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Research Article

Eudesman-Type Sesquiterpenoids from Stem Bark *Dysoxylum gaudichaudianum* and Cytotoxic Evaluation Against Human HeLa Cervical Cancer

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Abstract

Two eudesmane-type sesquiterpenoids were isolated from the stem bark of *Dysoxylum gaudichaudianum*: 6α-hydroxy-eudesm-4(15)-en-1-one (**1**) and eudesm-4(15),7-dien-1β-ol (**2**). This study represents the first report of these compounds not only from *D. gaudichaudianum* but also from the genus *Dysoxylum*. The cytotoxic potential of two sesquiterpenoids was assessed against human cervical carcinoma (HeLa) cells employing the Resazurin-based PrestoBlue assay. Using cisplatin as a positive control, compound **1** exhibited moderate cytotoxicity with an IC_{50} of 28.04 µM, whereas compound **2** showed comparatively weaker activity, with an IC_{50} of 58.37 µM. Their structures were elucidated through comprehensive spectroscopic analyses, including HR-ESI-MS, ^{1}H NMR, and ^{13}C NMR. Structure–activity relationship analysis indicates that hydroxylation at C-6 enhances cytotoxic activity, whereas the C-6/C-7 olefinic moiety reduces potency, likely due to increased molecular rigidity, highlighting key structural features for activity modulation in the eudesmane scaffold.

Keywords: *Dysoxylum gaudichaudianum,* eudesmane-type sesquiterpenoids, hela cancer cell, meliaceae

1. INTRODUCTION

The Meliaceae, or mahogany family, is a diverse group of about 740 species in 58 genera, widely distributed across tropical regions and extending into some subtropical areas[1,2]. Known for producing high-quality timber essential to industries such as construction and furniture making, the family also holds significant phytochemical and pharmacological value[3–5]. Although only around 24 genera have been extensively studied due to distribution and resource constraints, investigations have revealed a wealth of secondary metabolites, including sesquiterpenoids[6–9], triterpenoids[10], and limonoids[11–14], the latter being characteristic of the family. Many of these compounds exhibit notable biological activities such as cytotoxic[15–18], antidiabetic[19,20], and immunomodulatory effects, underscoring the dual importance of Meliaceae as both an economic resource and a reservoir of bioactive natural products with potential in drug discovery[21,22].

Within this family, the genus *Dysoxylum* represents a diverse group of tropical woody plants distinguished by their aromatic stems and bark[23]. The genus is widely distributed throughout Southeast Asia and the Pacific region, with Indonesia recognized as one of its biodiversity hotspots[24]. Approximately 80 species of *Dysoxylum* have been documented across Indonesian islands such as Java and Kalimantan, reflecting both ecological richness and phytochemical potential[25,26].

Phytochemical studies on *Dysoxylum* have revealed a broad spectrum of bioactive constituents, notably sesquiterpenoid[16,27–29],titerpenoids[30,31],limonoids[32,33], and steroids[34–37] which are predominantly isolated from the bark. In addition, other classes of compounds such as lignan have also been reported from different species of *Dysoxylum*, indicating the chemical diversity and pharmacological potential of this genus[38,39]. These metabolites have garnered considerable attention due to their broad range of pharmacological activities. Traditionally, species of this genus have long been incorporated into ethnomedicine. For example, the leaves of *D. binectariferum* are used in treating festering ulcers[40], while *D. richii* is employed for alleviating skin[41], irritations, and muscular stiffness[42]. Likewise, *D. gaudichaudianum* is valued among local communities as a traditional remedy for tuberculosis[43]. In Indonesia, certain species are also referred to by the local name "Kedoya". They are occasionally applied in women's health practices, particularly vaginal fumigation or steaming (*ratus*), which is believed to support reproductive well-being. Such practices highlight the cultural and therapeutic significance of the genus[44].

Previous chemical investigations and biological studies on *Dysoxylum gaudichaudianum* have demonstrated its potential as a rich source of terpenoid compounds with diverse pharmacological activities[45]. Several terpenoid derivatives, particularly limonoids isolated from the stem bark, have exhibited strong antiviral properties, including significant inhibition of respiratory syncytial virus (RSV)[46]. More recently, our group reported the isolation of triterpenoids bearing distinctive side-chain modifications that displayed notable cytotoxicity against cervical cancer cells, especially the HeLa cell line[31]. Building on these promising findings, the present study was designed to isolate and structurally characterize two sesquiterpenoid compounds **1** and **2**, from *D. gaudichaudianum* and to evaluate their cytotoxic activity against HeLa cervical cancer cells. Furthermore, this work aimed to investigate the impact of functional group modifications on bioactivity, thereby providing new insights into the structure–activity relationships (SAR) of *Dysoxylum*-derived terpenoids.

