Meroterpenoid Dimers from Ganoderma Mushrooms and Their Biological Activities Against Triple Negative Breast Cancer Cells

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(±)-Dimercochlearlactones A–J (1–10), ten pairs of novel meroterpenoid dimers and one known spirocochlealactone A (11), were isolated from Ganoderma mushrooms. The structural elucidation of new compounds, including their absolute configurations, depends on spectroscopic analysis and electronic circular dichroism (ECD) calculations. Biological studies showed that (+)- and (−)-2, (−)-3, and (+)- and (−)-11 are cytotoxic toward human triple negative breast cancer (TNBC) cells (MDA-MB-231) with IC_{50} values of 28.18, 25.65, 11.16, 8.18, and 13.02 μM, respectively. Wound healing assay revealed that five pairs of meroterpenoids (±)-5–(±)-8 and (±)-10 could significantly inhibit cell mobility at 20 μM in MDA-MB-231 cells. The results provide a new insight into the biological role of Ganoderma meroterpenoids in TNBC.

Keywords: Ganoderma cochlear, Ganoderma lucidum, meroterpenoid dimers, dimercochlearlactone A–J, triple negative breast cancer

INTRODUCTION

Triple negative breast cancer (TNBC), a subgroup of breast cancer, is often found as high grade of invasive ductal carcinoma with aggressive behavior (O’Reilly et al., 2021). The incidence rate of TNBC accounts for approximately 15%–20% of breast cancers (Chen et al., 2021; Chowdhury et al., 2021). “Triple negative” is regarded as the absence of the expression of three receptors, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2). It causes an about threefold shorter median overall survival (OS) comparing with other breast cancers (O’Reilly et al., 2021). In addition, the relapse and metastasis rate of TNBC is high, the relapse commonly found within 3 years, and the metastasis often occurs in visceral and brain (O’Reilly et al., 2021; Chen et al., 2021; Chowdhury et al., 2021). Due to the difficulties in treating TNBC, more potential molecules are needed.

Ganoderma is a traditional Chinese medicine and has been discovered numerous bioactivities as hypoglycemic effect, cardiovascular protection, anti-tumor, antioxidant, and brain injury prevention (Lin and Deng, 2019; Lin and Sun, 2019; Liu and Tie, 2019; Meng and Yang, 2019; Quan et al., 2019). All along, Ganoderma triterpenoids have been considered as the main active components with anti-tumor effects. In recent years, Ganoderma meroterpenoids, which process phenol moiety and terpene moiety, have been continuously excavated significant anti-tumor activities, such as toward human cancer cell lines (A549, KYSE30, BT549, and MDA-MB-231) (Qin et al., 2018; Cai et al., 2021; Zhang et al., 2021). For the purpose of discovering active agents toward TNBC from natural sources,
eleven meroterpenoid dimers including ten novel ones were isolated from *Ganoderma* (Figure 1). This paper deals with their isolation, structural elucidation, and biological evaluation for cytotoxicity and cell migration inhibition in TNBC cells.

**MATERIALS AND METHODS**

**General**

An Anton Paar MCP-100 digital polarimeter was used to collect optical rotations data. UV and CD spectra were measured on a Chirascan instrument. NMR spectra were collected by a Bruker Avance III 600 MHz or a 500-MHz spectrometer, and internal standard is TMS. HRESIMS were recorded on a Waters Xevo G2-XS QTOF or a Shimazu LC-20AD AB Sciex X500R MS spectrometer (Shimadzu Corporation, Tokyo, Japan). C-18 silica gel (40–60 μm; Daiso Co., Japan), MCI gel CHP 20P (75–150 μm, Mitsubishi Chemical Industries, Tokyo, Japan), Sephadex LH-20 (Amersham Pharmacia, Uppsala, Sweden), and Silica gel (Qingdao Marine Chemical Inc., Qingdao, China) were used for column chromatography. Preparative HPLC was carried out using a Chuangxin-Tongheng chromatograph equipped with a Thermo Hypersil GOLD-C18 column (250 mm × 21.2 mm, i.d., 5 μm). Semi-preparative HPLC was taken on a SEP-LC52 chromatograph with a YMC-Pack ODS-A column (250 mm × 10 mm, i.d., 5 μm). Chiral HPLC analysis was taken on an Agilent 1260 or SEP-LC52 chromatograph with a Daicel Chiralpak column (IC, 250 mm × 10 mm, i.d., 5 μm).

**Fungal Material**

*Ganoderma cochlear* were purchased from Guangzhou Tongkang Pharmaceutical Co. Ltd. (Guangdong Province, China) in July.
2014. *Ganoderma lucidum* were collected from Dayao County, Yunnan Province, China, in April 2018. Prof. Zhu-Liang Yang from Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, China, authenticated these fungi. The voucher specimens (CHXY-0589 for *G. cochlear* and CHXY-0615 for *G. lucidum*) are deposited at the School of Pharmaceutical Sciences, Shenzhen University Health Science Center, China.

