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# Chaeglobol A, an unusual octocyclic sterol with antifungal activity from the marine-derived fungus *Chaetomium globosum* HBU-45

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ABSTRACT

Chemical investigation of the marine-derived fungus *Chaetomium globosum* HBU-45 led to the discovery of chaeglobol A (**1**). Its structure was determined by spectroscopic analysis, computational electronic circular dichroism (ECD)/optical rotatory dispersion (ORD) methods, and X-ray crystallography. Compound **1** represents a new skeleton with an uncommon 6/6/6/5/6/5/6/5 octacyclic system, which is presumably biosynthesized *via* a [4 + 2] cycloaddition and an enzymatic cyclization. Chaeglobol A (**1**) exhibited inhibitory activity against *B. dothidea* by destroying cell membrane integrity and causing oxidative damage within the cells.



Natural products with novel skeletons not only possess unique chemical structures and remarkable pharmacological activities, but also frequently possess the potential to bind to novel drug target proteins *in vivo*, offering distinct mechanisms of action compared to existing clinical drugs [1,2]. Consequently, they represent a significant avenue for exploring new mechanism-based drug leads derived from natural sources [3–5]. Among these novel natural products, derivatives with structures derived from steroid skeletons have particularly promising potential [6,7]. Despite the ubiquity of steroid structures, the discovery of novel steroid derivatives with unique skeletons continues to yield compounds with significant pharmacological activities, including anti-microbial, anti-inflammatory, and anti-tumor activities [8,9]. For instance, two ergosteroids featuring a rearranged bicyclo[3.3.1]nonane motif, phomopsterones A and B, isolated from the fungus *Phomopsis* sp., exhibited anti-inflammatory activity [9]. Nevertheless, the exploration of structurally unique steroids remains in its infancy, and numerous steroids with novel carbon skeletons remain to be discovered. The ongoing exploration of uncommon steroids derived from natural sources will undoubtedly contribute to the development of new drugs.

The fungal genus *Chaetomium* is widely dispersed across both marine and terrestrial ecosystems, demonstrating a propensity to biosynthesize a myriad of novel compounds, such as steroids, cytochalasins, and azaphilones. These secondary metabolites exhibited a broad spectrum of pharmacological activities, including potent antifungal, cytotoxic, and antiviral properties [10]. In the course of our continuous exploration for structurally unique natural products from marine-derived fungi [11–13], an unusual octacyclic sterol, chaeglobol A (**1**), was isolated from the marine-derived fungus *Chaetomium globosum* HBU-45. The structure of **1**, inclusive of its absolute configuration, was meticulously elucidated through a combination of spectroscopic techniques, electronic circular dichroism (ECD) alongside optical rotatory dispersion (ORD) methods, and single-crystal X-ray diffraction analysis. Herein we report the isolation, structural determination, and anti-fungal activity assessment of **1**, along with discussing its putative biosynthetic origin.

Chaeglobol A (**1**) was obtained as colorless crystals, revealing its molecular formula of $C_{37}H_{48}O_6$, as confirmed by high resolution electrospray ionization mass spectroscopy (HRESIMS) analysis (*m/z* 611.3336 $[M+Na]^+$, calcd. for $C_{37}H_{48}NaO_6^+$ 611.3343), corresponding to 14 sites of unsaturation. The proton nuclear magnetic resonance ($^1$H NMR) data (Table 1) of **1** showed the presence of seven

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**Table 1**
$^{1}H$ (600 MHz) and $^{13}C$ (150 MHz) NMR data for **1** in $CDCl_3$.

