Phytochemistry 156 (2018) 106–115

Contents lists available at ScienceDirect

Phytochemistry

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

Armochaetoglasins A–I: Cytochalasan alkaloids from fermentation broth of *Chaetomium globosum* TW1-1 by feeding *L*-tyrosine

Weixi Gao[a], Weiguang Sun[a], Fengli Li[a], Chenwei Chai[a], Yan He[b], Jianping Wang[a], Yongbo Xue[a], Chunmei Chen[a], Hucheng Zhu[a], Zhengxi Hu[a,**], Yonghui Zhang[a,*]

[a] Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, People's Republic of China
[b] Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, People's Republic of China

ARTICLE INFO

Keywords:
Chaetomium globosum TW1-1
Chaetomiaceae
Cytochalasan alkaloids
Cytotoxic activity
Antibacterial activity

ABSTRACT

By feeding *L*-tyrosine into the culture medium, nine undescribed compounds, termed as armochaetoglasins A–I, together with three known analogues, namely armochaetoglobin E, chaetoglobosin V, and chaetoglobosin J, were isolated and identified from the medicinal terrestrial arthropod-derived fungus *Chaetomium globosum* TW1-1. Their structures were elucidated by means of NMR spectroscopy, single-crystal X-ray crystallography, and comparison of their electronic circular dichroism (ECD) spectra. Structurally, armochaetoglasin A represented the first tyrosine-derived cytochalasan alkaloid characterized by a 13-membered carbocyclic ring system; armochaetoglasins B and C possessed a rare 19,20-*seco*-chaetoglobosin skeleton. Armochaetoglasin B, chaetoglobosin V, and chaetoglobosin J showed weak cytotoxic activity with IC_{50} values ranging from 19.5 to 34.72 μM.

1. Introduction

Cytochalasan alkaloids represented a large and important group of polyketide synthase-nonribosomal peptide synthetase (PKS-NRPS) hybrid specialised metabolites, showing diverse biological properties, such as antitumor (Jiao et al., 2004; Zhang et al., 2014), anti-HIV (Rochfort et al., 2005), and immunomodulatory activities (Hua et al., 2013). Over the past five decades, cytochalasan alkaloids have received considerable attention from both chemists and pharmacologists, largely due to their architecturally complicated structures and promising bioactivities (Schümann and Hertweck, 2007; Scherlach et al., 2010; Ishiuchi et al., 2013; Hu et al., 2014). As far as we knew, more than 300 cytochalasan alkaloids have been identified hitherto, including a number of excellent studies reported in recent years (Xu et al., 2012; Zhang et al., 2013, 2015; Yan et al., 2016; Zhu et al., 2015, 2016; 2017; Wei et al., 2017). For instance, asperchalasine A, the first cytochalasan dimer, was discovered from *Aspergillus flavipes* (Zhu et al., 2015); afterwards, epicochalasines A and B, two bioactive merocytochalasans bearing caged epicoccine dimer units, were also discovered from this fungus (Zhu et al., 2016); most excitingly, asperflavipine A, the first cytochalasan heterotetramer, was discovered from *Aspergillus flavipes* QCS12 coming from a different origin (Zhu et al., 2017).

Previously, our research group has discovered a large range of bioactive cytochalasan alkaloids from *Chaetomium globosum* TW1-1, which was isolated from the medicinal terrestrial arthropod *Armadillidium vulgare* (Chen et al., 2015a, 2015b, 2016). Biosynthetically, these cytochalasan alkaloids might plausibly be traced backed to *L*-tryptophan, which inspired us to adequately excavate the chemical space by feeding *L*-tyrosine into the fermentation broth of fungus *C. globosum* TW1-1. As a result, nine undescribed compounds, termed as armochaetoglasins A–I (**1–9**) and three known analogues, namely armochaetoglobin E (**10**) (Chen et al., 2015a), chaetoglobosin V (**11**) (Thohinung et al., 2010), and chaetoglobosin J (**12**) (Sekita et al., 1977), were isolated and identified. Structurally, compound **1** represented the first tyrosine-derived cytochalasan alkaloid characterized by a 13-membered carbocyclic ring system; compounds **2** and **3** possessed a rare 19,20-*seco*-chaetoglobosin skeleton, and hitherto only four metabolites bearing this core skeleton have been reported (Chen et al., 2015a). Herein, the isolation, structure elucidation, and bioactivity evaluations of these compounds are described (Fig. 1).