**Extraction and Isolation**

Powdered fruiting bodies of *G. cochlear* (200 kg) were extracted using refluxing 80% EtOH (3 × 120 L, 4, 3, 3 h) to yield a crude extract. An aliquot (8 kg of the residue corresponding to 95 kg fungal material) was suspended in H2O and extracted three times with EtOAc. The EtOAc soluble residue (4 kg) was then separated by semi-preparative HPLC (MeOH/H2O, 70%) to obtain 13 fractions (Fr.1–Fr.13). Fr.13 (228.0 g) was cut by a silica gel column eluted by increasing acetone in petroleum ether (10:1) to give two parts (Fr.13.1 and Fr.13.2). The second part (50.9 g) was separated by vacuum liquid chromatography (VLC) with increasing acetone in petroleum ether (10:1–3:1) to give five parts (Fr.13.2.1–Fr.13.2.5). Among them, Fr.13.2.2 (2.5 g) was separated by preparative HPLC (aqueous MeOH, 40%–100%) to afford compounds (1–9). Of which, Compounds 1–3 were racemates, further purified by chiral column (Daicel Chiralpak IC, 250 mm × 10 mm, i.d., 5 μm) (flow rate: 3 ml/min) afforded their enantiomers (+)-1 (3.50 mg, tR = 14.8 min) and (−)-1 (3.60 mg, tR = 19.9 min) (n-hexane/ethanol, 90:10); (+)-2 (0.75 mg, tR = 8.6 min) and (−)-2 (0.79 mg, tR = 10.7 min) (n-hexane/ethanol, 85:15); (+)-3 (4.70 mg, tR = 20.6 min) and (−)-3 (4.50 mg, tR = 18.1 min) (n-hexane/ethanol, 92:8); (+)-4 (10.50 mg, tR = 18.1 min) and (−)-4 (10.80 mg, tR = 20.8 min) (n-hexane/ethanol, 95:5); (+)-5 (0.35 mg, tR = 12.3 min) and (−)-5 (0.38 mg, tR = 13.2 min) (n-hexane/ethanol, 90:10); (+)-6 (4.70 mg, tR = 24.4 min) and (−)-6 (4.50 mg, tR = 21.8 min) (n-hexane/ethanol, 90:10); (+)-7 (3.60 mg, tR = 17.6 min) and (−)-7 (3.40 mg, tR = 20.9 min) (n-hexane/ethanol, 90:10); (+)-8 (3.70 mg, tR = 11.9 min) and (−)-8 (3.50 mg, tR = 13.8 min) (n-hexane/ethanol, 90:10); (+)-9 (1.32 mg, tR = 19.7 min) and (−)-9 (1.33 mg, tR = 24.1 min) (n-hexane/ethanol, 95:5); (+)-10 (0.98 mg, tR = 22.6 min) and (−)-10 (1.01 mg, tR = 20.3 min) (n-hexane/ethanol, 95:5); (+)-11 (18.8 mg, tR = 17.2 min) and (−)-11 (18.5 mg, tR = 15.0 min) (n-hexane/ethanol, 96:4).

**Compound Characterization**

Dimerocochlearactone A (1): yellowish gum; [α]20 D +18.9 (c 0.09, MeOH); CD (MeOH) Δε350 + 0.9, Δε310 −2.5, Δε260 + 2.8, Δε236 −3.1; (+)-1; [α]20 D −11.0 (c 0.10, MeOH); CD (MeOH) Δε371 −0.4, Δε310 + 2.0, Δε260 −2.2, Δε15 + 1.5; (−)-1; UV (MeOH) λmax (logε) 369 (3.42), 284 (58), 254 (3.95), 233 (4.15), 209 (4.31)
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nm; HRESIMS m/z 625.2774 [M + Na]^+ (calcd for C_{36}H_{42}NaO_{8}, 625.2777). 1H and 13C NMR data, see Tables 1 and 2.

Dimercochlearlate B (2): yellowish gum; [α]_D^{20} +17.0 (c 0.11, MeOH); CD (MeOH) δ_{327} + 1.0, δ_{311} - 3.3, δ_{266} + 3.5, δ_{263} - 6.3; (+)-2; [α]_D^{20} - 14.7 (c 0.11, MeOH); CD (MeOH) δ_{326} - 0.4, δ_{329} + 1.7, δ_{266} - 2.6, δ_{214} + 2.8; (−)-2; UV (MeOH) λ_{max} (log_e) 369 (3.31), 285 (3.49), 259 (3.87), 233 (4.10), 201 (4.39) nm; HRESIMS m/z 693.3406 [M + Na]^+ (calcd for C_{41}H_{52}NaO_{8}, 693.3403). 1H and 13C NMR data, see Tables 1 and 2.

Dimercochlearlate C (3): yellowish gum; [α]_D^{20} +30.6 (c 0.12, MeOH); CD (MeOH) δ_{325} + 3.5, δ_{229} - 11.6; (+)-3; [α]_D^{20} - 57.6 (c 0.12, MeOH); CD (MeOH) δ_{330} - 4.2, δ_{321} + 7.8; (−)-3; UV (MeOH) λ_{max} (log_e) 356 (3.55), 283 (3.50), 254 (3.96), 221 (4.48), 203 (4.81) nm; HRESIMS m/z 669.3777 [M – H]^- (calcd for C_{42}H_{53}O_{7}, 669.3797). 1H and 13C NMR data, see Tables 1 and 2.

Dimercochlearlate D (4): yellowish gum; [α]_D^{20} +4.5 (c 0.17, MeOH); CD (MeOH) δ_{325} + 4.6, δ_{229} - 9.2, δ_{226} + 13.6, δ_{305} - 8.5; (+)-4; [α]_D^{20} - 4.7 (c 0.22, MeOH); CD (MeOH) δ_{325} - 5.5, δ_{280} + 9.1, δ_{226} - 14.4, δ_{224} + 8.8; (−)-4; UV (MeOH) λ_{max} (log_e) 350 (3.62), 225 (4.44) nm; HRESIMS m/z 667.3620 [M – H]^- (calcd for C_{42}H_{53}O_{7}, 667.3640). 1H and 13C NMR data, see Tables 1 and 2.

