

Communication

# Chalcomycins from Marine-Derived *Streptomyces* sp. and Their Antimicrobial Activities

Shutai Jiang <sup>1,†</sup>, Lili Zhang <sup>1,3,†</sup>, Xuechang Pei <sup>1</sup>, Fang Deng <sup>1</sup>, Dan Hu <sup>1</sup>, Guodong Chen <sup>1</sup>, Chuanxi Wang <sup>1,\*</sup>, Kui Hong <sup>2</sup>, Xinsheng Yao <sup>1</sup> and Hao Gao <sup>1,\*</sup>

<sup>1</sup> Institute of Traditional Chinese Medicine and Natural Products, College of Pharmacy/Guangdong Province Key Laboratory of Pharmacodynamic Constituents of Traditional Chinese Medicine & New Drug Research, Jinan University, Guangzhou 510632, China; vstjiang@stu2014.jnu.edu.cn (S.J.); qymuzinini@126.com (L.Z.); cyan2014@stu2014.jnu.edu.cn (X.P.); xff@stu2014.jnu.edu.cn (F.D.); thudan@jnu.edu.cn (D.H.); chgdong@jnu.edu.cn (G.C.); tyaoxs@jnu.edu.cn (X.Y.)

<sup>2</sup> Key Laboratory of Combinatorial Biosynthesis and Drug Discovery, Ministry of Education, and School of Pharmaceutical Sciences, Wuhan University, Wuhan 430071, China; kuihong31@whu.edu.cn

<sup>3</sup> Food and Drug Department, Qingyuan Polytechnic, Qingyuan 511510, China

\* Correspondence: tcxwang@jnu.edu.cn (C.W.); tghao@jnu.edu.cn (H.G.); Tel./Fax: +86-20-8522-8369 (C.W. & H.G.)

† These authors have contributed equally to this work.

Academic Editors: Tracy John Mincer, David C. Rowley and Orazio Tagliatela

Received: 8 March 2017; Accepted: 22 May 2017; Published: 29 May 2017

**Abstract:** Dihydrochalcomycin (**1**) and chalcomycin (**2**), two known chalcomycins, and chalcomycin E (**3**), a new compound, were isolated from marine-derived *Streptomyces* sp. HK-2006-1. Their structures were elucidated by detailed spectroscopic and X-ray crystallographic analysis. The antimicrobial activities against *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Aspergillus niger* of **1–3** were evaluated. Compounds **1–2** exhibited activities against *S. aureus* with minimal inhibitory concentrations (MICs) of 32 µg/mL and 4 µg/mL, respectively. The fact that **1–2** showed stronger activity against *S. aureus* 209P than **3** indicated that the epoxy unit was important for antimicrobial activity. This structure–activity tendency of chalcomycins against *S. aureus* is different from that of aldgamycins reported in our previous research, which provide a valuable example for the phenomenon that 16-membered macrolides with different sugars do not have parallel structure–activity relationships.

**Keywords:** marine-derived *Streptomyces*; secondary metabolite; 16-membered macrolide; chalcomycin E; antimicrobial activity

## 1. Introduction

Infectious diseases seriously imperil human health. Antibiotics are important medicines against infectious diseases [1]. However, the prolonged, extensive, and indiscriminate use of antibiotics has triggered widespread resistance [2]. The global epidemic of continually rising resistance has become a critical threat to human health and therefore the discovery of new antibiotics is urgently needed [2]. Macrolide antibiotics such as erythromycins, tylosins, avermectins, and milbemycins have significant activity against a broad spectrum of Gram-positive bacteria [3–5], playing an important role in the chemotherapy of infectious diseases [6,7]. Macrolides are usually characterized by a 12-, 14-, 16-, 18-, 20-, 22-, or 24-membered lactone ring with one or more sugar moieties [3,8]. Different types of macrolides have different structure–antimicrobial activity relationships. For example, 16-membered macrolides with different sugars have no parallel structure–activity tendencies. Omura reported that the structure–activity relationships of some 16-membered macrolides (rosamicins, angolamycins, and

neutamycins) differed from the evidence found in other 16-membered macrolides (leucomycins) [9]. The 16-membered macrolides with different sugar moiety for instance spiramycins, neospiramycins, and forocidins have different structure–activity relationships [10].

