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Isolation and Antitumoral Effect of a New Siphonochilone Derivative from African Ginger

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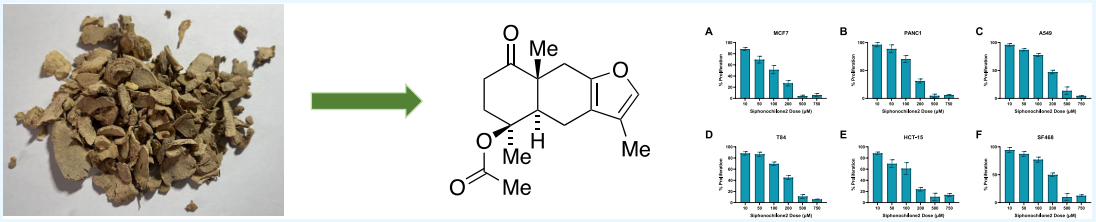

ABSTRACT: A new eusdesmane sesquiterpenoid, characterized as 3,5,8a-trimethyl-8-oxo-4,4a,5,6,7,8,8a,9-octahydronaphtho[2,3-*b*]furan-5-yl acetate (**1**), has been isolated from the rhizomes of the South African variety of wild ginger (*Siphonochilus aethiopicus* (Schweinf) B. L. Burtt). The compound was obtained by silica gel column chromatography. Its structure was elucidated by nuclear magnetic resonance spectroscopy (NMR) and mass-spectrometric (MS) analyses, including 1D-, 2D-NMR, and HR-LCMS. We also investigated the cytotoxic effect of **1** on a panel of cancer cell lines, human breast, pancreas, lung, colon, and central nervous system cancer lines. The data are not encouraging since its antitumor effect is poor. Nonetheless, the discovery of new molecules may provide a source of new compounds with important biological effects applicable to the field of medicine.

1. INTRODUCTION

Siphonochilus aethiopicus is a member of the family Zingiberaceae, and it is commonly known as African ginger or wild ginger. This plant is native of the western and southern tropical Africa. It is used for treating a variety of respiratory ailments[1] and plays significant roles in general well-being maintenance and poverty alleviation through sales of plant materials for income generation and sustainable livelihoods.[2] The roots and rhizomes, with similar essential oil composition, have been reported to have potent medicinal properties, with anti-inflammatory, antibacterial, and antifungal activities and are known to be used as a spice to flavor food and in traditional herbal medicine for treating fevers, colds, flu, sinusitis, coughs, headache, asthma, malaria, hysteria, candida, epilepsy, and menstrual cramps.[3−5] Consequently, African ginger is listed in the African Herbal Pharmacopoeia as one of the most important medicinal plants in sub-Saharan Africa,[6,7] and it is among the eight most traded and the most expensive plant species per kilogram at informal markets in some regions of Limpopo Province in South Africa.[8]

A chemotaxonomic survey of *S. aethiopicus* invariably yielded substantial quantities of an essential oil, with a low content of monoterpenoids, but with substantial amounts (up to 0.2% wet weight) of a major constituent, siphonochilone (**2**), isolated for the first time in 2002, accompanied by a minor compound, the 2-hydroxysiphonochilone **3**, while compound **4** has been prepared by acetylation (Ac_2O/Py) of siphonochilone.[9] To date, only one more furanoterpenoid from eudesmane family of sesquiterpenoids has been isolated from *S. aethiopicus*, being characterized as **5**.[10]

On the other hand, despite major advances in cancer screening, prevention, and treatment, cancer remains one of the leading causes of death in the world, with a high incidence rate among the population. In 2020, a total of 19.3 million new diagnoses and 10 million cancer-related deaths were estimated worldwide.[11] Cancer is characterized by uncontrolled cellular proliferation and growth, resulting from the accumulation of genetic mutations.[12] Conventional cancer treatments, such as radiotherapy, chemotherapy, and surgical resection, are commonly employed; however, their effectiveness is often limited by the emergence of cellular resistance mechanisms. Given the increasing number of cancer-related deaths, there is an urgent need to develop new prevention strategies and therapeutic approaches that can mitigate side effects and overcome treatment resistance.[13] Natural compounds have demonstrated a wide range of beneficial activities, including the enhancement of health and cancer treatment.[14] The history of anticancer drug discovery has been significantly influenced by

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natural products. Numerous widely used anticancer drugs, such as irinotecan, paclitaxel, vincristine, and etoposide, have been developed from natural products.[15] There is intense research into the discovery of new natural molecules with biological activity, their mechanisms of action,[16] their use as adjuvant therapy,[17] or their use as anticancer agents.[18] Based on the evidence of the increase in diagnoses and deaths caused by cancer and the need to develop new drugs to improve this problem, nature provides us with compounds that can be useful for developing new anticancer drugs, such as Siphonochilone isolated from *S. aethiopicus*.

