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RESEARCH PAPER

p-Terphenyl alcohols from a marine sponge-derived fungus, *Aspergillus candidus* OUCMDZ-1051

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Abstract

In order to discover structurally new and bioactive compounds from marine life, we studied the secondary metabolites of the marine-derived fungi associated with a marine sponge (XS-3) from the Xisha islands. As a result, 4-*O*-methylcandidusin A (**1**), a new *p*-terphenyl alcohol, along with nine known analogs (**2**–**10**), were isolated and identified from the marine sponge-derived fungus *Aspergillus candidus* OUCMDZ-1051. The structures of these compounds were determined by analyzing spectroscopic data, especially 1D and 2D NMR. The new compound **1** selectively inhibited the growth of the MDA-MB-468, BT474 and A431 human cancer cell lines with the IC_{50} values of 1.84, 6.05 and 0.98 μmol/L, respectively. Compound **1** also displayed a selective antimicrobial activity against *Escherichia coli* with an MIC value of 27.3 μmol/L. The results indicated 4-*O*-methylcandidusin A (**1**) as a potential lead in the new drug discovery for triple negative breast cancer, invasive ductal breast cancer and epidermoid cancer. The antimicrobial metabolites also evidenced a clue for chemical defense of sponges by their associated microorganisms.

Keywords Sponge-derived fungus · *Aspergillus candidus* · Natural products · *p*-Terphenyl · Cytotoxicity · Antimicrobial activity

Introduction

Marine sponges and their associated secondary metabolites have played a vital role in drug studies (Anjum et al. 2016) featuring compounds such as Cytarabine, Vidarabine, and Eribulin Mesylate. More and more data suggest that the real producers of the natural compounds from marine invertebrates are the symbiotic microorganisms which comprise about 40% by volume of the sponge, including strains that are cultivable and uncultivable (Wilson et al. 2014). Compared with the non-reproducible sponges, the renewable and inexhaustible microorganisms around them seem an eco-friendly source to discovery novel molecules bearing pharmaceutical potential (Brinkmann et al. 2017).

Statistically, symbiotic microorganisms within sponges accounted for 19% of new and bioactive marine natural products (MNPs) from marine fungi between 1951 and 2014 (Wang et al. 2019a; Zhu et al. 2015). Our research is also interested in the discovery of bioactive new compounds from marine sponge-associated fungi (Huang et al. 2019; Jia et al. 2019; Kong et al. 2015; Liu et al. 2005, 2019; Xin et al. 2005, 2007; Zhu et al. 2018). In our ongoing research, we obtained 47 fungi from an unidentified

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Dongyang Wang and Peng Qu made equal contributions to this work.

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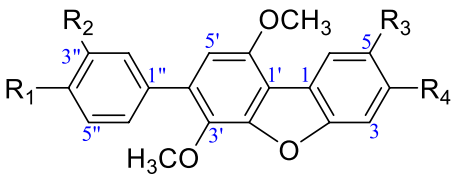
marine sponge (XS-3) from the Xisha islands, South China Sea. One of these fungal strains, *Aspergillus candidus* OUCMDZ-1051, produced bioactive metabolites which were cytotoxic to the murine lymphocytic leukemia cell line (P388) at 10 µg/ml and antibacterial to *Escherichia coli* at 10 µg/disk. Chemical isolation led to the identification of a new *p*-terphenyl alcohol, 4-*O*-methylcandidusin A (**1**) and nine known analogs, 4,5-di-*O*-methylcandidusin A (**2**) (Guo et al. 2012), candidusin A (**3**) (Kobayashi et al. 1982; Liu et al. 2012), prenylcandidusins B (**4**) and C (**5**) (Cai et al. 2011), candidusin C (**6**) (Rahbaek et al. 2000), 3-hydroxyterphenyllin (**7**) (Yen et al. 2001), terphenyllin (**8**) (Kamigauchi et al. 1998), 4″-deoxy-3-hydroxyterphenyllin (**9**) (Guo et al. 2012) and prenylterphenyllin B (**10**) (Cai et al. 2011) (Fig. 1). Compounds **1**–**3** and **8** exhibited antimicrobial activity against *E. coli*, *Enterobacter aerogenes*, *Candida albicans* and *Pseudomonas aeruginosa* with MIC (minimal inhibitory concentration) values of 27.3, 33.2, 37.2 and 71.7 µmol/L, respectively. The new compound **1** showed a broad-spectrum cytotoxic activity against 21 cancer cell lines among 26 human cancer cell lines tested with IC_{50} (half maximal inhibitory concentration) values between 0.98 and 19.1 µmol/L.

