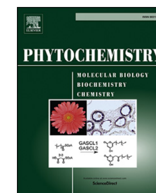
ARTICLE IN PRESS

Phytochemistry xxx (2017) 1–9

Contents lists available at ScienceDirect

Phytochemistry

journal homepage: www.elsevier.com/locate/phytochem



Antiproliferative cyclodepsipeptides from the marine actinomycete *Streptomyces* sp. P11-23B downregulating the tumor metabolic enzymes of glycolysis, glutaminolysis, and lipogenesis

Xuewei Ye [a], Komal Anjum [a], Tengfei Song [a], Wenling Wang [a], Ying Liang [a], Mengxuan Chen [a], Haocai Huang [a], Xiao-Yuan Lian [b, **], Zhizhen Zhang [a, *]

[a] *Ocean College, Zhoushan Campus, Zhejiang University, Zhoushan 316021, China*
[b] *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China*

ARTICLE INFO

Article history:
Received 20 January 2016
Received in revised form
7 December 2016
Accepted 13 December 2016
Available online xxx

Keywords:
Marine actinomycete
Streptomyces sp.
Cyclodepsipeptides
Antiproliferative agents
Glioma cells
Tumor metabolic regulators

ABSTRACT

Two cyclodepsipeptides and a known cyclodepsipeptide valinomycin were isolated from a culture of the marine actinomycete *Streptomyces* sp. P11-23B. Their structures were established based on NMR, HRESIMS, and MS-MS spectroscopic interpretation as well as by chemical degradation. Both streptodepsipeptides P11A and P11B inhibited proliferation of different glioma cell lines, with IC_{50} values ranging from 0.1 μM to 1.4 μM. Streptodepsipeptide P11A was found to block the cell cycle at the G_0/G_1 phase and induce apoptosis in glioma cells. Further investigation demonstrated that streptodepsipeptide P11A downregulated expression of HK2, PFKFB3, PKM2, GLS, and FASN, important tumor metabolic enzymes. Data from this study suggested that targeting multiple tumor metabolic regulators might be one anti-glioma mechanism of streptodepsipeptide P11A. A possible mechanism for this class of streptodepsipeptides is reported herein.

© 2016 Elsevier Ltd. All rights reserved.

1. Introduction

Gliomas are the most common and high death malignant brain tumors (Patil et al., 2013; Ru et al., 2013) and can be located at many important brain function areas, which make surgical resection extremely difficult. Therefore, chemotherapy has played a more important role in treatment and prevention of gliomas. However, so far very few drugs have been approved for treating gliomas including temozolomide (TMZ), carmustine, and lomustine. Of these, only TMZ has been independently used for treatment of gliomas. Furthermore, most current anti-glioma drugs are cytotoxicity-based alkylating agents with limited efficacy and serious side-effects (Chamberlain, 2010; Mittal et al., 2015). Therefore, there is an urgent need to discover lead compounds for development of novel anti-glioma drugs. Marine-derived natural products are important sources for discovery of new anticancer drug leads (Newman and Cragg, 2014; Petit and Biard, 2013; Schumacher et al., 2011).

Enhanced glycolysis, elevated glutaminolysis, and exacerbated lipogenesis, which are required for the rapid and unlimited proliferation of tumor cells, have been demonstrated as prominent hallmarks in glioma metabolism (Galluzzi et al., 2013; Guo et al., 2013; Vander Heiden, 2011; Ru et al., 2013). There are several important regulators (enzymes) in the glycolytic pathway, such as hexokinase 2 (HK2) (Vander Heiden, 2011; Wolf et al., 2011), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB3) (Kessler et al., 2008; Vander Heiden, 2011), and pyruvate kinase M2 (PKM2) (Kefas et al., 2010; Vander Heiden, 2011), that have been shown to be up-regulated in the glioma cells. These specific regulators are preferentially used by cancer cells (Vander Heiden, 2011). Glutamine metabolism (Daye and Wellen, 2012; Ru et al., 2013) and lipid metabolism (Guo et al., 2013; Ru et al., 2013; Santos and Schulze, 2012) have also been found to be largely altered in cancer cells. Both glutaminase (GLS, a key enzyme of glutaminolysis) (Daye and Wellen, 2012; Lu et al., 2010; Ru et al., 2013) and fatty acid synthase (FASN, a key lipogenic enzyme) (Menendez and Lupu, 2007; Ru et al., 2013) are up-regulated in gliomas. Accumulated

* Corresponding author.
** Corresponding author.
E-mail addresses: xylian@zju.edu.cn (X.-Y. Lian), zzhang88@zju.edu.cn (Z. Zhang).

http://dx.doi.org/10.1016/j.phytochem.2016.12.010
0031-9422/© 2016 Elsevier Ltd. All rights reserved.

