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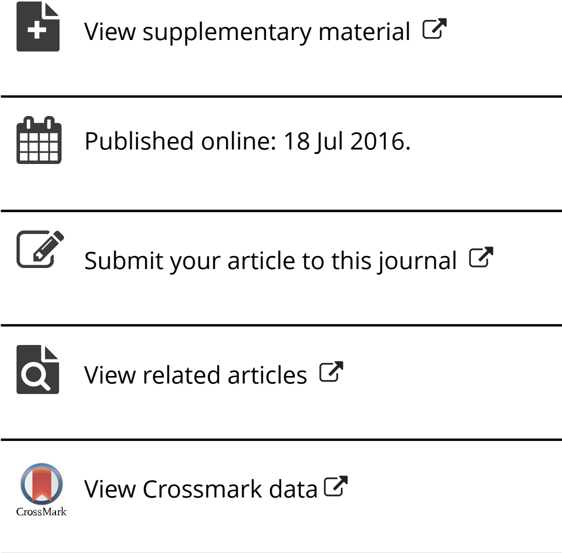

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Biologically active new metabolites from a Florida collection of *Moorea producens*

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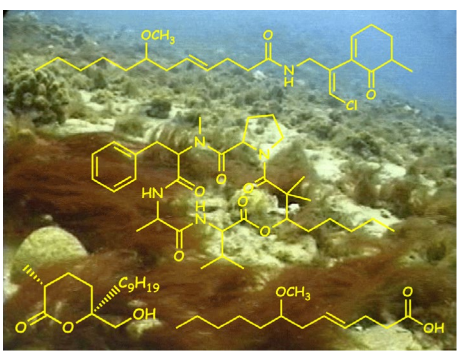
ABSTRACT

A bioassay-guided investigation (cancer cell cytotoxicity) of a *Moorea producens* collection from Key West, Florida, led to the discovery of two new bioactive natural products [(+)-malyngamide Y and a cyclic depsipeptide, (+)-floridamide]. Their planar structures were deduced through extensive analysis of 1D and 2D NMR spectroscopic data and supported by HRFAB mass spectrometry. The new cyclic depsipeptide contains four amino acids units, including *N*-methyl phenylalanine, proline, valine and alanine, beside the unique unit, 2,2-dimethyl-3-hydroxy-octanoic acid. In addition to the discovery of these two new compounds, two previously reported metabolites were also isolated and identified from this cyanobacterial collection; (−)-C-12 lyngbic acid and the antibacterial agent (−)-malyngolide.



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Moorea producens; cytotoxicity; malyngamide; floridamide

1. Introduction

A large number of collections of the marine cyanobacterium *Moorea producens* produce a class of lipopeptide metabolite known as the 'malyngamides'(Cardellina et al. 1978; Moore et al. 1978; Mynderse & Moore 1978; Ainslie et al. 1985; Wright et al. 1990; Gerwick et al. 1987; Engene et al. 2012). To date, more than 30 members belonging to this group of cyanobacterial metabolites have been discovered. There are two distinct and characteristic portions

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comprising the malyngamides; a methoxy fatty acid (known trivially as lyngbic acid) and a variety of functionalised amines, linked through an amide bond. These lyngbic acids have varying chain lengths, ranging from C-12 to C-20, with a methoxy group at C-7 as well as a trans double bond at C-4. The C-12 and C-14 lyngbic acids have also been detected in free form from marine cyanobacteria. The absolute stereochemistry of the lyngbic acids has been confirmed by total chemical syntheses (Praud et al. 1993; Orjala et al. 1995; Mesguiche et al. 1999). The marine cyanobacterium *M. producens* is known to be a rich source of unique and bioactive peptides. Examples include the antimicrobial and actin polymerisation-inhibiting lyngbyabellins A and B, the cytotoxic lyngbyastatin 2 and the pro-inflammatory lyngbyatoxins A and B (Cardellina et al. 1979; Fujiki et al. 1981; Aimi et al. 1990; Luesch et al. 1999; Luesch, Yoshida, Moore, & Paul 2000; Luesch, Yoshida, Moore, Paul, & Mooberry 2000; Milligan et al. 2000; Youssef et al. 2015). As part of our ongoing search for structurally and pharmacologically interesting substances from *M. producens*, a detailed examination of a Key West, Florida, collection was undertaken. During this study, two new compounds, (+)-malyngamide Y (**1**) and (+)-floridamide (**2**) have been isolated. In addition, two metabolites of known identity were isolated, namely the anti-microbial (–)-malyngolide (**3**) and the (–)-C-12 lyngbic acid (**4**).

