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Investigation on antimicrobial agents of the terrestrial *Streptomyces* sp. BCC71188

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Abstract The terrestrial actinomycete strain BCC71188 was identified as *Streptomyces* by its morphology (having spiral chain spore on the aerial mycelium), chemotaxonomy (containing *LL*-diaminopimelic acid in the cell wall), and 16S rRNA gene sequence analysis [showing high similarity values compared with *Streptomyces samsunensis* M1463^T (99.85 %) and *Streptomyces malaysiensis* NBRC 16446^T (99.40 %)]. The crude extract exhibited antimalarial against *Plasmodium falciparum* (IC_{50} 0.19 μg/ml), anti-TB against *Mycobacterial tuberculosis* (MIC 6.25 μg/ml), and antibacterial against *Bacillus cereus* (MIC 1.56 μg/ml) activities. Therefore, chemical investigation was conducted by employing bioassay-guided method and led to the isolation of 19 compounds including two cyclic peptides (**1**–**2**), five macrolides (**3**–**7**), new naphthoquinone (**8**), nahuoic acid C (**9**), geldanamycin derivatives (**10**–**13**), cyclooctatin (**14**), germicidins A (**15**) and C (**16**), actinoramide A (**17**), abierixin, and 29-*O*-methylabierixin. These isolated compounds were evaluated for antimicrobial activity, such as antimalarial, anti-TB, and antibacterial activities, and for cytotoxicity against both cancerous (MCF-7, KB, NCI-H187) and non-cancerous (Vero) cells. Compounds **1**–**7**, **10**–**14** exhibited antimalarial (IC_{50} 0.22–7.14 μg/ml), and elaiophylin analogs (**4**–**6**) displayed anti-TB (MIC 0.78–12.00 μg/ml) and *B. cereus* (MIC 0.78–3.13 μg/ml) activities. Compounds **1**, **2**, **14**, and abierixin displayed weak cytotoxicity, indicating a potential for antimicrobial agents.

Keywords *Streptomyces* · Secondary metabolites · Antimicrobial · Cytotoxicity

Introduction

The genus *Streptomyces* by far produces diverse secondary metabolites with various biological activities. Its complex morphological differentiation of *Streptomyces*, involving in the formation of a layer of hyphae, and signal molecule(s) production after cell wall breakdown may trigger the manufacture of different bioactive compounds (Chater and Chandra 2006). Moreover, *Streptomyces* can survive in assorted environments, which can stimulate a diverse secondary metabolites production. So far, over 600 species of *Streptomyces* have been recorded and proved to be the excellent sources of bioactive secondary metabolites (Genilloud et al. 2011). The terrestrial *Streptomyces* spp. have delivered multifarious chemical core-structures, such as linear polyketide (Raju et al. 2012), cyclobutane-bearing tricyclic lactam (Park et al. 2012), azoxide compounds (Ding et al. 2012), pyranonaphthoquinones (Wang et al. 2013), ansamysins (Lu et al. 2013), and sesquiterpene alblaflavenol B (Raju et al. 2015). In addition, several compounds have also been isolated from *Streptomyces* collected in various parts of Thailand, indicating a potential of *Streptomyces* as a source of bioactive

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compounds, for example, antimalarial C-glycosylated benz [α] anthraquinones (Supong et al. 2012), antimalarial samroiyotmycins A and B (Dramae et al. 2013), antibacterial streptophenazines (Bunbamrung et al. 2014), antimicrobial steffimycin C (Intaraudom et al. 2015).

In our continuing search for bioactive compounds from actinomycetes, we came across a terrestrial *Streptomyces* strain BCC71188, preliminarily identified by its morphology and 16S rRNA gene sequence analysis. The crude extract of the strain displayed a prolific secondary metabolic profile and exhibited antimicrobial activity against *Bacillus cereus* (MIC value 1.56 μg/ml), *Mycobacterium tuberculosis* (MIC 6.25 μg/ml), and *Plasmodium falciparum* (IC_{50} value 0.19 μg/ml). Therefore, the investigation was further conducted on identification of the strain by phenotypic chemotaxonomic and genotypic characteristics along with the isolation, structure elucidation, and biological evaluation of the secondary metabolites isolated from this strain.

Materials and methods

General experimental procedures

FT-IR spectra were measured on a Bruker ALPHA spectrometer. UV spectra were performed in MeOH on a Spekol 1200 spectrophotometer, Analytik Jena. Optical rotations were measured with JASCO P-1030 digital polarimeter. NMR spectra were recorded on Bruker Avance 500 MHz and Bruker Avance III 400 MHz NMR spectrometers using either acetone-d_6 or DMSO-d_6 as an internal standard. HRESIMS data were obtained from Bruker MicrOTOF spectrometer. Column chromatography was performed on Sephadex LH-20 column using 100 % MeOH as eluent. HPLC was performed on a Dionex-Ultimate 3000 series equipped with a binary pump, an autosampler, and diode array detector. Semi-preparative HPLC was performed on a Sunfire C18 column from Waters (5 μm, diam. 19 mm × 150 mm). Preparative HPLC was performed on a Sunfire C18 column from Waters (10 μm, diam. 19 mm × 250 mm).

Biological material

The actinomycete strain BCC71188 (original code KC138) was isolated from a soil sample collected from Nakhon Si Thammarat Province, Thailand, and deposited at BIOTEC Culture Collection (BCC), National Center for Genetic Engineering and Biotechnology (BIOTEC) with the registration number BCC71188. The 16S rRNA gene sequence (1346 nt) of this strain was deposited in DDBJ database with the accession number LC121598.

Isolation, characterization, and identification of actinomycete strain BCC71188

An actinomycete strain BCC71188 was isolated from a soil sample collected from Nakhon Si Thammarat Province, Thailand, and grown on a starch-casein nitrate agar, consisting of soluble starch 1 %, sodium caseinate 0.1 %, KH_2PO_4 0.05 %, $MgSO_4$ 0.05 %, and agar 1.8 % (pH 7.3). The agar plate was incubated at 30 °C for 21 days and actinomycete isolate was then purified on a ISP 2 agar medium, containing glucose 0.4 %, yeast extract 0.4 %, and malt extract 1 % (pH 7.3), at 30 °C in an incubator for 14 days. Then, the strain was grown on ISP 4 agar [containing soluble starch 1 %, K_2HPO_4 0.1 %, $MgSO_4$ 0.1 %, NaCl 0.1 %, $(NH_4)_2SO_4$ 0.2 %, $CaCO_3$ 0.2 %, and agar 1.8 % (pH 7.3)], incubated at 30 °C for 21 days, and observed by scanning electron microscopy (model JSM-5410 LV; JEOL). The carbon utilization of the strain was determined by using carbon utilization medium (ISP 9), consisting of 1 % sole carbon source (Shirling and Gottlieb 1966). The ISCC–NBS Color Charts standard sample no. 2106 was used for color designations (Kelly 1964). The tolerance of NaCl, pH, and the effect of temperature was determined by cultivating on ISP 2 medium. Gelatin liquefaction, nitrate reduction, and starch hydrolysis were determined by cultivation on various media, described by Arai (Arai 1975) and Williams and Cross (Williams and Cross 1971). For chemotaxonomic determination, dried cells of the strain were obtained from the cells grown in ISP 2 broth on a rotary shaker (200 rpm) at 30 °C for 4 days. Cells were then harvested by centrifugation, washed with distilled water, and freeze-dried. Cell wall peptidoglycan was prepared and hydrolyzed by the methods of Kawamoto et al. (Kawamoto et al. 1981) and the amino acid composition was analyzed by TLC (Staneck and Roberts 1974).

