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Perthamides C–F, potent human antipsoriatic cyclopeptides

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ABSTRACT

Two new cyclopeptides, perthamides E and F were isolated from the polar extracts of the sponge *Theonella swinhoei*. The new structures, featuring an unprecedented β-amino acid unit (AHMOA), were determined by interpretation of NMR and MS data. The absolute configuration of the AHMOA residue was proposed on the basis of quantum chemical calculation of NMR chemical shifts. Perthamides were proved to inhibit TNF-α and IL-8 release in primary human keratinocytes cells and therefore could represent potentially leads for the treatment of psoriasis.

1. Introduction

Psoriasis is a chronic autoimmune inflammatory skin disorder affecting approximately 2–3% of the general population in Europe and North America. Cutaneous and systemic overexpression of various proinflammatory cytokines (TNF-α, IL-8, IFN-γ, etc.) has been demonstrated in psoriatic patients.[1,2] Notably it has been postulated that TNF-α produced locally in psoriatic lesions creates a TNF-α positive feedback loop that amplifies and sustains the inflammatory process within plaques.[3] In fact, recently developed anti-inflammatory therapies based on blocking TNF-α signalling have been shown to be effective in the treatment of psoriasis and could become a highly promising option for the treatment of this skin condition.[4,5]

Recently, we reported the isolation and the chemical characterization of two cyclic octapeptides, which we named perthamides C (**1**) and D (**2**), from the Solomon marine sponge *Theonella swinhoei*.[6,7] Perthamide C has an unprecedented primary structure that comprises a 25-membered macrocycle with 6 out the 8 residues constituted by unusual amino acids: γ-methylproline, N^{δ}-carbamoyl-β-OSO_3asparagine, *o*-tyrosine, D-Abu, *O*-methylthreonine and the β-amino acid AHMHA (3-amino-2-hydroxy-6-methylheptanoic acid). Perthamide C (**1**), when tested in a well characterised model of inflammation in vivo, i.e., mouse paw oedema, significantly reduced carrageenan-induced paw oedema, displaying a dose-dependent anti-inflammatory activity.

Despite this promising activity, the mechanism of action at the molecular level of perthamide C is unknown. Although the modular peptidic nature and the ready chemical access to perthamide C may open the possibility to investigate new pharmacophores, the isolation of further natural derivatives represents an alternative approach to investigate the structure–activity relationships and to shed light on the biological target of this promise anti-inflammatory lead. In this respect, the sponge *T. swinhoei* (order Lithistida, family Theonellidae), recognized as one of the most prolific sources of bioactive secondary metabolites,[8] could represent a source of useful perthamide derivatives. Continuing investigation of the polar extracts of this sponge afforded a large amount of perthamide C together with two new derivatives, perthamides E (**3**) and F (**4**).

In this paper we describe the isolation, the structure elucidation including the stereochemical characterization and the biological activity of the new peptides (Fig. 1).

2. Results and discussion

The lyophilized sponge (400 g) was extracted with MeOH, and the combined extracts were fractionated according to the Kupchan

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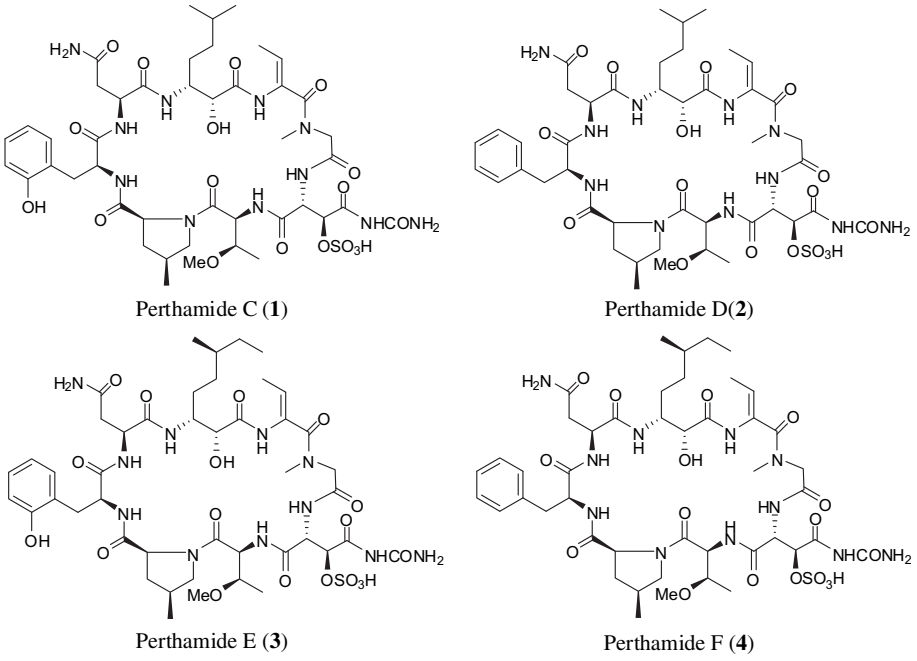