2. Results and discussion

A collection of *M. producens* (active in H460 cancer cell cytotoxicity assay) was obtained from Key West, Florida, extracted with 2:1 CH_2Cl_2/MeOH and fractionated over silica gel vacuum liquid chromatography (EtOAc/hexanes gradient). Successive reversed phase solid phase extraction (SPE) and HPLC fractionation resulted in the isolation of two new compounds (**1**, **2**), in addition to two previously known compounds (**3**, **4**). Analysis of their spectroscopic properties (UV, IR, LRMS, HRMS, 1D NMR and 2D NMR) allowed the unequivocal construction of their planar structures (Figure 1).

Malyngamide Y (**1**) was isolated as colourless oil from the cancer cell cytotoxic organic extract of *M. producens*. The isotope pattern observed for the molecular ion (FAB) indicated the presence of one chlorine atom, and HRFABMS established a molecular formula of $C_{23}H_{37}ClNO_3$ (6° of unsaturation). The IR spectrum of **1** showed absorption bands at 3301 and 1675 cm^{-1}, indicative of the presence of an amide functional group. Inspection of the ^1H NMR spectrum indicated the presence of an olefin proton triplet signal at δ 6.87 (H-9). Another sharp singlet at δ 6.18 was characteristic of the olefin proton associated with the vinyl chloride functionality found in most malyngamides (H-3). Additionally a broad triplet at δ 6.02 was observed for an amide proton coupled with a methylene group. Another two doublet of doublets at δ 4.20 and 4.06 ($H1_a$ and $H1_b$) were seen. A sharp three-proton singlet at 3.20 was observed which indicated the presence of a methoxy group (C-13′). Moreover, a sharp triplet at δ 3.14 was indicative of a proton attached to a carbon carrying oxygen (H-7′), and a 3H doublet at δ 1.16, suggested a methyl group attached to methine group. Finally, a terminal methyl triplet (δ 0.89) was observed (H_3-12).

The ^{13}C NMR spectrum in $CDCl_3$ confirmed the presence of 23 carbon atoms. Analysis of ^{13}C NMR, DEPT135 and DEPT90 data revealed the presence of 1 ketone resonance at δ 202.40 (C-5), an amide resonance at δ 172.40 (C-1′), 6 olefinic carbons (δ 149.0, 138.70, 138.40, 131.00, 127.00 and 120.10), 10 methylene groups (δ 63.94, 31.0, 36.9, 36.80, 33.74, 32.40, 29.10, 26.12, 25.37, 23.90), two aliphatic methine groups (81.1 and 42.5) and also 3 methyl groups (56.9, 15.48 and 14.5). This was in keeping with 5°of the 6° of unsaturation required

Figure 1. Structures of the isolated compounds from *Moorea producens*.

by the molecular formula and confirmed the need for one ring to accomodate the 6° of unsaturations.

