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Three new 16-membered macrolide compounds from a genetically engineered strain *S. avermitilis* MHJ1011

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ABSTRACT

Three new 16-membered macrolide compounds, 13α-*O*-α-L-oleandrosyl milbemycin β_3 (**1**), 13α-*O*-α-L-oleandrosyl-25-ethyl milbemycin β_3 (**2**), 13α-*O*-α-L-oleandrosyl-25-isopropyl milbemycin β_3 (**3**), were isolated from the genetically engineered strains *Streptomyces avermitilis* MHJ1011. Their structures were determined on the basis of spectroscopic analysis, including 1D and 2D NMR techniques as well as ESI-MS and comparison with data from the literature. Both compounds **1**–**3** displayed impressive acaricidal activity against larval mites with the IC_{50} values of 0.0327, 0.0276 and 0.0235 mg/L, respectively, which are higher than those of 13α-hydroxy milbemycin β_3 and 13α-hydroxy-25-ethyl milbemycin β_3.

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Microbial metabolites, especially 16-membered macrocyclic lactone antibiotics used as potential pesticides and veterinary drugs have attracted great interest due to their latent high activity and low toxicity, such as avermectins and milbemycins.[1–4] Such novel macrolides could in themselves provide the basis for new pharmaceuticals or could serve as scaffolds for new semisynthetic analogs.[5–7] In our previous paper,[8,9] we reported the isolation and characterization of five new 16-membered macrocyclic lactone antibiotics from the fermentation broth of the genetically engineered strain *Streptomyces avermitilis* MHJ1011.[10] In our continuing chemical study of this genetically engineered strain, three new milbemycin analogs, 13α-*O*-α-L-oleandrosyl milbemycin β_3 (**1**), 13α-*O*-α-L-oleandrosyl-25-ethyl milbemycin β_3 (**2**), 13α-*O*-α-L-oleandrosyl-25-isopropyl milbemycin β_3 (**3**) (Fig. 1) were isolated and purified from the fermentation broth of *S. avermitilis* MHJ1011.[11] In this Letter, we report the isolation, structural elucidation and acaricidal activity of the three new compounds.

The molecular formula of compound **1** was established to be $C_{38}H_{54}O_9$ as deduced from the high-resolution electrospray ionization (HRESI)-MS at *m*/*z* 655.2573 $[M+H]^+$(calcd for $C_{38}H_{55}O_9$ 655.2577) and ^{13}C NMR data (Table 1).[12] The ^1H NMR spectrum of **1** displayed four doublet aliphatic methyls (δ_H 0.82, 3H, d, J = 6.5 Hz, H_3-30; δ_H 1.14, 3H, d, J = 6.3 Hz, H_3-31; δ_H 1.16, 3H, d, J = 6.9 Hz, H_3-28; δ_H 1.28, 3H, d, J = 6.2 Hz, H_3-6′), one methoxy signal (δ_H 3.54, 3H, s), two olefinic methyl signals (δ_H 1.58, 3H, br s, H_3-29; δ_H 2.06, 3H, s, H_3-27), one aromatic methyl (δ_H 2.23, 3H, s, H_3-26), one trans-double bond (δ_H 5.43, 1H, dd, J = 14.9, 10.1 Hz, H-11; δ_H 6.08, 1H, dd, J = 14.9, 10.9 Hz, H-10) and two downfield proton signals (δ_H 6.61, 1H, s, H-6; δ_H 7.33, 1H, s, H-3). The ^{13}C NMR and HMQC spectra revealed 38 carbon resonances, including an ester carbonyl carbon at δ_C 169.7 (s), a ketal carbon at δ_C 97.7 (s), an acetal carbon at δ_C 94.8 (d), a methoxy carbon at δ_C 56.9 (q), nine aliphatic methines (8 oxygenated), six sp^2 methines, six sp^2 quaternary carbons, in addition to six aliphatic methylenes and seven methyl carbons. By detailed comparison of the ^1H and ^{13}C NMR data (Table 1) of **1** with those of **4**,[13] a metabolite previously isolated from *Streptomyces avermitilis* NEAU1069, it was revealed that compound **1** was structurally similar to compound **4** (Fig. 1). The differences between **1** and **4** were in C-23 and C-25. The ^1H–^1H COSY and HMBC spectra (Fig. 2) fulfilled the assignment of the structure of **1**. The correlation of H_3-31/H-25 in the ^1H–^1H COSY spectrum and the observed HMBC correlations from δ_H 1.14 to C-24, C-25, from δ_H 0.82 to C-23, C-24 and C-25 demonstrated that the oxymethine group at C-23 and the cyclohexyl moiety at C-25 in **4** were replaced by a methylene and a methyl, respectively, in **1**. As a result, the gross structure of **1** was established. The relative stereochemistry of **1** was assigned as occurring with that of tenvermectins A and B.[8]