Genomic DNA extraction was performed from the cells grew in ISP 2 broth according to the method described by Tamaoka (1994). PCR-mediated amplification of the 16S rRNA gene was carried out as described by Inahashi et al. (Inahashi et al. 2010) and sequencing of the PCR products (Macrogen) was done by using universal primers (Lane 1991). The 16S rRNA gene sequence was multiply aligned with selected sequences obtained from the GenBank/EMBL/DDBJ databases by using CLUSTAL W program, version 1.81 (Thompson et al. 1994). The alignment was manually verified and adjusted prior to the construction of a phylogenetic tree. The phylogenetic tree was constructed by using the neighbor-joining (Saitou and Nei 1987) with the genetic distances calculated by Kimura's 2-parameter model (Kimura 1980) in MEGA 6 software (Tamura et al. 2013). The confidence values for the branches of the phylogenetic tree were determined by using bootstrap analyses based on 1000 resamplings (Felsenstein 1985). 16S rRNA gene sequence similarities among the closely related strains were calculated manually after obtaining pair-wise alignments using CLUSTAL_X (Thompson et al. 1997).

Fermentation and isolation of secondary metabolites

The culture plate of strain BCC71188 was used for the stock culture, which grown on ISP 2 agar medium at 30 °C for 4 days. The stock culture was inoculated into 250-ml Erlenmeyer flasks, containing 150 ml of seed medium (ISP 2 broth). The seed culture of strain BCC71188 was cultivated on a rotary shaker (200 rpm) at 30 °C for 4 days. Then, the seed culture (20 flasks) was transferred into 80 × 1-l Erlenmeyer flasks, which each contained 250 ml of wheat germ-starch production medium, comprising (*w*/*v*) soluble starch 2 %, glycerol 0.5 %, defatted wheat germ 1 %, meat extract 0.3 %, yeast extract 0.3 %, and $CaCO_3$ 0.3 % (pH 7.3). The production culture (20 l) was cultivated for 14 days at 30 °C on rotary shakers (200 rpm). After 14 days of the cultivation, the whole culture was extracted three times with an equal volume of EtOAc and then the extract was dried over Na_2SO_4. EtOAc was evaporated to dryness to yield a crude extract (10.1 g), which was fractionated through a Sephadex LH-20 column to give seven fractions (F1–F7).

Fraction F1 (2.5 g) was purified by a preparative HPLC, eluted with a linear gradient system of 30–95 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to furnish compounds **3** (4.8 mg), **4** (0.10 g), and **6** (13.6 mg). Fraction F2 (1.2 g) was further purified by a preparative HPLC, eluted with a linear gradient system of 30–95 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to give two subfractions (F2F1-F2F2). Subfraction F2F1 (78.5 mg) was further purified by a preparative HPLC, eluted with a linear gradient system of 30–95 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to yield compounds **3** (4.7 mg) and **4** (17.8 mg). Subfraction F2F2 (47.6 mg) was further purified by semi-preparative HPLC, eluted with a linear gradient system of 45–95 % CH_3CN in H_2O over 35 min at the flow rate of 10 ml/min, to afford abierixin (11.1 mg) and 29-*O*-methylabierixin (13.6 mg).

Fraction F3 (0.8 g) was purified by a preparative HPLC, eluted with a linear gradient system of 45–95 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to give compound **9** (7.1 mg) and a mixture (35.9 mg). The mixture was purified by another semi-preparative HPLC, eluted with a linear gradient system of 40–95 % CH_3CN in H_2O over 35 min at the flow rate of 10 ml/min, to obtain compounds **4** (3.1 mg), **5** (4.7 mg), and **7** (11.2 mg).

Fraction F4 (2.9 g) was re-chromatographed on a Sephadex LH-20 column, eluted with 100 % MeOH to give two subfractions (F4F1-F4F2). Subfraction F4F1 (0.37 g) was purified by a preparative HPLC, eluted with a linear gradient system of 10–85 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to give compound **9** (3.2 mg). Subfraction F4F2 (1.1 g) was purified by a preparative HPLC, eluted with a linear gradient system of 10–95 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to yield compounds **1** (35.6 mg), **2** (4.1 mg), **7** (15.9 mg), **9** (15.2 mg), **14** (12.7 mg), and **17** (6.2 mg).

Fraction F5 (1.3 g) was re-chromatographed on another Sephadex LH-20 column to give two subfractions (F5F1-F5F2). Subfraction F5F1 (37.5 mg) was purified by a semi-preparative HPLC, eluted with a linear gradient system of 10–90 % CH_3CN in H_2O over 35 min at the flow rate of 10 ml/min, to afford compound **1** (15.4 mg). Subfraction F5F2 (0.50 g) was purified by a preparative HPLC, eluted with a linear gradient system of 10–95 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to afford compounds **14** (20.9 mg), **15** (10.2 mg), and **16** (10.9 mg).

Fraction F6 (1.1 g) was re-chromatographed on a Sephadex LH-20 column, to give three subfractions (F6F1-F6F3). Subfraction F6F1 (65.5 mg) was purified by preparative HPLC, eluted with a linear gradient system of 30–80 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to obtain compounds **10** (47.5 mg) and **11** (6.1 mg). Subfraction F6F2 (0.50 g) was purified by a semi-preparative HPLC, eluted with a linear gradient system of 50–90 % CH_3CN in H_2O over 30 min at the flow rate of 10 ml/min, to yield compounds **15** (10.2 mg) and **16** (17.5 mg). Subfraction F6F3 (0.83 g) was purified by a preparative HPLC, eluted with a linear gradient system of 10–80 % CH_3CN in H_2O over 40 min at the flow rate of 15 ml/min, to give compounds **4** (4.6 mg), **10** (28.8 mg), **12** (7.2 mg), **13** (16.1 mg), and **14** (34.7 mg). In addition, compound **9** (6.9 mg) was obtained from the fraction F7 by a semi-preparative HPLC, eluted with a linear gradient system of 10–70 % CH_3CN in H_2O over 30 min at the flow rate of 10 ml/min.

Monoglycosylelaiolide (**3**): Colorless solid; $[\alpha]_D^{27}$ + 6.3 (*c* 0.12, MeOH); UV λ_{max} (log ε, MeOH) 249 (4.22) nm; IR (ν_{max}, cm^{-1}) 34,251, 2967, 2933, 1696, 1638, 1462, 1384, 1304, 1282, 1261, 1224, 1183, 1149, 1112, 1087, 1017, 1001, 902, 879, 803, and 755; ^1H (500 MHz) and ^{13}C NMR (125 MHz) data in acetone-d_6 (see Table 1, Figs. S1–S6); HRESIMS *m/z* 917.5241 $[M + Na]^+$ (calcd. for $C_{48}H_{78}O_{15}Na$, 917.5233).

2-Amino-6-hydroxyl-7-methyl-1,4-naphthoquinone (**8**): Red solid; UV λ_{max} (log ε, MeOH) 222 (4.08), 272 (4.08), 276 (4.08), and 324 (3.92) nm; IR (ν_{max}, cm^{-1}) 3464, 3352, 2924, 2854, 1683, 1621, 1597, 1562, 1467, 1341, 1300, 1213, 1160, 1071, 1040, 1011, and 827; ^1H NMR (400 MHz, DMSO-d_6) (Figs. S7 and S10) 2.19 (s, 7-CH_3), 5.67 (s, H-3), 7.10 (br s, OH), 7.26 (s, H-5), 7.69 (s, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) (Figs. S8 and S10) 16.3 (7-**C**H_3), 101.8 (3-CH), 111.3 (5-CH), 122.4 (8a-C), 128.7 (7-C), 129.5 (8-CH), 134.5 (4a-C), 151.2 (2-C), 162.5 (6-C), 180.9 (1-C), 182.4 (4-C); HRESIMS *m/z* 202.0514 $[M - H]^-$ (calcd. for $C_{11}H_8O_3N$, 202.0510).