| No. | $\delta_C$ | $\delta_H$ ($J$ in Hz) |
|---|---|---|
| 1 | 33.6, $CH_2$ | 1.54, m |
| | | 1.46, m |
| 2 | 29.0, $CH_2$ | 1.67, m |
| | | 2.07, m |
| 3 | 68.0, CH | 4.40, t (7.8) |
| 4 | 126.7, CH | 5.28, s |
| 5 | 139.0, C | |
| 6 | 40.5, CH | 3.03, s |
| 7 | 38.6, CH | 3.03, s |
| 8 | 132.3, C | |
| 9 | 44.9, CH | 1.64, m |
| 10 | 35.5, C | |
| 11 | 19.4, $CH_2$ | 1.57, m |
| | | 1.66, m |
| 12 | 37.4, $CH_2$ | 2.00, s |
| | | 1.23, m |
| 13 | 42.5, C | |
| 14 | 148.6, C | |
| 15 | 43.0, CH | 2.72, m |
| 16 | 35.2, $CH_2$ | 1.87, m |
| | | 1.66, m |
| 17 | 54.7, CH | 1.24, m |
| 18 | 21.1, $CH_3$ | 0.92, s |
| 19 | 19.5, $CH_3$ | 0.93, s |
| 20 | 39.3, CH | 2.10, m |
| 21 | 21.1, $CH_3$ | 1.03, d (6.6) |
| 22 | 135.2, CH | 5.22, dd |
| | | (15.0, 7.2) |
| 23 | 132.8, CH | 5.25, dd |
| | | (15.0, 7.2) |
| 24 | 43.0, CH | 1.87, m |
| 25 | 33.3, CH | 1.47, m |
| 26 | 20.1, $CH_3$ | 0.85, d (7.2) |
| 27 | 19.8, $CH_3$ | 0.84, d (6.6) |
| 28 | 17.9, $CH_3$ | 0.94, d (7.2) |
| 1′ | 63.5, C | |
| 2′ | 158.1, C | |
| 3′ | 127.6, C | |
| 4′ | 199.3, C | |
| 5′ | 88.7, C | |
| 6′ | 199.0, C | |
| 7′ | 84.4, CH | 4.28, d (7.8) |
| 8′ | 97.8, CH | 6.13, s |
| 9′ | 11.7, $CH_3$ | 2.00, s |
| 5′-OH | | 3.86, s |

methyl groups at $\delta_H$ 0.84 (d, $J$ = 6.6 Hz, $H_3$–27), 0.85 (d, $J$ = 7.2 Hz, $H_3$–26), 0.92 (s, $H_3$–18), 0.93 (s, $H_3$–19), 0.94 (d, $J$ = 7.2 Hz, $H_3$–28), 1.03 (d, $J$ = 6.6 Hz, $H_3$–21), and 2.00 (s, $H_3$–9′), two oxymethines at $\delta_H$ 4.28 (d, $J$ = 7.8 Hz, H-7′) and 4.40 (t, $J$ = 7.8 Hz, H-3), three olefinic hydrogen at $\delta_H$ 5.22 (dd, $J$ = 15.0, 7.2 Hz, H-22), 5.25 (dd, $J$ = 15.0, 7.2 Hz, H-23), and 5.28 (s, H-4), and one hemiacetal oxymethine at $\delta_H$ 6.13 (s, H-8′). By combining its heteronuclear single quantum coherence (HSQC) data with the $^{13}C$ NMR of **1**, a total of 37 carbon resonances were observed, divided into two saturated ketones ($\delta_C$ 199.0 and 199.3), eight olefinic carbon atoms including three methine groups ($\delta_C$ 126.7, 132.8, and 135.2) and five quaternary carbons ($\delta_C$ 127.6, 132.3, 139.0, 148.6, and 158.1), seven methyl groups, five $sp^3$ methylene groups, eleven $sp^3$ methine groups including two oxygenated carbons($\delta_C$ 68.0 and 84.4) and one hemiacetal carbon ($\delta_C$ 97.8), and four quaternary carbons including one oxygenated carbon ($\delta_C$ 88.7). The above NMR data accounted for six degrees of unsaturation, suggesting that **1** should be an octacyclic compound.

