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SHORT REPORT

Euphebranone F, a new acetophenone derivative from the *Euphorbia fischeriana*

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Abstract: Phytochemical investigation of the roots of *Euphorbia fischeriana* led to the isolation of a novel acetophenone derivative, named Euphebranone F (**1**), along with three known acetophenone analogs (**2–4**). The structure of the new compound, featuring a C-C linkage between the C-9 of the acetophenone unit and C-8′ of the phenylpropanoid moiety, was elucidated by extensive NMR and HRESIMS analysis, and its absolute configuration was determined by ECD calculations. Cytotoxic activity screening against human gastric cancer cell lines (MKN-45 and AGS) revealed that only compound **2** exhibited moderate antiproliferative activity against MKN-45 cells.

Keywords: *Euphorbia fischeriana* Steud, structure elucidation, Euphebranone F, acetophenone derivative

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1 Plant Source

Euphorbia fischeriana Steud., belonging to the Euphorbiaceae family, is one of the primary botanical origins of the traditional Chinese medicine "Langdu." The dried roots of *E. fischeriana* used in this study were collected in Inner Mongolia in May 2024. The species was authenticated by Prof. Shanqing Yang from the School of Pharmacy, Anhui University of Chinese Medicine. A voucher specimen (specimen No.: efs-20240525) has been deposited in the Laboratory of Chinese Materia Medica and Natural Medicinal Chemistry, Anhui University of Chinese Medicine.

2 Previous Studies

Euphorbia fischeriana is a classic medicinal plant employed in various ethnic traditional medicine systems. In traditional practice, its dried roots are processed to reduce toxicity and used primarily for treating skin infections (e.g., tinea corporis and eczema), scrofula, rheumatoid arthritis, and abdominal distension caused by parasitic infections (Kemboi et al., 2020). Modern pharmacological studies have demonstrated that ethanol and ethyl acetate extracts of the roots exhibit a wide range of bioactivities—such as antiviral, antitumor, antibacterial, anti-inflammatory, analgesic, and other therapeutic properties (Sun et al., 2021; Du et al., 2020; Sun et al., 2023)—which are highly consistent with its traditional uses (Li et al., 2021). In this context, phytochemical investigations of *E. fischeriana* have largely concentrated on its bioactive constituents. Terpenoids have been identified as the principal active compounds, with particular research emphasis placed on the antitumor and antiviral effects of diterpenoids (Jian et al., 2018; Shen et al., 2017; Gao & Han, 2018). However, another characteristic class of components—acetophenones—has received considerably less attention. Moreover, our previous work on the related species *E. ebracteolata* led to the identification of structurally novel acetophenones with promising antitumor activity (Xu et al., 2025).

3 Present Study

The dried roots of *E. fischeriana* (30.0 kg) were powdered and repeatedly macerated at room temperature with a mixture of methanol-dichloromethane (1:1) until exhaustion. The combined extracts were concentrated under reduced pressure to afford a crude extract devoid of methanol odor. This extract was then dissolved in purified water (3.0 L) and successively partitioned with petroleum ether (PE) and ethyl acetate (EtOAc), each for three cycles. The respective PE and

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EtOAc solutions were collected and concentrated to yield the PE-soluble and EtOAc-soluble fractions, respectively.

A portion of the EtOAc fraction (723 g) was subjected to silica gel column chromatography (CC) and eluted with a stepwise gradient of dichloromethane-methanol (100:0 to 0:100, v/v). Fractions were monitored by thin-layer chromatography (TLC), and those with similar compositions were combined to yield ten major fractions, designated as A–J. Fraction C (41.3 g) was further separated by medium-pressure reversed-phase (MP-RP) CC using a methanol-water gradient (10:90 to 100:0, v/v). Based on TLC analysis, 15 subfractions (Fr. C1–C15) were obtained. Fr. C3 was purified over a Sephadex LH-20 column eluted with methanol, yielding eight fractions (Fr. C3.1–C3.8). **2** (152.3 mg) was obtained from Fr. C3.3 via precipitation and crystallization. Fraction E (70.3 g) was fractionated by MP-RP CC with a methanol-water gradient (30:70 to 100:0, v/v), yielding 18 subfractions (Fr. E1–E18). Fr. E3 was purified by preparative high-performance liquid chromatography (prep-HPLC) using a gradient of acetonitrile and 0.1% formic acid in water (45% to 60% over a specified runtime; flow rate: 8 mL/min) to afford **4** (5.7 mg, t_R = 21.9 min). Fr. E6 was subjected to further MP-RP CC separation with a methanol-water gradient (60:40 to 100:0, v/v), resulting in 12 subfractions (Fr. E6.1–E6.12). Fr. E6.2 was then chromatographed over a Sephadex LH-20 column, yielding eight fractions (Fr. E6.2.1–E6.2.8). Subsequent purification of Fr. E6.2.2 by prep-HPLC (acetonitrile/0.1% aqueous formic acid, 55% to 70%; 8 mL/min) afforded **1** (5.4 mg, t_R = 19.32 min). Similarly, Fr. E6.2.5 was processed by prep-HPLC under identical conditions to yield **3** (1.8 mg, t_R = 23.17 min).