Please cite this article in press as: Ye, X., et al., Antiproliferative cyclodepsipeptides from the marine actinomycete *Streptomyces* sp. P11-23B downregulating the tumor metabolic enzymes of glycolysis, glutaminolysis, and lipogenesis, Phytochemistry (2017), http://dx.doi.org/10.1016/j.phytochem.2016.12.010

studies have demonstrated that the above mentioned metabolic enzymes are promising targets for discovery of novel anticancer drugs.

As part of an ongoing project for discovery of novel anti-glioma and antibacterial compounds from marine resources (Chen et al., 2015; Liang et al., 2016; Xin et al., 2012; Yu et al., 2014, 2015), a crude extract prepared from the culture of marine bacterium strain P11-23B was found to significantly inhibit proliferation of human glioma cells. Chemical investigation of this active extract led to isolation of two new cyclodepsipeptides, which were named as streptodepsipeptides P11A (**2**) and P11B (**3**), together with known valinomycin (**1**) (Fig. 1). This study described the isolation and culture of the strain P11-23B, the isolation and structural elucidation of new compounds, and their bioactivity against glioma cells and effect on the tumor metabolic regulators.

2. Results and discussion

Strain P11-23B was isolated from a marine mud sample and assigned as *Streptomyces* sp. P11-23B based on the analysis of its 16S rDNA gene sequence, which matched (99% identity for a 1361 bp stretch of sequence) those of seven *Streptomyces* strains (Supplementary Data, Figure S_1 and Table S_1). Culture of this marine actinomycete was grown in Gause's liquid medium (50.0 L). The extract prepared from the culture of P11-23B showed significant activity against the proliferation of human glioma cells with inhibitions of 87.17% for glioma U87-MG cells and 86.84% for U251 cells. Separation of this active extract by ODS column chromatography, following by HPLC purification, afforded three compounds **1**–**3**.

Compound **1** was proved to be the known cyclodepsipeptide valinomycin based on its NMR and HRESIMS data, melting point, optical rotation value, the analysis of its acidic hydrolysates by chiral HPLC and GC analyses, and the comparison with literature data (Pettit et al., 1999; Tabeta and Saito, 1985). Valinomycin (**1**) was previously isolated from several *Streptomyces* species (Heisey et al., 1988; Lim et al., 2007; Park et al., 2008; Pettit et al., 1999) and is well known to enhance the K^+ permeability of several membrane systems including mitochondria, erythrocytes, and lipid bilayers (Bhattacharyya et al., 1971; Haynes et al., 1969). This cyclodepsipeptide was also reported to have activities against tumors, bacteria, fungi (Lim et al., 2007; Park et al., 2008; Pettit et al., 1999), and severe acute respiratory-syndrome coronavirus (Wu et al., 2004). Valinomycin (**1**) is composed of four units of D-valine (D-Val), L-valine (L-Val), D-α-hydroxyisovaleric acid (D-Hiv), and L-lactate (L-Lac) with a trimer structure of cyclo-(D-Val-L-Lac-L-Val-D-Hiv)$_3$. For its ^{13}C and ^{1}H NMR spectroscopic data assignments, see Table S_2 (Supplementary Data). It was noted that each of the four units displayed characteristic NMR signals, which allowed for differentiation of the four units. The unit L-Lac was easily recognized by its NMR signals of δ_C 172.7 (C-1), 70.4 (C-2), 17.3 (C-3) and δ_H 5.32 (1H, q, J = 7.0 Hz, H-2) and 1.44 (3H, d, J = 7.0 Hz, H-3), while D-Hiv had its characteristic signals of δ_C 171.0 (C-1), 78.7 (C-2), 30.4 (C-3), 16.8 (C-4) and δ_H 5.02 (1H, d, J = 3.11 Hz, H-2). The D-Val and L-Val could be distinguished from their chemical shifts of C-1, C-2, H-2 and the coupling constant values of $^3J_{CH\text{-}NH}$. The unit D-Val was indicated by its characteristic NMR signals at δ_C 170.2 (C-1), 59.1 (C-2) and δ_H 4.10 (1H, dd, J = 10.0, 8.1 Hz, H-2), 7.88 (1H, d, J = 8.1 Hz, NH-2), as compared with their counterparts of L-Val at δ_C 172.0 (C-1), 60.6 (C-2) and δ_H 3.96 (1H, dd, J = 10.2, 6.2 Hz, H-2), 7.80 (1H, d, J = 6.2 Hz, NH-2). All of these characteristic NMR signals mentioned above are very helpful for the structure elucidation of the new compounds of streptodepsipeptides P11A (**2**) and P11B (**3**), which had very complicated NMR signals.