Many interesting strains were obtained in our continuing investigations on active components from microorganisms. Among our recent discoveries [11–21], we recently reported that a strain of *Streptomyces* sp. HK-2006-1 produced both aldamycins and chalcomycins, which are 16-membered macrolides [11,21]. Chalcomycin and seven aldamycins were isolated from this strain, and chalcomycin showed more potent antibacteria activity against *Staphylococcus aureus* than aldamycins [11]. Chalcomycin, the first member of chalcomycins, was reported with its activity against bacteria as early as 1962 [22]. However, there have only been seven chalcomycins (chalcomycin, chalcomycins B-D, dihydrochalcomycin, 8-deoxy-chalcomycin, 250-144C) reported until now [23–27], and there is no discussion on the structure-antimicrobial activity relationship of chalcomycins against *S. aureus*. Thus, in this study, the fermentation volume of this strain *Streptomyces* sp. HK-2006-1 was scaled up in search of more chalcomycins. The crude extract of the culture of the strain was subjected to column chromatography (CC) over silica gel, Sephadex LH-20, octadecylsilane (ODS), and high performance liquid chromatography (HPLC), yielding three chalcomycins, dihydrochalcomycin (1), chalcomycin (2), and a new compound, chalcomycin E (3) (Figure 1). In addition, their antimicrobial activities against two bacteria, Gram-positive *S. aureus* 209P and Gram-negative *Escherichia coli* ATCC0111, as well as two fungi, *Candida albicans* FIM709 and *Aspergillus niger* R330, were evaluated. Details of the isolation, structural elucidation, and antimicrobial activities of compounds 1–3 are presented herein.

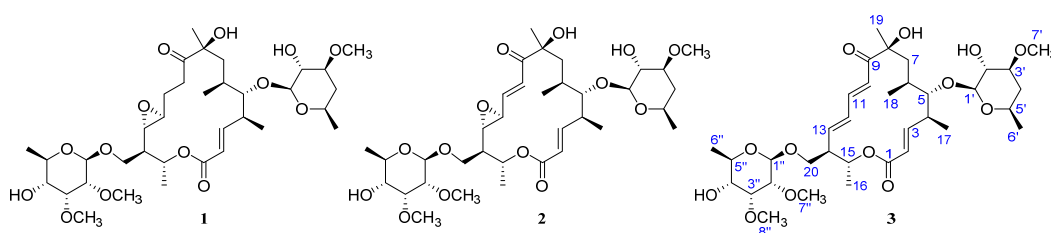


Figure 1. The structures of compounds 1–3.

## 2. Results and Discussion

Compounds 1 and 2 were established as dihydrochalcomycin and chalcomycin respectively by precisely comparing the nuclear magnetic resonance (NMR) data with literature values [11,24,28]. The single-crystal X-ray crystallographic analysis of dihydrochalcomycin (1) was reported for the first time (Figure 2). Chalcomycin (2) was also obtained and identified in our previous study on the strain of *Streptomyces* sp. HK-2006-1 [11].

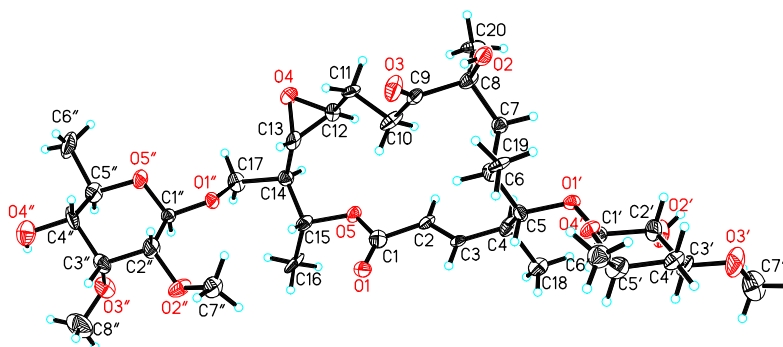
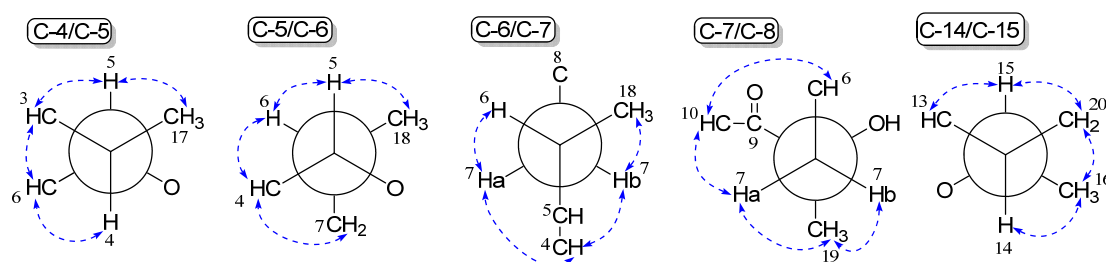


Figure 2. X-ray structure of 1.