The planar structure of **1** was rigorously determined through a comprehensive interpretation of its $^{1}H$–$^{1}H$ correlation spectroscopy (COSY) and $^{1}H$ detected heteronuclear multiple bond correlation (HMBC) spectra (Fig. 1). The $^{1}H$–$^{1}H$ COSY correlations observed for $H_2$–1/$H_2$–2/H-3/H-4, H-6/H-7, H-9/$H_2$–11/$H_2$–12, and H-15/$H_2$–16/H-17, when combined with key HMBC correlations such as those from $H_3$–19 to C-1/C-5/C-9/C-10, from $H_3$–18 to C-12/C-13/C-14/C-17, from H-4 to C-2/C-6, from H-9 to C-7, and from $H_2$–11/H-15 to C-8, unequivocally confirmed the presence of A/B/C/D-rings system. Furthermore, the $^{1}H$–$^{1}H$ COSY correlations involving $H_3$–21/H-20/H-22/H-23/H-24/H-25/$H_3$–26, H-24/$H_3$–28, and H-25/$H_3$–27, indicated the presence of 22,23-dihydro-24-methyl C9 side chain. This side chain was shown to be attached to C-17, based on the $^{1}H$–$^{1}H$ COSY correlation between H-17 and H-20, and the HMBC correlation from $H_3$–21 to C-17. The HMBC correlations from OH-5′ to C-4′/C-5′/C-6′, from H-7′ to C-6′, from H-8′ to C-1′/C-3′/C-7′, and from H-9′ to C-2′/C-3′/C-4′ were sufficient to establish the "E + F" 6/5-membered ring system. Finally, the integration of the E/F-ring system with the A/B/C/D-ring system was proposed to occur *via* bonds between C-5′ and C-6, C-1′ and C-7, and C-7′ and C-15, forming the novel "G + H" 5/6-membered rings. This proposal was supported by the $^{1}H$–$^{1}H$ COSY correlation between H-7′ and H-15, as well as the HMBC correlations from H-6 to C-4′ and from H-15 to C-1′/C-7′. Thus, the planar structure of **1** was unambiguously established, featuring a unique 6/6/6/5/6/5/6/5 octacyclic ring system. To validate the novel skeleton of **1**, we employed the *gauge*-independent atomic orbital (GIAO) method [14] for $^{13}C$ NMR chemical shift calculation (Fig. 2). The high correlation coefficient ($R^2$) of 0.9986 and all deviation ($|\Delta\delta|$) between experimental and calculated chemical shifts being less than 5.4 ppm, confirmed the proposed octacyclic structure of **1**.

The relative configuration of the 12 stereogenic centers C-3, C-6, C-7, C-9, C-10, C-13, C-15, C-17, C-1′, C-5′, C-7′, and C-8′ in **1** was assigned through a meticulous analysis of its nuclear overhauser effect spectroscopy (NOESY) spectrum (Fig. 3). The NOESY correlations of H-1$\alpha$/H-3, H-1$\alpha$/H-9, H-9/OH-5′, H-1$\beta$/$H_3$–19, $H_3$–19/H-

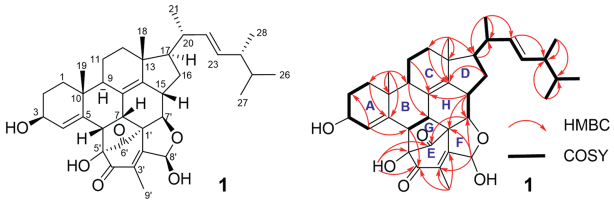



**Fig. 1.** Chemical structure, the key HMBC and COSY correlations of chaeglobol A (**1**).

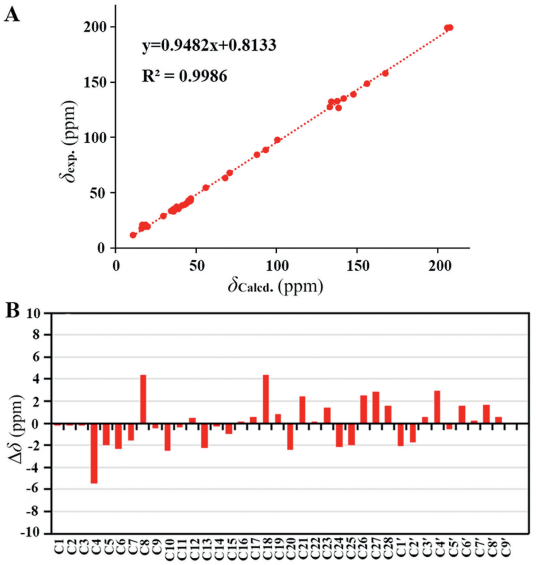



**Fig. 2.** (A) Regression analysis and (B) individual deviations of experimental *versus* calculated $^{13}C$ NMR chemical shifts of **1**.