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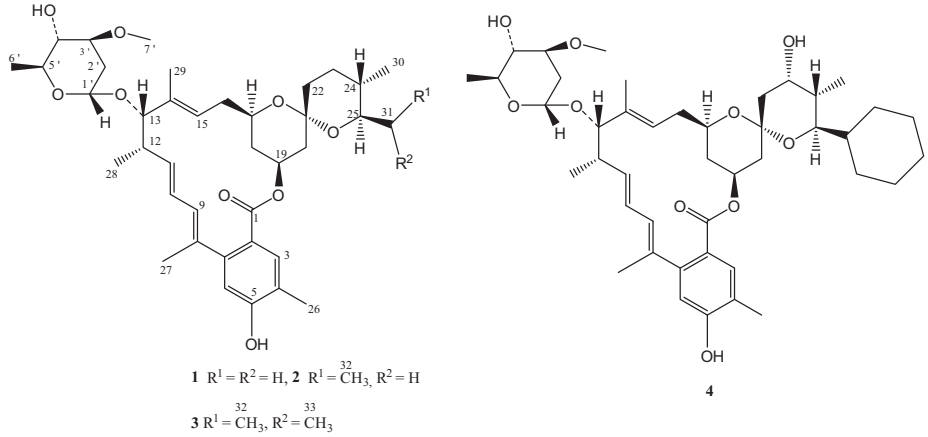

Figure 1. The structures of compounds **1**–**4**.

Table 1
^{1}H and ^{13}C NMR data of compounds **1**–**3** (coupling constants in parenthesis)

No.	1		2		3	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		169.7 s		169.6 s		169.6 s
2		124.1 s		123.7 s		123.6 s
3	7.33 s	131.9 d	7.38 s	132.1 d	7.39 s	132.1 d
4		122.5 s		122.6 s		122.6 s
5		155.6 s		155.9 s		155.9 s
6	6.61 s	114.1 d	6.62 s	114.1 d	6.60 s	114.1 d
7		144.0 s		144.2 s		144.3 s
8		134.5 s		134.7 s		134.7 s
9	5.72 d (11.0)	128.6 d	5.73 d (10.8)	128.4 d	5.71 d (10.9)	128.4 d
10	6.08 dd (14.9, 11.0)	126.9 d	6.10 dd (15.1, 10.8)	127.0 d	6.08 dd (15.0, 10.9)	127.0 d
11	5.43 dd (14.9, 10.1)	135.8 d	5.47 dd (15.1, 10.2)	135.7 d	5.46 dd (15.0, 10.0)	135.7 d
12	2.52 m	41.0 d	2.53 m	40.9 d	2.52 m	40.9 d
13	4.00 br s	82.7 d	4.02 br s	82.5 d	4.00 br s	82.9 d
14		134.0 s		134.1 s		134.1 s
15	4.96 d (10.4)	118.8 d	4.94 d (9.4)	118.8 d	4.92 d (10.0)	118.9 d
16	2.29 m	33.4 t	2.30 m	33.3 t	2.26 m	33.3 t
	2.42 m		2.40 m		2.33 m	
17	3.75 m	67.5 d	3.75 m	67.5 d	3.76 m	67.4 d
18	1.97 m	36.9 t	1.98 m	36.8 t	1.94 m	36.8 t
	0.73 t (12.0)		0.76 t (12.0)		0.75 t (12.3)	
19	5.56 m	67.9 d	5.54 m	68.1 d	5.50 m	68.2 d
20	1.94 m	41.1 t	1.96 m	41.3 t	1.92 m	41.3 t
	1.39 m		1.43 d (12.0)		1.39 m	
21		97.7 s		97.6 s		97.6 s
22	1.54 m	35.8 t	1.52 m	35.8 t	1.49 m	35.8 t
	1.62 m		1.67 m		1.64 m	
23	1.50 m	27.4 t	1.52 m	28.0 t	1.50 m	28.1 t
24	1.27 m	36.6 d	1.38 m	34.3 d	1.31 m	34.4 d
25	3.33 m	71.3 d	3.13 t (7.6)	75.8 d	3.10 dd (8.9, 1.6)	78.2 d
26	2.23 s	15.2 q	2.24 s	15.3 q	2.22 s	15.3 q
27	2.06 s	18.1 q	2.07 s	18.2 q	2.05 s	18.2 q
28	1.16 d (6.9)	19.7 q	1.19 d (6.8)	19.7 q	1.16 d (6.8)	19.6 q
29	1.58 br s	15.6 q	1.59 br s	15.6 q	1.58 br s	15.6 q
30	0.82 d (6.5)	17.9 q	0.83 d (6.4)	17.7 q	0.85 d (6.6)	19.2 q
31	1.14 d (6.3)	19.5 q	1.39 m	25.7 t	1.47 m	28.3 d
			1.69 m			
32			1.00 t (7.2)	9.9 q	1.03 d (6.8)	20.8 q
33					0.79 d (6.0)	17.4 q
1′	4.85 d (3.5)	94.8 d	4.85 d (3.2)	94.9 d	4.83 d (3.5)	94.9 d
2′	1.51 m	34.0 t	1.53 m	34.2 t	1.55 m	34.2 t
	2.35 t (7.5)		2.36 t (7.6)		2.35 t (7.7)	
3′	3.58 m	78.3 d	3.60 m	78.3 d	3.60 m	78.3 d
4′	3.17 t (9.1)	76.2 d	3.19 t (9.1)	76.2 d	3.18 t (9.1)	76.2 d
5′	3.88 dd (9.5, 6.6)	67.8 d	3.90 dd (9.4, 6.3)	67.9 d	3.89 dd (9.4, 6.3)	67.9 d
6′	1.28 d (6.2)	17.7 q	1.29 d (6.1)	17.8 q	1.28 d (6.2)	17.7 q
7′	3.54 s	56.9 q	3.54 s	56.8 q	3.51 s	56.8 q

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