We here report our results on the isolation of furanoterpenoids from *S. aethiopicus* and their activity against tumoral and nontumoral cell lines. A new compound was isolated by column chromatography and identified as compound **1** by NMR and mass-spectrometric analyses.

2. MATERIALS AND METHODS

2.1. General Techniques. The chemical identity of siphonochilone was confirmed by electron-impact spectrometry (PerkinElmer Clarus SQ8C spectrometer coupled to a PerkinElmer Gas Chromatograph Clarus 690, using 70 eV electron-impact ionization, EI), electrospray ionization mass spectrometry (HPLC-ESI-MS; Orbitrap Q-Exactive, Thermo Scientific S. L., Bremen, Germany), and nuclear magnetic resonance (NMR; Avance III 500 MHz, Bruker, Switzerland). For NMR analyses, the ^{1}H spectra were recorded at 500 MHz and the ^{13}C spectra at 125 MHz, and the compound was dissolved in deuterated dimethyl sulfoxide (DMSO-d_6), with residual solvent peaks at δ_H = 2.50 (DMSO) ppm for ^{1}H and δ_C = 39.5 (DMSO) ppm for ^{13}C.

2.2. Plant Material. Rhizomes and roots of *S. aethiopicus* were obtained locally in Málaga, Spain, from nursery plants grown as ornamentals, sliced, and air-dried. Since *S. aethiopicus* is the only indigenous member of the family in South Africa, and since it has such a unique and distinctive morphology[4] and organoleptic characteristics, no voucher specimen was collected.

2.3. Extraction and Isolation. Dry crushed plant (PM, *S. aethiopicus*, 500 g) was extracted with methanol (2.5 L) at room temperature for 3 days under slow shaking. After this period, the mixture was filtered, and the methanolic solution was concentrated to dryness under vacuum to obtain a syrup (45 g). This syrup was flash chromatographed on silica gel eluting with a mixture of ethyl ether:EtOAc (8:2). Two fractions were collected (F1: Rf = 0.6, 3.5 g, 0.7% PM, and F2: Rf = 0.5, 1.0 g, 0.2% PM). After one more chromatography, compound **2** was isolated as a colorless solid, while compound **1** was isolated as a colorless syrup. It is worth mentioning that after 7 days in an amber vial, **1** became slightly yellow. Compound **1**: $[\alpha]_D^{22}$ +87.5 (MeOH *c* 0.07). ^{1}H NMR (400 MHz, $CDCl_3$, Table 1) and ^{13}C NMR (100 MHz, $CDCl_3$, Table 2). EI-MS *m*/*z* (rel. int.): 290 (24, M^+), 230 (62), 215 (100), 197 (58), 187 (85), 172 (70). HREI-MS *m*/*z*: 290.1519 ($C_{17}H_{22}O_4$ requires 290.1518).

2.4. Cell Culture. Human cancer cell lines including MCF7 (breast), PANC1 (pancreas), A549 (lung), T84 and HCT15 (colon), and SF268 (central nervous system) were cultured in Dulbecco's Modified Eagle's Medium (DMEM)-high glucose (Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS) (Gibco) and 1% penicillin/streptomycin (Sigma-Aldrich). Cells were grown in monolayer culture and maintained under standard conditions at 37 °C with a 5% CO_2 humidified atmosphere.

Table 1. ^{1}H NMR Data for Compounds 1 and 2[9] (Siphonochilone)[a]

	1		2	
H	δ_H (ppm)	*J* (Hz)	δ_H (ppm)	*J* (Hz)
2	7.07, s		7.02, br m	137.8
4	2.66, dd	14.2, 10.0	2.68, ddd	15.7, 5.4, 1.6
4′	2.47, m		2.12, dddd	15.7, 18.4, 3.0, 1.4
4a	2.42, m		1.81, ddd	10.8, 10.2, 5.4
5			2.40, dqdd	10.2, 7.1, 2.7, 2.1
6	2.91, dt	13.9, 4.6	6.66, dd	10.1, 2.1
6′	2.13, td	13.9, 4.6		
7	2.43, dt	13.9, 4.6	5.91, dd	10.1, 2.7
7′	2.66, m			
9	2.81, br d	16.9	2.73 dd	16.7, 1.4
9′	2.58, d	16.9	2.64, br d	16.7
3-Me	1.95, s		1.90, d	1.3
5-Me	1.81, s		1.21, d	7.1
8a-Me	1.15, s		1.02, s	
OCOMe	1.96, s			

[a] ^{1}H NMR spectra are included in the SI.