Results

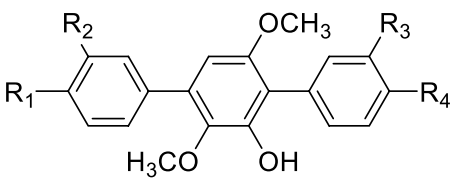
Compound **1**, a white powder, was established to have the molecule formula $C_{21}H_{18}O_6$ from the HRESIMS peak at *m/z* 367.1166 $[M+H]^+$ (Supplementary Fig. S1) that is 14 Da more than candidusin A (**3**). ^{1}H-NMR (Table 1 and Supplementary Table S1) and ^{1}H-^{1}H-COSY (Fig. 2 and Supplementary Fig.S5) showed the structure containing one 1,2,4,5-tetrasubstituted benzene ring [$\delta_{H\text{-}3}$ 7.37(s), $\delta_{H\text{-}6}$ 7.41(s)], one 1,4-disubstituted benzene ring [$\delta_{H\text{-}2''/6''}$ 7.42 (d, $J=8.8$ Hz), $\delta_{H\text{-}3''/5''}$ 6.86 (d, $J=8.8$ Hz)], one pentasubstituted benzene ring [$\delta_{H\text{-}5'}$ 6.72 (s)], and three methoxy groups [$\delta_{H\text{-}6'\text{-}OCH3}$ 3.97(s), $\delta_{H\text{-}4\text{-}OCH3}$ 3.87(s), $\delta_{H\text{-}3'\text{-}OCH3}$ 3.77(s)]. ^{13}C-NMR (Table 1, Supplementary Figs. S3, S4 and S6) gave 18 aromatic carbons between 96.2 and 156.8 ppm including 11 aromatic nonprotonated carbons and seven aromatic methine carbons. These NMR data featured molecule **1** as a *p*-terphenyl skeleton fused a furan moiety between rings B and C that is very closely related to candidusin A (**3**) (Liu et al. 2012). The major difference was presented in benzene ring C (Table 1, Supplementary Tables S1 and S2). Except for an additional methoxy signal at $\delta_{H/C}$ 3.87/56.1, C-2–C-4 and H-3 had obvious shifts and the shift values were +1.3, +2.9, −1.6 and −0.26 ppm, respectively. These data indicated a 4-*O*-methylation that was further supported by the following 2D NMR experiment. The key HMBC correlations (Fig. 2, Supplementary Figs. S7 and S8) of H-5′ (δ_H 6.72) to C-1″ (δ_C 128.6), H-3″/5″ (δ_H 6.86) to C-1″ and H-2″/6″ (δ_H 7.42) to C-4′ (δ_C 131.0) indicated a connection of benzene rings A and B by a C-1″–C-4′ single bond. The key HMBC correlations of H-5′ to C-1′ (δ_C 113.9), H-6 (δ_H 7.41) to C-1′ and H-3 (δ_H 7.37) to C-1 (δ_C 114.6) indicated a connection of benzene rings B and C by a C-1′–C-1 single bond. The HMBC correlations of 3′-OCH_3 (δ_H 3.77) to C-3′ (δ_C 136.0), 6′-OCH_3 (δ_H 3.97) to C-6′ (δ_C 149.6) and 4-OCH_3 (δ_H 3.87) to C-4 (δ_C 148.0) located the positions of these three methoxy groups. Thus, compound **1** was established as 4-*O*-methylcandidusin A. The known compounds **2**–**10** were identified by comparing their NMR data (Supplementary Tables S1–S3) and Physical properties (see Physical properties of compounds **2**–**10** in Supporting material).