Dimercochlearlate E (5): yellowish gum; [α]_D^{20} +26.9 (c 0.30, MeOH); CD (MeOH) ε_{280} + 0.9, δ_{229} + 1.5, δ_{325} - 1.0, δ_{320} + 1.7, δ_{229} - 6.7, δ_{216} + 2.9; δ_{226} - 3.0; (+)-5; [α]_D^{20} - 19.0 (c 0.32, MeOH); CD (MeOH) ε_{280} - 0.9, δ_{280} - 1.5, δ_{264} + 1.4, δ_{249}...
-1.4, $\Delta \varepsilon_{233} + 7.9$, $\Delta \varepsilon_{216} -4.0$, $\Delta \varepsilon_{204} + 3.7$; UV (MeOH) $\lambda_{\text{max}}$ (log $c$) 369 (3.36), 285 (3.34), 255 (3.87), 222 (4.28), 203 (4.50) nm; HRESIMS $m/z$ 781.3580 [M + C$_4$H$_5$F$_3$O$_9$, 781.5369]. $^1$H and $^{13}$C NMR data, see Table 1 and 2.

Dimercochlearlactone F (6): yellowish gum; $[\alpha]_{D}^{20} +38.2$ (c 0.10, MeOH); CD (MeOH) $\varepsilon_{381} -5.7$, $\Delta \varepsilon_{319} + 5.5$, $\Delta \varepsilon_{255} + 3.6$, $\Delta \varepsilon_{215} -3.5$; (+)-6; $[\alpha]_{D}^{20} -16.4$ (c 0.11, MeOH); CD (MeOH) $\varepsilon_{380} + 4.7$, $\Delta \varepsilon_{320} -4.0$, $\Delta \varepsilon_{256} -3.8$, $\Delta \varepsilon_{214} + 2.0$; (+)-6; UV (MeOH) $\lambda_{\text{max}}$ (log $c$) 368 (3.94), 262 (4.24), 229 (4.40), 203 (4.64) nm; HRESIMS $m/z$ 783.3727 [M + C$_4$H$_5$COO]$^-$ (calcld for C$_{44}$H$_{54}$F$_3$O$_9$, 783.7325). $^1$H and $^{13}$C NMR data, see Tables 2 and 3.

Dimercochlearlactone G (7): yellowish gum; $[\alpha]_{D}^{20} +18.6$ (c 0.09, MeOH); CD (MeOH) $\Delta \varepsilon_{206} + 12.1$; (+)-7; $[\alpha]_{D}^{20} -20.2$ (c 0.10, MeOH); CD (MeOH) $\Delta \varepsilon_{207} -14.2$; (+)-7; UV (MeOH) $\lambda_{\text{max}}$ (log $c$) 380 (3.42) 259 (3.95) nm; HRESIMS $m/z$ 723.3501 [M + Na]$^+$ (calcld for C$_{42}$H$_{52}$NaO$_9$, 723.3509). $^1$H and $^{13}$C NMR data, see Tables 2 and 3.

Dimercochlearlactone H (8): yellowish gum; $[\alpha]_{D}^{20} +17.6$ (c 0.09, MeOH); CD (MeOH) $\Delta \varepsilon_{230} + 1.7$; $\Delta \varepsilon_{210} -8.4$; (+)-8; $[\alpha]_{D}^{20} -18.9$ (c 0.10, MeOH); CD (MeOH) $\Delta \varepsilon_{228} -2.0$; $\Delta \varepsilon_{209} + 6.4$; (+)-8; UV (MeOH) $\lambda_{\text{max}}$ (log $c$) 316 (3.85), 242 (4.33), 203 (4.79) nm; HRESIMS $m/z$ 765.3633 [M + C$_4$H$_5$COO]$^-$ (calcld for C$_{42}$H$_{52}$F$_3$O$_9$, 765.3620). $^1$H and $^{13}$C NMR data, see Tables 2 and 3.

Dimercochlearlactone I (9): yellowish gum; $[\alpha]_{D}^{20} +10.1$ (c 0.08, MeOH); CD (MeOH) $\Delta \varepsilon_{244} -17.7$, $\Delta \varepsilon_{213} -9.4$; (+)-9; $[\alpha]_{D}^{20} -5.1$ (c 0.07, MeOH); CD (MeOH) $\Delta \varepsilon_{239} + 13.9$, $\Delta \varepsilon_{239} + 13.7$; (+)-9; UV (MeOH) $\lambda_{\text{max}}$ (log $c$) 373 (3.39), 296 (3.35), 254 (3.82),...
209 (4.42) nm; HRESIMS m/z 569.2154 [M + Na]⁺ (calcld for C₃₂H₃₄NaO₈, 569.2152). ¹H and ¹³C NMR data, see Tables 2 and 3.

Dimercochlearlactone J (10): yellowish gum; [α]D²⁰ +85.8 (c 0.09, MeOH); CD (MeOH) Δε₂₁₀ –4.4, Δε₂₂₆ + 31.5; (+)-10; [α]D¹⁰ –47.1 (c 0.10, MeOH); CD (MeOH) Δε₂₅₈ + 7.5, Δε₂₆₆ –31.8; (-)-10; UV (MeOH) λₘₐₓ (logε) 372 (3.66), 297 (3.57), 254 (4.08), 203 (4.45) nm; HRESIMS m/z 569.2149 [M + Na]⁺ (calcld for C₃₂H₃₄NaO₈, 569.2152). ¹H and ¹³C NMR data, see Tables 2 and 3.

