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Stellettapeptins A and B, HIV-inhibitory cyclic depsipeptides from the marine sponge *Stelletta* sp.

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ABSTRACT

Two new HIV-inhibitory depsipeptides, stellettapeptins A (**1**) and B (**2**), were isolated from an extract of the marine sponge *Stelletta* sp., collected from northwestern Australia. Structures of these cyclic nonribosomal peptides were elucidated on the basis of extensive NMR data analysis, and chemical degradation and derivatization studies. Stellettapeptins contain numerous nonproteinogenic amino acid residues and they are the first peptides reported to contain a 3-hydroxy-6,8-dimethylnon-4-(*Z*)-enoic acid moiety. Compounds **1** and **2** potently inhibit infection of human T-lymphoblastoid cells by HIV-1_{RF} with EC_{50} values of 23 and 27 nM, respectively.

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Marine sponges in the genus *Stelletta* have proven to be an extremely rich source of structurally diverse and biologically active natural products.[1–3] Marine sponges frequently contain nonribosomal peptides that have unusual amino acid residues and aliphatic moieties reminiscent of the mixed nonribosomal peptide synthetase (NRPS)–polyketide synthase (PKS) pathways of microorganisms, which suggests the involvement of symbiotic microbes in their production.[4] In the course of our search for bioactive metabolites from marine organisms, we obtained two new cyclic depsipeptides from a sponge of the genus *Stelletta*. We report herein the isolation, structure determination, and HIV-inhibitory properties of stellettapeptins A (**1**) and B (**2**).

Stellettapeptin A (**1**) was isolated as an amorphous solid, which had a molecular formula of $C_{67}H_{108}N_{16}O_{23}$ from analysis of HRESIMS data coupled with ^{1}H and ^{13}C NMR spectral data (Table 1). The presence of a large number of exchangeable amide NH protons (δ_H 6.80–9.98 ppm) and carbonyl resonances (δ_C 170.0–182.4 ppm) in the ^{1}H and ^{13}C NMR spectra of **1** was characteristic of a peptide derivative. Detailed analysis of 2D NMR data enabled us to assign 11 amino acid residues: *N*-methylalanine (*N*MeAla), β-methoxytyrosine (β-*O*MeTyr), *N*-methylglutamine (*N*MeGln), leucine (Leu), glycine (Gly), 3-methoxyalanine (3-*O*MeAla), threonine (Thr), 3,4-dimethylglutamine (3,4-DiMeGln), 2,3-diaminobutanoic acid (Dab), 3-hydroxyglutamine (3-OHGln), and 3-hydroxyasparagine (3-OHAsn) (Table 1). Additionally, a 3-hydroxy-6,8-dimethylnon-4-enoic acid (Hdna) moiety was identified (Fig. 1).

The sequence of amino acid residues in stellettapeptin A (**1**) was deduced from inter-residue NH/CHα ROE interactions, acquired in CD_3OH, and HMBC correlations as shown in Figure 2. The Hdna unit was defined by ^{1}H–^{1}H COSY and heteronuclear correlation NMR data, and its double bond assigned *Z* geometry based on the 10.5 Hz vicinal coupling between the H-4 (δ_H 5.37) and H-5 (δ_H 5.21) olefin protons. The Hdna moiety was linked to the N-terminus of the 3-OHAsn residue by an HMBC correlation from the 3-OHAsn NH (δ_H 8.25) to the carbonyl (δ_C 175.2) of Hdna. This linkage was also supported by ROESY correlations between the 3-OHAsn amide proton and the Hdna H_2-2 (δ_H 2.36, 2.61) methylene protons. The secondary amide NH signal (δ_H 7.88) of 3-OHGln correlated with the C-1 carbonyl (δ_C 171.8) of 3-OHAsn in the HMBC spectrum, which connected these residues, while the 3-OHGln α-methine (δ_H 4.52) showed a ROESY correlation with the amide NH (δ_H 8.75) of Dab. The amino acid sequence was

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Table 1
NMR spectral data for **1** (600 MHz, CD_3OH)

Position	δ_C	δ_H (J in Hz)	HMBC
*N*MeAla			
1	171.4		
2	51.9	5.42 q (7.0)	1, 3, N-Me, $1_{3\text{-OMeTyr}}$
3	13.3	1.28 d (7.0)	1, 2
N-Me	29.5	2.68 s	2, $1_{3\text{-OMeTyr}}$
3-*O*MeTyr			
1	170.0		
2	53.8	4.92[b] dd (10.5, 9.8)	1, 3
3	84.4	4.53[a] d (9.8)	1, 2, 4, 5, 9
3-OMe	56.9	3.10 s	3
4	129.5		
5, 9	131.5	7.17 d (8.3)	3, 6, 7, 8
6, 8	116.2	6.80 d (8.3)	4, 7
7	158.8		
NH		8.23 d (10.5)	2, 1_{NMeGln}
*N*MeGln			
1	170.8		
2	55.8	4.76[a] m	1, 4, N-Me, 1_{Leu}
3	25.1	1.29 m	5
		1.54 m	2, 4, 5
4	32.1	1.61 m	2, 3, 5
		1.69 m	2, 3, 5
5	177.9		
5-NH_2		6.80 br s	4, 5
		7.05 br s	5
N-Me	30.4	2.93 s	2, 1_{Leu}
Leu			
1	174.0		
2	49.4	4.72 m	3, 1_{Gly}
3	40.7	1.23 m	
		1.61 m	5
4	26.2	1.66 m	3
5	21.5	0.90[a] d (6.5)	3, 4, 6
6	23.6	0.95 d (6.5)	3, 4, 5
NH		7.20 d (9.2)	1_{Gly}
Gly			
1	172.3		
2	44.2	3.51 dd (17.0, 5.2)	1, $1_{3\text{-OMeAla}}$
		3.95 dd (17.0, 6.1)	1, $1_{3\text{-OMeAla}}$
NH		9.08 dd (6.1, 5.2)	2, $1_{3\text{-OMeAla}}$
3-OMeAla			
1	172.8[a]		
2	55.4	4.48 q (7.2)	1, 3, 1_{Thr}
3	71.6	3.74 m	1, 2, 3-OMe
		3.79 m	1, 2, 3-OMe
3-OMe	59.5	3.39 s	3
NH		8.47 d (7.2)	2, 3, 1_{Thr}
Thr			
1	172.9[a]		
2	57.4	5.20 dd (10.2, 2.8)	1, 3, 4
3	71.6	5.60 dq (6.6, 2.6)	4, 1_{NMeAla}
4	14.8	1.18 d (6.3)	2, 3
NH		8.93 d (10.2)	2, $1_{3,4\text{-DiMeGln}}$
3,4-DiMeGln			
1	174.1		
2	59.3	4.09 dd (9.3, 2.9)	1, 3, 3-Me, 4
3	36.8	2.47 m	2, 3-Me, 4-Me, 5
3-Me	17.3	1.28 d (6.9)	2, 3, 4
4	44.9	2.72 m	2, 3, 3-Me, 4-Me, 5
4-Me	14.0	1.32 d (7.1)	3, 4, 5
5	182.4		
5-NH_2		7.14 br s	4, 5
		7.87[a] br s	5
NH		9.98 br s	1_{Dab}
Dab			
1	171.6		
2	56.4	4.56 t (6.1)	1, 3, 4, $1_{3\text{-OHGln}}$
3	49.5	3.95 m	
3-NH_2		7.73 2H, br s	
4	16.8	1.43 d (6.8)	2, 3
NH		8.75 d (6.9)	2, 3, $1_{3\text{-OHGln}}$