The cytotoxic activity of new compound **1** against 26 human tumor cell lines (Table 2 and Bioassay Protocol in Supporting material) were tested by the Cell Titer Glo (CTG) assay and doxorubicin (Dox) was used as the positive control. The results indicated that 4-*O*-methylcandidusin A (**1**) was active against 21 tumor cell lines with IC_{50} values of 0.98–19.1 µmol/L in the 26 tested tumor cell lines (Table 2). Especially, compound **1** showed a stronger or comparable inhibitory activity to the positive control (doxorubicin) against the triple negative breast cancer (MDA-MB-468),



1: R_1=R_3= OH, R_2= H, R_4= OCH_3
2: R_1= OH, R_2= H, R_3=R_4= OCH_3
3: R_1=R_3=R_4= OH, R_2= H

4: R_1= OH, R_2= $CH_2CH=C(CH_3)_2$, R_3=R_4= OCH_3
5: R_1=R_3= OH, R_2= $CH_2CH=C(CH_3)_2$, R_4= OCH_3
6: R_1= OCH_3, R_2= H, R_3=R_4= OH



7: R_1=R_3=R_4= OH, R_2= H
8: R_1=R_4= OH, R_2=R_3= H
9: R_1=R_2= H, R_3=R_4= OH
10: R_1=R_4= OH, R_3= H, R_2= $CH_2CH=C(CH_3)_2$

Fig. 1 Structures of compounds **1**–**10**

Table 1 The ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR data for compound **1** in DMSO-d_6

No.	δ_H (J in Hz)	δ_C, type
1		114.6, C
2		148.7, C
3	7.37, s	96.2, CH
4		148.0, C
5		143.6, C
6	7.41, s	107.0, CH
4-OMe	3.87, s	56.1, CH_3
1′		113.9, C
2′		149.3, C
3′		136.0, C
4′		131.0, C
5′	6.72, s	105.7, CH
6′		149.6, C
3′-OMe	3.77, s	60.6, CH_3
6′-OMe	3.97, s	55.9, CH_3
1″		128.6, C
2″	7.42, d (8.8)	130.4, CH
3″	6.86, d (8.8)	115.1, CH
4″		156.8, C
5″	6.86, d (8.8)	115.1, CH
6″	7.42, d (8.8)	130.4, CH

the breast invasive ductal carcinoma (BT474), and the epidermoid carcinoma (A431) cell lines, with the IC_{50} values of 1.84, 6.05, and 0.98 μmol/L, respectively (Table 2).

The antimicrobial activities of *p*-terphenyl alcohols **1**–**10** against human pathogenic bacteria, *Enterobacter aerogenes* (ATCC 13408), *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC11775) and *Pseudomonas aeruginosa* (ATCC10145) and fungus *Candida albicans* (ATCC 10231), were evaluated using the filter disk method. Ciprofloxacin and ketoconazole were used as the positive controls for bacteria and fungus, respectively. The results (Table 3) showed that new compound **1** and the known compounds **2**, **3** and **8** displayed a weak antimicrobial activity against *E. coli*, *E. aerogenes*, *C. albicans and P. aeruginosa* with MIC values of 27.3, 33.2, 37.2 and 71.7 μmol/L, respectively.

Discussion

p-Terphenyl alcohols are a kind of natural products mainly derived from fungi. The structural core is a C-18 tricyclic skeleton formed by three benzene rings that the two phenyl groups (rings A and C) connect at the 1,4-positions of the middle benzene ring (ring B) (Wang et al. 2019b). The structural diversity of the natural *p*-terphenyls mainly resulted from the variation of the ring B, the number and the position of hydroxy groups, and the changes of the phenol to quinone functions. Approximately 230 natural *p*-terphenyls have been identified from the year 1877 to 2018 (Li et al. 2018; Liu 2006), and this number is growing every year (Kalansuriya et al. 2019; Kalvo et al. 2018; Lin et al. 2019; Lu et al. 2019; Narmani et al. 2019; Ren et al. 2018; Sangsopha et al. 2019; Song et al. 2019; Wang et al. 2019b; Xu et al. 2018). Our present work isolated and identified a new *p*-terphenyl alcohol with a dibenzofuran moiety from the marine sponge-derived fungus *A. candidus* OUCMDZ-1051, as well as nine known *p*-terphenyl alcohols. The strong and selective inhibition of compound **1** on MDA-MB-468, BT474 and A431 tumor cell lines indicated the potential use of 4-*O*-methylcandidusin A (**1**) as a lead for inhibiting triple negative breast cancer, invasive ductal breast cancer and epidermoid cancer. The antimicrobial activity of metabolites **1**, **2**, **3** and **8** hints at chemical protection of symbiotic microbes for sponge against pathogenic microorganisms.