**RESULTS AND DISCUSSION**

Dimercochlearlactone A (1) was determined to have a molecular formula as C₃₆H₄₂O₈ from its positive HRESIMS (m/z 625.2774 [M + Na]⁺, calcld for C₃₆H₄₂NaO₈, 625.2777). Two typical ABX spin systems (δH 7.14, d, J = 3.0 Hz, H-3; δH 6.98, d, J = 2.9 Hz, H-9) were observed by its ¹H NMR data (Table 1). The ¹³C NMR spectra show 36 carbon signals, which were assigned as 5 methyl, 7 methylene, 10 methine, and 14 nonprotonated carbons (10 aromatic including 4 oxygenated, 1 oxygenated aliphatic, 2 ketones, and 1 carbonyl). When consideration of the NMR data of the previous reported meroterpenoids (Qin et al., 2018), the above signals suggest that dimercochlearlactone A (1) might be a dimeric meroterpenoid. The structure of dimercochlearlactone A (1) contains two parts (Parts A and B in Figure 1), which were

### Biological Activity Assay on TNBC Cell Lines (MDA-MB-231)

TNBC cell line MDA-MB-231 was purchased from Procell (Procell Life Science & Technology Co. Ltd., Wuhan, China). Cell culture, cell viability, and wound healing assays were conducted following the reported protocols (Cai et al., 2021).
mainly determined by 2D NMR spectra. For the structure of part A, the $^1$H-$^1$H COSY correlations from H$_2$-12 ($\delta$H 1.97 and 1.83) to H$_2$-11 ($\delta$H 1.86 and 1.74) and H-13 ($\delta$H 5.03), and from H$_2$-17 ($\delta$H 2.00) to H$_2$-16 ($\delta$H 1.91) and H-18 ($\delta$H 5.07), along with the HMBC correlations (Figure 2) from H$_3$-20 ($\delta$H 1.54) and H$_3$-21 ($\delta$H 1.55) to C-18 ($\delta$C 122.5) and C-19 ($\delta$C 130.6), from H$_3$-20 to C-21 ($\delta$C 25.3), from H$_3$-15 ($\delta$H 1.52) and H$_2$-16 to C-13 ($\delta$C 122.4) and C-14 ($\delta$C 135.5), from H$_3$-15 to C-16 ($\delta$C 39.1), and from H$_2$-12 to C-14 suggest the presence of two isoprenyl moieties in dimercochlearlactone A (1). In addition, the HMBC correlations from H-8 ($\delta$H 3.92 and 3.57) to C-7 ($\delta$C 199.1), C-9 ($\delta$C 88.2) and C-10 and the above-mentioned HMBC correlations from H-8 to C-9 and C-10 imply another isoprenyl residue. Furthermore, HMBC correlation between H-3 ($\delta$H 7.14) and C-7 indicates that the sesquiterpenoid moiety is attached to the ring A via C-7 to C-2. Thus, the structure of part A was determined as shown.

Part B was also elucidated by 2D NMR experiments ($^1$H-$^1$H COSY, HSQC and HMBC). The HMBC correlations from H-3' ($\delta$H 7.10) to C-7', from H-8' ($\delta$H 8.77) to C-2' ($\delta$C 122.5), C-7' ($\delta$C 115.0), C-9 and C-10 and the above-mentioned HMBC correlations from H-8 to C-9 and C-10 not only imply the presence of ring B but also indicate that C-2' is attached to the ring C. The structure of side chain in part B was confirmed by $^1$H-$^1$H COSY correlations observed from H$_2$-11'($\delta$H 2.26) to H$_2$-10' ($\delta$H 2.51) and H-12'($\delta$H 5.09) and HMBC correlations from H$_3$-14' ($\delta$H 1.55) and H$_2$-15' ($\delta$H 1.63) to C-12' ($\delta$C 123.9) and C-13' ($\delta$C 132.2), and from H$_2$-11' and H$_2$-10' to C-9' ($\delta$C 171.2). Since the carboxyl group (C-9') in the side chain of part B needs form an ester with the phenolic hydroxyl group to meet the molecular formula requirement, the position of the side chain in part B linkage can be determined by the following evidence. In the 2D NMR experiments, the HMBC correlations of 1-OH ($\delta$H 10.75)/C-1 ($\delta$C 153.0), 4-OH ($\delta$H 9.17)/C-4 ($\delta$C 149.4), and 4'-OH ($\delta$H 9.50)/C-4'/($\delta$C 139.5) and ROESY correlations between 1-OH with H-6, 4-OH with H-3, and 4'-OH with H-6 led to the determination of the side chain linkage at the C-1' position. This conclusion was further secured by the ROESY correlation (Figure 3) between H$_2$-10' and H-6'. Thus, the 2D structure of 1 was assigned.

In the ROESY spectrum, the correlation between H-13 and H-1-6 demonstrates that the $\Delta^{13(14)}$ double bond is E configuration. Dimercochlearlactone A (1) was found to be a racemate, the separation by chiral-phase HPLC afforded enantiomers (+)-dimercochlearlactone A (1) and (-)-dimercochlearlactone A (1). Computational ECD spectral methods at time-dependent density functional theory (TDDFT) were employed to define the absolute configurations of (+)-dimercochlearlactone A (1) and (-)-dimercochlearlactone A (1). Due to the structure flexibility of dimercochlearlactone A (1), the model compound (1a) was constructed to ECD
calculations. The result showed that the experimental CD spectrum of (+)-dimercochlearlactone A (1) exhibited similar Cotton effects with calculated ECD spectrum (Figure 4) of (9R)-1a. Accordingly, the absolute configurations as 9R for (+)-dimercochlearlactone A (1) and 9S for (−)-dimercochlearlactone A (1) were determined.