2. Results and discussion

Compound **1** was obtained as a white powder. It was determined to

* Corresponding author.
** Corresponding author.
E-mail addresses: hzx616@126.com (Z. Hu), zhangyh@mails.tjmu.edu.cn (Y. Zhang).

https://doi.org/10.1016/j.phytochem.2018.09.004
Received 2 June 2018; Received in revised form 24 August 2018; Accepted 21 September 2018

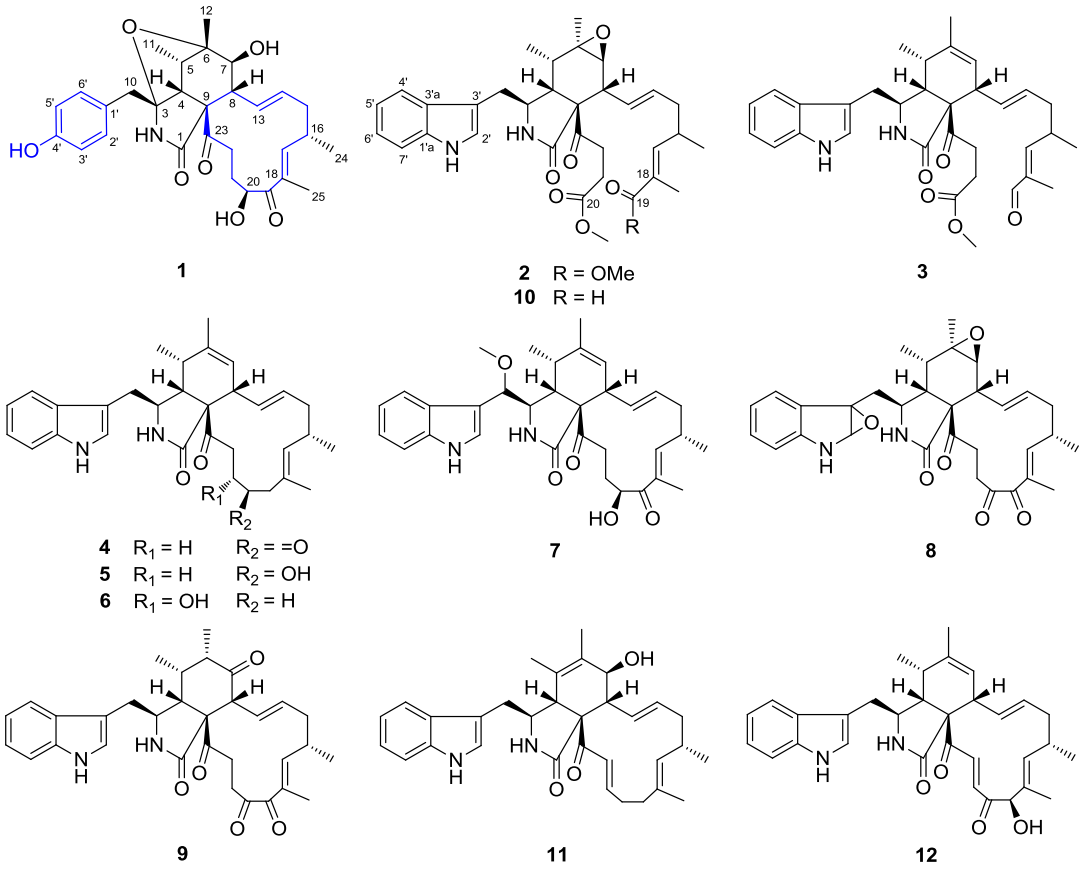

Fig. 1. Chemical structures of compounds **1–12**.

