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Nagelamides M and N, new bromopyrrole alkaloids from sponge *Agelas* species

Takaaki Kubota [a], Atsushi Araki [a], Junji Ito [b], Yuzuru Mikami [b], Jane Fromont [c], Jun'ichi Kobayashi [a,*]

[a] *Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan*
[b] *Medical Mycology Research Center, Chiba University, Chiba 260-0856, Japan*
[c] *Western Australian Museum, Locked Bag 49, Welshpool DC, WA 6986, Australia*

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ABSTRACT

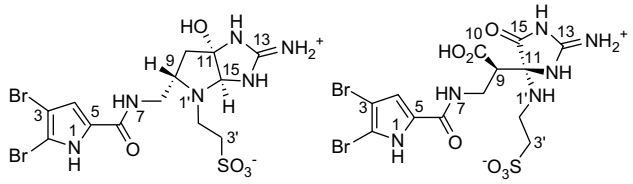
Two new bromopyrrole alkaloids, nagelamides M (**1**) and N (**2**), have been isolated from an Okinawan marine sponge *Agelas* species, and the structures and stereochemistry were elucidated from the spectroscopic data. Nagelamide M (**1**) is a novel bromopyrrole alkaloid possessing a 2-amino-octahydropyrrolo[2,3-*d*]imidazole ring with a taurine unit, while nagelamide N (**2**) is a new bromopyrrole alkaloid possessing a 2-amino-tetrahydroimidazole-4-one ring with a taurine unit and 3-(dibromopyrrole-2-carboxamido)propanoic acid moiety. Nagelamides M (**1**) and N (**2**) exhibited antimicrobial activity.

1. Introduction

Bromopyrrole alkaloids are known to be one of the most common metabolites contained in marine sponges.[1] During our search for bioactive substances from marine organisms, we previously isolated several bromopyrrole alkaloids with unique cyclic skeletons from sponges of *Agelas* or *Hymeniacidon* sp.[2] More recently, two new bromopyrrole alkaloids, nagelamides M (**1**) and N (**2**), have been isolated from an Okinawan marine sponge *Agelas* sp. (SS-1134). Here we describe the isolation and structure elucidation of **1** and **2**.

2. Results and discussion

The sponge *Agelas* sp. (SS-1134) collected off Seragaki beach, Okinawa, was extracted with MeOH. BuOH-soluble materials of the extract were subjected to silica gel and C_{18} column chromatographies followed by C_{18} HPLC to yield nagelamides M (**1**, 0.00069%, wet weight) and N (**2**, 0.0016%) together with known related alkaloids, tauroacidin A,[3] taurodispacamide A,[4] and nagelamides C[5] and K.[2]



1 **2**

The ESIMS spectrum of nagelamide M (**1**) showed the pseudomolecular ion peaks at *m*/*z* 527, 529, and 531 (1:2:1), indicating the presence of two bromine atoms, and the molecular formula of **1** was revealed to be $C_{13}H_{18}N_6O_5Br_2S_1$ by HRESIMS data [*m*/*z* 526.9340 $(M-H)^-$, Δ −0.8 mmu]. The UV absorption [λ_{max} 275 nm (ε 18,000)] was attributed to a pyrrole chromophore,[6] while the IR absorption (1684 cm^{-1}) indicated the existence of amide carbonyl functionality.

The ^1H NMR (Table 1) spectrum included five D_2O-exchangeable signals (δ_H 12.65, 9.02, 8.64, 8.30, and 7.95) attributed to amino and/or amide protons. The ^{13}C NMR (Table 1) spectrum disclosed 13 signals due to one amide carbonyl carbon, four sp^2 quaternary carbons, one sp^2 methine, one sp^3 quaternary carbon, two sp^3 methine, and four sp^3 methylenes. Among the ^{13}C signals of **1**, one amide carbonyl (159.10), three sp^2 quaternary carbons (127.98, 104.41, and 97.91), and one sp^2 methine (δ_C 113.29) were ascribed to a 2,3-dibromopyrrole carbonyl moiety (N-1–C-6) by comparison with those of known bromopyrrole alkaloids,[2] while one sp^3 quaternary carbon (δ_C 94.36) and one sp^3 methine (δ_C 81.26) were assigned as those bearing two hetero atoms such as oxygen and nitrogen atoms.