Materials and methods

General experimental procedures

Analytical HPLC were carried out on a Shimadzu LC-6AD equipped with a Shimadzu SPD-M10A detector (250 mm × 4.6 mm YMC-Pack ODS-A column). Preparative HPLC was performed on a Waters 1525 equipped with Waters 2487 Dual λ Absorbance Detector (250 mm × 10 mm YMC-Pack ODS-A column); UV data were obtained on a NanoDrop One Microvolume UV–Vis Spectrophotometer. IR spectra were measured in KBr disks on a Nicolet Nexus 470 spectrophotometer. NMR spectra were recorded on a JNM-ECP600 spectrometer, and the residual DMSO signals at $\delta_{H/C}$ 2.50/39.52 were used to reference the chemical shifts. HRESIMS data were measured using a Q-TOF ULTIMA GLOBAL GAA076 LC mass spectrometer. TLC (thin-layer chromatography) plates pre-coated with silica gel GF254 (10–40 μm) and silica gel H (Qingdao Marine Chemical Factory) were respectively used for TLC, column chromatography (CC), and vacuum liquid chromatography (VLC). Sephadex LH-20 (Amersham Biosciences) was soaked overnight in a CH_2Cl_2/MeOH (1:1) mixture before use.

Strain information

Strain OUCMDZ-1051 was isolated from an unidentified sponge sample (No. XS-3) collected from Xisha islands, South China Sea in 2009, by a serial dilution method using a PDA agar medium that was prepared by dissolving 200 g Potato infusion, 20 g glucose and 20 g agar in 1 L natural sea water supplemented with 0.02% chloramphenicol.

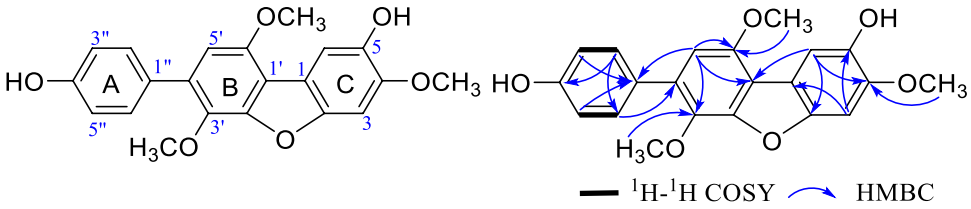


Fig. 2 The key 2D NMR correlations of compound **1**

Table 2 Cytotoxicity of compound **1** against 26 human cancer cell lines (IC_{50} μmol/L)

Cell line[a]	**1**	Dox
N87	6.05 ± 0.24	0.05 ± 0.01
A673	16.75 ± 0.42	0.10 ± 0.01
MV4-11	1.66 ± 0.05	0.16 ± 0.01
K562	23.12 ± 1.19	0.02 ± 0.01
A549	5.42 ± 0.08	0.11 ± 0.01
BT474	6.05 ± 0.04	1.90 ± 0.01
H1299	5.56 ± 0.34	0.50 ± 0.03
HUCCT1	9.55 ± 0.86	0.05 ± 0.01
MDA-MB-468	1.84 ± 0.02	> 100
H1975	8.45 ± 0.41	0.09 ± 0.01
HL-60	4.16 ± 0.01	0.20 ± 0.01
Karpas299	> 100	0.38 ± 0.01
U87	> 100	0.11 ± 0.01
A431	0.98 ± 0.02	0.16 ± 0.01
U251	19.10 ± 0.53	0.17 ± 0.01
HCC1954	4.93 ± 0.07	0.05 ± 0.01
MCF-7	7.75 ± 0.10	0.10 ± 0.01
MKN-45	7.52 ± 0.45	0.19 ± 0.01
DU145	1.79 ± 0.11	0.05 ± 0.01
SPC-A1	9.25 ± 0.67	0.18 ± 0.01
HCT116	9.31 ± 0.16	0.10 ± 0.01
MDA-MB-231	1.89 ± 0.10	0.18 ± 0.01
143B	5.86 ± 0.13	0.10 ± 0.01
B16F10	> 100	0.02 ± 0.01
H2228	> 100	0.10 ± 0.01
Hep3B	> 100	16.29 ± 1.39