Chemical shift arguments, ^{1}H–^{1}H COSY and TOCSY correlations supported by MS data and HMBC, allowed the assignment of the planar structure of **1**. From the ^{1}H–^{1}H COSY NMR spectrum of **1**, it was possible to differentiate three discrete spin systems. A continuous spin system was evident in which a broad amide proton triplet (*δ* 6.02) was coupled to two mutually coupled midfield methylene resonances (*δ* 4.2 and 4.0 H-1a and H-1b), which in turn, showed couplings to an olefinic ^{1}H resonance (*δ* 6.1, H-3). The proton signal at *δ* 6.8 (H-9) was coupled to the proton at *δ* 2.4 (H-8) which by itself was coupled to the methylene proton at *δ* 2.0 (H-7). The latter proton was found to couple with the methine proton at *δ* 2.4 (H-6) which completed the second spin system.

The third spin system was the C-12 chain of lyngbic acid. This spin system began with the terminal methyl protons at *δ* 0.88 (H_3-12′) which were found to couple with the methylene group at *δ* 1.23 (H_2-11′). The latter proton signal was coupled to the protons at *δ* 1.22 (H_2-10′), which in turn was coupled to the methylene protons at *δ* 1.35 (H_2-9′). The H_2-9′ protons were adjacent to the methylene proton at *δ* 1.6 (H_2-8′) which coupled with a methine proton at *δ* 3.12; by chemical shift, this C-7′methine carbon also carried the methoxy group. The latter proton signal was coupled to the methylene protons at *δ* 2.15 (H_2-6′) which was adjacent to the olefinic proton at *δ* 5.4 (H-5′).

Coupling of H-5′with the second olefinic proton H-4′ and of H4′ to the final methylene (H_2-3′) completed the third spin system. These connections were confirmed by TOCSY correlations. HMBC correlations from *δ* 4.0/4.2 ($H_{a/b}$-1) to C-2, C-3 and C-4 combined with complementary HMBC correlations from H-3 to C-1, C-2 and C-4, firmly established the C-1/C-2/C-3/C-4 fragment of **1**. HMBC correlations from the methyl singlet at *δ* 1.12 (H_3-10) to C-5, C-6, C-7 and C-8 confirmed this connectivity deduced from COSY data. Securing of the cyclohexene ring structure was possible by placement of the carbonyl at C-5 due to HMBC correlations from the methyl group at *δ* 1.12 to C-5, C-6, C-7 and C-8. The C-2 (*δ* 138.7)/ C-3 (*δ* 120.1) double bond was determined as being terminal with the chlorine at C-3 by HMBC correlations from H-4 to C-1 (*δ* 39.4), C-2 and C-3.

Further HMBC correlations from $H_{a/b}$-1 to C-1′ established the C-1/N–H/C-1′ connection. ^{13}C NMR and 2D NMR established the fatty acid as a 12-carbon chain with unsaturation at the 4′-position. Placement of the methoxy group (δ_H 3.4 and δ_C 56.9) was possible through a HMBC correlation from the methoxy proton singlet to C-7' (δ 81.1). Strong HMBC correlations from δ 6.1 (H-3) to C-1 confirmed the stereochemistry of the vinyl chloride group to be *E*, and completed the planar structure of malyngamide Y (**1**) (McPhail & Gerwick 2003).

Floridamide (**2**) was isolated as a colourless oil with a molecular formula of $C_{33}H_{50}N_4O_6$ as determined by HRFABMS (observed $[M + Na]^+$ at *m/z* 621.9). The IR spectrum of floridamide (**2**) gave characteristic absorption bands at 3293, 1734, 1650, 1625 cm^{-1}, indicative of ester/amide carbonyl functionalities. Of the 11° of unsaturation inherent to the molecular formula, four could be accounted for by a phenyl group as suggested in the ^{1}H NMR spectrum. In addition, the peptidic nature of **2** was indicated by exchangeable NH protons resonating at δ 8.6 and δ 6.7. One distinct *N*-CH_3 proton singlet was also observed in the ^{1}H NMR data at δ 2.95. Two other high-field CH_3 proton singlets were also observed at δ 0.92 and δ 1.4. Thirty-three carbon signals were observed in the ^{13}C NMR data of floridamide (**2**), which included signals for a mono-substituted phenyl ring as well as five signals belonging to amide/ester carbonyls in the 169–173 ppm range. One oxygenated sp^3 carbon resonating at δ 77.9 was also detected in the HSQC spectrum.