Detailed analyses of the ^1H–^1H COSY and HMQC spectra disclosed three structural fragments, N-7 to C-10, C-2′ to C-3′, and N-14 to C-15. The presence of a 2,3-dibromopyrrole moiety was suggested by HMBC cross-peaks of NH-1 to C-3 and C-4, and H-4 to C-2 and C-5 (Fig. 1). The NOESY correlation for NH-7/H-4 indicated that the 2,3-dibromopyrrole moiety was attached to N-7 through an amide bond. The presence of a 2-amino-octahydropyrrolo[2,3-*d*]imidazole ring was deduced from analysis of the HMBC spectrum of **1**. Connections among C-10, N-12, and C-15 via C-11 were implied by HMBC cross-peaks for H_2-10 and H-15 to C-11, and NH-12 to C-15. HMBC correlations for NH-12, NH-14, and H-15 to C-13, and

* Corresponding author. Tel.: +81 11 706 3239; fax: +81 11 706 4989.
E-mail address: jkobay@pharm.hokudai.ac.jp (J. Kobayashi).

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Table 1
^{1}H and ^{13}C NMR data of nagelamide M (**1**) in DMSO-d_6

Position	δ_H		δ_C
1	12.65	brs	—
2	—		104.41
3	—		97.91
4	7.02	brs	113.29
5	—		127.98
6	—		159.10
7	8.30	brdd 7.7, 4.2	—
8a	3.67	m	37.40
8b	3.18	m	—
9	2.94	m	59.50
10a	2.11	dd 12.1, 4.7	40.67
10b	1.77	brt 11.5	
11	—		94.36
12	9.02	brs	—
13	—		157.54
13-NH_2	7.95 (2H)	brs	—
14	8.64	brs	—
15	4.93	brs	81.26
2′a	3.16	m	48.34
2′b	2.86	m	—
3′a	2.82	m	40.78
3′b	2.72	m	

NH-12 to C-15 indicated the connection of N-12 and N-14 via C-13. The connectivity of C-9 and C-15 through N-1′ was implied by the HMBC cross-peak of H-15 to C-9, while HMBC correlations for NH-14 to C-11 indicated the connection of C-11 and N-14 via C-15. In addition, NOESY correlations for H_2-8/H-2′ and H-15/H_2-2′ suggested that a taurine unit was attached to N-1′. Thus, the gross structure of nagelamide M was elucidated to be **1**.

Relative stereochemistry of the bicyclic system in **1** was deduced from *J*-values and NOESY correlations as shown in Figure 2. The NOESY correlation for H-10b/H-15 indicated that H-10b and H-15 was α-oriented, while NOESY cross-peaks of H-9/H-10a, and H-10a/NH-12 suggested that these hydrogen atoms were β-oriented. The cis ring junction of the bicyclic ring system and an α-orientation of 11-OH were implied by data described above.

The ESIMS spectrum of nagelamide N (**2**) showed the pseudomolecular ion peaks at *m*/*z* 557, 559, and 561 (1:2:1), suggesting the presence of two bromine atoms. The molecular formula of **2** was revealed to be $C_{13}H_{15}N_6O_7Br_2S_1$ from HRESIMS data [*m*/*z* 556.9105 $(M-H)^-$, Δ +1.5 mmu]. The UV absorption [λ_{max} 275 nm (ε 10,000)] indicated the presence of pyrrole chromophore, while IR absorptions (3388, 1700, and 1678 cm^{-1}) suggested the existence of hydroxyl and carbonyl functionalities.

The ^{1}H NMR (Table 2) spectrum included six D_2O-exchangeable signals (δ_H 12.75, 9.84, 9.15, 9.07, 8.31, and 7.92) attributed to amino and/or amide protons. The ^{13}C NMR (Table 2) spectrum disclosed 13 signals due to seven sp^2 quaternary carbons, one sp^2 methine, one sp^3 methine, one sp^3 quaternary carbon, and three sp^3 methylenes.