[a]The details of the 26 cell lines are listed in the supplementary material

In brief, the washed and ground sponge tissue (1 g) was added into 9 ml of sterile natural seawater. Then, 100 μl of suspension was deposited on a PDA age plate incubated at 28 °C for 3 days. The fungus was purified using the same media and characterized as *A. candidus* (GenBank accession no. MN582997) by the comparison of its 18S rRNA gene sequence with the type strains. The strain was preserved in our Laboratory at − 80 °C, Ocean University of China.

Production, extraction and purification

Spores of the strain, grown on PDA agar plates, were inoculated into 1-L Erlenmeyer flasks; each contained 300 ml liquid medium (20 g mannitol, 10 g glucose, 20 g maltose, 3 g yeast extract, 10 g glutamate, 1 g corn syrup, 20 g $CaCO_3$, 0.5 g KH_2PO_4, 0.3 g $MgSO_4 \cdot 7H_2O$ and 1 L natural seawater). After 35 days of static culture at room temperature, the mycelium was separated from the liquid by gauze. The 69 L ferment liquor was extracted three times with equal volume of ethyl acetate (EtOAc). The EtOAc layers were combined and evaporated to dryness at 37 °C using a rotary evaporator. The mycelium was extracted three times by 80% acetone aqueous, each for 1 h in an ultrasonic cleaning instrument. The acetone was removed from extracting solution at 37 °C using the rotary evaporator and the residual solution was extracted three times using triple volume of EtOAc. A total of 42 g crude extract was obtained.

The extract was separated by VLC using a CH_2Cl_2/MeOH mixture solvent gradient from 100% CH_2Cl_2 to 100% MeOH, resulting in 11 fractions (Fr.1–Fr.11). Fr.4 (4.3 g) was separated into 12 subfractions (Fr.4.1–Fr.4.12) via a silica gel flash column eluting with petroleum ether (PE) and acetone mixture gradient. Fr.4.10 was purified on a semi-preparation ODS column eluting with 80% MeOH to obtain compound **5** (12.0 mg, t_R 9.8 min). Fr.4.9 was purified by semi-preparation HPLC on an ODS column using the solvent system of 75% MeOH to yield compounds **1** (7.9 mg, t_R 5.0 min) and **10** (5.9 mg, t_R 8.0 min). Fr.4.4 was separated into four subfractions (Fr.4.4.1–Fr.4.4.4) on Sephadex LH-20 eluting with a CH_2Cl_2/MeOH (1:1) mixture. Fr.4.4.3 was further purified by semi-preparation HPLC on an ODS Column using 82% MeOH to obtain compounds **4** (12.3 mg, t_R 15.0 min) and **6** (6.2 mg, t_R 6.9 min). Fr.3 (1.4 g) was separated into five subfractions (Fr.3.1–Fr.3.5) via a silica gel flash column eluting with a PE/acetone mixture gradient. Fr.3.4 was separated into three subfractions (Fr3.4.1–Fr3.4.3) on Sephadex LH-20 eluting with a CH_2Cl_2/MeOH (1:1) mixture. Fr3.4.2 and Fr3.4.3 were respectively purified by HPLC on an ODS column using 80% MeOH and 60% MeOH to yield compounds **2** (21 mg, t_R 13.0 min) and **9** (4.5 mg, t_R 17.0 min). Fr.5 was purified on an LH-20 column eluting with a CH_2Cl_2/MeOH (1:1) mixture to yield compound **8** (132.0 mg). Fr.7 was separated into 10 subfractions (Fr.7.1–Fr.7.10) via a silica gel

Table 3 The MIC values (μmol/L) of *p*-terphenyl alcohols **1**–**10** against pathogenic microbes