Compound **1** was obtained as a pale yellow powder. Its molecular formula was determined to be $C_{19}H_{22}O_8$ by HRESIMS, corresponding to 9 degrees of unsaturation. The ^{1}H NMR spectrum revealed signals in the aromatic region consistent with an ABX coupling system [δ_H 6.81 (1H, d, J = 2.1, H-2′), 6.78 (1H, d, J = 8.0 Hz, H-5′), and 6.70 (1H, dd, J = 8.0, 2.1 Hz, H-6′)] and an isolated aromatic proton [δ_H 6.03 (1H, s, H-5)]. In the upfield region, one methoxy signal and one singlet methyl signal [δ_H 2.60 (1H, s, H-8)] were observed (Table 1). The ^{13}C NMR and DEPT spectra (Table 1), in addition to confirming the carbon signals associated with the aforementioned protons, displayed signals for two methylene groups (one of which was an oxygenated methylene, δ_C 63.6, C-9′), two methine groups (one of which was an oxygenated methine, δ_C 81.4, C-7′), and nine quaternary carbon signals. Among these quaternary carbons, three were aromatic carbons at approximately 160 ppm, and one was a ketone carbonyl carbon (δ_C 204.6, C-7). Combined with the characteristic signals, these data indicated the presence of an acetophenone moiety (Figure 1), a common and typical structural feature in *E. ebracteolata*. This assignment was confirmed by key HMBC correlations from H-5 to C-1/C-3/C-4/C-6, from H-8 to C-1/C-7, and from H-9 to C-2/C-4 (Figure 2).

Subsequent analysis of the remaining NMR signals led to the identification of a C6-C3 skeleton characteristic of a simple phenylpropanoid. This was supported by an ^{1}H-^{1}H COSY correlation between H-8′ and H-7′/H-9′, along with the classic ABX coupling pattern of the aromatic ring. Furthermore, an HMBC correlation from H-7′ to C-2′/C-6′ confirmed this partial structure. Based on the NMR data patterns of previously reported acetophenone derivatives from *E. ebracteolata* in our research group (Xu et al., 2025), it was hypothesized that the two structural fragments were likely connected via the C-9 position. Re-examination of the 2D NMR data (Figure 2) revealed a key ^{1}H-^{1}H COSY correlation between H-9 and H-8′. Additionally, HMBC correlations from both H-7′ and H-9′ to C-9 were observed, definitively establishing the connection between the two fragments at the C_9–$C_{8'}$ position.

The stereochemistry of compound **1** involved the chiral centers at C-7′ and C-8′ of the phenylpropanoid unit. This structural motif is analogous to that found in 8,4′-oxyneolignans (Ding et al., 2025; Zhao et al., 2023). Therefore, an empirical rule from the literature, based on the chemical shift difference ($\Delta\delta$) between the H-9′a and H-9′b protons ($\Delta\delta_{H\text{-}9'a\text{-}H\text{-}9'b}$ = 0.13 ppm < 0.15 ppm in CD_3OD), was applied to determine the relative configuration. This analysis indicated an *erythro* relative configuration for the C-7′ and C-8′

Table 1. ^{1}H and ^{13}C NMR spectroscopic data for **1** (600 MHz) in CD_3OD (δ in ppm and J in Hz)

No.	δ_H	δ_C, type	No.	δ_H	δ_C, type
1		106.4, C	1′		132.3, C
2		165.6, C	2′	6.81 (d, J = 2.1 Hz)	114.8, CH
3		103.4, C	3′		146.5, C
4		162.9, C	4′		146.5, C
5	6.03 (s)	91.9, CH	5′	6.78 (d, J = 8.0 Hz)	116.2, CH
6		162.8, C	6′	6.70 (dd, J = 8.0, 2.1 Hz)	119.6, CH
6-OCH_3	3.88 (s)	56.1, CH_3	7′	4.85 (d, J = 8.4 Hz)	81.4, CH
7		204.6, C	8′	2.15 (m)	41.0, CH
8	2.60 (s)	33.1, CH_3	9′	3.35 (dd, J = 10.9, 6.8 Hz)	63.6, CH_2
				3.48 (dd, J = 10.9, 4.5 Hz)	
9	2.52 (dd, J = 16.7, 9.5 Hz)	22.0, CH_2			
	2.79 (dd, J = 16.7, 5.4 Hz)				

