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Amphimedonoic acid and psammaplysene E, novel brominated alkaloids from *Amphimedon* sp.

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ABSTRACT

Examination of the CH_2Cl_2-MeOH (1:1) extract from the Madagascan sponge *Amphimedon* sp. highlighted two new brominated alkaloids, amphimedonoic acid (**1**) and psammaplysene E (**2**), along with the known 3,5-dibromo-4-methoxybenzoic acid (**3**). Their structures were elucidated by 1D and 2D NMR spectroscopy and HRESIMS data.

Marine sponges have been reported as a major source of bioactive secondary metabolites with a wide variety of unusual structures.[1] The genus *Amphimedon* has been known to produce various potent bioactive compounds, especially alkaloids with unique structures.[2–4] As part of our continued search for structurally unique metabolites from marine invertebrates,[5–7] the sponge *Amphimedon* sp., collected from the Mitsio Islands, Madagascar, was investigated. These investigations afforded two new brominated alkaloids, amphimedonoic acid (**1**) and psammaplysene E (**2**), along with the known 3,5-dibromo-4-methoxybenzoic acid (**3**).[8,9] Herein, the isolation and structure elucidation of **1**–**3** are described.

The sponge *Amphimedon* sp. (36.2 g, wet weight) collected off the Mitsio Islands, Madagascar, was extracted with CH_2Cl_2/MeOH (1:1). The crude extract (1.5 g) was subjected to MPLC over silica gel and separated into ten fractions (F1-F10) using a combination of isohexane, EtOAc and MeOH of increasing polarity. F9 (15 mg) was subjected to a subsequent reversed phase semi-preparative HPLC separation to yield pure compound **2** (0.7 mg). F10 (32 mg) was subjected to a reversed phase semi-preparative HPLC separation and led to the isolation of pure compounds **1** (2.8 mg), **2** (1.3 mg) and **3** (1.0 mg) (Fig. 1).

Amphimedonoic acid (**1**) was obtained as a colorless oil. The high resolution electrospray mass spectrum exhibited a molecular ion $[M+H]^+$ as a cluster of peaks *m/z* 302.0388/304.0388 in a 1:1 ratio, an isotope pattern characteristic of a brominated compound. Accordingly, based on HRESIMS, the molecular formula $C_{12}H_{16}BrNO_3$ (calcd for $C_{12}H_{17}{}^{79}BrNO_3^+$, 302.0386), with five degrees of unsaturation, was determined. The ^1H and ^{13}C NMR data displayed resonances and correlations for one carboxylic acid group, one 1,2,4-trisubstituted aromatic ring, three methylenes, one of which was oxygenated and two *N*-methyl groups (Table 1). The benzoic acid moiety was suggested by HMBC correlations from H-3 (δ_H 8.10) to C-1 (δ_C 172.6), C-4 (δ_C 111.7), C-5 (δ_C 157.6), C-7 (δ_C 131.1), from H-6 (δ_H 6.97) to C-2 (δ_C 132.2), C-4, C-5 and from H-7 (δ_H 7.83) to C-3 (δ_C 135.3) and C-5 (Fig. 2). The chemical shift (δ_C 111.7) of the quaternary carbon C-4 placed the bromine substituent at C-4. The substitution of C-5 was suggested by its chemical shift (δ_C 157.6) and also by the HMBC correlation from H-8 (δ_H 4.21) to C-5. Interpretation of the ^1H–^1H COSY correlations between H-8, H-9 and H10, revealed the propyl spin system C-8–C-9–C-10. The substitution of the amine moiety was determined by HMBC correlations from H-10 (δ_H 3.21) to C-11, C-12 (δ_C 43.9) and from H-11, H-12 (δ_H 2.81) to C-10 (δ_C 56.7), C-11 and C-12 (Fig. 2).

Psammaplysene E (**2**) was obtained as a colorless oil. The high resolution electrospray mass spectrum showed four isotopic peaks

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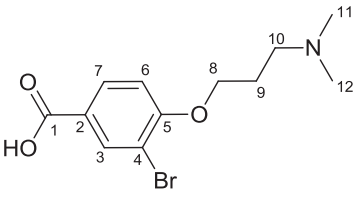
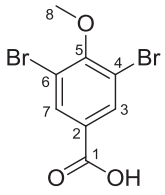
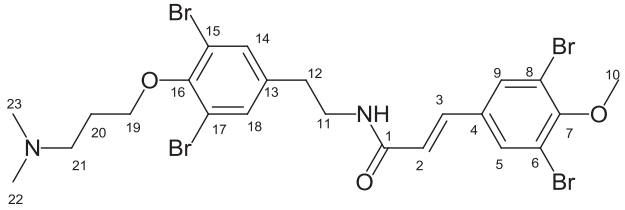


amphimedonoic acid (**1**)



3,5-dibromo-4-methoxybenzoic acid (**3**)



psammaplysene E (**2**)

Fig. 1. Structures of isolated compounds **1**–**3**.