The NMR data of dimercochlearlactone B (2) resemble those of dimercochlearlactone A (1) revealing that the structure of dimercochlearlactone B (2) similar to that of dimercochlearlactone A (1). Only difference appears at their side chains, which is a 7-carbon side chain in dimercochlearlactone A (1) was attached an isopentenyl to form a 12-carbon side chain in dimercochlearlactone B (2), supporting by the 1H-1H COSY correlations from H2-16′ (δH 2.00) to H2-15′ (δH 1.92) and H-17′ (δH 5.04) and the HMBC correlations (Figure 2) from H2-19′ (δH 1.54) and H2-20′ (δH 1.62) to C-17′ (δC 123.9) and C-18′ (δC 130.0), from H2-14′ (δH 1.56) to C-12′ (δC 122.2), C-13′ (δC 135.8) and C-15′ (δC 39.0). In the ROESY experiment, correlations between H-13 and H2-16 and between H-12′ and H2-15′ suggest that both double bonds Δ13(14) and Δ12′(13′) are E-from configurations (Figure 3). Racemic dimercochlearlactone B (2) was separated by chiral HPLC to yield (+)-dimercochlearlactone B (2) and (−)-dimercochlearlactone B (2). Their absolute configurations were deduced as 9R for (+)-dimercochlearlactone B (2) and 9S for (−)-dimercochlearlactone B (2) by using the above-mentioned ECD calculations (Figure 4).

Compounds 1 and 2 bear a same skeleton, which are different from the previously isolated *Ganoderma* meroterpenoids, a plausible pathway for the biogenesis of 2 was proposed (Figure 5). At first, fornincin C (Niu et al., 2006) undergoes a series of oxidation, ring formation, and reduction reactions to form intermediates A and B, respectively, which further form intermediate C via aldol condensation reaction. Intermediate C
undergoes a reduction and substitution reaction to form D, which then give hemiacetal E via a substitution addition reaction. After a decarboxylation reaction, hemiacetal E can produce intermediate F. Finally, F undergoes intermediates G and H through dehydration and C-C bond cracking to form 2.

Dimercochlearlactone C (3) has the molecular formula C_{42}H_{54}O_{7} (16 degrees of unsaturation) deduced by the HRESIMS analysis at m/z 669.3777 [M-H]^- (calc for C_{42}H_{53}O_{7}, 669.3797). The 1H NMR spectrum of dimercochlearlactone C (3) exhibits signals for two typical ABX systems (δH 7.16, d, J = 3.0 Hz, H-3; δH 7.06, dd, J = 8.9, 3.0 Hz, H-5; δH 7.01, d, J = 8.9 Hz, H-6; δH 6.57, d, J = 2.7 Hz, H-3'; δH 6.54, dd, J = 8.6, 2.7 Hz, H-5'; δH 6.51, d, J = 8.6 Hz, H-6'). It was found 42 carbon signals including 6 methyl, 11 methylene, 11 methine, and 14 nonprotonated carbons (11 aromatic including 4 oxygenated, 1 oxygenated aliphatic, 1 ketone, and 1 carbonyl) by analyzing its 13C NMR and DEPT spectra. Like compound dimercochlearlactone A (1), the NMR data of
dimercochlearlactone C (3) suggest a meroterpenoid dimer. The data of part A are very similar to those of ganotheaecolumol A (Luo et al., 2018), differing in that C-20 is a hydroxymethylene in ganotheaecolumol A, while the same position in part A of dimercochlearlactone C (3) is a methyl group. This deduction is supported by the HMBC correlations between H3-20 (δH 1.58) with C-18 (δC 125.5), C-19 (δC 132.5), and C-21 (δC 26.1).

The analysis of 2D NMR spectra (See Supplementary Figures S30–S33) of dimercochlearlactone C (3) reveals that the structure of part B is similar to that of ganomycin F (Cheng et al., 2018). Thus, there are four possibilities for the connection between part A and part B of dimercochlearlactone C (3), C-4-O-C-1′, C-4-O-C-4′, C-9-O-C-1′, and C-9-O-C-4′. In the 1H NMR spectrum, signals of two phenolic hydroxyl groups (δH 9.51, s and δH 9.41, s) are observed, it could be concluded that the connections between part A and part B in dimercochlearlactone C (3) are C-9-O-C-1′ or C-9-O-C-4′. Furthermore, the ROESY correlations (observed in DMSO-d6) between 4-OH with H-3 and 4′-O with H-3′ are indicative of phenolic hydroxyl attaching to C-4 and C-4′, which indicate that C-9 and C-1′ are connected via oxygen atom to form phenolic ester. The ROESY correlation between H-8′ (δH 5.13) and H2-11′ (δH 2.14) suggests that the double bond Δ13(14) is Z-form configuration. Furthermore, ROESY correlations between H-13 with H2-16 and H-13′ with H2-16′ demonstrate that both Δ13(14) and Δ13′(14′) double bonds are E configuration. Racemic dimercochlearlactone C (3) was segregated into (+)-dimercochlearlactone C (3) and (-)-dimercochlearlactone C (3) by using chiral HPLC. Since the calculated ECD curve of (9S)-3a (Model structure) agrees with the experimental CD spectrum of (+)-dimercochlearlactone C (3) (Figure 4), the absolute configurations at the stereogenic center were established as 9S for (+)-dimercochlearlactone C (3) and 9R for (-)-dimercochlearlactone C (3).