Table 2. ^{13}C NMR Data for Compounds 1 and 2[9] (Siphonochilone)[a]

C	**1**, δ_C (ppm)	**2**, δ_C (ppm)
2	137.8	137.5
3	119.3	119.0
3a	115.4	114.6
4	18.3	22.5
4a	49.3	45.0
5	83.0	34.2
6	35.3	154.2
7	35.0	126.6
8	212.8	204.0
8a	47.5	44.9
9	34.9	31.9
9a	148.7	149.3
3-Me	8.2	8.1
5-Me	19.7	18.7
8a-Me	19.0	16.6
OCOMe	22.6	
OCOMe	170.2	

[a] ^{13}C NMR spectra are included in the SI.

2.5. Proliferation Assay. Cell lines were seeded into 48-well plates at varying densities: 2.5 × 10^3 cells/well for MCF7, 3 × 10^3 cells/well for SF268, 5 × 10^3 cells/well for A549 and T84, 7 × 10^3 cells/well for HCT15, and 8 × 10^3 cells/well for PANC1. After a 24 h incubation period, the cells were exposed to increasing concentrations (10−750 μM) of **1** for 72 h. Subsequently, the cells were fixed using 10% cold trichloroacetic acid (TCA) (Sigma-Aldrich) at 4 °C for 20 min. Following fixation, staining was carried out with Sulforhodamine B (SRB) (Sigma-Aldrich) at a concentration of 0.08%, diluted in 1% glacial acetic acid (PanReac AppliChem) for 20 min at room temperature. The dye was then solubilized using Trizma (10 mM, pH 10.5) (Sigma-Aldrich). Finally, the optical density (OD) was measured at a wavelength of 492 nm using an 800 TS Absorbance Reader (BioTek). Cell viability (%) was calculated using the following formula

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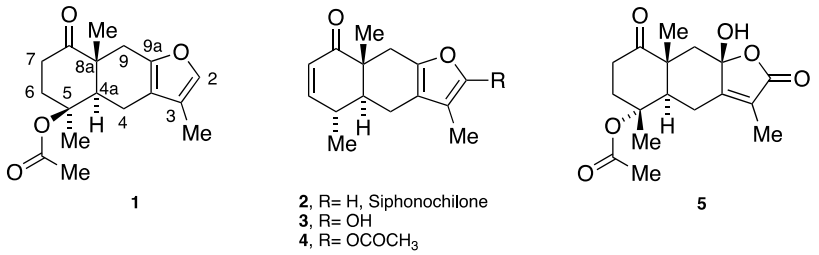

Figure 1. Chemical structures of natural furanoterpenoids from *Siphonochilous*.

