.0 ppm), one hemiketal carbon (δ 110.3 ppm), and the absence of a ^{1}H NMR peak (even in a spectral window of 20 ppm) attributable to a hydrogen-bonded enolic proton, a common feature in these systems.[2] In addition to the phenyl ketone, other readily identifiable pendant residues were: (a) the gem-dimethyl group (C_{26} and C_{27}) correlating by HMBC to each other and to C_6 on the main skeleton; (b) the gem-dimethyl group (C_{38} and C_{39}) correlating by HMBC to each

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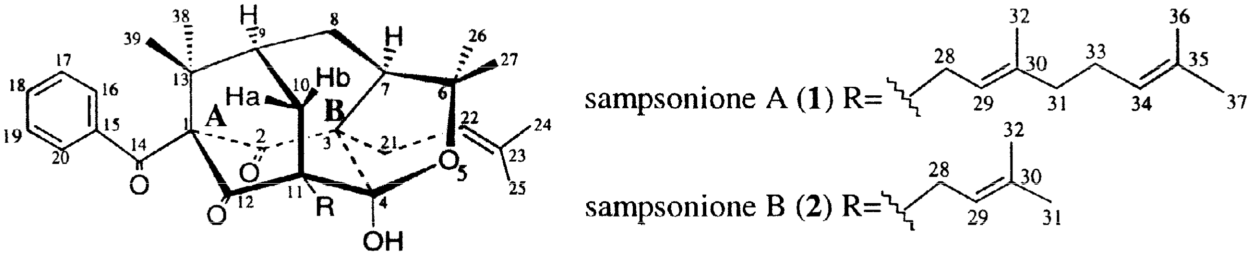
other and to C_{13} on the main skeleton; (c) a geranyl side chain (C_{28} to C_{37}) linked to the basic skeleton at a quaternary position; (d) a 3-methyl-2-butenyl side chain (C_{21} to C_{25}) linked to the basic skeleton at a quaternary position.



sampsonione A (**1**) R=

sampsonione B (**2**) R=

The structure of tetracyclic core of the molecule was determined by tracing the connectivities shown in the HMBC spectrum. Starting with the gem-dimethyl at C_{13}, cross peaks were observed between protons of both methyls groups and: (i) the quaternary carbon signal at δ 81.8 (C_1) which, from its deshielded position, had to be flanked by three carbonyl groups (shown as C_2, C_{12}, and C_{14}); (ii) the methine carbon at δ 43.5 (C_9). Moreover, one of the C_{10} methylene protons at δ 2.27 was correlated with the quaternary carbon signal at δ 48.0 (C_{13}), and the other of the C_{10} methylene protons at δ 2.25 was correlated with the carbonyl carbon at δ 209.1 (C_{12}), as well as the hemiketal carbon at δ 110.3 (C_4), and the quaternary carbon at δ 59.1 (C_{11}), Therefore, carbons 1, 12, 11, 10, 9 and 13 formed the six-membered ring A.

The seven-membered ring B comprising carbons 1, 13, 9, 8, 7, 3 and 2 was established from the HMBC cross peaks between: i) the quaternary carbon bearing the gem-dimethyl group, C_{13} (δ 48.0), and one of the C_8 methylene protons at δ 1.98; ii) the C_7 methine proton at δ 2.59 and the quaternary carbon signal at δ 64.6 (C_3), as well as the hemiketal carbon at δ 110.3 (C_4), the methylene carbon at δ 25.7 (C_8), and the methine carbon at δ 43.5 (C_9).

The protons of both methyls at C_6 showed distinct correlations with C_6 (δ 84.1) and C_7 (δ 46.5), therefore the linkage $C_4/C_3/C_7/C_6$ should be present. The chemical shift of C_6 carbon (δ 84.1) indicated it was an oxygen-bearing quaternary carbon. So the last ring of the tetracyclic core is a furan ring, comprising carbons 4, 3, 7, 6 and one oxygen 5.

The ^1H-^1H COSY spectrum, which showed correlations between H-10 (δ 2.27 and 2.25) and H-9 (δ 1.70); H-9 and H-8 (δ 1.98 and 1.96); H-8 and H-7 (δ 2.59), indicated that the four protonated carbons in the core of sampsonione A are contiguous.

The C_{28} methylene protons showed heteronuclear correlation to C_{12} (δ 209.1), C_{11} (δ 59.1), C_4 (δ 110.3) and C_{10} (δ 33.5) and NOE interactions with C_{32} methyls, while the C_{29} olefinic proton correlated with C_{31} and showed NOE enhancements with the C_{31} methylene protons. This allowed assignment of a geranyl moiety at C_{11} and revealed that the geometry of the C_{29}-C_{30} olefin was *E*. HMBC correlations observed between the C_{21} methylene protons and C_4 (δ 110.3), C_3 (δ 64.6), and C_2 (δ 207.0) established that the 3-methyl-2-butenyl moiety was located at C_3.