Compound	*E. aerogenes*	*S. aureus*	*P. aeruginosa*	*E. coli*	*C. albicans*
1	> 200	> 200	> 200	27.3	> 200
2	33.2	> 200	> 200	> 200	> 200
3	71.7	> 200	71.7	143.4	> 200
4	> 200	> 200	> 200	55.8	55.8
5	> 200	115.0	> 200	> 200	> 200
6	> 200	> 200	> 200	> 200	> 200
7	> 200	141.0	> 200	141.0	> 200
8	> 200	> 200	> 200	148.8	37.2
9	> 200	> 200	> 200	> 200	> 200
10	> 200	> 200	123.0	> 200	> 200
Ciprofloxacin	3.2	0.4	13.0	0.1	–
Ketoconazole	–	–	–	–	9.4

flash column eluting with a PE/acetone mixture gradient. Fr.7.8 was performed on an LH-20 column eluting with a CH_2Cl_2/MeOH (1:1) mixture to give five subfractions (Fr.7.8.1–Fr.7.8.5). Fr.7.8.3 was separated into compound **3** (11.7 mg, t_R 8.0 min) and a subfraction (Fr.7.8.5.1) on an ODS column using 65% MeOH; Fr.7.8.5.1 was further purified on the same column eluting with 65% MeOH to give compound **7** (35.0 mg, t_R 10.0 min).

*4-O-Methylcandidusin A (**1**)* White powder; UV (MeOH) λ_{max} (log ε) 218 (4.40), 281 (4.15), 295 (4.12), 325 (4.20), 334 (4.24) nm; IR ν_{max} (KBr) 3417, 2938, 2838, 2766, 1635, 1610, 1522, 1483, 1459, 1393, 1357, 1338, 1267, 1230, 1190, 1130, 1105, 1025, 913, 824, 586 cm^{-1}; ^1H and ^{13}C NMR data (Table 1); HRESIMS *m/z* 367.1166 $[M+H]^+$ (calcd for $C_{21}H_{19}O_6$, 367.1176).

Cytotoxicity and antimicrobial assay

4-*O*-Methylcandidusin A (**1**) was evaluated for cytotoxicity against 26 human cancer cell lines by the CTG assay (Shen et al. 2019; Wang et al. 2019b). The cell suspensions were prepared at 37 °C by growing cells in RPMI-1640 medium supplemented with 10% fetal bovine serum and 1% penicillin–streptomycin solution under a humidified atmosphere of 5% CO_2 and 95% air. The cell suspension (100 μl) at a density of 20 cell/μl and 90 μl fresh medium was plated into a well of a 96-well microtiter plate and incubated overnight. Then, 10 μl of the compound solution in DMEM with varying concentrations from 100.0 to 0.032 μM by a consecutive twofold dilution was added and incubated for 72 h. To each well was added 100 μl of CTG solution and incubated in the dark for 10 min at room temperature. The absorbance of each well was recorded by a BioTek Synergy H1m multimode microplate reader.

The antimicrobial activities against four human pathogenic bacteria (*E. aerogenes*, *S. aureus*, *P. aeruginosa* and *E. coli*) and one pathogenic fungus (*C. albicans*) were evaluated using the paper disk method as we previously described (Wang et al. 2017). In brief, the tested compounds and positive controls were respectively dissolved into methanol with the initial concentration of 0.1 mg/ml (> 200 μM). Only those samples with obvious inhibition zones to pathogenic microbes were further tested for MICs (presented as μM) by a double dilution method.

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Authors Contributions D. Wang identifies the structures and write the draft of the manuscript. P. Qu isolates the fungus and compounds. J. Zhou and L. Wang test the bioactivities. Y. Wang identifies the fungus. W. Zhu designes the study and revises the manuscript and the proof.