From 1D and 2D NMR data, including HMBC and TOCSY, the presence of two conformers of compound **2** were observed in a ratio of 2:1. Five substructures were assembled for the major conformer of floridamide (**2**), including four amino acids (*N*-methyl phenylalanine (*N*-MePhe), proline (Pro), valine (Val) and alanine (Ala)) and one hydroxy acid, 2,2-dimethyl-3-hydroxy-octanoic acid (Dhoaa). The latter hydroxy acid, Dhoaa, is a unique unit previously reported from cyanobacterial depsipeptides and was deduced in floridamide from HMBC and TOCSY data. The sequence of these five residues in floridamide (**2**) was established mainly from CIMS and HMBC correlations. Sequential HMBC correlations in CD_2Cl_2 were observed between H-3, H-28, H-1/C-4; H-17, H-3, *N*H (δ 6.7)/C-19; H-12, H-3/C-11; H-3, H-9, H-10, H-1/C-1 and H-17, H-12, *N*H (δ 8.6)/C-16 which gave rise to the Pro/*N*-MePhe/Ala/Val/Dhoaa sequence. The overall cyclic structure of floridamide (**2**) was deduced by consideration of the downfield chemical shifts of alpha protons for each residue and consideration of the overall molecular formula. The absolute stereochemistry of floridamide (**2**) was not determined due to lack of available material.

Malyngamide Y (**1**) was found to have cytotoxic activity ($EC_{50} = 1.45 \times 10^{-5}$ μM/mL) to a human lung cancer cell line (NCI-H460) as well as to the mouse neuro-2a neuroblastoma cell line. However, floridamide (**2**) had weaker cytotoxic activity ($EC_{50} = 1.89 \times 10^{-5}$ μM/mL) in these cell lines. Neither of these compounds was found to have blocking or activating activity in a sodium channel modulation assay (Manger & Leja 1995).

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a Perkin-Elmer 141 polarimeter. IR and UV spectra were recorded on Nicolet 510 and Beckman DU640B spectrophotometers, respectively. NMR spectra were recorded on a Bruker DPX400 spectrometer, with the solvent ($CDCl_3$ at δ_C 77.2, δ_H 7.26) used as an internal standard. Mass spectra were recorded on a Kratos MS50TC mass spectrometer and HPLC isolations were performed using Waters Millipore model 515 pumps and a Waters 969 diode array detector.

3.2. Cyanobacterial collection

The marine cyanobacterium *M. producens* (voucher specimen available as collection number KWN-18/NOV/05-01) was collected by hand using SCUBA in Key West Florida, USA. The material was stored in 2-propanol at −3 °C until extraction.

3.3. Extraction and isolation

Approximately 40 g dry weight of the cyanobacterium was extracted repeatedly with 2:1 CH_2Cl_2/MeOH to produce 0.99 g of crude organic extract. A portion of the extract (0.97 g) was then fractionated by silica gel vacuum liquid chromatography. The fractions eluting with 60% EtOAc in hexanes was further purified with a C_{18} SPE cartridge (8:2 MeOH/H_2O) and reversed-phase HPLC (9:1 CH_3OH/H_2O, Phenomenex Sphereclone 5 µ ODS) to yield 2.4 mg of C-12 lyngbic acid (**3**), 1.3 mg of malyngamide Y (**1**) and 1.0 mg of malyngolide (**4**). A second fraction eluting with 80% EtOAc in hexanes was further purified with a C_{18} SPE cartridge (8:2 MeOH/H_2O) and reversed-phase HPLC (9:1 CH_3OH/H_2O, Phenomenex Sphereclone 5 µ ODS) to yield 2.0 mg of floridamide (**2**).