Inspection of the ^{1}H–^{1}H COSY and HMQC spectra of **2** revealed two structural fragments, N-7 to C-9 and N-1′ to C-3′. The presence

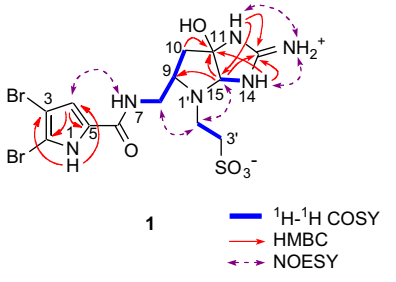

Figure 1. Selected 2D NMR correlations for nagelamide M (**1**).

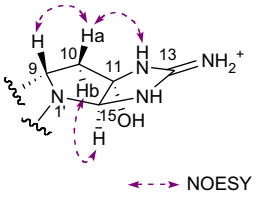

Figure 2. Selected NOESY correlations and relative stereochemistry for the bicyclic core in nagelamide M (**1**).

of 2,3-dibromopyrrole moiety was suggested by HMBC cross-peaks of NH-1 to C-3 and C-4, and H-4 to C-2 and C-5. The ROESY correlation for NH-7/H-4 indicated that the 2,3-dibromopyrrole moiety was attached to NH-7 through an amide bond. The HMBC correlation for H-9 to C-10 indicated that a carboxy group was attached to C-9. The presence of an aminoimidazole ring was deduced from HMBC correlations for NH-12 to C-11, C-13, and NH-12 and NH-14 to C-15, and ROESY cross-peaks for 13-NH_2/NH-12 and NH-14. The HMBC correlation for H-9 to C-11 and the ROESY cross-peak of NH-1′/H-9 revealed that both C-9 and NH-1′ were attached to C-11. Thus, the gross structure of nagelamide N was assigned as **2** (Fig. 3).

The relative stereochemistry of **2** was deduced from ROESY data. The relative stereochemistry for C-9 and C-11 in **2** was elucidated by ROESY correlations of NH-1′/H-8a and H-9, and NH-12/H-8b as shown in Figure 4.

A plausible biogenetic path for nagelamides M (**1**) and N (**2**) is proposed as shown in Scheme 1. Nagelamide M (**1**) could be produced by oxidation of intermediate **A**, which might be derived from taurodispacamide A[4] through cyclization, while nagelamide N (**2**) could be generated from hydrolysis and oxidation of intermediate **B**, which might be derived from taurodispacamide A through Baeyer–Villiger oxidation and cyclization.

Nagelamide M (**1**) is a novel bromopyrrole alkaloid possessing a 2-amino-octahydropyrrolo[2,3-*d*]imidazole ring with a taurine unit, while nagelamide N (**2**) is a new bromopyrrole alkaloid consisting of a 2-amino-tetrahydroimidazole-4-one ring with a taurine unit and 3-(dibromopyrrole-2-carboxamido)propanoic acid moiety. Nagelamides M (**1**) and N (**2**) showed inhibitory activity against *Aspergillus niger* (MIC, 33.3 μg/mL, each).

Table 2
^{1}H and ^{13}C NMR data of nagelamide N (**2**) in DMSO-d_6

Position	δ_H		δ_C
1	12.75	brs	—
2	—		105.07
3	—		98.05
4	6.89	s	113.12
5	—		127.91
6	—		159.09
7	8.31	brt	—
8a	3.02	m	36.57
8b	3.29	m	—
9	3.12	dd 12.2, 4.0	51.91
10	—		172.13
11	—		90.40
12	9.07	brs	—
13	—		167.55
13-NH_2	7.92 (2H)	brs	—
14	9.15	brs	—
15	—	brs	178.60
1′	9.84	brt	—
2′a	3.58		40.24
2′b	3.68	s	—
3′	3.82 (2H)	t 7.6	49.17