Compliance with ethical standards

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

Animal and human rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

References

Anjum K, Abbas SQ, Shah SA, Akhter N, Batool S, Hassan SS (2016) Marine sponges as a drug treasure. Biomol Ther (Seoul) 24:347–362

Brinkmann CM, Marker A, Kurtböke DI (2017) An overview on marine sponge-symbiotic bacteria as unexhausted sources for natural product discovery. Diversity 9:40–70

Cai S, Sun S, Zhou H, Kong X, Zhu T, Li D, Gu Q (2011) Prenylated polyhydroxy-*p*-terphenyls from *Aspergillus taichungensis* ZHN-7-07. J Nat Prod 74:1106–1110

Guo ZK, Yan T, Guo Y, Song YC, Jiao RH, Tan RX, Ge HM (2012) *p*-Terphenyl and diterpenoid metabolites from endophytic *Aspergillus* sp. YXf3. J Nat Prod 75:15–21

Huang X, Kong F, Zhou S, Huang D, Zheng J, Zhu W (2019) *Streptomyces tirandamycinicus* sp. nov., a novel marine sponge-derived actinobacterium with antibacterial potential against *Streptococcus agalactiae*. Front Microbiol 10:482

Jia Q, Du Y, Wang C, Wang Y, Zhu T, Zhu W (2019) Azaphilones from the marine sponge-derived fungus *Penicillium sclerotiorum* OUCMDZ-3839. Mar Drugs 17:260

Kalansuriya P, Khalil ZG, Salim AA, Capon RJ (2019) Talarophenol sulfate and talarophilones from the Australian mud dauber wasp-associated fungus, *Talaromyces* sp. CMB-W045. Tetrahedron Lett 60:151157

Kalvo D, Broberg A, Menkis A (2018) Secondary metabolites from the root rot biocontrol fungus *Phlebiopsis gigantea*. Molecules (Basel, Switzerland) 23:1417

Kamigauchi T, Sakazaki R, Nagashima K, Kawamura Y, Yasuda Y, Matsushima K, Tani H, Takahashi Y, Ishii K, Suzuki R, Koizumi K, Nakai H, Ikenishi Y, Terui Y (1998) Terprenins, novel immunosuppressants produced by *Aspergillus candidus*. J Antibiot 51:445–450

Kobayashi A, Takemura A, Koshimizu K, Nagano H, Kawazu K (1982) Candidusin A and B: new *p*-terphenyls with cytotoxic effects on sea urchin embryos. Agric Biol Chem 46:585–589

Kong F, Zhao C, Hao J, Wang C, Wang W, Huang X, Zhu W (2015) New α-glucosidase inhibitors from a marine sponge-derived fungus, *Aspergillus* sp. OUCMDZ-1583. RSC Adv 5:68852

Li W, Li X, Lou H (2018) Structural and biological diversity of natural *p*-terphenyls. J Asian Nat Prod Res 20:1–13

Lin Y, Xie C, Xing C, Wang B, Tian X, Xia J, Jia L, Pan Y, Yang X (2019) Cytotoxic *p*-terphenyls from the deep-sea-derived *Aspergillus candidus*. Nat Prod Res. https://doi.org/10.1080/14786419.2019.1633651

Liu J (2006) Natural terphenyls: developments since 1877. Chem Rev 106:2209–2223

Liu R, Cui CB, Duan L, Gu QQ, Zhu WM (2005) Potent in vitro anticancer activity of metacycloprodigiosin and undecylprodigiosin from a sponge-derived *Actinomycete Saccharopolyspora* sp. nov. Arch Pharm Res 28:1341–1344

Liu SS, Zhao BB, Lu CH, Huang JJ, Shen YM (2012) Two new *p*-terphenyl derivatives from the marine fungal strain *Aspergillus* sp. AF119. Nat Prod Comm 7:1057–1062

Liu H, Zhu G, Zhao S, Fu P, Zhu W (2019) Bioactive natural products from the marine sponge-derived *Nocardiopsis dassonvillei* OUCMDZ-4534. Chin J Org Chem 39:507–514

Lu D, Ren J, Du Q, Song Y, Lin S, Li X, Li E, Xie W (2019) p-Terphenyls and actinomycins from a *Streptomyces* sp. associated with the larva of mud dauber wasp. Nat Prod Res. https://doi.org/10.1080/14786419.2019.1639177

Narmani A, Teponno RB, Arzanlou M, Surup F, Helaly SE, Wittstein K, Praditya DF, Babai-Ahari A, Steinmann E, Stadler M (2019) Cytotoxic, antimicrobial and antiviral secondary metabolites produced by the plant pathogenic fungus *Cytospora* sp. CCTU A309. Fitoterapia 134:314–322

Rahbaek L, Frisvad JC, Christophersen C (2000) An amendment of *Aspergillus* section *Candidi* based on chemotaxonomical evidence. Phytochemistry 53:581–586