The molecular formula of dimercochlearlactone D (4) was deduced as C42H52O7 by its negative HRESIMS. In 1H NMR spectrum of dimercochlearlactone D (4), the signals at (δH 6.70, d, J = 8.5 Hz, H-6; 6.61, d, J = 8.5 Hz, H-5; δH 8.00, d, J = 3.0 Hz, H-3′; δH 6.57, d, J = 3.0 Hz, H-5′) suggest that a 1,2,3,4-tetrasubstituted benzene ring and a 1,3,4,5-tetrasubstituted benzene ring in the structure of dimercochlearlactone D (4). The 13C NMR and DEPT spectra of dimercochlearlactone D (4) show 42 carbons including 6 methyl, 9 methylene, 12 methine, and 15 nonprotonated carbons (14 aromatic including 4 oxygenated and 1 carbonyl). The structure of dimercochlearlactone D (4) was mainly determined by 2D NMR spectra. The observation correlations from H2-12 to H2-11 and H-13, and from H2-17 to H2-16 and H-18 in 1H-1H COSY spectrum, along with the HMBC correlations from H3-20 and
H3-21 to C-18 and C-19, from H3-20 to C-21, from H3-15 and H-16 to C-13 and C-14, and from H3-15 to C-16 indicate the presence of two isoprenyl moieties. Another isoprenyl residue is supported by the observation of 1H-1H COSY correlation between H-7 with H-8 and the HMBC correlations from H-10 and H-11 to C-8 and C-9, from H-10 to C-11, and from H-7 to C-9. Further observation of HMBC correlations from H-7 and H-8 to C-2 suggests that C-7 is connected to C-2. Similarly, the 1H-1H COSY correlations from H2-7′ to H-8′, from H2-12′ to H2-11′ and H-13′, and from H2-17′ to H2-16′ and H-18′ along with the HMBC correlations from H2-20′, and H2-21′ to C-18′ and C-19′, from H-20′ to C-21′, from H3-15′ and H-16′ to C-13′ and C-14′, from H3-15′ to C-16′, from H-10′ and H-11′ to C-8′ and C-9′, and from H-10′ to C-11′ indicates substructure consisting of three isoprenyl groups in part B of 4. Moreover, the correlation from H-6′ to C-7′ in HMBC spectrum suggests that the side chain and benzene ring of part B are linked via C-7′-C-6′. Finally, the two meroterpenoids are linked via C-2′-C-3 and C-8-O-C-1′ supported by the key HMBC correlations from H-3′ to C-2 and from H-8 to C-1′. The ROESY correlations from H-8 to H-10, from H-13 to H-16, and from H-13′ to H-16′ indicate that three double bonds (Δ8(9), Δ13(14), and Δ13′(14′)) are E-form, and that between H-8′ and H2-11′ suggests Δ8′(9′) double bond is Z form.

Racemic 4 was submitted to chiral HPLC to afford their enantiomers. The absolute configurations were determined to be 7S for (-)-4 and 7R for (+)-4 by using computational ECD methods (Figure 4).

The NMR data of dimercochlearlactone E (5) are similar to those of the known spirocochlealactone A (Qin et al., 2018). Careful analysis of their structures showed that compound 5 is
formed by the reduction of nonprotonated carbon (δ\textsubscript{C} 88.3) and a carbonyl group (δ\textsubscript{C} 173.0) in spirocochlealactone A to a methine (δ\textsubscript{C} 40.1) and an aldehyde group (δ\textsubscript{C} 194.0), respectively. The \textsuperscript{1}H-\textsuperscript{1}H COSY correlation between H-7′ and H-8′, and the HMBC correlations from H-7′ to C-8′ and C-9′, and from H-8′ to C-9′, C-10′ and C-11′ supports the above conclusions. In the ROESY spectrum, correlations from H-8′ to H-10′, from H-13′ to H-16′, and from H-13 to H-16 indicate that three double bonds (Δ\textsubscript{8′}(9′), Δ\textsubscript{13′}(14′), and Δ\textsubscript{13′}(14)) are E-form. Furthermore, the relative configuration of dimercochlearlactone E (5) was assigned as 9\textsuperscript{R},7\textsuperscript{S}, gaining support from the ROESY correlation of Hb-8/H-7′. Dimercochlearlactone E (5) was also separated by chiral HPLC to afford (+)-dimercochlearlactone E (5) and (−)-dimercochlearlactone E (5). Their absolute configurations were assigned as 9\textsuperscript{R},7\textsuperscript{S} for (+)-dimercochlearlactone E (5) and 9\textsuperscript{S},7\textsuperscript{R} for (−)-dimercochlearlactone E (5) by comparing their CD curves with the calculated ones. Thus, the structure of 5 was determined.

Dimercochlearlactone F (6) has the molecular formula C\textsubscript{42}H\textsubscript{54}O\textsubscript{7} based on HRESIMS analysis (m/z 783.3727 [M + CF\textsubscript{3}COO]\textsuperscript{−}; calcld for 783.3725). The \textsuperscript{1}H NMR spectrum of 6 contains signals for one typical ABX system (δ\textsubscript{H} 7.11, d, J = 2.7 Hz, H-3; δ\textsubscript{H} 6.99, dd, J = 8.9, 2.7 Hz, H-5; δ\textsubscript{H} 6.80, d, J = 8.9 Hz, H-6) and a 1,2,4,5-tetrasubstituted benzene ring (δ\textsubscript{H} 6.58, s, H-3′ and δ\textsubscript{H} 7.08 s, H-5′). The \textsuperscript{13}C NMR and DEPT spectra contain the resonances for 42 carbons including 6 methyl, 11 methylene, 10 methine, and 15 nonprotonated carbons (12 aromatic including 4 oxygenated, 1 oxygenated aliphatic, 2 ketones). The above signals suggest that compound 6 is also a meroterpenoid dimer, and its structure consists of parts A and B. The substructure of part A in 6 is similar to that of part A in 1 as they have very similar NMR data. The substructure of part B is very similar to ganomycin F (Cheng et al., 2018). The difference is that the 3-position of the benzene ring in part A is connected to the other additional substructures, which is a hydrogen atom in ganomycin F. The HMBC correlation from H-6′ to C-10 suggests that C-10 is connected to C-5′. Although no HMBC correlations are observed to support C-9-O-C-3 fragment, the presence of ring A is confirmed due to the observation of characteristic chemical shift of C-4 (δ\textsubscript{C} 166.2) in the benzene ring (Ring B).
phenomenon was observed in other such kind of benzofuran structures, such as cochlereol I and spiroplanatuminones A-Q (Luo et al., 2017; Wang et al., 2019). The ROESY correlations from H-13′ to H-16′ and from H-13 to H-16 indicate that both double bonds (Δ13(14)= 2.9 Hz, H-3) and Δ13(14)= 8.9 Hz, H-6) are E-form. Further correlation from H-8′ to H-11′ observed in ROESY spectrum suggests a E-form double bond (Δ8(9)= 9.0 Hz). Chiral separation by HPLC afforded (+)-6 and (-)-6. Their absolute configurations were determined as 9S and 9R, respectively, when comparing their experimental CD curves with the calculated ones. As a result, the structure of 6 was assigned.