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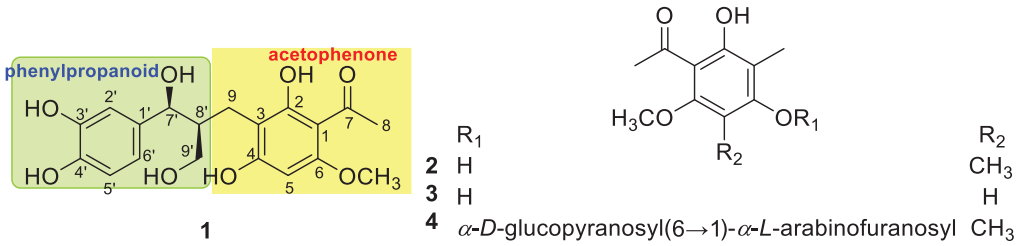

Figure 1. The structure of compounds **1–4**

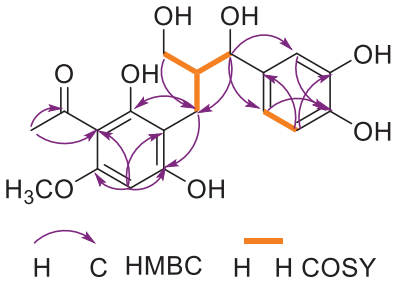

Figure 2. The key ^{1}H-^{1}H COSY and HMBC correlations of compound **1**

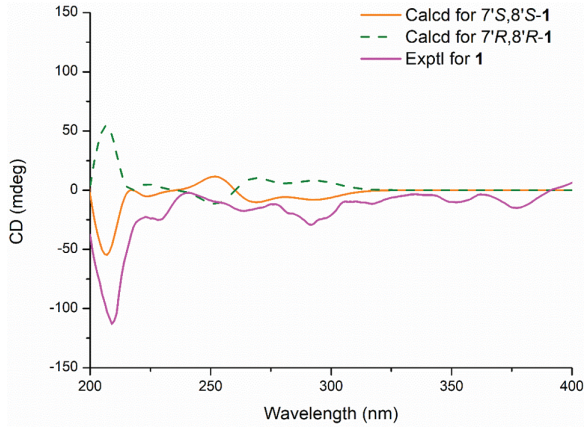

Figure 3. Experimental and calculative ECD curves of **1**

positions in compound **1**. Finally, the absolute configuration was determined to be 7′S, 8′S by comparison of the experimental ECD spectrum with the calculated ECD data (Figure 3).

The known compounds (Figure 1) isolated were identified as 2,4-dihydroxy-6-methoxy-3-methyl-acetophenone (**2**) (Wang et al., 2012), 4,6-dihydroxy-2-methoxyacetophenone (**3**) (Wang et al., 2022), 2,4-dihydroxy-6-methoxy-3-methyl acetophenone 4-O-α-L arabinofuranosyl (6→1)-β-D-glucopyranoside (**4**) (Yin et al., 2005), by comparing their NMR and HRESIMS data with reported data.

Euphebranone F (**1**): pale yellow powder; $C_{19}H_{22}O_8$, $[\alpha]_D^{20}$ + 14 (*c* 0.5, CH_3OH); UV (CH_3OH) λ_{max} (logε): 206.0 (4.22) and 292.0 (4.03) nm; 1D NMR data (CD_3OD), Table **1**; HRESIMS *m/z* 377.1237 $[M - H]^-$ (calculated for $C_{19}H_{21}O_8^-$ 377.1242).

Table 2. In vitro tumor growth IC_{50} of compounds against MKN-45 and AGS cells

Samples	MKN-45	AGS
	IC_{50} ± SD (μM)	
1	>50.00	>50.00
2	42.27 ± 0.27	>50.00
3	>50.00	>50.00
4	>50.00	>50.00
[a]Cisplatin	2.71 ± 0.33	3.81 ± 0.34

Note: [a]Positive control.

Numerous studies report acetophenone derivatives (benzene hydroxyl/methoxy, C-3 methyl, mostly from Euphorbia spp. et al.) exhibit cytotoxicity, such as 2,4-dihydroxy-6-methoxy-3-methylacetophenone has antitumor effects on BEL-7402/5-FU et al. tumor cells (Dong et al., 2021; Huang et al., 2017). To further explore this potential, we evaluated the cell proliferation inhibitory effects of the isolated compounds in vitro using the CCK-8 assay. In line with our previous research, the assessment was conducted on two human gastric cancer cell lines, MKN-45 and AGS. The results revealed that only compound **2** possessed moderate inhibitory activity against the proliferation of MKN-45 cells (Table 2).

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Author Contributions

Funding acquisition, Resources, M.M. Li, and Y. Yu; Writing—original draft, M.M. Li, N.W. Xu; Data curation, Formal analysis, N.W. Xu, Y. Yu; Investigation, Supervision, B.X. Cai, J.T. Wang; Writing—review & editing, Y. Yu. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. The further data will be made available on request.

Ethics Approval

This study focuses solely on plant compound isolation and preliminary cell activity screening, and does not involve any animal experiments, human subjects, or research activities requiring ethical review. As such, an ethics approval statement is not applicable to this work, and it would be appreciated if this section could be omitted accordingly.

Conflicts of 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.

Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products.

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