Bioassays

Antibacterial activity against *B. cereus* was tested by resazurin microplate assay (REMA) (Sarker et al. 2007). Vancomycin

Table 1 The ^{1}H and ^{13}C NMR spectral data of compound **3** (monoglycosylelaiolide)

Position	Compound **3** in acetone-d_6[a]		Monoglycosylelaiolide in $CDCl_3$[b]	
	δ_C (ppm)	δ_H (ppm), multiplicity (*J* in Hz)	δ_C (ppm)	δ_H (ppm), multiplicity (*J* in Hz)
1/1′	169.2	–	170.0	–
2/2′	121.7	5.85, d (15.4)	120.9	[f]
3/3′	145.3	6.95, dd (15.4, 11.2)	145.0	[f]
4/4′	132.0	6.25, dd (11.2, 15.1)	132.0	[f]
5/5′	144.8	5.74, dd (15.1, 9.7)	141.3	[f]
6/6′	41.2	2.58–2.67, m	[f]	[f]
7/7′	77.4	4.91, d (10.2)	[f]	4.73, br d (10.0)
8/8′	36.4	1.97–2.05, m	[f]	[f]
9/9′	70.6/70.8	4.14, dd (9.8, 4.3)	[f]	4.10–4.15, m
10/10′	42.2	1.68–1.77, m	[f]	[f]
11/11′	99.3/99.4	–	99.0/99.1	–
12	43.8	1.15–1.21, m/2.17, dd (12.0, 4.7)	[f]	2.30, dd (12.0, 5.0)
12′	38.6	1.01–1.12, m/2.41, dd (12.0, 4.6)		2.39, dd (12.0, 5.0)
13/13′	65.9[c]/69.4	3.78–3.87, m/3.88–3.99, m	[f]	3.85–4.05, m
14/14′	51.5/48.9	0.95–1.02, m/1.10–1.18, m	[f]	[f]
15/15′	66.5[d]/67.0	3.88–3.99, m	[f]	3.85–4.05, m
16/16′	19.1/19. 0	1.07, d (6.1)/1.08, d (6.0)	[f]	[f]
17/17′	19.4/19.3	1.42–1.53, m/1.63–1.70, m	[f]	[f]
18/18′	8.7[e]	0.86, t, 6.3	[f]	[f]
6-/6′-CH_3	14.8	1.06, d (6.7)	[f]	[f]
8-/8′-CH_3	8.8[e]	0.85, d (6.8)/0.86, d (6.3)	[f]	[f]
10-/10′-CH_3	6.5(0)/6.5(4)	0.99, d (7.4)/1.00, d (7.5)	[f]	[f]
1″	93.4	5.02, d (3.5)	93.2	5.06, br s
2″	33.3	1.58, dd (12.5, 5.0)/1.85–1.93, m	33.6	[f]
3″	65.6[c]	3.88–3.99, m	[f]	[f]
4″	66.6[d]	3.88–3.99, m	[f]	[f]
5″	71.2	3.55, s	[f]	[f]
6″	16.8	1.18, d (6.6)	[f]	[f]
9-OH/9′-OH		4.27, t (5.6)		4.10–4.15, m
11-OH/11′-OH		5.17, d (1.8)/5.21, d (1.8)		5.06, br

[a] 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR

[b] 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR

[c, d, e] Interchangeable

[f] Signals were referred to those reported for elaiolide (Bindseil and Zeeck 1993)

was used as a positive control. The green fluorescent protein microplate assay (GFPMA) was used for evaluation of cytotoxicity against Vero cell (African green monkey kidney fibroblasts, ATCC CCL-81) and of antituberculosis against *M. tuberculosis* strain H37Ra (Changsen et al. 2003). Ellipticine was used as a positive control for cytotoxicity against Vero cell. Isoniazid, ofloxacin, rifampicin, streptomycin, and ethambutol were used as the positive controls for antitubercular activity. Antimalarial assay against *P. falciparum* (K-1, multidrug-resistant strain) was performed by using the microculture radioisotope technique (Desjardins et al. 1979). Dihydroartemisinin and mefloquine were used as positive controls for antimalarial assay. Cytotoxicity against KB (oral human epidermoid carcinoma, ATCC CCL-17), MCF-7 (human breast cancer, ATCC HTC-22), and NCI-H187 (human small-cell lung cancer, ATCC CRL-5804) cell lines were evaluated by using the resazurin microplate assay (REMA) (O'Brien et al. 2000). Ellipticine and doxorubicin were used as the positive controls for anti-KB activity. Tamoxifen and doxorubicin were used as the positive controls for anti-MCF-7 activity. Doxorubicin was used as a positive control for anti-NCI-H187 activity. Minimum inhibitory

concentration (MIC) represents the lowest concentration that inhibited 90 % growth of bacteria and IC_{50} represents the concentration that caused 50 % reduction in cell growth.

Results

Identification and characterization of actinomycete strain BCC71188

Based on morphology, the strain produced grayish yellow substrate mycelium and greenish gray aerial mycelium on ISP 2 agar. The spiral chain spore was developed on the aerial mycelium. The surface of the spores was rough (Fig. 1). Strain BCC71188 grew well on ISP 2, ISP 3, ISP 4, ISP 5, ISP 6, ISP 7, and nutrient agars. The strain could utilize L-arabinose, D-fructose, D-glucose, D-mannitol, D-melibiose, *myo*-inositol, raffinose, L-rhamnose, and D-xylose as carbon sources. The strain could hydrolyze soluble starch, peptonize milk, and reduce nitrate to nitrite. Strain BCC71188 could grow on the medium in a presence of salt 0–4 % (*w*/*v*) NaCl, at pH 5–12, and at temperature in a range of 15–40 °C. For cell wall analysis, the isomer of diaminopimelic acid (DAP) in the peptidoglycan was identified as *LL*-DAP. Based on morphological and pattern of *LL*-DAP, the strain BCC71188 was identified as a member in the family *Streptomycetaceae*. In addition, the strain did not show diagnostic sugars in whole-cell hydrolysates and contained phospholipid type II, indicating that the strain BCC71188 could be classified as the genus *Streptomyces* (Manfio et al. 1995).

The 16S rRNA gene sequence (1346 nt) of strain BCC71188 was deposited in DDBJ database with the accession number LC121598. The sequence analysis indicated that BCC71188 was closely related to the genus *Streptomyces* and showed high level of similarity values compared with *Streptomyces samsunensis* M1463^T (99.85 %) and *Streptomyces malaysiensis* NBRC 16446^T (99.40 %). In addition, neighbor-joining phylogenetic tree, constructed based on 16S rRNA gene sequences and its closest relatives, also confirmed that the strain belonged to the genus *Streptomyces* that formed the subclade and clustered with *S. samsunensis* M1463^T and *S. malaysiensis* NBRC 16446^T (Fig. 2). The strain was deposited at BIOTEC Culture Collection (BCC), National Center for Genetic Engineering and Biotechnology (BIOTEC) with the registration number BCC71188.

Isolation and structure elucidation of secondary metabolites from the strain BCC71188

An EtOAc crude extract was purified on a Sephadex LH-20 column and followed by HPLC to yield 19 compounds, including cyclic peptides (**1** and **2**), macrolide alaiophylin derivatives (**3**–**7**), naphthoquinone (**8**), nahuoic acid C (**9**), geldanamycin analogs (**10**–**13**), diterpene cyclooctatin (**14**), polyketide germicidins B (**15**) and A (**16**), a peptide actinoramide A (**17**), and two polyethers (abierixin, and 29-*O*-methylabierixin). The chemical structures of these compounds were determined by using spectroscopic techniques including NMR, Mass, IR, UV spectroscopy, and the isolated compounds were also evaluated for biological activity.

Compound **3** was obtained as a white solid. The molecular formula $C_{48}H_{78}O_{15}$ was deduced by the analysis of HRESIMS spectrum, giving the mass ion peak at *m/z* 917.5241 $[M + Na]^+$. Partial spectroscopic information from the ^1H and ^{13}C NMR spectra data were identical to those reported for monoglycosylelaiolide (Table 1), which was synthesized from elaiophylin (Bindseil and Zeeck 1993). This is the first report of monoglycosylelaiolide from a natural source. The complete ^1H and ^{13}C NMR spectral data were given in Table 1.