Ren F, Chen S, Zhang Y, Zhu S, Xiao J, Liu X, Su R, Che Y (2018) Hawaiienols A-D, highly oxygenated *p*-terphenyls from an insect-associated fungus, *Paraconiothyrium hawaiiense*. J Nat Prod 81:1752–1759

Sangsopha W, Lekphrom R, Schevenels FT, Saksirirat W, Bua-Art S, Kanokmedhakul K, Kanokmedhakul S (2019) New *p*-terphenyl and benzoquinone metabolites from the bioluminescent mushroom *Neonothopanus nambi*. Nat Prod Res. https://doi.org/10.1080/14786419.2019.1578763

Shen J, Fan Y, Zhu G, Chen H, Zhu W, Fu P (2019) Polycyclic macrolactams generated via intramolecular Diels-Alder reactions from an antarctic *Streptomyces* species. Org Lett 21:4816–4820

Song Y, Zheng H, Peng A, Ma J, Lu D, Li X, Zhang H, Xie W (2019) Strepantibins A-C: hexokinase II inhibitors from a mud dauber wasp associated *Streptomyces* sp. J Nat Prod 82:1114–1119

Wang SM, Han JJ, Ma K, Jin T, Bao L, Pei YF, Liu HW (2014) New α-glucosidase inhibitors with p-terphenyl skeleton from the mushroom *Hydnellum concrescens*. Fitoterapia 98:149–155

Wang D, Wang C, Gui P, Liu H, Khalaf S, Elsayed EA, Wadaan M, Hozzein WN, Zhu W (2017) Identification, bioactivity, and productivity of actinomycins from the marine-derived *Streptomyces heliomycini*. Front Microbiol 8:1147

Wang C, Mei X, Wang D, Zhu W (2019a) Marine natural products from marine sponge microorganisms. In: Li Z (ed) Symbiotic microbiomes of coral reefs sponges and corals. Springer, Dordrecht, pp 263–310

Wang D, Wang Y, Ouyang Y, Fu P, Zhu W (2019b) Cytotoxic *p*-Terphenyls from a marine-derived *Nocardiopsis* species. J Nat Prod 82:3504–3508

Wilson MC, Mori T, Rückert C, Uria AR, Helf MJ, Takada K, Gernert C, Steffens UA, Heycke N, Schmitt S, Rinke C, Helfrich EJ, Brachmann AO, Gurgui C, Wakimoto T, Kracht M, Crüsemann M, Hentschel U, Abe I, Matsunaga S et al (2014) An environmental bacterial taxon with a large and distinct metabolic repertoire. Nature 506:58–62

Xin H, Zhu W, Gu Q, Fang Y, Duan L, Cui C (2005) A new cytotoxic compound from *Penicillium auratiogriseum*, symbiotic or epiphytic fungus of sponge *Mycale plumose*. Chin Chem Lett 16:1227–1229

Xin ZH, Fang Y, Du L, Zhu T, Duan L, Chen J, Gu QQ, Zhu WM (2007) Aurantiomides A-C, quinazoline alkaloids from the sponge-derived fungus *Penicillium aurantiogriseum* SP0-19. J Nat Prod 70:853–855

Xu K, Gao Y, Li Y, Xie F, Zhao Z, Lou H (2018) Cytotoxic *p*-terphenyls from the endolichenic fungus *Floricola striata*. J Nat Prod 81:2041–2049

Yen GC, Chang YC, Sheu F, Chiang HC (2001) Isolation and characterization of antioxidant compounds from *Aspergillus candidus* broth filtrate. J Agric Food Chem 49:1426–1431

Zhu TH, Ma YN, Wang WL, Chen ZB, Qin SD, Du YQ, Wang AY, Zhu WM (2015) New marine natural products from the marine-derived fungi other than *Penicillium* sp. and *Aspergillus* sp. (1951–2014). Chin J Mar Drugs 34:56–108

Zhu G, Kong F, Wang Y, Fu P, Zhu W (2018) Cladodionen, a cytotoxic hybrid polyketide from the marine-derived *Cladosporium* sp. OUCMDZ-1635. Mar Drugs 16:71