Compound **3** was obtained as a white amorphous powder. The quasi-molecular ion at  $m/z$  707.3616  $[M + Na]^+$  by high resolution electrospray ionization mass spectroscopy (HRESIMS) indicated that the molecular formula of **3** was  $C_{35}H_{56}O_{13}$  (eight degrees of unsaturation), which was 16 atomic mass unit (O) less than **2**. Analysis of its  $^1H$  and  $^{13}C$  NMR spectroscopic data (Table 1) revealed nearly identical structure features to **2**, except that two mono-oxygenated methine carbons at  $\delta_C$  59.0 and 58.7 disappeared, and two olefinic carbons at  $\delta_C$  143.3 and 133.0 appeared. Analysis of  $^1H$ - $^1H$  COSY and the coupling values of the protons revealed the presence of the spin system C-10–C-11–C-12–C-13–C-14(C-20)–C-15–C-16. Therefore, **3** was the reduction product of **2** at C-12/C-13. The geometrical configuration of the double bond moiety (C-12/C-13) was deduced as *E* on the basis of the coupling constant of the olefinic protons ( $J_{12,13} = 14.1$  Hz). Thus, compound **3** can be recognized as a new member of the chalcomycin family, consisting of the 16-membered lactone ring, mycinose, and chalcose, and its structure was further confirmed by two-dimensional NMR (2D NMR) data (Table 1 and Table S1). The observed rotating frame overhauser effect spectroscopy (ROESY) correlations (Figure 3) were consistent with the stereochemistry of the 16-membered lactone ring. All the reported mycinose and chalcose units in natural products have D configurations. The mycinose and chalcose units in the isolated macrolides from the strain of *Streptomyces* sp. HK-2006-1 also had D configurations [11]. Therefore, the absolute configurations of the mycinose and chalcose units in **3** were assumed to be D. The relative configurations of the two units were established as  $\beta$  from the coupling constants of the anomeric protons (H-1' and H-1''). Thus, the structure of **3** was elucidated as (3*E*,5*S*,6*S*,7*S*,9*S*,11*E*,13*E*,15*R*,16*R*)-9-hydroxy-15-(((2*R*,3*R*,4*R*,5*R*,6*R*)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2*H*-pyran-2-yloxy)methyl)-6-(((2*S*,3*R*,4*S*,6*R*)-3-hydroxy-4-methoxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-5,7,9,16-tetramethyloxacyclohexadeca-3,11,13-triene-2,10-dione, and named as chalcomycin E.



**Figure 3.** The observed rotating frame overhauser effect spectroscopy (ROESY) correlations (dashed double arrow in blue) of C-4–C-5–C-6–C-7–C-8 and C-14–C-15 in **3**.

Until now, only seven chalcomycins had been reported. The discovery of chalcomycin E (**3**) adds a new member to chalcomycins. The single-crystal X-ray crystallographic analysis of dihydrochalcomycin (**1**) was firstly reported. Compounds **1**–**3** were tested for antimicrobial activities against two bacteria, Gram-positive *S. aureus* 209P and Gram-negative *E. coli* ATCC0111, as well as two fungi, *C. albicans* FIM709 and *A. niger* R330 (Table 2). Compounds **1**–**2** showed activities against *S. aureus*, but no activity against the other test strains. The fact that **1** and **2** exhibited stronger activity against *S. aureus* 209P than **3** suggested that the epoxy unit was important for antimicrobial activity. However, the replacement of the double bond in C-10 to C-13 by the epoxy unit in aldgamycins is not beneficial for antimicrobial activity. The difference in structure between aldgamycins and chalcomycins is just the sugar type at C-5, but the two types of macrolides have different structure–activity tendencies. Our findings provide a valuable example for the phenomenon that 16-membered macrolide antibiotics with different sugars do not have parallel structure–activity relationships [9,10].