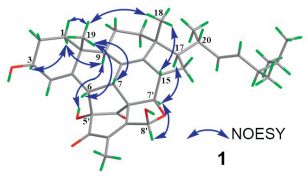



**Fig. 3.** NOESY correlations of chaeglobol A (**1**).

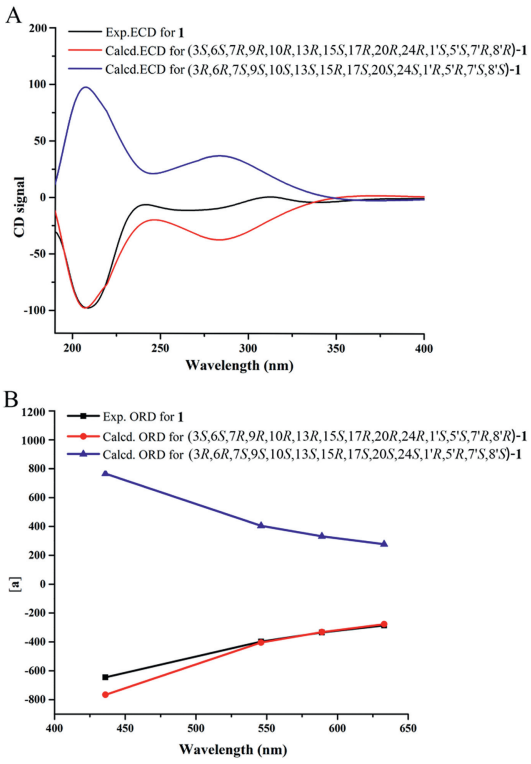



**Fig. 4.** (A) Experimental *versus* calculated ECD and (B) ORD spectra of **1**.

6, $H_3$–19/H-7, $H_3$–19/$H_3$–18, $H_3$–18/H-15, H-17/H-7′, and H-7′/H-8′, provided compelling evidence for the proposed relative configuration of the A/B/C/D/E/F/G/H rings: 3*S**, 6*S**, 7*R**, 9*R**, 10*R**, 13*R**, 15*S**, 17*R**, 1′*S**, 5′*S**, 7′*R**, and 8′*R**. Furthermore, the relationship between H-22 and H-23 was ascertained to be *E* configuration based on their coupling constant ($J = 15.0$ Hz). Additionally, the configurations of C-20 and C-24 were tentatively determined as *R* and *R* since ergosterols of these configurations are commonly found in natural sources [15,16].

To determine the absolute configuration of **1**, a comprehensive spectral analysis was conducted. The experimental electronic circular dichroism (ECD) and optical rotatory dispersion (ORD) spectra of **1** were compared with the corresponding computed ECD and ORD curves for the structures of (3*S*,6*S*,7*R*,9*R*,10*R*,13*R*,15*S*,17*R*,20*R*,24*R*,1′*S*,5′*S*,7′*R*,8′*R*)−**1** and (3*R*,6*R*,7*S*,9*S*,10*S*,13*S*,15*R*,17*S*,20*S*,24*S*,1′*R*,5′*R*,7′*S*,8′*S*)−**1** (Fig. 4). Notably, the predicted ECD and ORD curves for the (3*S*,6*S*,7*R*,9*R*,10*R*,13*R*,15*S*,17*R*,20*R*,1′*S*,5′*S*,7′*R*,8′*R*)−**1** matched exquisitely with the measured ECD and ORD spectra of **1**, suggesting that the absolute configuration of **1** could be assigned as 3*S*,6*S*,7*R*,9*R*,10*R*,13*R*,15*S*,17*R*,20*R*,24*R*,1′*S*,5′*S*,7′*R*,8′*R*. Finally, the single-crystal X-ray diffraction analysis (Fig. 5) using Cu K$\alpha$ radiation with a Flack parameter of 0.00(12) (CCDC 2249834) not only validated the novel 6/6/6/5/6/5/6/5 skeleton of **1** but also authenticated its absolute configuration as 3*S*,6*S*,7*R*,9*R*,10*R*,13*R*,15*S*,17*R*,20*R*,24*R*,1′*S*,5′*S*,7′*R*,8′*R*.

