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Nagelamide J, a Novel Dimeric Bromopyrrole Alkaloid from a Sponge *Agelas* Species

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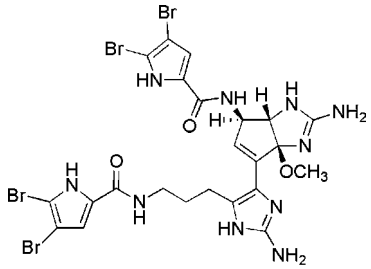
ABSTRACT



nagelamide J (1)

A novel dimeric bromopyrrole alkaloid, nagelamide J (1), with antimicrobial activity has been isolated from an Okinawan marine sponge *Agelas* species, and the structure and stereochemistry were elucidated from spectroscopic data. Nagelamide J (1) is the first bromopyrrole alkaloid possessing a cyclopentane ring fused to an amino imidazole ring.

Bromopyrrole alkaloids are known to be one of the common metabolites from marine sponges of several genera. During our search for bioactive substances from marine organisms,[1] we have isolated some bromopyrrole alkaloids with unique cyclic skeletons from sponges of the genus *Agelas* or *Hymeniacidon*.[2] Recently, we investigated extracts of an Okinawan marine sponge *Agelas* sp. (SS-1077) and isolated a novel dimeric bromopyrrole alkaloid, nagelamide J (**1**).[3] Nagelamide J (**1**) is the first bromopyrrole alkaloid possessing a cyclopentane ring fused to an amino imidazole ring. Here we describe the isolation and structure elucidation of **1**.

The sponge *Agelas* sp. (SS-1077) collected off Unten-Port, Okinawa, was extracted with MeOH. EtOAc-soluble materials of the extract were subjected to silica gel and C_{18} column chromatographies followed by C_{18} HPLC to yield nagelamide J (**1**, 0.0011% wet weight) as a colorless amorphous solid together with known related alkaloids, longamide A,[4] tauroacidin A,[5] taurodispacamide A,[6] mauritiamine,[7] and nagelamides B, C, and H.[8]

The ESIMS spectrum of nagelamide J (**1**) showed the pseudomolecular ion peaks at *m*/*z* 805, 807, 809, 811, and 813 (1:4:6:4:1), indicating the presence of four bromine atoms, and the molecular formula of **1** was revealed to be

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(3) Nagelamide J (**1**): colorless amorphous solid; $[\alpha]^{20}_{D}$ −19 (*c* 0.2, MeOH); UV (MeOH) λ_{max} 216 nm (ϵ 32 000) and 279 nm (18 000); IR (KBr) ν_{max} 3420, 1680, and 1640 cm^{-1}; ESIMS (pos.) *m*/*z* 805, 807, 809, 811, and 813 [1:4:6:4:1, $(M + H)^+$]; HRESIMS (pos.) *m*/*z* 808.8799 [$(M + H)^+$, calcd for $C_{23}H_{25}N_{10}O_3{}^{79}Br_2{}^{81}Br_2$, 808.8803].
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$C_{23}H_{25}N_{10}O_3Br_4$ by HRESIMS data [*m*/*z* 808.8799 $(M + H)^+$, Δ −0.4 mmu]. The UV absorption [λ_{max} = 279 nm (ϵ 18 000)] was attributed to a substituted pyrrole chromophore,[9] while IR absorptions indicated the existence of OH and/or NH (3420 cm^{-1}) and amide carbonyl (1680 cm^{-1}) functionalities. The ^{13}C NMR (Table 1) spectrum disclosed 23 signals

Table 1. ^1H and ^{13}C NMR Data of Nagelamide J (**1**) in DMSO-d_6

position	δ_H	δ_C
1	12.75 (br s)	
2		105.3
3		98.0
4	7.02 (s)	113.6
5		127.4
6		158.6
7	8.68 (d, 7.0)	
8	4.82 (m)	60.3
9	6.08 (d, 2.2)	130.9
10		137.4
11		103.5
11-OMe	3.26[b] (s)	49.8
12	9.71 (br s)	
13		157.2
13-NH_2	8.02[a] (br s)	
14	9.18 (br s)	
15	4.31 (br s)	66.8
1′	12.65 (br s)	
2′		104.5
3′		97.8
4′	6.89 (s)	112.5
5′		128.1
6′		158.9
7′	8.20 (t, 5.6)	
8′	3.21[a] (m)	38.9
9′	1.73[a] (m)	28.8
10′	2.58[a] (m)	21.9
11′		126.7
12′	11.50 (br s)	
13′		146.9
13′-NH_2	7.43[a] (br s)	
14′	12.62 (br s)	
15′		113.9

[a] 2H. [b] 3H.

due to 13 sp^2 quaternary carbons (δ_C 158.9, 158.6, 157.2, 146.9, 137.4, 128.1, 127.4, 126.7, 113.9, 105.3, 104.5, 98.0, and 97.8), one sp^3 quaternary carbon (δ_C 103.5), three sp^2 methines (δ_C 130.9, 113.6, and 112.5), two sp^3 methines (δ_C 66.8 and 60.3), three sp^3 methylenes (δ_C 38.9, 28.8, and 21.9), and a methoxy carbon (δ_C 49.8). The ^1H NMR (Table 1) spectrum included ten D_2O-exchangeable signals [δ_H 12.75, 12.65, 12.62, 11.50, 9.71, 9.18, 8.68, 8.20, 8.02 (2H), and 7.43 (2H)] attributable to amino and/or amide protons. Comparison of the NMR data for **1** with those of known bromopyrrole alkaloids such as nagelamide C[8] indicated the presence of two 2,3-dibromopyrrole carbonyl moieties (N-1−C-6 and N-1′−C-6′) and a 4,5-disubstituted 2-aminoimidazole ring (C-11′−C-15′).