**Table 1.** NMR (600 MHz, CDCl<sub>3</sub>) data for 3.

Position	$\delta_C$ , Mult.	$\delta_H$ (J in Hz) <sup>§</sup>	<sup>1</sup> H, <sup>1</sup> H-COSY	HMBC	ROESY
aglycone					
1	165.6, C	–	–	–	–
2	121.4, CH	5.75 d (15.4)	3	4	4, 17
3	151.7, CH	6.62 dd (15.4, 9.5)	2, 4	1	5, 6, 17
4	41.0, CH	2.66	3, 5, 17	2, 3	2, 6, 7a, 7b
5	88.1, CH	3.19	4, 6	3, 4, 6, 7, 17, 18, 1'	3, 6, 17, 18, 1'
6	34.0, CH	1.30	5, 7a, 7b, 18	–	3, 4, 5, 7a, 10
7	37.4, CH <sub>2</sub>	1.89, Ha 1.83, Hb	6, 7b 6, 7a	6, 8, 9, 18 6, 18	4, 6, 10, 19 4, 18, 19
8	78.3, C	–	–	–	–
9	202.0, C	–	–	–	–
10	122.0, CH	6.18 d (15.1)	11	8, 9, 11, 12	6, 7a, 19
11	144.1, CH	7.30 dd (15.1, 10.1)	10, 12	9, 12, 13	–
12	133.0, CH	6.15 dd (14.1, 10.1)	11, 13	10, 11, 13, 14	–
13	143.3, CH	6.14 dd (14.1, 9.2)	12, 14	11, 12, 14, 20	15, 20b
14	51.2, CH	2.47	13, 15, 20a, 20b	12, 13, 15	16, 20a
15	69.2, CH	5.06 dq (10.2, 6.2)	14, 16	1, 13, 14	13, 20a, 20b
16	18.6, CH <sub>3</sub>	1.36 d (6.3)	15	14, 15	14, 20a, 20b
17	19.2, CH <sub>3</sub>	1.18 d (6.9)	4	3, 4, 5	2, 3, 5, 1'
18	19.3, CH <sub>3</sub>	1.00 d (6.9)	6	5, 6, 7	5, 7b
19	27.9, CH <sub>3</sub>	1.38 s	–	7, 8, 9	7a, 7b, 10
20	68.4, CH <sub>2</sub>	4.04 dd (9.6, 3.7), Ha 3.57 dd (9.6, 6.1), Hb	14, 20b 14, 20a	13, 14, 15, 1'' 13, 14, 15, 1''	14, 15, 16, 20b, 1'' 13, 15, 16, 20a, 1''
β-D-chalcosyl unit					
1'	103.0, CH	4.19 d (7.6)	2'	5, 5'	5, 17, 3', 5'
2'	75.1, CH	3.32 dd (8.8, 7.6)	1', 3'	1', 3', 4'	4'b
3'	80.4, CH	3.22	2', 4'a, 4'b	1', 2', 4', 7'	1', 4'a, 5'
4'	36.8, CH <sub>2</sub>	2.04 ddd (12.7, 4.9, 1.9), Ha 1.25, Hb	3', 4'b, 5'	2', 3'	3', 5', 6'
5'	67.8, CH	3.48	3', 4'a, 5' 4'a, 4'b, 6'	2', 3', 5' 1'	2', 6' 1', 3', 4'a
6'	20.9, CH <sub>3</sub>	1.23 d (6.2)	5'	4', 5'	4'a, 4'b
7'	56.7, CH <sub>3</sub>	3.41 s	–	3'	–
β-D-mycinosyl unit					
1''	101.1, CH	4.58 d (7.8)	2''	20, 3'', 5''	20a, 20b, 5'', 8''
2''	81.9, CH	3.04 dd (7.8, 3.1)	1'', 3''	1'', 7''	3'', 4'', 7''
3''	79.8, CH	3.76 t (3.1)	2'', 4''	1'', 2'', 4'', 5'', 8''	2'', 4'', 8''
4''	72.7, CH	3.18	3'', 5''	2''	2'', 3'', 6''
5''	70.6, CH	3.52	4'', 6''	3'', 4''	1''
6''	17.8, CH <sub>3</sub>	1.27 d (6.2)	5''	4'', 5''	4''
7''	59.8, CH <sub>3</sub>	3.52 s	–	2''	2''
8''	61.8, CH <sub>3</sub>	3.62 s	–	3''	1'', 3''