The HRESIMS spectrum of compound **2** displayed ions at m/z 1095.6051 ($[M-H]^-$) and 1097.6227 ($[M+H]^+$), corresponding to the molecular formula of $C_{53}H_{88}N_6O_{18}$. Its ^{13}C NMR spectrum showed 53 carbon resonances, which were distributed in six zones. The first zone displayed 12 carbonyl carbon (C=O) signals at δ_C 170.28–172.80. Six carbon signals at δ_C 70.41–78.93 in the second zone were assigned to six oxymethines (α–CH–O) and six resonances at δ_C 58.98–60.75 in the third zone were contributed to six nitrogenated methines (α–CH–N). The fourth zone exhibited eight methines (β-CH) at δ_C 28.49–30.41 and one carbon signal at δ_C 25.16 in the fifth zone was assigned to a methylene (β-CH_2). The remaining 20 carbons, which appeared at δ_C 9.41–19.92 in the sixth zone, were assigned to 20 methyls (γ-CH_3 or β-CH_3). The ^{1}H NMR spectrum of **2** also showed six NH signals at δ_H 7.89 (d, 7.9 Hz), 7.84 (d, 6.0 Hz), 7.83 (d, 8.0 Hz), 7.83 (d, 8.0 Hz), 7.77 (d, 6.2 Hz), and 7.76 (d, 5.8 Hz). All of the above data suggested that compound **2** was composed of 12 units, including six amide groups (amino acids) and six ester groups. Acid hydrolysis of **2** produced D-Val, L-Val, D-Hiv, L-Lac, D-2-hydroxybutanoic acid (D-Hba) as determined by chiral HPLC and GC analyses using the standard compounds as references. Detailed COSY, HSQC, and HMBC spectroscopic analyses confirmed the presence of 12 units including three L-lactates, three L-valines, three D-valines, two D-α-hydroxyisovaleric acids, and one D-2-hydroxybutanoic acid (D-Hba). As shown in Fig. 2, the α-NH and α-CH protons of each valine had a COSY correlation, while the α-CH proton of each unit displayed a COSY correlation with the β-CH (or β-CH_2 for D-Hba, or β-CH_3 for L-Lac) proton, which was correlated with the γ-CH_3 proton. HMBC correlations (see Table 1 and Fig. 2) further supported the structure of each unit. According to the foregoing NMR correlations and the NMR data comparison of

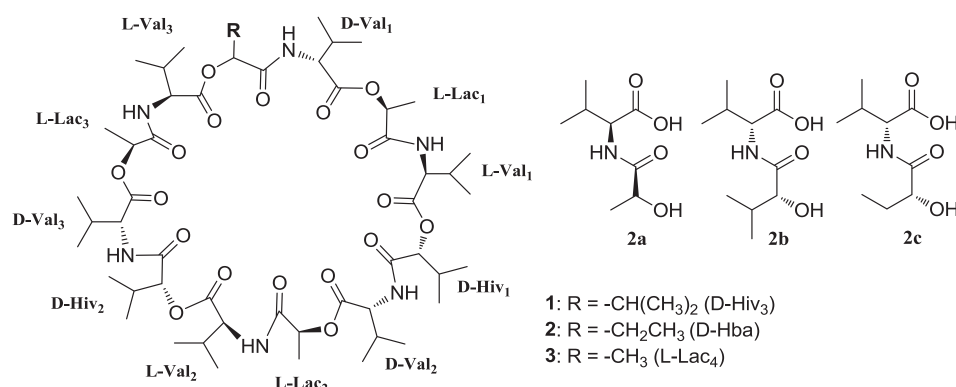


Fig. 1. Structures of compounds **1**–**3**, **2a**, **2b**, and **2c**.

Please cite this article in press as: Ye, X., et al., Antiproliferative cyclodepsipeptides from the marine actinomycete *Streptomyces* sp. P11-23B downregulating the tumor metabolic enzymes of glycolysis, glutaminolysis, and lipogenesis, Phytochemistry (2017), http://dx.doi.org/10.1016/j.phytochem.2016.12.010

Download English Version:

https://daneshyari.com/en/article/5164046

Download Persian Version:

https://daneshyari.com/article/5164046

Daneshyari.com