Compound **8** was obtained as a red solid and had the molecular formula of $C_{11}H_9NO_3$ by showing a mass ion peak at *m/z* 202.0514 $[M - H]^-$ in HRESIMS spectrum (Fig. S12). The ^1H NMR spectrum gave signals of one methyl at δ_H 1.44 (s) and three aromatic protons at δ_H 5.67 (s), 7.26 (s), and 7.69 (s). The ^{13}C NMR spectrum (Fig. S8), together with DEPT-135 spectrum (Fig. S9), displayed 11 signals comprising one methyl (δ_C 16.3), three aromatic methine (δ_C 101.8, 111.32, 129.5), seven sp^2 quaternary (δ_C 122.4, 128.7, 134.5, 151.2, 162.5, 180.9, 182.4) carbons. Two sp^2 quaternary carbons resonating at δ_C 180.9 and 182.4 were carbonyl carbons of 1,4-naphthoquinones, supported by the absorption at ν_{max}

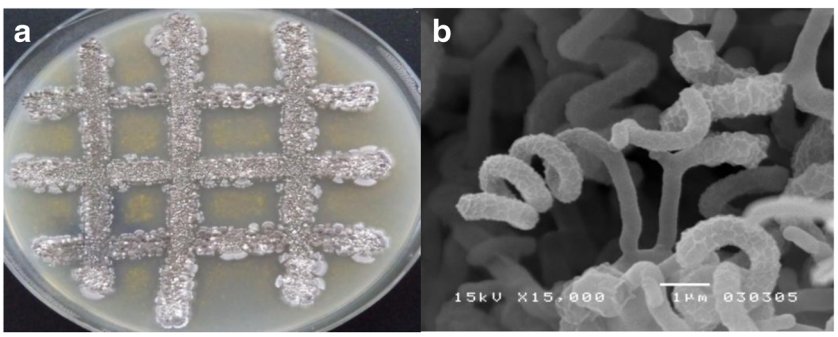

Fig. 1 Colony characteristic of strain BCC711888 appearance on ISP 3 (**a**) and scanning electron micrograph on ISP 4 (**b**)

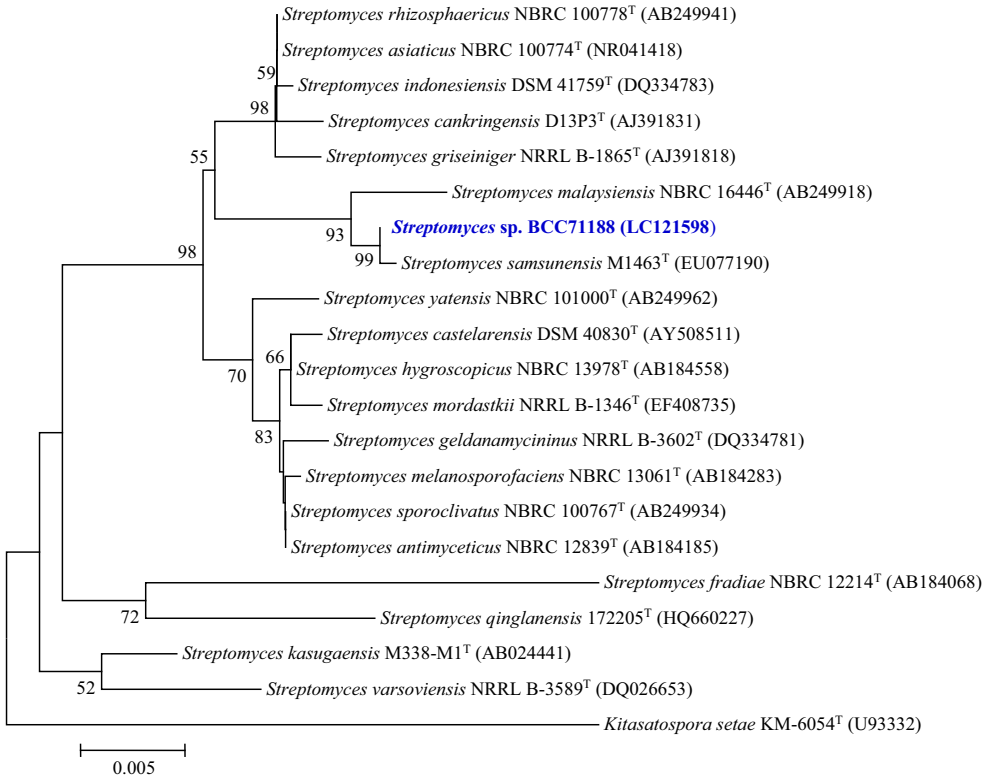

Fig. 2 Neighbor-joining phylogenetic tree based on 16S rRNA gene sequences of the strain BCC71188 and closely related *Streptomyces* strains. The numbers on the branches indicate the percentage bootstrap values of 1000 replicates; only values >50 % are indicated

1683 cm^{-1} in IR spectrum. The HMBC spectrum (Fig. S11), showed correlations from the methyl proton at 7-CH_3 (δ_H 1.44) to C-6, C-7, and C-8; from H-8 (δ_H 7.69) to C-1, C-4a, C-6, and 7-CH_3; from H-5 (δ_H 7.26) to C-4, C-6, C-7, C-8a; from H-3 (δ_H 5.67) to C-1, C-2, and C-4a. In the ^{13}C NMR spectrum, C-2 and C-6 resonated at δ_C 151.2 and δ_C 162.5, respectively, together with HRESIMS data, suggested the presence of an amino and a hydroxyl groups at C-2 and C-6, respectively. Therefore, compound **8** was 2-amino-6-hydroxyl-7-methyl-1,4-naphthoquinone and possessed the chemical structure as shown in Fig. 3. Compound **8** is a new 1,4-naphthoquinone derivative with a presence of amino group at the 2 position.

The ^1H and ^{13}C NMR spectral data of the known compounds (**1**, **2**, **4**–**7**, **9**–**17**, abierixin, and 29-*O*-methylabierixin) were agreed with those previously reported for nocardamine (**1**) (Lee et al. 2005), dehydroxynocardamine (**2**) (Lee et al. 2005), elaiophylin or azalomycin (**4**) (Kaiser and Keller-Schierlein 1981; Nair et al. 1994), 11, 11′-*O*-dimethylelaiophylin (**5**) (Ritzau et al. 1998; Wu et al. 2013), efomycin G (**6**) (Frobel et al. 1990), oxohygrolidin (**7**) (Carr et al. 2010; Kretschmer et al. 1985), nahuoic acid C (**9**) (Nong et al. 2016), geldanamycin (**10**) (DeBoer et al. 1970), 17-*O*-demethylgeldanamycin (**11**) (Yin et al. 2011), 17-demethoxyreblastatin (**12**) (Stead et al. 2000), 4,5-dihydrothiazinogeldanamycin (**13**) (Wu et al. 2012), cyclooctatin (**14**) (Aoyagi et al. 1992; Zhao et al. 2013), germicidins B (**15**) and A (**16**) (Petersen et al. 1993), actinoramide A or padanamide A (**17**) (Nam et al. 2011), abierixin, and 29-*O*-methylabierixin (Supong et al. 2016). The absolute configuration at the asymmetric carbon of compound **16** was determined to be "*S*" as giving a positive sign of specific rotation ($[\alpha]_D^{24}$ +27.86, MeOH), versus the specific rotation ($[\alpha]_D$ +22.0, MeOH) reported in the literature (Aoki et al. 2011). In addition, these previously reported compounds were also confirmed by HRESIMS data, their physicochemical properties, and chemical means for compound **9**.

The results showed that *Streptomyces* sp. strain BCC71188 is as an excellent producer of secondary metabolites. The strain provided two naturally new compounds, which were compounds **3** and **8**, and also produced diverse compounds that derived from different biosynthetic pathways.