Table 1
^{1}H NMR (400 MHz) spectroscopic data (δ in ppm, J in Hz) for compounds **1–5**.

no.	1[a,d]	2[a,d]	3[a,d]	4[b,d]	5[c,d]
3		3.84, ddd (6.8, 4.9, 3.5)	3.46, q (4.6)	3.37, m	3.28, m
4	2.72, s	2.76, dd (6.8, 3.8)	2.64, t (4.5)	2.65, m	2.45, dd (3.5, 1.5)
5	2.18, m	1.86, m	2.36, m	2.50, m	2.24, s
7	3.37, d (8.7)	2.82, d (5.4)	5.42, m	5.37, s	5.26, s
8	2.55, t (9.6)	2.72, m	3.15, d (9.4)	2.74, br. s	2.54, br. s
10	3.18, d (14.3); 2.90, d (14.3)	2.96, dd (14.3, 4.9); 2.89, dd (14.3, 6.9)	3.00, dd (14.6, 5.1); 2.91, dd (14.6, 4.6)	2.97, dd (14.6, 3.4); 2.62, dd (14.6, 6.3)	2.83, dd (14.5, 4.1); 2.59, dd (14.5, 3.6)
11	1.17, d (7.1)	0.83, d (7.4)	1.10, d (7.3)	1.29, d (7.2)	1.12, d (7.2)
12	1.26, s	1.21, s	1.76, s	1.74, s	1.70, s
13	5.53, m	5.95, m	5.82, dd (15.2, 9.2)	6.00, dd (15.1, 10.2)	5.83, dd (15.2, 10.1)
14	5.30, ddd (14.7, 11.0, 2.7)	5.43, dt (14.8, 7.0)	5.27, dt (15.2, 7.1)	5.08, m	4.82, ddd (15.2, 11.0, 3.6)
15	2.43, m; 2.01, m	2.10, ddd (14.9, 9.4, 4.1)	2.11, dq (15.3, 7.2)	2.18, d (13.6); 1.90, d (12.6)	2.06, d (7.2); 1.63, m
16	2.79, m	2.59, m	2.75, dt (15.5, 7.0)	2.39, m	2.24, m
17	6.26, dd (9.0, 1.6)	6.52, dd (9.9, 1.5)	6.37, dd (9.9, 1.5)	5.13, d (8.9)	4.66, d (8.0)
19				3.04, d (15.3); 2.76, d (15.5)	2.09, d (8.4); 1.77, dd (14.2, 4.3)
20	4.87, m				3.29, m
21	1.83, m; 1.55, m	2.21, m	2.01, q (6.8, 5.9)	3.33, m; 1.98, m	0.93, m
22	2.48, m; 2.23, m	2.68, m; 2.32, m	2.49, dt (19.1, 6.1); 1.76, m	2.45, m; 1.99, m	2.40, m; 0.55, m
24	1.02, d (6.7)	0.98, d (6.7)	1.02, d (6.7)	0.90, d (6.7)	0.81, d (6.7)
25	1.79, s	1.81, s	1.67, s	1.55, s	1.55, s
2′	7.07, d (8.6)	7.15, s	7.12, s	6.94, s	7.04, d (2.3)
3′	6.73, d (8.6)				
4′		7.55, d (7.7)	7.55, m	7.47, d (7.8)	6.95, m
5′	6.73, d (8.6)	7.09, m	7.03, m	7.12, m	7.51, d (7.8)
6′	7.07, d (8.6)	7.03, m	7.08, m	7.18, m	7.00, m
7′		7.32, d (7.7)	7.31, m	7.36, d (8.0)	7.28, d (7.9)
19-OCH_3		3.71, s			
20-OCH_3		3.65, s	3.61, s		

[a] Measured in CD_3OD.
[b] Measured in $CDCl_3$.
[c] Measured in DMSO-d_6.
[d] "m" means overlapped or multiplet with other signals.