2. RESEARCH METHODS

Instruments and Materials

Infrared (IR) spectra were recorded using a PerkinElmer Spectrum-100 Fourier Transform Infrared (FT-IR) spectrometer, with potassium bromide (KBr) as the medium (Thermo Fisher Scientific, Madison, WI, USA). High-resolution mass spectrometric (HRMS) data were acquired with a Waters QTOF-HRTOFMS-XEVOTM instrument (Waters, Milford, MA, USA), which provided accurate mass determination and fragmentation patterns essential for structural elucidation. Nuclear Magnetic Resonance (NMR) analyses were conducted on a Bruker Ascend spectrometer equipped for both one-dimensional and two-dimensional experiments. The ^{1}H-NMR spectra were measured at 700 MHz, whereas the ^{13}C-NMR spectra were recorded at 175 MHz, and DEPT experiments were obtained at 135 MHz. All NMR measurements were referenced to the residual solvent signals of $CDCl_3$ (δ_H 7.26 ppm; δ_C 77.2 ppm).

For compound isolation, chromatographic separation was carried out using silica gel 60 with particle sizes of 70–230 mesh and 200–400 mesh (Merck, Darmstadt, Germany), as well as octadecylsilane-bonded silica (ODS) material (Chromatorex® C18 DM1020T, 100–200 mesh; Fuji Sylisia Chemical Ltd., Japan). Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates (Merck, Darmstadt, Germany) and reversed-phase RP-18 F254 plates (Merck KGaA, Darmstadt, Germany). Spots on the chromatographic plates were initially visualized under ultraviolet light at wavelengths of 254 and 365 nm, followed by spraying with 10% sulfuric acid in ethanol and heating, which enhanced the detection of separated constituents.

In June 2021, the stem bark of the *D. gaudichaudianum* [A Juss.] Miq plant was collected from the National Forest of Pangandaran in West Java, Indonesia (Latitude 70°42'18.82'' S, Longitude 108°39'33.56''E). The specimen labeled 41/HB/07/2021 was identified and confirmed as *D. gaudichaudianum* (A. Juss.) Miq by Mr. Joko Kusmoro, Department of Biology, Universitas Padjadjaran.

Extraction and Isolation

The dried stem bark of *D. gaudichaudianum*, weighing 2.8 kg, was subjected to extraction by maceration with methanol for six days. This process produced about 393 g of crude extract, which was subsequently subjected to solvent evaporation. The concentrated methanol extract was suspended in water and subjected to sequential partitioning with *n*-hexane, ethyl acetate, and *n*-butanol. The organic layers were subjected to evaporation under reduced pressure, resulting in crude extracts of 9.8 g from *n*-hexane, 98.7 g from ethyl acetate, and 135.9 g from *n*-butanol, respectively. The *n*-hexane extract underwent further purification via normal-phase chromatography, yielding five fractions through gradient elution with a 10% v/v mixture of *n*-hexane and ethyl acetate. Fraction D was purified via normal-phase column chromatography (CC) utilizing a gradient of n-hexane, dichloromethane, and ethyl acetate in a ratio of 8:1:1,

yielding four sub-fractions (D1-D4). Subsequent chromatographic examination of Fraction D3 (28.3 mg) was performed using reverse-phase CC (methanol: H_2O, 1:1, isocratic), which resulted in the isolation of compound **1** (4.1 mg). Furthermore, Fraction D4 (34.7 mg) underwent reverse-phase CC (MeOH: H_2O, 6:4, isocratic), leading to the separation of compound **2** (4.3 mg).

Cytotoxic activity assay

Both sesquiterpenoids were examined for their cytotoxicity against HeLa cervical cancer cells using the PrestoBlue assay, with cisplatin serving as a positive control, as described previously[30]. Notably, the HeLa cell line is one of the most abnormally fast-growing cervical cancer cells compared with another cervical cancer and has been reported to be resistant to current drugs. The cell was cultured in 96-well plates and incubated for 48 h with Roswell Park Memorial Institute Medium (RPMI) (Biosera, France) supplemented with 10% Fetal Bovine Serum (FBS) (Gibco, USA) and 1 µL/mL of antibiotic (1% penicillin) (Gibco, USA) at an initial cell density of approximately 1.7 x 10^4 cells/well, and incubated for 24 h. All incubation processes were maintained at 37 °C with 5% CO_2.

Subsequently, the cells were washed and treated with the test compounds at eight final concentrations: 1.56, 3.13, 6.25, 12.5, 25.0, 50.0, 100, and 200 µg/mL. The plates were incubated for 48 hours, after which the medium was replaced with 10% PrestoBlue reagent and incubated for 1-2 hours. Cell viability was assessed by measuring the absorbance at 570 nm with a reference wavelength of 600 nm using an Emax Microplate Reader (Molecular Devices, Sunnyvale, CA, USA). Percent inhibition was calculated relative to the vehicle control, and IC_{50} values were obtained by fitting the concentration-response data to a four-parameter logistic (4PL) model using non-linear regression in GraphPad Prism. The obtained IC50 values were subsequently converted into micromolar (µM). In Table 3, all compounds exhibited cytotoxic activity against the HeLa cell line, classified as moderate to weak.