Fig. 1.

partitioning procedure.[9] The *n*-BuOH extract was purified by DCCC (*n*-BuOH/Me_2CO/H_2O, descending mode) followed by reverse-phase HPLC to afford perthamides C–F.

Perthamide E (**3**) was isolated as a colourless amorphous solid and showed the pseudomolecular ion peak at *m*/*z* 1080.4361 $[M-H]^-$ in the HRESIMS spectrum, corresponding to the molecular formula $C_{45}H_{67}N_{11}O_{18}S$ and indicating the presence of one additional carbon atom with respect to perthamide C (**1**).

A careful analysis of the NMR data (Table 1), including COSY, HSQC, TOCSY, indicated the presence of the same α-amino acid residues found in **1** and a variation of the β-amino acid unit (AHMHA in perthamide C). Even if from ^{1}H NMR and HSQC data an additional methylene group with respect to perthamide C was easily detected (δ_C 28.7, δ_H 1.03, 1.22), the analysis of the proton spin system of this amino acid unit was not straightforward due to the heavy overlap in the ^{1}H NMR high field region and to the absence of some scalar coupling in the COSY spectrum. The ^{1}H and ^{13}C NMR resonances of C-1/C-5 nuclei relative to this portion were almost superimposable with the corresponding values found for the 3-amino-2-hydroxy-6-methylheptanoic acid (AHMHA) residue in perthamide C. Additionally, inspection of ^{1}H NMR spectrum indicated the presence of one methyl doublet (0.74, d, *J*=6.2 Hz) and

Table 1
NMR data (700 MHz, DMSO-d_6) of perthamides E (**3**) and F (**4**)

Position	Perthamide E (**3**)		Position	Perthamide F (**4**)	
	δ_H (*J* in Hz)[a]	δ_C[a]		δ_H (*J* in Hz)[a]	δ_C[a]
ThrOMe			*ThrOMe*		
1	—	170.9	1	—	170.9
2	4.91d (9.5)	55.4	2	4.81d (9.6)	55.4
3	4.16m	72.9	3	4.14–4.22m	72.9
4	1.23d (5.9)	14.3	4	1.21d (5.8)	14.4
OMe	3.26s	54.7	OMe	3.25s	54.5
NH	9.01d (9.1)		NH	8.90d (8.8)	
γMePro			*γMePro*		
1	—	170.7	1	—	170.7
2	3.89dd (11.1, 6.6)	63.4	2	3.98dd (11.0, 6.7)	63.3
3	0.71m, 2.05–2.13m	36.2	3	1.09 ovl, 2.14–2.18m	36.3
4	2.20–2.30m	33.2	4	2.19–2.27m	33.5
5	3.39 ovl, 4.11 ovl	53.2	5	3.38 ovl, 4.10 ovl	53.2
6	1.03d (5.8)	15.8	6	1.01d (5.7)	15.6
o-Tyr			*Phe*		
1	—	170.6	1	—	170.6
2	4.11 ovl	56.4	2	4.28–4.36m	55.8
3	2.86dd (13.2, 3.2), 2.93t (13.2)	30.7	3	2.83dd (13.5, 3.5), 3.14 ovl	36.2
1′	—	124.3	1′	—	137.8
2′	—	154.6	2′	7.19d (7.4)	128.0
3′	6.87d (7.8)	114.5	3′	7.30t (7.4)	128.3
4′	7.10t (7.8)	128.0	4′	7.22d (7.3)	126.3
5′	6.80t (7.3)	119.9	5′	7.30t (7.4)	128.3
6′	7.16 ovl	130.5	6′	7.19d (7.4)	128.0
NH	7.20 ovl		NH	6.91d (8.0)	

(*continued on next page*)