Table 1
^{1}H and ^{13}C NMR data for amphimedonoic acid (**1**), psammaplysene E (**2**) and 3,5-dibromo-4-methoxybenzoic acid (**3**) (^{1}H 500 MHz, ^{13}C 125 MHz, CD_3OD).

Position	**1**		**2**		**3**	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	172.6	–	167.6	–	171.0	–
2	132.2	–	123.6	6.52 (1H, d, 15.7)	–	–
3	135.3	8.10 (1H, d, 1.9)	138.1	7.37 (1H, d, 15.7)	134.7	8.12 (1H, s)
4	111.7	–	135.1	–	118.0	–
5	157.6	–	132.8	7.79 (1H, s)	156.6	–
6	112.9	6.97 (1H, d, 8.5)	119.3	–	118.0	–
7	131.1	7.83 (1H, dd, 8.6, 2.0)	156.1	–	134.7	8.12 (1H, s)
8	67.2	4.21 (2H, t, 5.7)	119.3	–	60.8	3.87 (3H, s)
9	25.9	2.23 (2H, m)	132.8	7.79 (1H, s)	–	–
10	56.7	3.21 (2H, t, 7.4)	60.9	3.88 (3H, s)	–	–
11	43.9	2.81 (3H, s)	41.5	3.51 (2H, t, 7.1)	–	–
12	43.9	2.81 (3H, s)	34.9	2.82 (2H, t, 7.0)	–	–
13	–	–	139.9	–	–	–
14	–	–	134.2	7.50 (1H, s)	–	–
15	–	–	118.7	–	–	–
16	–	–	152.3	–	–	–
17	–	–	118.7	–	–	–
18	–	–	134.2	7.50 (1H, s)	–	–
19	–	–	71.6	4.07 (2H, t, 5.8)	–	–
20	–	–	27.4	2.15 (2H, m)	–	–
21	–	–	57.1	3.07 (2H, t, 7.3)	–	–
22	–	–	44.3	2.63 (3H, s)	–	–
23	–	–	44.3	2.63 (3H, s)	–	–

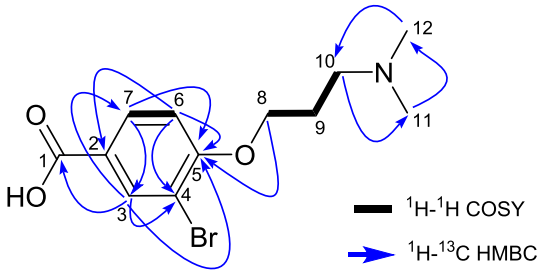


Fig. 2. Key ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMBC correlations for **1**.

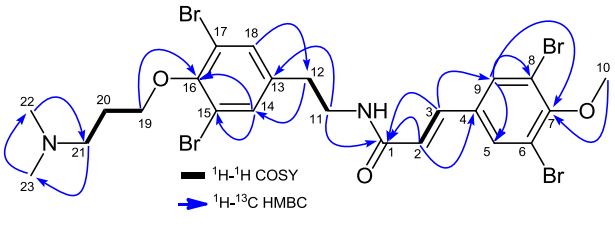


Fig. 3. Key ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMBC correlations for **2**.

at m/z 694.8758, 696.8740, 698.8723, 700.8702, 702.8691 $[M+H]^+$ in a 1:4:6:4:1 ratio, respectively, indicating the presence of two bromine atoms in the molecule. The HRESIMS allowed assignment of the molecular formula as $C_{23}H_{27}Br_4N_2O_3^+$ (calcd for $C_{23}H_{27}{}^{79}Br_4N_2O_3^+$, 694.8750) requiring ten degrees of unsaturation. The ^{1}H and ^{13}C NMR data of **2** displayed the resonances of a *trans*-α,β-unsaturated carbonyl group, two symmetrical 1,2,4,6-tetrasubstituted aromatic rings, five methylenes, one of which was oxygenated, two *N*-methyl groups and one *O*-methyl group (Table 1).