<sup>§</sup> Indiscernible signals owing to overlapping or having complex multiplicity are reported without designating multiplicity. NMR: nuclear magnetic resonance; <sup>1</sup>H, <sup>1</sup>H COSY: <sup>1</sup>H, <sup>1</sup>H chemical shift correlated spectroscopy; HMBC: heteronuclear multiple-bond correlation; ROESY: rotating frame overhauser effect spectroscopy.

**Table 2.** Antimicrobial activities of 1–3 (minimal inhibitory concentrations (MICs): µg/mL).

Compound	Bacteria		Fungi	
	<i>S. aureus</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
1	32	>512	>512	>512
2	4	>512	>512	>512
3	>512	>512	>512	>512
Tobramycin	0.4	2	NT	NT
Actidione	NT	NT	64	32

NT: not tested.

### 3. Conclusions

Two known chalomycins, dihydrochalomycin (**1**) and chalomycin (**2**), together with a new one, chalomycin E (**3**) were isolated from marine-derived *Streptomyces* sp. HK-2006-1. Their structures were determined by detailed spectroscopic and X-ray crystallographic analysis. The discovery of chalomycin E (**3**) adds a new member to chalomycins. The antimicrobial activities of **1–3** were tested against *S. aureus*, *E. coli*, *C. albicans*, and *A. niger*. Compounds **1–2** showed activities against *S. aureus* with minimal inhibitory concentrations (MICs) of 32 µg/mL and 4 µg/mL, respectively. Compounds **1–2** showed stronger activity against *S. aureus* 209P than **3**, which suggested a different structure–activity tendency against *S. aureus* from that of aldgamycins. This case indicated that 16-membered macrolide antibiotics with different sugars do not have parallel structure–activity relationships.

**Supplementary Materials:** The following are available online at [www.mdpi.com/1660-3397/15/6/153/s1](http://www.mdpi.com/1660-3397/15/6/153/s1), materials and methods, one-dimensional NMR (1D NMR) data and spectra for **1** and **2**, and 1D/2D NMR, ultraviolet (UV), and HRESIMS spectra for **3**.

**Acknowledgments:** This work was financially supported by grants from the National Natural Science Foundation of China (81373306, 81422054), Fok Ying Tung Education Foundation (121039) from the Ministry of Education of China, the Guangdong Natural Science Funds for Distinguished Young Scholar (S2013050014287), Guangdong Special Support Program (2016TX03R280), Guangdong Province Universities and Colleges Pearl River Scholar Funded Scheme (Hao Gao, 2014), Wong Kwan Cheng Education Foundation (Hao Gao, 2016), and “Challenge Cup” National Undergraduate Curricular Academic Science and Technology Works of Jinan University (16112001).

**Author Contributions:** H.G. and X.Y. initiated and coordinated the project. H.G. and C.W. wrote the paper. S.J., L.Z., and C.W. performed the extraction, isolation, and structural identification of the compounds. K.H. supplied the strain. K.H. and D.H. performed the identification of the strain. G.C. performed the X-ray crystallographic analysis. X.P. and F.D. performed the fermentation of the strain.