Dimercochlearlactone G (7) has a molecular formula C42H52O6 based on its HRESIMS, 13C NMR, and DEPT data. Two ABX aromatic coupling systems at δH 7.07 (d, J = 3.0 Hz, H-3), 7.01 (dd, J = 8.9, 3.0 Hz, H-5), 6.82 (d, J = 8.9 Hz, H-6), 6.35 (d, J = 2.9 Hz, H-3′, 6.55 (dd, J = 8.6, 2.9 Hz, H-5′), and 6.69 (d, J = 8.6 Hz, H-6′) were observed in its 1H NMR spectrum. Its 13C NMR and DEPT spectra revealed the presence of 42 carbons ascribed to 6 methyl, 9 methylene, 12 methine, and 15 nonprotonated carbons. Analysis of the NMR data of 7 found that part A is similar to daoyaolingzhiol K (Zhang et al., 2021). The molecular formula of compound dimercochlearlactone J was specified as C32H48O8 based on the analysis of its positive HRESIMS ([M + Na]+, m/z 569.2154, calc 569.2151). The 1H NMR spectrum exhibits two typical ABX spin systems δH 7.14, d, J = 2.9 Hz, H-3; 7.08, dd, J = 8.9, 2.9 Hz, H-5; 6.84, dd, J = 8.9 Hz, H-6; δH 6.98, d, J = 8.9 Hz, H-6′; 6.85, dd, J = 8.9, 2.9 Hz, H-5′; 6.45, d, J = 2.9 Hz, H-3′. The 13C NMR and DEPT spectra of 9 display 4 methyl, 5 methylene, 9 olefinic methine, 14 nonprotonated carbons (11 aromatic including 4 oxygenated, 2 carbonyl, and a ketone group). These data are very similar to those of spirocochlealactone B (Qin et al., 2018). The difference between 9 and spirocochlealactone B is that the chemical shift of C-19 is 71.5 ppm in the ROESY correlation between H3-21 and H-8 and H-11 suggests that the double bond in 9 is different from C-2′. The molecular weight and the unsaturation of the molecule need to form another ring to be satisfied. There are three possible ring formations, which are C-1- O-C-1′ C-1′-O-C-10 or C-1-O-C-10. In the 1H NMR spectrum (DMso-d6), there are two free phenolic hydroxyl signals at δH 9.42 (s, 4-OH), 9.29 (s, 4′-OH). The ROESY correlations from 4-OH to H-3 and H-5 and from 4′-OH to H-3′ and H-5′ fix phenolic hydroxy at C-4′ and C-4′, confirming the formation of ring C. Furthermore, the ROESY correlations from H-13′ to H-16′ and from H-13 to H-16 suggest that double bonds Δ13(14) and Δ13(14) are E-form. Additional ROESY correlation between H-8′ and H-11′ suggests a E-form double bond Δ8(9)= 9.0 Hz. The absolute configurations of 9 were determined to be 7R for (+)-8 and 7S for (+)-8′ by using ECD calculation methods.

The molecular formula of 9 was specified as C32H48O8 based on the analysis of its positive HRESIMS ([M + Na]+, m/z 569.2154, calc 569.2151). The 1H NMR spectrum exhibits two typical ABX spin systems δH 7.14, d, J = 2.9 Hz, H-3; 7.08, dd, J = 8.9, 2.9 Hz, H-5; 6.84, dd, J = 8.9 Hz, H-6; δH 6.98, d, J = 8.9 Hz, H-6′; 6.85, dd, J = 8.9, 2.9 Hz, H-5′; 6.45, d, J = 2.9 Hz, H-3′. The 13C NMR and DEPT spectra of 9 display 4 methyl, 5 methylene, 9 olefinic methine, 14 nonprotonated carbons (11 aromatic including 4 oxygenated, 2 carbonyl, and a ketone group). These data are very similar to those of spirocochlealactone B (Qin et al., 2018). The difference between 9 and spirocochlealactone B is that the chemical shift of C-19 is 71.5 ppm in the ROESY correlation between H3-21 and H-8 and H-11 suggests that the double bond in 9 is different from C-2′. The molecular weight and the unsaturation of the molecule need to form another ring to be satisfied. There are three possible ring formations, which are C-1- O-C-1′ C-1′-O-C-10 or C-1-O-C-10. In the 1H NMR spectrum (DMso-d6), there are two free phenolic hydroxyl signals at δH 9.42 (s, 4-OH), 9.29 (s, 4′-OH). The ROESY correlations from 4-OH to H-3 and H-5 and from 4′-OH to H-3′ and H-5′ fix phenolic hydroxy at C-4′ and C-4′, confirming the formation of ring C. Furthermore, the ROESY correlations from H-13′ to H-16′ and from H-13 to H-16 suggest that double bonds Δ13(14) and Δ13(14) are E-form. Additional ROESY correlation between H-8′ and H-11′ suggests a E-form double bond Δ8(9)= 9.0 Hz. The absolute configurations of 9 were determined to be 7R for (+)-8 and 7S for (+)-8′ by using ECD calculation methods.