3.4. Spectral data

3.4.1. Malyngamide Y (1)

Colourless oil; $[\alpha]_D^{25}$ +14° (*c* 0.09, $CHCl_3$); UV (MeOH) λ_{max} 250 (ε = 174); IR v_{max}(film) 3301, 2928, 2859, 1675, 1537, 1455, 1370, 1095 cm^{-1}; ^{1}H and ^{13}C NMR data in $CDCl_3$, see Table S1; HRFABMS (3-NBA) obsd $[M + H]^+$ *m/z* 410.2467 (Calcd for $C_{23}H_{37}ClNO_3$ 410.2462).

3.4.2. Floridamide (2)

Colourless oil; $[\alpha]_D^{25}$ +56° (*c* 0.1, $CHCl_3$); UV (MeOH) λ_{max} 220 (log ε = 5.467), 278 (log ε = 4.453); IR v_{max} (film) 3293, 2924, 2854, 2360, 2337, 1734,1650, 1625, 1510, 1458, 1175 cm^{-1}; ^{1}H and ^{13}C NMR data in $CDCl_3$, see Table S2; HRFABMS $[M + H]^+$ *m/z* 599.3815 (Calcd for $C_{33}H_{51}N_4O_6$ 599.3808).

3.4.3. (−)-Malyngolide (3)

Colourless oil, $[\alpha]_D^{25}$ −10° (*c* 0.10, $CHCl_3$), literature value −12.0°;[1] UV, IR, ^{1}H, ^{13}C NMR and MS data were similar to literature values (Cardellina & Moore 1979).

3.4.4. (−)-C-12 lyngbic acid (4)

Colourless oil; $[\alpha]_D^{25}$ −8° (*c* 0.1, $CHCl_3$); with remaining physical and spectroscopic properties identical to those previously reported (Kwan et al. 2010).

3.5. Cytotoxicity against NCI-H460 human lung cancer and neuro-2a neuroblastoma cell line (Alley & Scudiero 1988)

The method of Alley et al. was used to determine cell viability in NCI-H460 human lung tumour cells and mouse neuro-2a blastoma cells by MTT reduction. Cells were seeded in 96-well plates at 5000 and 8000 cells/well in 180 µL for H460 and neuro-2a cells, respectively. Twenty-four hours later, the test chemical dissolved in DMSO and diluted into medium without foetal bovine serum was added at 3 µg/well. DMSO was less than 1% final concentration. After 48 h, the medium was removed and cell viability determined.

3.6. Sodium channel modulation (Alley & Scudiero 1988)

Isolated compounds, were evaluated for their capacity to either activate or block sodium channels using the following modifications to the cell-based bioassay of Manger et al. Twenty-four hours prior to chemical testing, mouse neuro-2a blastoma cells were seeded in 96-well plates at 8×10^4 cells/well in a volume of 30 µL. Test chemicals dissolved in DMSO were serially diluted in medium without foetal bovine serum and added at 10 µL/well. DMSO was less than 1% final concentration. Plates to evaluate sodium channel activating activity received 3 µL/well of either a mixture of 3 mM quabain and 0.3 mM veratridine (Sigma Chemical Co) in 5 mM HCl in addition to the test chemical. Plates were incubated for 18 h and results were compared to similarly treated solvent controls with 10 µL medium added in lieu of the test chemical. The sodium channel activator brevetoxin PbTx-1 (Calbiochem) was used as the positive control and added at 10 ng/well in 10 µL medium. Sodium channel blocking activity was assessed in a similar manner except that ouabain and veratridine were 5.0 and 0.5 mM, respectively, and the sodium channel blocker saxitoxin (Calbiochem) was used as the positive control. Plates were incubated for approximately 22 h.

4. Conclusions

Bioassay-guided investigation (cancer cell cytotoxicity) of a *M. producens*, led to the discovery of (+)-malyngamide Y and (+)-floridamide. The new cyclic depsipeptide contains four amino acids units, including *N*-MePhe, Pro, Val and Ala, beside the unique unit, Dhoaa.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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