**Conflicts of Interest:** The authors declare no conflict of interest.

### References

1. Aminov, R. History of Antimicrobial Drug Discovery: Major Classes and Health Impact. *Biochem. Pharmacol.* **2017**, *133*, 4–19. [[CrossRef](#)] [[PubMed](#)]
2. Chaudhary, A.S. A Review of Global Initiatives to Fight Antibiotic Resistance and Recent Antibiotics Discovery. *Acta Pharm. Sin. B* **2016**, *6*, 552–556. [[CrossRef](#)] [[PubMed](#)]
3. Gamerding, M.; Deuerling, E. Macrolides: The Plug Is Out. *Cell* **2012**, *151*, 469–471. [[CrossRef](#)] [[PubMed](#)]
4. Kwiatkowska, B.; Maslinska, M. Macrolide Therapy in Chronic Inflammatory diseases. *Mediat. Inflamm.* **2012**, *2012*, 1–7. [[CrossRef](#)] [[PubMed](#)]
5. Hansen, J.L.; Ippolito, J.A.; Ban, N.; Nissen, P.; Moore, P.B.; Steitz, T.A. The Structures of Four Macrolide Antibiotics Bound to the Large Ribosomal Subunit. *Mol. Cell* **2002**, *10*, 117–128. [[CrossRef](#)]
6. Blondeau, J.M.; DeCarolis, E.; Metzler, K.L.; Hansen, G.T. The macrolides. *Expert Opin. Investig. Drugs* **2002**, *11*, 189–215. [[CrossRef](#)] [[PubMed](#)]
7. Zuckerman, J.M.; Qamar, F.; Bono, B.R. Review of Macrolides (Azithromycin, Clarithromycin), Ketolids (Telithromycin) and Glycylcyclines (Tigecycline). *Med. Clin. N. Am.* **2011**, *95*, 761–791. [[CrossRef](#)] [[PubMed](#)]
8. Elshahawi, S.I.; Shaaban, K.A.; Kharel, M.K.; Thorson, J.S. A comprehensive review of glycosylated bacterial natural products. *Chem. Soc. Rev.* **2015**, *44*, 7591–7697. [[CrossRef](#)] [[PubMed](#)]
9. Omura, S.; Nakagawa, A. Chemical and biological studies on 16-membered macrolide antibiotics. *J. Antibiot.* **1975**, *28*, 401–433. [[CrossRef](#)] [[PubMed](#)]
10. Corcoran, J.W.; Hahn, F.E. *Antibiotics, Vol. 3: Mechanism of Action of Antimicrobial and Antitumor Agents*; Springer: Berlin/Heidelberg, Germany, 1975; pp. 459–479.
11. Wang, C.X.; Ding, R.; Jiang, S.T.; Tang, J.S.; Hu, D.; Chen, G.D.; Lin, F.; Hong, K.; Yao, X.S.; Gao, H. Aldgamycins J–O, 16-membered Macrolides with a Branched Octose Unit from *Streptomyces* sp. and their Antibacterial Activities. *J. Nat. Prod.* **2016**, *79*, 2446–2454. [[CrossRef](#)] [[PubMed](#)]
12. Zhao, H.; Chen, G.D.; Zou, J.; He, R.R.; Qin, S.Y.; Hu, D.; Li, G.Q.; Guo, L.D.; Yao, X.S.; Gao, H. Dimericbiscognienyne A: A meroterpenoid dimer from *Biscogniauxia* sp. with new skeleton and its activity. *Org. Lett.* **2017**, *19*, 38–41. [[CrossRef](#)] [[PubMed](#)]