Biological activity of isolated compounds

Nocardamine analogs **1** and **2** exhibited antimalarial activity against *P. falciparum*, K-1 strain—the multidrug-resistant strain, with IC_{50} values of 3.20 and 2.63 μg/ml, respectively, and also showed cytotoxicity against NCI-H187 cell line with IC_{50} values of 17.76 and 9.16 μg/ml, respectively. Moreover, elaiophylin derivatives **4**–**6** displayed antimicrobial activity against *B. cereus* (MIC 0.78 3.13 μg/ml), *M. tuberculosis* (MIC 0.78 12.0 μg/ml), and *P. falciparum* (IC_{50} 0.22 2.37 μg/ml), while monoglycosylelaiolide (**3**) showed only antimalarial activity with IC_{50} value of 2.46 μg/ml.

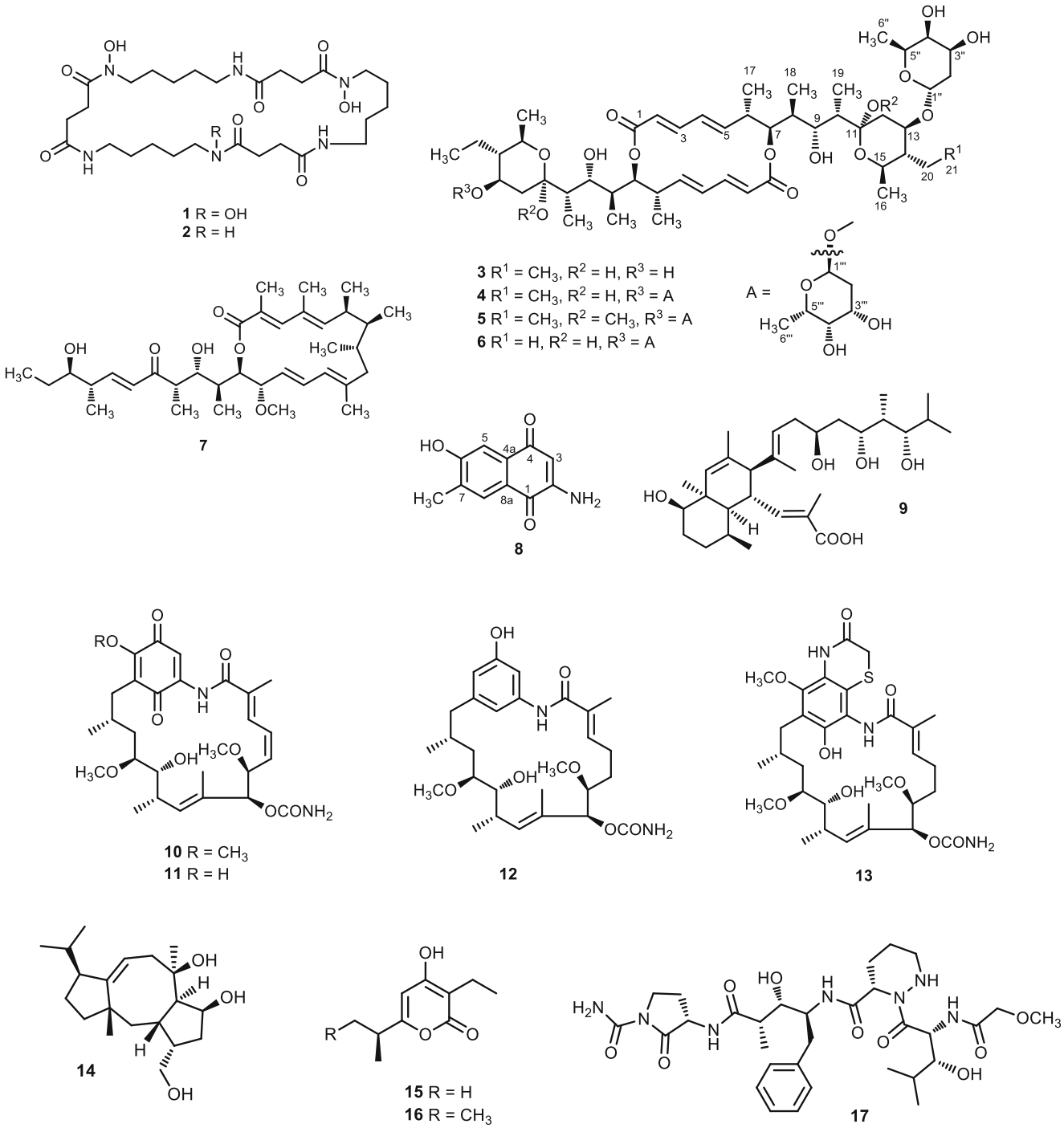

Fig. 3 Chemical structures of secondary metabolites isolated from the strain BCC71188

However, compounds **3**–**6** also showed cytotoxicity against both cancerous and non-cancerous cells (Table 2). Geldanamycin derivatives (**10**–**12**) showed antimalarial activity with IC_{50} values in a range of 0.31–1.90 μg/ml. Compound **10** had strong cytotoxicity against both cancerous and non-cancerous cells (Table 2), while compounds **11** and **12** displayed non-cytotoxicity against KB and MCF-7 cells. Cyclooctatin (**14**) showed antimicrobial activity against *B. cereus* (MIC 25.0 μg/ml) and *P. falciparum* (IC_{50} 7.14 μg/ml) with relatively low cytotoxicity. Moreover, compounds **8**, **9**, **13**, **15**, and **16** were inactive for all tests except that compound **9** displayed low cytotoxicity against NCI-H187 cell line with IC_{50} value of 28.53 μg/ml. Compound **7**, abierixin, and 29-*O*-methylabierixin were earlier reported from our group for antimicrobial activity against *B. cereus*, *M. tuberculosis*, and *P. falciparum* along with the cytotoxicity

Table 2 Biological activity of isolated compounds from *Streptomyces* sp. BCC71188

Compound	Anti-*B. cereus* MIC (μg/ml)	Anti-*M. tuberculosis* MIC (μg/ml)	Anti-*P. falciparum* IC_{50} (μg/ml)	Cytotoxicity IC_{50} (μg/ml)			
				NCI-H187	KB	MCF-7	Vero
1	>25.0	>50.0	3.20	17.76	>50.0	>50.0	>50.0
2	>25.0	>50.0	2.63	9.16	>50.0	>50.0	>50.0
3	>25.0	>50.0	2.46	2.67	3.35	9.80	5.31
4	0.78	0.78	0.22	0.46	0.64	1.82	0.62
5	1.56	3.13	1.47	0.65	0.67	1.43	1.13
6[a]	3.13	12.0	2.37	1.56	5.16	7.86	3.68
7[a]	>25.0	50.0	2.30	2.96	4.70	12.89	15.47
8	>25.0	>50.0	>10.0	>50.0	>50.0	>50.0	>50.0
9	>25.0	>50.0	>10.0	28.53	>50.0	>50.0	>50.0
10	>25.0	>50.0	0.35	0.032	1.63	3.30	0.59
11	>25.0	>50.0	1.90	1.11	>50.0	>50.0	14.97
12	>25.0	>50.0	0.31	0.28	>50.0	>50.0	10.55
13	>25.0	>50.0	>10.0	>50.0	>50.0	>50.0	>50.0
14	25.0	>50.0	7.14	47.82	34.66	>50.0	32.78
15	>25.0	>50.0	>10.0	>50.0	>50.0	>50.0	>50.0
16	>25.0	>50.0	>10.0	>50.0	>50.0	>50.0	>50.0
Abierixin[a]	25.0	>50.0	2.58	22.50	>50.0	>50.0	16.68
29-*O*-Methylabierixin[a]	25.0	50.0	1.40	10.12	16.86	22.27	4.29
Vancomycin	2.00	–	–	–	–	–	–
Rifampicin	–	0.013	–	–	–	–	–
Streptomycin	–	0.313	–	–	–	–	–
Isoniazid	–	0.047	–	–	–	–	–
Ofloxacin	–	0.391	–	–	–	–	–
Ethambutol	–	0.938	–	–	–	–	–
Dihydroartemisinin	–	–	7.17×10^{-4}	–	–	–	–
Mefloquine	–	–	0.013	–	–	–	–
Ellipticine	–	–	–	3.11	2.60	–	1.12
Doxorubicin	–	–	–	0.12	0.35	8.59	–
Tamoxifen	–	–	–	–	–	8.14	–

[a] The data were taken from the previously published results (Supong et al. 2016)

against both cancerous and non-cancerous cells (Supong et al. 2016).

