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Kakeromamide A, a new cyclic pentapeptide inducing astrocyte differentiation isolated from the marine cyanobacterium *Moorea bouillonii*

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ABSTRACT

Kakeromamide A (**1**), a new cyclic pentapeptide encompassing a thiazole ring moiety and a β-amino acid, was isolated from the marine cyanobacterium *Moorea bouillonii*. Its structure was elucidated by the spectral analysis and the modified Marfey's method. Compound **1** induced differentiation of neural stem cells into astrocytes at the concentration of 10 μM.

Introduction

Marine cyanobacteria are known to be a rich source of peptides such as lyngbyabellin B[1] and dolastatin 10.[2,3] In this study, a new cyclic peptide named kakeromamide A (**1**) was isolated from the marine cyanobacterium *Moorea bouillonii* collected at Kakeroma Island in Kagoshima prefecture of the southern part of Japan. This peptide shares the common amino acid sequence with that of a cyclic depsipeptide ulongamide D[4] in which valine was replaced by hydroxy isovaleric acid. Ulongamide D showed cytotoxicity against KB and LoVo cells with the IC_{50} values of 1 and 5 μM, respectively, while compound **1** showed only a moderate cytotoxicity against HeLa cells with the IC_{50} value of 10 μM. However, we found a unique biological activity in compound **1** to induce differentiation of neural stem cells into astrocytes at 10 μM in the *in vitro* differentiation model using mouse ES cells.[5,6] In this letter, we report the isolation, structure elucidation, and biological activities of kakeromamide A (**1**).

The frozen specimen of *Moorea bouillonii* (128 g wet weight), collected by hand using SCUBA at Kakeroma Island in Kagoshima prefecture (N 28° 04.67′, E 129° 18.42′), was extracted with MeOH. The combined methanolic extract was evaporated *in vacuo* and partitioned between H_2O and $CHCl_3$. The organic layer was subjected to ODS flash chromatography and followed by the reversed-phase HPLC, yielding 1.2 mg of kakeromamide A (**1**) as the colorless amorphous solid (9.4×10^{-6}% yield based on the wet weight).

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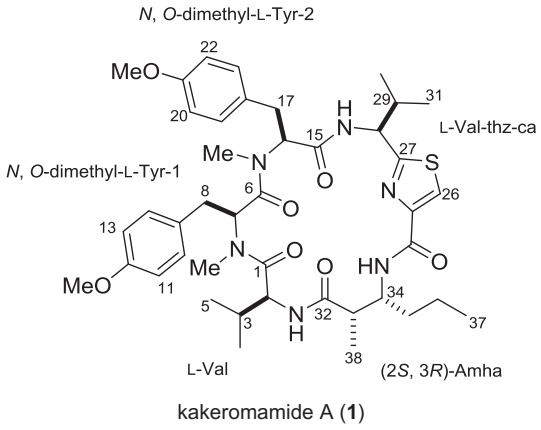

Kakeromamide A (**1**) with the optical rotation of $[\alpha]_D^{23.8}$ + 6.2° (*c* 0.065, MeOH), had a molecular formula of $C_{42}H_{58}N_6O_7S$ as determined by HRFABMS analysis (*m*/*z* 791.4171 $[M+H]^+$, calcd for $C_{42}H_{59}N_6O_7S$ *m*/*z* 791.4166, Δ +0.5 mDa). The IR absorption at 1647, 1612, and 1541 cm^{-1} indicated the presence of amide bonds.