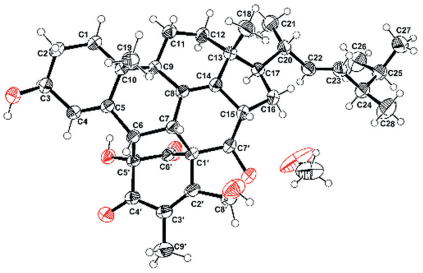
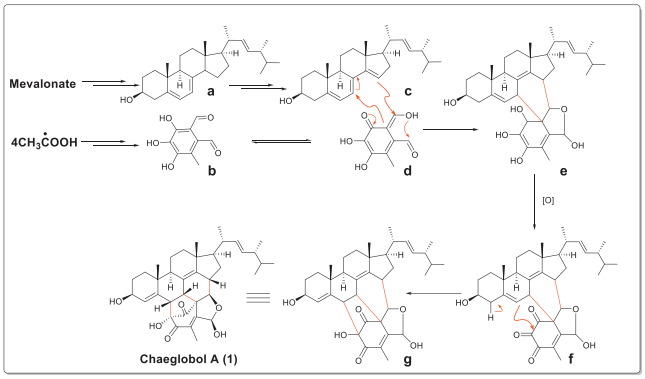


**Fig. 5.** X-ray structure of **1**.




**Scheme 1.** Proposed biosynthetic pathway of **1**.

Chaeglobol A (**1**) represents an unparalleled C37 sterol, characterized by a unique 6/6/6/5/6/5/6/5 octacyclic system, prompting the proposal of a plausible biosynthetic pathway (Scheme 1). Initially, mevalonate and $CH_3COOH$ underwent a series of enzymatic catalytic processes to produce ergosterol (**a**) and 1,2-benzenedicarboxaldehyde-3,4,5-trihydroxy-6-methyl (**b**), respectively, previously isolated from the fungal genus *Chaetomium* [17,18]. Then, the oxidative transformation of **a** would produce intermediate **c**, while structural resonance of **b** would produce intermediate **d**. Subsequently, a pivotal [4 + 2] cycloaddition reaction between the **c** and **d** was envisioned to form intermediate **e**. Ensuing enolization and oxidation of **e** led to the formation of **f**. Ultimately, the intermediate **f** would be transformed into the **1** by an enzymatic cyclization reaction between C-6 and C-5′.

Chaeglobol A (**1**) was evaluated for its antifungal activity against *Botryosphaeria dothidea* (Fig. 6). It was observed that **1** displayed potential inhibitory effect against *B. dothidea*, with inhibition rates of 37% and 45% at concentrations of 12.5 and 25.0 μg/mL, respectively (Fig. 6A). Carbendazim was used as the positive control with the half maximal inhibitory concentration ($IC_{50}$) values of 13.6 μg/mL. To explore the antifungal mechanism of **1**, scanning electron microscopy (SEM), transmission electron microscopy (TEM), and propidium iodide (PI) and 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) staining experiments were conducted. In SEM experiment, it was observed that the hyphae of the blank control group were uniform and smooth, while those treated with **1** exhibited shrinkage and protrusion (Figs. 6B and C). The TEM experiment revealed that the cell wall, cell membrane, and organelle structures of the blank control group were clearly visible and orderly. However, after treatment with **1**, there were observable changes such as cell deformation, cell membrane damage, and organelle dissolution (Figs. 6D and E). The SEM and TEM results indicated that **1** could affect the normal growth of *B. dothidea* and potentially inhibited hyphal growth by damaging the cell membrane of *B. dothidea*. The PI and DCFH-DA staining experiments further confirmed that the cell membrane integrity of