Discussion

The genus *Streptomyces* is the major group of filamentous actinobacteria that has been isolated from various environments. An ability to produce bioactive compounds, especially antibiotics, of this genus is well recognized. An actinomycetes strain BCC71188 was identified by its morphological, chemotaxonomic, and genotypic characteristics as *Streptomyces*, which closely related to *S. samsunensis* M1463^T (99.85 %) and *S. malaysiensis* NBRC 16446^T (99.40 %). The crude extract of this strain exhibited strong antimicrobial activity including anti-*B. cereus* (MIC 1.56 μg/ml), anti-*M. tuberculosis* (MIC 6.25 μg/ml), and anti-*P. falciparum* (IC_{50} 0.19 μg/ml). Nineteen compounds, including two naturally new and 17 known, have been isolated and identified from *Streptomyces* sp. BCC71188. Nocardamine or deferrioxamine E (**1**) was originally reported from various strains of bacteria such as *Nocardia* sp., *Pseudomonas stutzeri*, and *S. hydroscopicus* var. *geldanus* (Lee et al. 2005; Maehr et al. 1977; Wang et al. 2000). Dehydroxynocardamine or terragine E (**2**) was earlier isolated from engineered *S. lividans* (Wang et al. 2000) and later isolated from a marine-derived bacterium of the genus *Streptomyces* (Lee et al. 2005) and *S. avermitilis* K139 (Ueki et al. 2009). Compounds **1** and **2** were inactive against various strains of Gram-positive and Gram-negative bacteria at the

concentration of 200 μg/ml and several fungal strains (Lee et al. 2005). Monoglycosylelaiolide (**3**) was semi-synthesized from elaiophylin (Bindseil and Zeeck 1993) and its biological activity has never been reported. Elaiophylin or azalomycin B or gopalamycin (**4**) and 11,11′-*O*-dimethylelaiophylin (**5**) was formerly isolated from *S. melanosporus*, *S. violaceoniger* (Arai 1960) and *Streptomyces* spp. strains HKI-0113 and HKI-0114 (Ritzau et al. 1998). Compounds **4** and **5** had antibacterial activity against Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus faecium* with MIC in a range of 0.78–3.13 μg/ml (Hammann et al. 1990) and also showed cytotoxicity against L-929, K562, and HeLa cell lines (Ritzau et al. 1998). Efomycin G (**6**) was formerly isolated from soil *Streptomyces* sp. BS 1261 (Frobel et al. 1990), from the marine-derived *Streptomyces* sp. 7-145 (Wu et al. 2013), and from endophytic *Streptomyces* sp. BCC72023 (Supong et al. 2016). It displayed antimicrobial activity with cytotoxicity against both cancerous and non-cancerous cells (Supong et al. 2016; Wu et al. 2013). Oxohygrolidin (**7**) was isolated from *Streptomyces* spp. from various sources (Kretschmer et al. 1985; Supong et al. 2016) and antimicrobial activity was also reported (Supong et al. 2016). Nahuoic acid C (**9**), a polyketide with a decalin ring, was first isolated from the marine *Streptomyces* SCSGAA 0027 (Nong et al. 2016) and was failed to display biological activity including acetylcholinesterase assay, antibacterial assay, and cytotoxicity against several cancer cell lines such as H1975, K562, BGC823, MCF-7, HL60, and Huh-7 (Nong et al. 2016). However, it had weak cytotoxicity against NCI-H187 (IC_{50} 28.53 μg/ml, Table 2). Geldanamycin analogs with varying substituents at the C-17, such as tanespimycin (or 17-*N*-allylamino-17-demethoxygeldanamycin, 17-AAG), have been developed for anticancer agents due to their ability to inhibit the chaperone activity of heat shock protein 90 (Hsp90) (Lin et al. 2011). Due to the limitation on the hepatotoxicity and low water solubility, more analogs of geldanamycin are, therefore, required for further study. Geldanamycin (**10**) was previously isolated from *S. hygroscopicus* var. *geldanus* var. *nova* and had broad spectrum of antimicrobial activity (MIC 2 – >100 μg/ml), showed anti-phytopathogenic fungal activity against *Alternaria*, *Pythium*, *Botrytis*, and *Penicillium* (<500 ppm), and possessed strong anticancer activity against KB and L1210 cells (DeBoer et al. 1970). 17-*O*-demethylgeldanamycin (**11**) was first reported from *S. autolyticus* CGMCC 0516 with inactivated the *gdmMT* gene to study gene encoding C-17 *O*-methyltransferase of geldanamycin biosynthesis (Yin et al. 2011). Moreover, this is the first report of compound **11** directly obtained from a natural source and it exhibited antimalarial activity (IC_{50} 1.90 μg/ml) and anti-NCI-H187 activity (IC_{50} 1.11 μg/ml). 17-Demethoxylreblastatin (**12**) was formerly isolated from *Streptomyces* sp. S6619 and *S. hygroscopicus* JCM4427 (Wu et al. 2012). Compound **12** inhibited oncostatin M (OSM)-driven sPAP (secreted placenta alkaline phosphatase) production in HepG2B6 cells with IC_{50} value of 0.7 mM (Stead et al. 2000) and Hsp90 ATPase with IC_{50} value of 1.82 μM (Wu et al. 2012). Compound **13**, geldanamycin with a thiazino-moiety in hydroquinone ring at C-19, was first isolated from the *gdmP* mutant in *Streptomyces hygroscopicus* 17997 (Lin et al. 2011) and later from *S. hygroscopicus* JCM4427 (Wu et al. 2012). It had 33-fold higher water solubility than compound **10** and possessed moderate anti-HSV-1 virus activity toward infected Vero cells with IC_{50} value of 0.252 μM (Lin et al. 2011). Compound **13** was inactive to all our biological tests (Table 2). Cyclooctatin (**14**), a tricyclic diterpene with 5-8-5-fused ring system, was previously isolated from *Streptomyces* spp., such as *S. melanosporofaciens* MI614-43F2 (Aoyagi et al. 1992) and *Streptomyces* sp. LZ35 (Zhao et al. 2013), and was inactive toward antimicrobial activity at 100 μg/ml but inhibited lyso-phospholipase enzyme with low cytotoxicity in mice (Aoyama et al. 1992). Moreover, in our assay, compound **14** exhibited weak antimalarial (IC_{50} 7.14 μg/ml) and anti-*B. cereus* (MIC 25.0 μg/ml) activities (Table 2). Pyrone derivatives known as germicidins B (**15**) and A (**16**) were formerly isolated from *S. viridochromogens* NRRL B-1551 (JCM4265) (Petersen et al. 1993) and *S. coelicolor* A3(2) (Aoki et al. 2011). Compound **16** inhibited spore germination of several *Streptomyces* strains at a concentration of 40 pg/ml (Petersen et al. 1993) and of the producing strain at concentration above 1 μg/ml (Aoki et al. 2011). In addition, germicidin A (**16**) was inactive against various Gram-positive and Gram-negative bacteria and various fungi (Petersen et al. 1993). Actinoramide A or padanamide A (**17**), having a unique embodiment of the unusual amino acids, was earlier isolated from a marine bacterium, which closely related to the genus *Streptomyces* spp. (Nam et al. 2011; Williams et al. 2011) and showed cytotoxic to Jurkat T lymphocyte cells (ATCC TIB-152) in vivo with IC_{50} value of 60 μg/ml (Williams et al. 2011). However, compound **17** was inactive against HCT-116 (human colon carcinoma) cells, methicillin-resistant *S. aureus*, and the breast cancer-related enzyme aromatase (Nam et al. 2011). Abierixin and 29-*O*-methylabierixin were previously produced by various *Streptomyces* spp. such as *S. albus* NRRL B-1865 (David et al. 1985), *S. hygroscopicus* XM201 (Wu et al. 2009), and endophytic *Streptomyces* sp. BCC72023 (Supong et al. 2016) and was earlier reported by our group to exhibit antimicrobial activity with weak cytotoxicity (Supong et al. 2016).