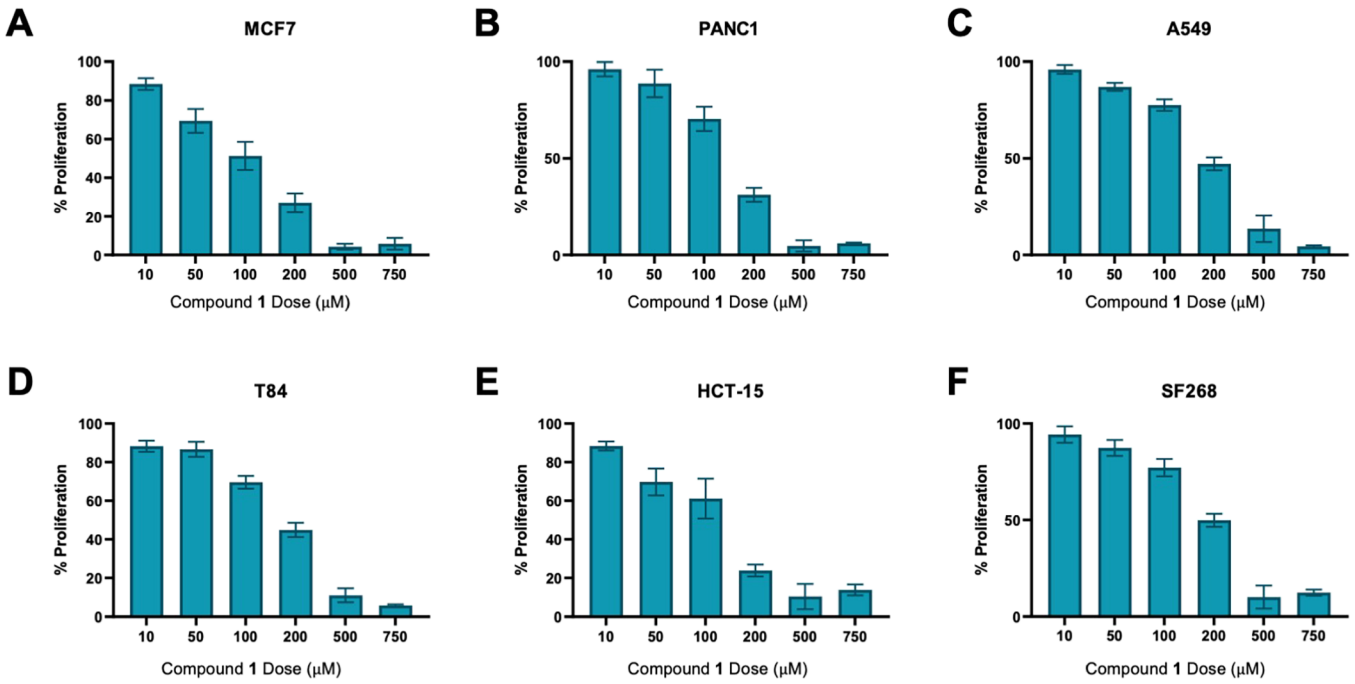

Figure 2. Antiproliferative effect of siphonochilone derivative **1** against human cancer cell lines. Relative proliferation is expressed as % of proliferation in MCF7 (A), PANC1 (B), A549 (C), T84 (D), HCT15 (E), and SF268 (F). Data are represented as the mean ± standard deviation (SD) of triplicate experiments.

$$\%\ \text{cell viability} = \frac{\text{OD sample} - \text{blank}}{\text{OD negative control} - \text{blank}} \times 100$$

2.6. Statistical Analysis. Statistical analyses and image processing were conducted using GraphPad Prism 9 software. For the cytotoxicity analysis, nonlinear regression was applied, and the logEC50 was calculated.

3. RESULTS AND DISCUSSION

3.1. Isolation and Identification of Compound 1, A New Sesquiterpene. Dried *S. aethiopicus* was extracted with methanol at room temperature to afford a syrup, which was 9% PM. After sequential silica gel flash chromatography, two fractions were isolated, the first, and major one, was identified as siphonochilone (**2**) by comparison with the reported data,[9] and the second identified as compound **1**, according to its spectroscopic data (Tables 1 and 2).

The ^{1}H NMR (SI and Table 1) and ^{1}H−^{1}H COSY (SI) data of compound **1** displayed the characteristic signals associated with the siphonochilone skeleton, including three methyl groups (3-Me, 5-Me, and 8a-Me), one AB system of two geminal hydrogens (H-9 and H-9′), one ABX system of three protons (H-4, H-4′, and H-4a), and one singlet that does not interchange with deuterated water, assigned to the olefinic proton H-2, indicating an unsubstituted C-2 position in the furan ring.

Additionally, ^{1}H NMR (Table 1) showed one system of two diasterotopic methylene groups in the interval 2.1−2.9 ppm, which was assigned to protons H-6,6′ and H-7,7′, meaning the absence of the double bond of the siphonochilone skeleton. The ^{1}H−^{1}H COSY spectrum showed correlations among H-6, H-6′, H-7, and H-7′ with large geminal and *trans*-diaxial coupling constants (J = 13.9 Hz). Moreover, the characteristic dqdd, corresponding to H-5 in **2**, is not observed, suggesting the presence of one more substituent in C-5.

^{13}C (Table 2 and SI) and DEPT NMR (SI) data of compound **1** revealed 17 carbon signals, including those for three methyl groups (3-Me, 5-Me, and 8a-Me), two methylenes (C-4 and C-9), one methine (C-4a), the C-2 of the unsubstituted furane moiety (C-2, C-3, C-3a, and C-9a), one sp^3 quaternary carbon atom (C-8a), and one ketone group (C-8). The presence of two additional diastereotopic methylene groups was confirmed by the signals at δ_C 35.3 and 35.0 ppm (C-6 and C-7, respectively, Table 2 and DEPT). The presence of C-5 as a quaternary heteroatom-substituted carbon was also confirmed since the chemical shift of C-5 moved downfield from δ_C 34.2 ppm in **2** to 83.0 ppm in **1** (DEPT). The presence of four signals corresponding to four methyl groups in ^{1}H NMR, instead of

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the three present in siphonochilone, all being singlets, and the characteristic signal at δ_C 170.2 ppm, which can be attributed to one carbonyl carbon of an ester group, suggested the presence of an acetate group in position C-5. This fact was confirmed by the NOESY spectrum of **1** (SI) that shows the interaction among OCOMe and H-4a, and H-6,6′ and H-4,4′. On the other hand, NOESY does not show NOE correlation between 8a-Me and 5-Me, which confirms a *trans* configuration between these methyl groups, similar to that found in siphonochilone (**2**). HSQC spectrum enabled the exact assignment of all ^{1}H and ^{13}C NMR signals.