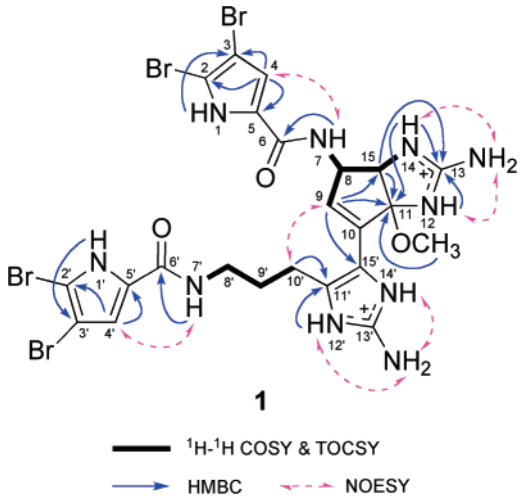

Figure 1. Selected 2D correlations for nagelamide J (**1**).

Detailed analyses of the $^1H-^1H$ COSY, TOCSY, and HMQC spectra disclosed connectivities from NH-7 to C-9 and NH-14 and from NH-7′ to C-10′. The HMBC spectrum showed correlations for NH-7 (δ_H 8.68)/C-6 (δ_C 158.6) and NH-7′ (δ_H 8.20)/C-6′ (δ_C 158.9), indicating that two 2,3-dibromopyrrole moieties were attached to NH-7 and NH-7′ through an amide bond. The connection of a 4,5-disubstituted 2-aminoimidazole ring (C-11′-C-15′) to C-10′ was deduced

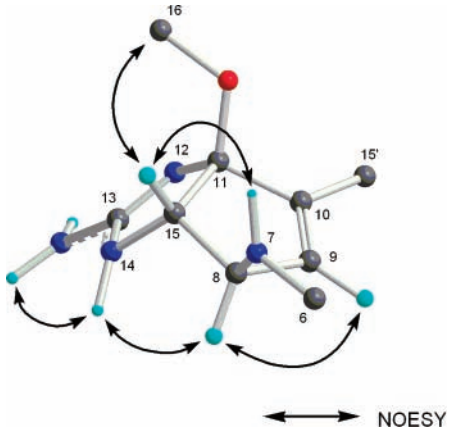

Figure 2. Selected NOESY correlations and relative stereochemistry for bicyclic moiety in nagelamide J (**1**).

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from HMBC correlations for H_2-10′ (δ_H 2.58)/C-11′ (δ_C 126.7) and NH-12′ (δ_H 11.5)/C-11′. The existence of a 4,4,5-trisubsituted 2-amino-4,5-dihydroimidazole ring was deduced from HMBC correlations for NH-12 (δ_H 9.71)/C-13 (δ_C 157.2), NH-14 (δ_H 9.18)/ C-11 (δ_C 103.5), NH-14/C-13, H-15 (δ_H 4.31)/C-11, and H-15/C-13. Since a methoxy proton signal (δ_H 3.26) showed a correlation to C-11 in the HMBC spectrum and the chemical shift for C-11 was observed at a relatively lower field, C-11 was suggested to connect to an oxygen (11-O) and a nitrogen (N-12) atoms. HMBC correlations for H-9 (δ_H 6.08) to C-11 and C-15′ (δ_C 113.9) in the 4,5-disubstituted 2-aminoimidazole ring indicated that C-9 was attached to C-11 and C-15′ through a remaining sp^2 quaternary carbon C-10 (δ_C 137.4). Thus, the gross structure of nagelamide J was assigned as **1**, possessing a cyclopentane ring fused to an amino imidazole ring at C-11 and C-15.

The relative stereochemistry of the cyclopentane ring fused to the amino imidazole ring at C-11 and C-15 in **1** was deduced from detailed analysis of NOESY data as follows. The NOESY correlation for NH-7/H-15 suggested an *anti* relation for H-8 and H-15. The NOESY spectrum showed a correlation for 11-OCH_3/H-15, suggesting a *syn* relation for the ring junction at C-11 and C-15.

Nagelamide J (**1**) is a novel dimeric bromopyrrole alkaloid with a connection between C-10 and C-15′ of each monomer unit (C-1∼C-15/C-1′∼C-15′). To the best of our knowledge, **1** is the first bromopyrrole alkaloid possessing a cyclopentane ring fused to an amino imidazole ring. Biogenetically, nagelamide J (**1**) might be generated from nagelamide A type alkaloid[8] by a bond formation between C-8 and C-15. Nagelamide J (**1**) exhibited antimicrobial activity against *Staphylococcus aureus* (MIC, 8.35 μg/mL) and *Cryptococcus neoformans* (MIC, 16.7 μg/mL).

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Supporting Information Available: One- and two-dimensional NMR spectra for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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