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Aoki Y, Matsumoto D, Kawaide H, Natsume M (2011) Physiological role of germicidins in spore germination and hyphal elongation in *Streptomyces coelicolor* A3(2). J Antibiot 64(9):607–611. doi:10.1038/ja.2011.59

Aoyagi T, Aoyama T, Kojima F, Hattori S, Honma Y, Hamada M, Takeuchi T (1992) Cyclooctatin, a new inhibitor of lysophospholipase, produced by *Streptomyces melanosporofaciens* MI614-43F2. Taxonomy, production, isolation, physico-chemical properties and biological activities. J Antibiot 45(10):1587–1591

Aoyama T, Naganawa H, Muraoka Y, Aoyagi T, Takeuchi T (1992) The structure of cyclooctatin, a new inhibitor of lysophospholipase. J Antibiot 45(10):1703–1704

Arai M (1960) Azalomycins B and F, two new antibiotics. I. Production and isolation. J Antibiot 13:46–50

Arai T (1975) Culture media for actinomycetes. The Society for Actinomycetes Japan, Tokyo, pp. 1–131

Bindseil KU, Zeeck A (1993) Chemistry of unusual macrolides. 1. Preparation of the aglycons of concanamycin A and elaiophylin. J Org Chem 58(20):5487–5492. doi:10.1021/jo00072a036

Bunbamrung N, Dramae A, Srichomthong K, Supothina S, Pittayakhajonwut P (2014) Streptophenazines I–L from *Streptomyces* sp. BCC21835. Phytochem Lett 10:91–94

Carr G, Williams DE, Diaz-Marrero AR, Patrick BO, Bottriell H, Balgi AD, Donohue E, Roberge M, Andersen RJ (2010) Bafilomycins produced in culture by *Streptomyces* spp. isolated from marine habitats are potent inhibitors of autophagy. J Nat Prod 73:422–427

Changsen C, Franzblau SG, Palittapongarnpim P (2003) Improved green fluorescent protein reporter gene-based microplate screening for antituberculosis compounds by utilizing an acetamidase promoter. Antimicrob Agents Chemother 47(12):3682–3687

Chater KF, Chandra G (2006) The evolution of development in *Streptomyces* analysed by genome comparisons. FEMS Microbiol Rev 30(5):651–672. doi:10.1111/j.1574-6976.2006.00033.x

David L, Leal Ayala H, Tabet JC (1985) Abierixin, a new polyether antibiotic. Production, structural determination and biological activities. J Antibiot 38(12):1655–1663

DeBoer C, Meulman PA, Wnuk RJ, Peterson DH (1970) Geldanamycin, a new antibiotic. J Antibiot 23(9):442–447

Desjardins RE, Canfield CJ, Haynes JD, Chulay JD (1979) Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique. Antimicrob Agents Chemother 16(6): 710–718

Ding L, Ndejouong Ble S, Maier A, Fiebig HH, Hertweck C (2012) Elaiomycins D-F, antimicrobial and cytotoxic azoxides from *Streptomyces* sp. strain HKI0708. J Nat Prod 75:1729–1734

Dramae A, Nithithanasilp S, Choowong W, Rachtawee P, Prabpai S, Kongsaeree P, Pittayakhajonwut P (2013) Antimalarial 20-membered macrolides from *Streptomyces* sp. BCC33756. Tetrahedron 69(38):8205–8208. doi:10.1016/j.tet.2013.07.034

Felsenstein J (1985) Confidence limits on phylogenies: an approach using the bootstrap. Evolution 39(4):783–791. doi:10.2307/2408678

Frobel K, Muller H, Bischoff E, Salcher O, de Jong A, Berschauer F, Scheer M (1990) Efomycin G and it's use as yield promoter in animals. US Patent US 4927810:22

Genilloud O, Gonzalez I, Salazar O, Martin J, Tormo JR, Vicente F (2011) Current approaches to exploit actinomycetes as a source of novel natural products. J Ind Microbiol Biotechnol 38(3):375–389. doi:10.1007/s10295-010-0882-7

Hammann P, Kretzschmar G, Seibert G (1990) Secondary metabolites by chemical screening. 7. I. Elaiophylin derivatives and their biological activities. J Antibiot 43(11):1431–1440

Inahashi Y, Matsumoto A, Danbara H, Omura S, Takahashi Y (2010) *Phytohabitans suffuscus* gen. nov., sp. nov., an actinomycete of the family Micromonosporaceae isolated from plant roots. Int J Syst Evol Microbiol 60(Pt 11):2652–2658. doi:10.1099/ijs.0.016477-0

Intaraudom C, Bunbamrung N, Dramae A, Danwisetkanjana K, Rachtawee P, Pittayakhajonwut P (2015) Antimalarial and antimycobacterial agents from *Streptomyces* sp. BCC27095. Tetrahedron Lett 56(49):6875–6877. doi:10.1016/j.tetlet.2015.10.098

Kaiser H, Keller-Schierlein W (1981) Stoffwechselprodukte von mikroorganismen. 202. Mitteilung. Strukturaufklärung von elaiophylin: Spektroskopische untersuchungen und abbau. Helv Chim Acta 64(2):407–424. doi:10.1002/hlca.19810640206

Kawamoto I, Oka T, Nara T (1981) Cell wall composition of *Micromonospora olivoasterospora*, *Micromonospora sagamiensis*, and related organisms. J Bacteriol 146(2):527–534

Kelly K (1964) Inter-society color council–national bureau of standard color name charts illustrated with centroid colors. US Government Printing Office, Washington, DC

Kimura M (1980) A simple method for estimating evolutionary rates of base substitutions through comparative studies of nucleotide sequences. J Mol Evol 16(2):111–120

Kretschmer A, Dorgerloh M, Deeg M, Hagenmaier H (1985) The structures of novel insecticidal macrolides: bafilomycins D and E, and oxohygrolidin. Agric Biol Chem 49(8):2509–2511. doi:10.1271/bbb1961.49.2509

Lane DJ (1991) 16S/23S rRNA sequencing. In: Stackebrandt E, Goodfellow M (eds) Nucleic acid techniques in bacterial systematics. John Wiley & Sons, Chichester, pp. 115–148

Lee H-S, Shin HJ, Jang KH, Kim TS, Oh K-B, Shin J (2005) Cyclic peptides of the nocardamine class from a marine-derived bacterium of the genus *Streptomyces*. J Nat Prod 68(4):623–625. doi:10.1021/np040220g

Lin L, Ni S, Wu L, Wang Y, Wang Y, Tao P, He W, Wang X (2011) Novel 4,5-dihydro-thiazinogeldanamycin in a gdmP mutant strain of *Streptomyces hygroscopicus* 17997. Biosci Biotechnol Biochem 75(10):2042–2045. doi:10.1271/bbb.110361

Lu C, Li Y, Deng J, Li S, Shen Y, Wang H, Shen Y (2013) Hygrocins C-G, cytotoxic naphthoquinone ansamycins from gdmAI-disrupted *Streptomyces sp*. LZ35. J Nat Prod 76(12):2175–2179. doi:10.1021/np400474s

Maehr H, Benz W, Smallheer J, Williams Thomas H (1977) Mikrobielle produkte, I NMR-spektren von nocardamin und massenspektrum des tri-O-methyl-nocardamins/Microbiological products, I NMR spectra of nocardamine and mass spectra of tri-O-methyl-nocardamine. Z Naturforsch B 32(8):937–942. doi:10.1515/znb-1977-0819

Manfio GP, Zakrzewska-Czerwinska J, Atalan E, Goodfellow M (1995) Towards minimal standards for the description of *Streptomyces* species. Biotekhnologia 7:242–253