Finally, the electron-impact mass spectrum (EI-MS, see the SI) showed the molecular ion at m/z 290. The labile acetate group loss affords the fragment at m/z 233 ($C_{15}H_{18}O_2$), and subsequent loss of a methyl affords the one at m/z 215 ($C_{14}H_{16}O_2$), this peak being the base peak. Peaks at m/z 197, 187, and 172 are reported for furanoeudesmane structures (Figure 1).

Based on ^{1}H, ^{13}C, EI-MS, and NMR-correlation data, which are in concordance with a furanoeudesmane skeleton with structural similarity with siphonochilone (**2**),[9] we propose structure **1** for the new siphonochilone derivative.

3.2. Compound 1 Reduces Viability in Several Tumor Cell Lines. Siphonochilone is one of the main constituents of *S. aethiopicus*, an African plant that has been reported to have numerous health benefits. The number of cancer-related diagnoses and deaths is increasing worldwide. So, it is mandatory to develop and discover new drugs. Nature provides a diverse array of compounds that can be explored for potential anticancer properties. The cytotoxic effect of **1** was assessed across an array of six tumor cell lines, originating from diverse tissues including breast, pancreas, lung, colon, and central nervous system. The evaluation was conducted following a 72 h exposure to **1** and is represented in Figure 2.

The compound displayed a half-maximal inhibitory concentration (IC_{50}) range from 97.1 to 188.8 μM in the studied cell lines, as presented in Table 3. Notably, the human lung (A549) and central nervous system (SF268) cancer cell lines exhibited the highest resistance, with an IC_{50} value of 188.8 μM. Conversely, the MCF7 human breast cancer cell line displayed the highest sensitivity to **1**, manifesting the lowest IC_{50} value at 97.1 μM.

Table 3. Determination of IC_{50} (μM)[a] of 1 in Different Cell Lines

organ	cell line	1[a]
breast	MCF7	97.1 ± 20.4
pancreas	Panc1	141.8 ± 11.5
lung	A549	188.8 ± 21
colon	T84	166.2 ± 12.6
colon	HCT15	108.7 ± 8
central nervous system	SF268	188.8 ± 14.4

[a]Half-maximal inhibitory concentration (IC_{50}) values calculated from dose−response curves as the concentration of **1** that inhibits cell survival by 50% compared to control. Data are shown as mean ± SD of each triplicate.

Product **1** is a new compound that has been isolated for the first time from *S. aethiopicus*. Therefore, there are no previous data on antitumor activity. However, other furanoterpenoids present in this plant have been shown to have a slight cytotoxic effect against tumor lines. In their study, Igoli et al.[19] found that sesquiterpenes epicurzerenone and furanodienone, isolated from *S. aethiopicus*, did not demonstrate cytotoxic activity at a concentration of 100 μg/mL. However, they reported selective cytotoxicity of the compound 8(17),12E-labdadiene-15,16-dial against SH-SY5Y (neuroblastoma), and Jurkat (leukemia) human cancer cell lines were also reported. This compound exhibited a moderate impact on nontumoral cell line Hs 27.[19] In addition, Lategan et al. showed that the effect of three furanoterpenoids isolated from this African plant caused a lower cytotoxic effect than an extract made with ethyl acetate.[20] Therefore, there are no revealing data on the effect of furanoterpenoids isolated from *S. aethiopicus* and it is the first time that we show the cytotoxic effect of this newly isolated compound **1**.

4. CONCLUSIONS

As of the available literature, there is a lack of comprehensive data regarding the cytotoxic effects of furanoterpenoids isolated from *S. aethiopicus*. However, we have isolated for the first time the siphonochilone derivative **1**, characterized its structure, and determined its cytotoxic effect against human breast, pancreas, lung, colon, and central nervous system cancer lines. The data are not encouraging since its antitumor effect is poor. Nonetheless, the discovery of new molecules may provide us with a source of new compounds with important biological effects that can be applied to the field of medicine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c01914.

^{1}H NMR, ^{13}C NMR, DEPT, NOESY, COSY, HSQC, and EI-MS spectra of the new compound **1** (PDF)

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Notes

The authors declare no competing financial interest.

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