Molecular models disclosed that, by its formation, the tetracyclic system itself sets up the relative configurations at the chiral centres C_1, C_3, C_4, C_7, C_9 and C_{11}, which were confirmed by the 2 D NOESY spectrum.

Table 1: NMR data for sampsoniones A (**1**) and B (**2**).

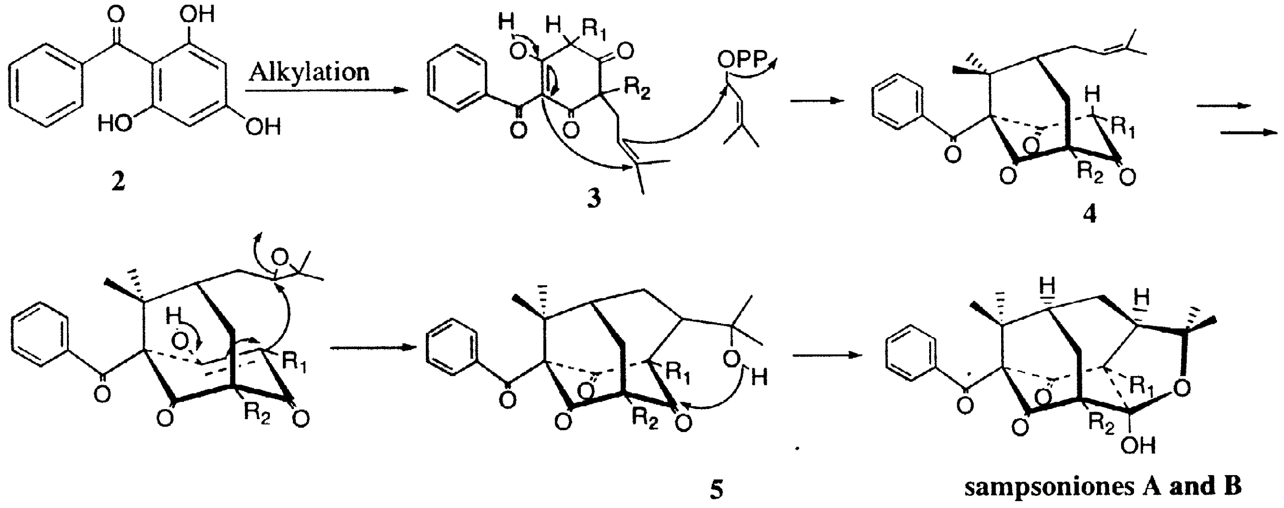
	sampsonione A (**1**)				sampsonione B (**2**)	
Position	^{1}H[a]	^{13}C[b]	HMBC[c]	NOESY	^{1}H[a]	^{13}C[b]
1		81.8				81.8
2		207.0				206.9
3		64.6				64.5
4		110.3				110.3
6		84.1				84.1
7	α 2.59 dd (6.4, 2.5)	46.5	3, 4, 8, 9, 21, 26	8α, 22, 26, 27	α 2.59 dd (6.2, 2.6)	46.6
8	α 1.98 m	25.7	6, 7, 9, 10, 13	7α, 9, 38	α 1.98 m	25.8
	β 1.96 m		3, 6, 7, 9, 13	7α, 9, 27	β 1.96 m	
9	1.70 m	43.5	8, 10, 13, 38, 39	8α, 8β, 10a, 10b, 38, 39	1.70 m	43.5
10	a 2.25 m	33.5	4, 8, 9,11, 12, 13	9, 39	a 2.27 dd (16.1, 2.9)	33.5
	b 2.27 m			9, 27, 28	b 2.29 dd (16.0, 6.1)	
11		59.1				59.0
12		209.1				209.0
13		48.0				48.0
14		194.2				194.2
15		136.0				136.0
16	7.61 d (7.3)	128.9	14, 18, 20	4-OH, 17, 21	7.60 d (7.2)	128.9
17	7.31 t (7.7)	127.9	15, 18, 19	16, 18	7.33 t (7.6)	127.9
18	7.39 t (7.3)	131.8	16, 119, 20	17, 19	7.39 t (7.2)	131.8
19	7.31 t (7.7)	127.9	15, 17, 18	18, 20	7.33 t (7.6)	127.9
20	7.61 d (7.3)	128.9	14, 16, 18	4-OH, 19, 21	7.60 d (7.2)	128.9
21	a 2.84 dd (16.8, 8.0)	33.7	2, 3, 4, 22, 23	21b, 22, 25	a 2.84 dd (16.7, 7.4)	33.6
	b 2.50 dd (16.7, 7.7)		3, 22, 23	21a, 22, 25	b 2.50 dd (16.7, 6.8)	
22	5.53 m	121.2	21, 24, 25	7α, 21, 24, 26	5.50 m	121.1
23		133.0				133.1
24	1.68 s	26.1	22, 23, 25	22, 25	1.67 s	26.0
25	1.44 s	17.8	22, 23, 24	21, 24	1.45 s	17.8
26	1.44 s	32.0	6, 7, 27	7α, 21, 27	1.46 s	32.1
27	1.47 s	28.0	6, 7, 26	8β, 10b, 26	1.45 s	28.0
28	a 2.69 dd (14.2, 7.4)	28.7	10, 11, 12, 29, 30	4-OH, 10, 28b, 29, 32	a 2.68 dd (14.7, 7.9)	28.8
	b 2.44 dd (14.1, 7.8)		4, 10, 11, 12, 29, 30	10, 28a, 29, 32	b 2.43 dd (14.8, 8.0)	
29	5.54 m	120.3	28, 30, 31, 32	4-OH, 10, 28b, 28b, 31	5.52 m	120.3
30		139.0				135.5
31	2.05 m	39.9	29, 30, 33	29, 32, 33	1.74 s	26.0
32	1.69 s	16.0	29, 30, 31	28, 31	1.70 s	17.8
33	2.07 m	26.4	31, 34, 35	31, 34, 36		
34	5.07 t (6.8)	123.9	35, 36, 37	33, 37		
35		131.6				
36	1.59 s	17.6	34, 35, 37	33, 37		
37	1.68 s	25.8	34, 35, 36	34, 36		
38	1.22 s	22.3	1, 9, 13, 39	6α, 9, 39	1.22 s	22.3
39	1.39 s	24.9	1, 9, 13, 38	9, 10α, 38	1.39 s	24.9
4-OH	3.84 s			16, 20, 21, 28, 29, 36	3.84 s	