Nair MG, Chandra A, Thorogood DL, Ammermann E, Walker N, Kiehs K (1994) Gopalamicin, an antifungal macrodiolide produced by soil actinomycetes. J Agric Food Chem 42(10):2308–2310. doi:10.1021/jf00046a043

Nam SJ, Kauffman CA, Jensen PR, Fenical W (2011) Isolation and characterization of actinoramides A-C, highly modified peptides from a marine *Streptomyces* sp. Tetrahedron 67(35):6707–6712. doi:10.1016/j.tet.2011.04.051

Nong XH, Zhang XY, Xu XY, Wang J, Qi SH (2016) Nahuoic acids B-E, polyhydroxy polyketides from the marine-derived *Streptomyces* sp. SCSGAA 0027. J Nat Prod 79:141–148

O'Brien J, Wilson I, Orton T, Pognan F (2000) Investigation of the alamar blue (resazurin) fluorescent dye for the assessment of mammalian cell cytotoxicity. Eur J Biochem 267(17):5421–5426

Park S-H, Moon K, Bang H-S, Kim S-H, Kim D-G, Oh K-B, Shin J, Oh D-C (2012) Tripartilactam, a cyclobutane-bearing tricyclic lactam from a *Streptomyces* sp. in a dung beetle's brood ball. Org Lett 14(5):1258–1261. doi:10.1021/ol300108z

Petersen F, Zahner H, Metzger JW, Freund S, Hummel RP (1993) Germicidin, an autoregulative germination inhibitor of *Streptomyces viridochromogenes* NRRL B-1551. J Antibiot 46(7):1126–1138

Raju R, Gromyko O, Fedorenko V, Luzhetskyy A, Plaza A, Müller R (2012) Juniperolide A: a new polyketide isolated from a terrestrial actinomycete, *Streptomyces* sp. Org Lett 14(23):5860–5863. doi:10.1021/ol302766z

Raju R, Gromyko O, Fedorenko V, Luzketskyy A, Muller R (2015) Albaflavenol B, a new sesquiterpene isolated from the terrestrial actinomycete, *Streptomyces* sp. J Antibiot 68(4):286–288. doi:10.1038/ja.2014.138

Ritzau M, Heinze S, Fleck WF, Dahse HM, Grafe U (1998) New macrodiolide antibiotics, 11-O-monomethyl- and 11, 11-O-dimethylelaiophylins, from *Streptomyces* sp. HKI-0113 and HKI-0114. J Nat Prod 61(11):1337–1339. doi:10.1021/np9800351

Saitou N, Nei M (1987) The neighbor-joining method: a new method for reconstructing phylogenetic trees. Mol Biol Evol 4(4):406–425

Sarker SD, Nahar L, Kumarasamy Y (2007) Microtitre plate-based antibacterial assay incorporating resazurin as an indicator of cell growth, and its application in the in vitro antibacterial screening of phytochemicals. Methods 42:321–324

Shirling EB, Gottlieb D (1966) Methods for characterization of *Streptomyces* species. Int J Syst Bacteriol 16:313–340. doi:10.1099/00207713-16-3-313

Staneck JL, Roberts GD (1974) Simplified approach to identification of aerobic actinomycetes by thin-layer chromatography. Appl Microbiol 28:226–231

Stead P, Latif S, Blackaby AP, Sidebottom PJ, Deakin A, Taylor NL, Life P, Spaull J, Burrell F, Jones R, Lewis J, Davidson I, Mander T (2000) Discovery of novel ansamycins possessing potent inhibitory activity in a cell-based oncostatin M signalling assay. J Antibiot 53(7):657–663

Supong K, Thawai C, Suwanborirux K, Choowong W, Supothina S, Pittayakhajonwut P (2012) Antimalarial and antitubercular C-glycosylated benz [α] anthraquinones from the marine-derived *Streptomyces* sp. BCC45596. Phytochem Lett 5(3):651–656. doi:10.1016/j.phytol.2012.06.015

Supong K, Thawai C, Choowong W, Kittiwongwattana C, Thanaboripat D, Laosinwattana C, Koohakan P, Parinthawong N, Pittayakhajonwut P (2016) Antimicrobial compounds from endophytic *Streptomyces* sp. BCC72023 isolated from rice (*Oryza sativa* L.). Res Microbiol. doi:10.1016/j.resmic.2016.01.004

Tamaoka J (1994) Determination of DNA base composition. In: Goodfellow M, O'Donnel AG (eds) Chemical methods in prokaryotic systematics. John Wiley & Sons, Chichester, pp. 463–470

Tamura K, Stecher G, Peterson D, Filipski A, Kumar S (2013) MEGA6 molecular evolutionary genetics analysis version 6.0. Mol Biol Evol 30(12):2725–2729. doi:10.1093/molbev/mst197

Thompson JD, Higgins DG, Gobson TJ (1994) CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position specific gap penalties and weight matrix choice. Nucleic Acids Res 22:4673–4680

Thompson JD, Gibson TJ, Plewniak F, Jeanmougin F, Higgins DG (1997) The CLUSTAL_X windows interface: flexible strategies for multiple sequence alignment aided by quality analysis tools. Nucleic Acids Res 25(24):4876–4882

Ueki M, Suzuki R, Takamatsu S, Takagi H, Uramoto M, Ikeda H, Osada H (2009) Nocardamin production by *Streptomyces avermitilis*. Actinomycetologica 23(2):34–39. doi:10.3209/saj.SAJ230203

Wang GY, Graziani E, Waters B, Pan W, Li X, McDermott J, Meurer G, Saxena G, Andersen RJ, Davies J (2000) Novel natural products from soil DNA libraries in a streptomycete host. Org Lett 2(16):2401–2404

Wang X, Shaaban KA, Elshahawi SI, Ponomareva LV, Sunkara M, Zhang Y, Copley GC, Hower JC, Morris AJ, Kharel MK, Thorson JS (2013) Frenolicins C-G, pyranonaphthoquinones from *Streptomyces* sp. RM-4-15. J Nat Prod 76(8):1441–1447. doi:10.1021/np400231r

Williams ST, Cross T (1971) Actinomycetes. In: Booth C (ed) Methods in microbiology vol 4. Academic Press, London, pp. 295–334

Williams DE, Dalisay DS, Patrick BO, Matainaho T, Andrusiak K, Deshpande R, Myers CL, Piotrowski JS, Boone C, Yoshida M, Andersen RJ (2011) Padanamides A and B, highly modified linear tetrapeptides produced in culture by a *Streptomyces* sp. isolated from a marine sediment. Org Lett 13(15):3936–3939. doi:10.1021/ol2014494

Wu Z, Bai L, Wang M, Shen Y (2009) Structure–antibacterial relationship of nigericin derivatives. Chem Nat Comp 45(3):333–337. doi:10.1007/s10600-009-9350-x

Wu CZ, Jang JH, Ahn JS, Hong YS (2012) New geldanamycin analogs from *Streptomyces hygroscopicus*. J Microbiol Biotechnol 22(11):1478–1481

Wu C, Tan Y, Gan M, Wang Y, Guan Y, Hu X, Zhou H, Shang X, You X, Yang Z, Xiao C (2013) Identification of elaiophylin derivatives from the marine-derived actinomycete *Streptomyces* sp. 7-145 using PCR-based screening. J Nat Prod 76(11):2153–2157. doi:10.1021/np4006794

Yin M, Lu T, Zhao L-X, Chen Y, Huang S-X, Lohman JR, Xu L-H, Jiang C-L, Shen B (2011) The missing C-17 *O*-methyltransferase in geldanamycin biosynthesis. Org Lett 13(14):3726–3729. doi:10.1021/ol201383w

Zhao GS, Li SR, Wang YY, Hao HL, Shen YM, Lu CH (2013) 16,17-Dihydroxycyclooctatin, a new diterpene from *Streptomyces* sp. LZ35. Drug Discov Ther 7(5):185–188