13. Sun, T.Y.; Zou, J.; Chen, G.D.; Hu, D.; Wu, B.; Liu, X.Z.; Yao, X.S.; Gao, H. A set of interesting sequoiatones stereoisomers from a wetland soil-derived fungus *Talaromyces flavus*. *Acta Pharm. Sin. B* **2017**. [[CrossRef](#)] [[PubMed](#)]
14. Wang, C.X.; Chen, G.D.; Feng, C.C.; He, R.R.; Qin, S.Y.; Hu, D.; Chen, H.R.; Liu, X.Z.; Yao, X.Z.; Gao, H. Same Data, different structures: diastereoisomers with substantially identical NMR data from nature. *Chem. Commun.* **2016**, *52*, 1250–1253. [[CrossRef](#)] [[PubMed](#)]
15. Gao, Y.M.; Sun, T.Y.; Ma, M.; Chen, G.D.; Zhou, Z.Q.; Wang, C.X.; Hu, D.; Chen, L.G.; Yao, X.S.; Gao, H. Adeninealkylresorcinol, the first alkylresorcinol tethered with nucleobase from *Lasiodiplodia* sp. *Fitoterapia* **2016**, *112*, 254–259. [[CrossRef](#)] [[PubMed](#)]
16. Sun, T.Y.; Kuang, R.Q.; Chen, G.D.; Qin, S.Y.; Wang, C.X.; Hu, D.; Wu, B.; Liu, X.Z.; Yao, X.S.; Gao, H. Three pairs of new isopentenyl dibenzo[b,e]oxepinone enantiomers from *Talaromyces flavus*, a wetland soil-derived fungus. *Molecules* **2016**, *21*, 1184. [[CrossRef](#)] [[PubMed](#)]
17. He, J.W.; Wang, C.X.; Yang, L.; Chen, G.D.; Hu, D.; Guo, L.D.; Yao, X.S.; Gao, H. A pair of new polyketide enantiomers from three endolichenic fungal strains *Nigrospora sphaerica*, *Alternaria alternata*, and *Phialophora* sp. *Nat. Prod. Commun.* **2016**, *11*, 829–831. [[PubMed](#)]
18. Zhao, Q.; Wang, C.X.; Yu, Y.; Wang, G.Q.; Zheng, Q.C.; Chen, G.D.; Lian, Y.Y.; Lin, F.; Guo, L.D.; Gao, H. Nodulisporipyrones A–D, new bioactive  $\alpha$ -pyrone derivatives from *Nodulisporium* sp. *J. Asian Nat. Prod. Res.* **2015**, *17*, 567–575. [[CrossRef](#)] [[PubMed](#)]
19. Zou, J.; Li, J.; Wu, Z.Y.; Zhao, Q.; Wang, G.Q.; Zhao, H.; Chen, G.D.; Sun, X.; Guo, L.D.; Gao, H. New  $\alpha$ -pyrone and phthalide from the Xylariaceae fungus. *J. Asian Nat. Prod. Res.* **2015**, *17*, 705–710. [[CrossRef](#)] [[PubMed](#)]
20. Wu, Y.H.; Chen, G.D.; Wang, C.X.; Hu, D.; Li, X.X.; Lian, Y.Y.; Lin, F.; Guo, L.D.; Gao, H. Pericoterpene A, a new bioactive cadinane-type sesquiterpene from *Periconia* sp. *J. Asian Nat. Prod. Res.* **2015**, *17*, 671–675. [[CrossRef](#)] [[PubMed](#)]
21. Tang, X.L.; Dai, P.; Gao, H.; Wang, C.X.; Chen, G.D.; Hong, K.; Hu, D.; Yao, X.S. A Single Gene Cluster for Chalcomycins and Aldgamycins: Genetic Basis for Bifurcation of Their Biosynthesis. *ChemBioChem* **2016**, *17*, 1241–1249. [[CrossRef](#)] [[PubMed](#)]
22. Frohardt, R.P.; Pittillo, R.F.; Ehrlich, J. Chalcomycin and Its Fermentative Production. U.S. Patent US 3065137, 20 November 1962.
23. Hauske, J.R.; Dibrino, J.; Guadiana, M.; Kostek, G. Structure Elucidation of a New Neutral Macrolide Antibiotic. *J. Org. Chem.* **1986**, *51*, 2808–2814. [[CrossRef](#)]
24. Kim, S.D.; Ryoo, I.J.; Kim, C.J.; Kim, W.G.; Kim, J.P.; Kong, J.Y.; Koshino, H.; Uramoto, M.; Yoo, I.D. GERI-155, a New Macrolide Antibiotic Related to Chalcomycin. *J. Antibiot.* **1996**, *49*, 955–957. [[CrossRef](#)] [[PubMed](#)]
25. Goo, Y.M.; Lee, Y.Y.; Kim, B.T. A New 16-membered Chalcomycin Type Macrolide Antibiotic, 250-144C. *J. Antibiot.* **1997**, *50*, 85–88. [[CrossRef](#)] [[PubMed](#)]
26. Asolkar, R.N.; Maskey, R.P.; Helmke, E.; Laatsch, H. Chalcomycin B, a New Macrolide Antibiotic from the Marine Isolate *Streptomyces* sp. B7064. *J. Antibiot.* **2002**, *55*, 893–898. [[CrossRef](#)] [[PubMed](#)]
27. Ding, L.; Qin, S.; Li, F.; Zhang, W.; Lachi, H. Method for Preparation of Chalcomycin-like Compounds from Marine *Streptomyces* and Its Application as Antitumor Agents. C.N. Patent CN 101624413, 2010.
28. Morisaki, N.; Hashimoto, Y.; Furihata, K.; Yazawa, K.; Tamura, M.; Mikami, Y. Glycosylative Inactivation of Chalcomycin and Tylosin by a Clinically Isolated *Nocardia asteroides* Strain. *J. Antibiot.* **2001**, *54*, 157–165. [[CrossRef](#)] [[PubMed](#)]