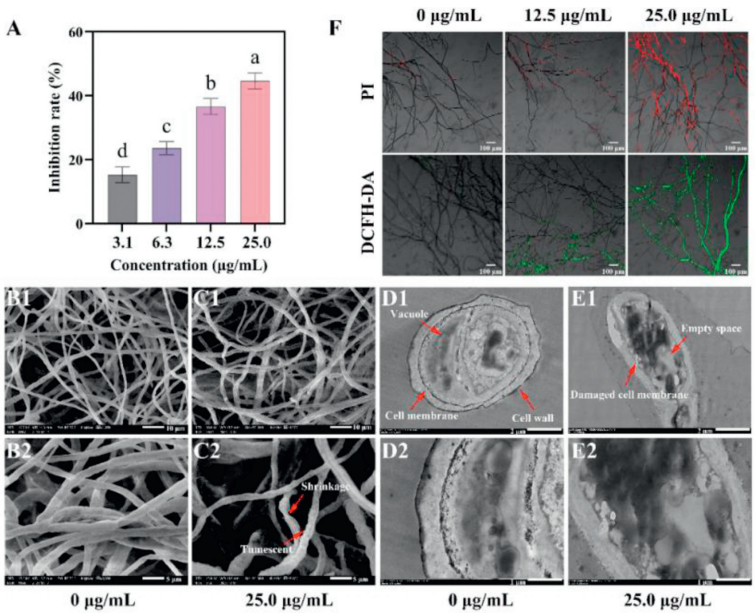



**Fig. 6.** Inhibitory effects of **1** on *B. dothidea*. (A) Inhibition rate of mycelial growth on potato dextrose agar (PDA) medium. Data are presented as mean ± standard deviation (SD) ($n = 3$). Values with different letters (a–d, at 7 days) are statistically significantly different ($P < 0.05$). (B, C) SEM microscopic observations of the *B. dothidea* mycelia. B1 and B2, control; C1 and C2, **1** of 25.0 μg/mL. Scale bars: 10 μm (B1, C1) and 5 μm (B2, C2), respectively. (D, E) TEM microscopic observations of the *B. dothidea* mycelia. Scale bars: 2 μm (D1, E1) and 1 μm (D2, E2), respectively. D1 and D2, control; E1 and E2, **1** of 25.0 μg/mL. (F) Effect of **1** treatment on the cell membrane and oxidative stress of *B. dothidea*. Scale bars: 100 μm.

*B. dothidea* was damaged after treatment with **1** and that oxidative damage occurred in the hyphae (Fig. 6F). These findings indicated that **1** can inhibit the growth of *B. dothidea* by destroying its cell membrane integrity and causing oxidative damage within the cells.

In summary, the fungal genus *Chaetomium* is renowned for its production of diverse natural products with novel skeletons [19]. To the best of our knowledge, previous research has primarily focused on the discovery of novel cytochalasins and azaphilones [20–22]. In the present study, we isolated an unprecedented C37 sterol (**1**) from the marine-derived fungus *C. globosum* HBU-45, characterized by a unique 6/6/6/5/6/5/6/5 octacyclic system that is highly fascinating to the organic chemistry community. Notably, compound **1** exhibited potent antifungal activity against *B. dothidea*, offering remarkable potential for agricultural fungicide development.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Yun-Feng Liu:** Writing – original draft. **Hui-Fang Du:** Visualization, Project administration, Investigation. **Ya-Hui Zhang:** Formal analysis. **Zhi-Qin Liu:** Supervision. **Xiao-Qian Qi:** Methodology. **Du-Qiang Luo:** Writing – review & editing. **Fei Cao:** Writing – review & editing, Supervision, Funding acquisition.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109858.

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