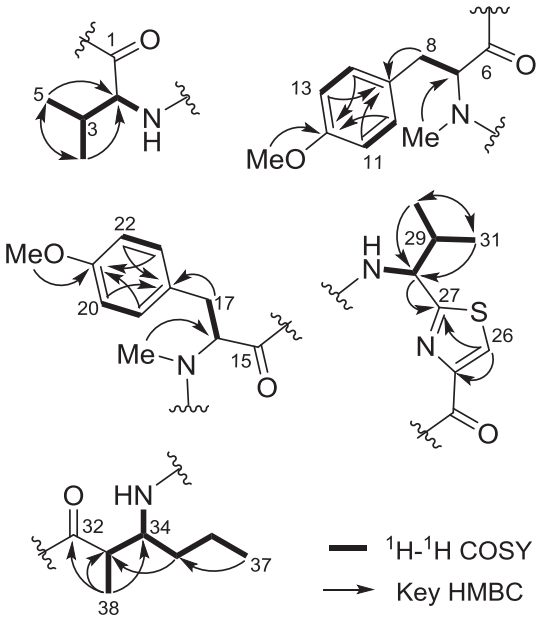

Fig. 1. Substructure of kakeromamide A (**1**).

Table 1
NMR spectral data for kakeromamide A (**1**) in CD_3CN (400 MHz and 600 MHz).

Unit	Position	δ_C	δ_H mult. (*J* in Hz)	COSY	HMBC
Val	1	176.8			
	2	57.2	4.30 dd (9.8, 7.3)	NH-2, H-3	
	3	32.0	1.80 dqq (9.8, 6.8, 6.7)	H-2, H-4, H-5	
	4	18.9	0.79 d (6.8)	H-3	C-2, C-5
	5	20.2	0.89 d (6.7)	H-3	C-2, C-4
	2-NH		6.53 d (7.3)	H-2	C-32[a]
N,*O*-diimethyl-Tyr-1	6	174.0			
	7	52.3	5.53 dd (11.3, 4.6)	H-8	C-6[a], C-8[a]
	8	33.4	1.38 dd (16.4, 4.6)	H-7	C-7[a], C-9
			2.70 dd (16.4, 11.3)	H-7	
	9	130.1			
	10/14	130.0	6.88 d (8.7)	H-11/13	C-8, C-12
	11/13	114.9	6.77 d (8.7)	H-10/14	C-9
	12	159.2			
	N-CH_3	31.7	3.05 s		C-1, C-7
	O-CH_3	55.9	3.73 s		C-12
N,*O*-dimethyl-Tyr-2	15	169.9			
	16	63.7	5.25 dd (9.7, 5.2)	H-17	C-15[a], C-17[a]
	17	34.6	2.61 dd (14.4, 9.7)	H-16	C-16[a], C-18
			2.97 dd (14.4, 5.2)	H-16	
	18	131.0			
	19/23	131.3	6.99 d (8.6)	H-20/22	C-17, C-21
	20/22	115.2	6.56 d (8.6)	H-19/23	C-18
	26	159.5			
	N-CH_3	29.7	2.86 s		C-6, C-16
	O-CH_3	55.7	3.48 s		C-21
Val-thz-ca	24	161.4			
	25	150.4			
	26	123.6	8.01 s		C25[a], C-27[a]
	27	170.0			
	28	57.2	5.33 dd (9.3, 5.5)	NH-28, H-29	C-27[a], C-29
	29	36.8	2.01 dqq (5.5, 6.8, 6.8)	H-28, H-30, H-31	
	30	17.8	0.78 d (6.8)	H-29	C-28, C-31
	31	20.8	0.94 d (6.8)	H-29	C-28, C-30
	28-NH		8.60 d (9.3)	H-28	
Amha	32	173.3			
	33	44.6	2.60 dq (3.4, 7.0)	H-34, H-38	
	34	52.8	4.09 dddd(12.0, 10.4, 3.4, 2.5)	H-33, H-35, NH-34	
	35	31.9	1.07 m, 1.70 dddd (14.1, 9.2, 7.0, 2.5)	H-34, H-36	C-33
	36	20.2	1.27 m, 1.45 m	H-35, H-37	
	37	14.6	0.97 t (7.5)	H-36	C-35, C-36
	38	14.4	1.09 d (7.0)	H-33	C-32, C-33, C-34
	34-NH		8.51 d (10.4)	H-34	

[a] observed only in the spectrum recorded on the spectrometer (600 MHz).