The molecular formula of 9 was specified as C32H48O8 based on the analysis of its positive HRESIMS ([M + Na]+, m/z 569.2154, calc 569.2151). The 1H NMR spectrum exhibits two typical ABX spin systems δH 7.14, d, J = 2.9 Hz, H-3; 7.08, dd, J = 8.9, 2.9 Hz, H-5; 6.84, dd, J = 8.9 Hz, H-6; δH 6.98, d, J = 8.9 Hz, H-6′; 6.85, dd, J = 8.9, 2.9 Hz, H-5′; 6.45, d, J = 2.9 Hz, H-3′. The 13C NMR and DEPT spectra of 9 display 4 methyl, 5 methylene, 9 olefinic methine, 14 nonprotonated carbons (11 aromatic including 4 oxygenated, 2 carbonyl, and a ketone group). These data are very similar to those of spirocochlealactone B (Qin et al., 2018). The difference between 9 and spirocochlealactone B is that the chemical shift of C-19 is 71.5 ppm in the ROESY correlation between H3-21 and H-8 and H-11 suggests that the double bond in 9 is different from C-2′. The molecular weight and the unsaturation of the molecule need to form another ring to be satisfied. There are three possible ring formations, which are C-1- O-C-1′ C-1′-O-C-10 or C-1-O-C-10. In the 1H NMR spectrum (DMso-d6), there are two free phenolic hydroxyl signals at δH 9.42 (s, 4-OH), 9.29 (s, 4′-OH). The ROESY correlations from 4-OH to H-3 and H-5 and from 4′-OH to H-3′ and H-5′ fix phenolic hydroxy at C-4′ and C-4′, confirming the formation of ring C. Furthermore, the ROESY correlations from H-13′ to H-16′ and from H-13 to H-16 suggest that double bonds Δ13(14) and Δ13(14) are E-form. Additional ROESY correlation between H-8′ and H-11′ suggests a E-form double bond Δ8(9)= 9.0 Hz. The absolute configurations of 9 were determined to be 7R for (+)-8 and 7S for (+)-8′ by using ECD calculation methods.

The molecular formula of compound dimercochlearlactone J (10) is similar to that of 9. Careful examination of 2D NMR (see Supplementary Figures S81–S84, S91–S94) data between 10 and 9 indicates that they have the same planar structure. The observed ROESY correlation (see Supplementary Figure S94) of H-8′ (δH 7.16)/H-8 (δH 3.68, 3.07) in 10 suggests 9R,7′S* relative configurations at chiral centers. The absolute configurations of 10 were determined as 9R,7′R* for (+)-dimerochechlearactone 10 and 9R,7′S* for (−)-dimerochechlearactone 10 by comparing their experimental CD spectra to (+)-spirocochlealactone A and
(−)-spirochlealactone A (Qin et al., 2018). Thus, the structure of 10 was assigned.

Compound 11 was identified as spirochlealactone A by comparing its NMR and MS data with the literature data (Qin et al., 2018). This compound has been isolated by us from 10 kg of *G. cochlear*, and in this experiment, it was isolated from *G. lucidum*.

To investigate the anti-TNBC effects of the isolated compounds, we used the MDA-MB-231 cells for our analyses. All 22 dimer meroterpenoid enantiomers were evaluated for their suppressive effect toward MDA-MB-231 cells. It was found that (+)-2, (−)-2, (−)-3, (+)-11, and (−)-11 significantly decreased the cell viability in MDA-MB-231 cells (Figure 6A). Moreover, the morphological and density changes were observed in MDA-MB-231 cells upon exposure of the compounds (Supplementary Figure S98). To further analyze the effects of the compounds on MDA-MB-231 cells, the dose-response studies were performed. The cell viability of MDA-MB-231 cells was substantially inhibited by treatment with compounds for 48 h in a dose-dependent manner. As shown in Figure 6B, similar to the positive control (cisplatin), compound treatment dose-dependently inhibits MDA-MB-231 cells growth. The IC<sub>50</sub> of compounds for MDA-MB-231 cells are 28.18, 25.65, 11.16, 8.18, and 13.02 μM, respectively. The remaining compounds showed negligible inhibitory effects on cell viability at 20 μM (Figure 6A). Interestingly, although all the remaining compounds have rather low cytotoxicities toward MDA-MB-231 cells, ten of the isolates (+)−5, (−)−5, (+)−6, (−)−6, (+)−7, (−)−7, (+)−8, (−)−8, (+)−10, and (−)−10 significantly inhibit the migration ability of MDA-MB-231 cells (Figure 7), suggesting that they might be promising lead compounds for the development of anti-cancer drugs against metastasis of TNBC.

**CONCLUSION**

To conclude, this study resulted in the isolation of ten pairs of novel meroterpenid dimers and one pair of known compounds from *Ganoderma* species. Biological results revealed the importance of (+)-2, (−)-2, (−)-3, (+)-11, and (−)-11 in the development of the anti-TNBC drugs. Furthermore, (+)-5, (−)-5, (+)-6, (−)-6, (+)-7, (−)-7, (+)-8, (−)-8, (+)-10, and (−)-10 significantly inhibit the migration ability of MDA-MB-231 cells, thereby providing promising compounds for the development of anti-TNBC drugs.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

Y-XC designed the research. FQ conducted chemical experiments (isolated compounds 1–10). Y-YC conducted biological experiments in vitro. JZ isolated compound 11. FQ, Y-YC, JZ and Y-XC analyzed data. FQ and Y-XC wrote and revised the manuscript. All authors discussed the results and commented on the manuscript at all stages.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2022.888371/full#supplementary-material

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