[a] Recorded in $CDCl_3$ at 300 MHz. [b] Recorded in $CDCl_3$ at 75 MHz. [c] Carbons that correlate with the proton resonance.

The other minor constituent, sampsonione B[3] (**2**) (1.3 mg, 0.000026%), HRMS $[M]^+$ 518.30131, calcd. for $C_{33}H_{42}O_5$, 518.30322, had UV and IR spectral features similar to those of **1**. A comparison of the ^{1}H and ^{13}C NMR spectra of **2** and those of **1** revealed that the only difference was in the side chain at C_{11}, the geranyl group in **1** replaced by the 3-methyl-2-butenyl in **2**. Its structure was confirmed by its ^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY spectra.

Sampsoniones A and B are the first pair of polyprenylated benzophenone derivatives[2, 4-9] possessing a novel rigid 5-oxatetracyclo[7.3.1.0^{3,7}.0^{4,11}]tridecane-2,12-dione skeleton. They are presumably biosynthesized from the biogenetically acceptable 2,4,6-trihydroxybenzophenone **2**.

C-alkylation of **2** by geranyl pyrophosphate and 3,3-dimethylallyl pyrophosphate yields the intermediate **3**, which in turn could react with one more prenyl group as indicated leading to a bicyclo[3.3.1]nonanetrione **4**, that subsequently epoxidizes and intramolecularly cyclizes to form a tricyclo[4.3.1.1]undecanetrione **5**. In this ring system the carbonyl carbon on the bridge and the hydroxyl group are close to each other, thereby leading to a favourable relationship for hemiketal formation to the oxatetracyclo-system (Figure 1).



sampsonione A (**1**) R_1=3-methyl-2-butenyl, R_2=geranyl
sampsonione B (**2**) R_1=3-methyl-2-butenyl, R_2=3-methyl-2-butenyl

Figure 1. Possible biosynthesis pathway of sampsoniones A and B

Sampsonione A has been tested for its cytotoxicity on P388 cell line, where it was found to be active with an ED_{50} of 13 ug/mL.

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[3] Sampsonione B (2): colourless oil; $[\alpha]_D^{31.2}$ -57.69 (*c*, 0.026, $CHCl_3$); IR (film) ν_{max} 3408 (OH), 1719 (unconjugated carbonyl), 1684 (conjugated carbonyl) cm^{-1}; UV (MeOH) λ_{max} (log ε) 320 (2.94), 276 (3.44), 244 (4.08), 214 (3.99) nm.

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