3. RESULT AND DISCUSSION

Compound **1** (**Figure 1**) was obtained as a colorless oil, characterized by its molecular composition, $C_{15}H_{26}O_2$, as determined by HR-TOFMS. This showed a hydrogen ion peak at *m/z* 237.1850 $[M+H]^+$ (calculated mass of 237.1999), indicating three degrees of unsaturation. The IR spectra showed absorption peaks at 3397 cm^{-1} (-OH), 1456 and 1386 cm^{-1} (*gem*-dimethyl), and 1061 cm^{-1} (C-O stretching). The ^{1}H-NMR ($CDCl_3$ 700 MHz) spectrum showed the presence of three methyl groups, including one angular methyl δ_H 0.64 (3H, s, CH_3-14) and two secondary methyl δ_H 0.98 (3H, d, *J*= 6.8, CH_3-12) and 0.99 (3H, d, *J*=6.8 Hz, CH_3-13), three methines, including two nonprotonated methines δ_H 2.14 (d, *J*=9.8, H-5), δ_H 1.25 (m, H-7), and one oxymethine at δ_H 3.81 (t, *J*=9.7, H-6). The ^{13}C-NMR with detailed analysis of DEPT (Table 1) of 1 presented a total 15 carbon implying three tertiary methyl groups [δ_C 21.1 (C-12), 16.2 (C-13), 18.0 (C-14)], five methylenes including four sp^3 methylenes and one sp^2 methylenes [δ_C 38.3 (C-2), 35.3 (C-3), 17.9 (C-8), 31.5 (C-9), 110.2 (C-15)], four methines including three sp^2 methines and one oxygenated methines (δ_C 55.6 (C-5), 67.1 (C-6), 49.0 (C-7), 26.0 (C-11), and three quartenary carbons comprising one nonprotonated carbon, one terminal double bond, one ketonic group [δ_C 213.4 (C-1), 144.3 (C-4)].

Based on the results, the presence of three methyls, five methylenes, four methines, two non-protonated quaternary carbons (one olefinic group), and one ketonic group indicated that the structural planar of **1** was a bicyclic sesquiterpenoid group. By ^{1}H-NMR, 1 showed proton signals at δ_C 5.00 ppm (CH_3-15α) and δ_C 5.26 ppm (CH_3-15β), both of which appeared as singlets with a coupling constant of $J = 0$ Hz. The absence of coupling indicates geminal protons, suggesting that the splitting pattern originates from an exocyclic double bond or terminal alkene group (C=CH_2). These spectral characteristics are in agreement with the structural features of sesquiterpenoids belonging to the eudesmane-type. Furthermore, this observation is in line with the biosynthetic origin of eudesmane-type sesquiterpenoids, which are derived from farnesyl pyrophosphate (FPP). In the biosynthetic pathway, FPP undergoes cyclization to form germacrene intermediates, followed by rearrangements that establish the eudesmane skeleton, often incorporating exocyclic double bonds as observed in the present compound.

The biosynthetic pathway approach indicates that Me-14 at δ_C 50.2 ppm (C-10) adopts a β-orientation. This interpretation is corroborated by the chemical shift at δ_C 55.6 ppm (C-5), which is likewise consistent with a β-orientation configuration. Analysis of the vicinal coupling constant (^3J) provided insight into the stereochemistry of the hydroxyl methine at C-6. Protons in an axial–axial relationship (Ø ≈ 180°) typically exhibit ^3J = 8–10 Hz, whereas equatorial–equatorial or axial–equatorial protons (Ø ≈ 60°) display lower ^3J values of 1–7 Hz. The methine proton at δ_C 67.1 ppm (C-6) exhibited a vicinal coupling constant (^3J = 8–10 Hz), consistent with an axial–axial interaction, thereby supporting the assignment of the hydroxyl substituent at this position in the α-configuration. In addition, the methine proton at C-7 displayed a multiplet splitting pattern, indicative of δ_C 26.0 ppm (C-11) occupying an equatorial orientation,

which in turn establishes the isopropyl substituent as adopting a *β*-orientation. A comparison of NMR data revealed that compound **1** exhibited high similarity to previously reported compounds from *Aglaia lawii* [47]. **Table 1** shows the NMR shift and coupling constant values. Based on the results, compound **1** was isolated from the *Dysoxylum* genus and identified as a known 6α-hydroxy-eudesm-4(15)-en-1-one.

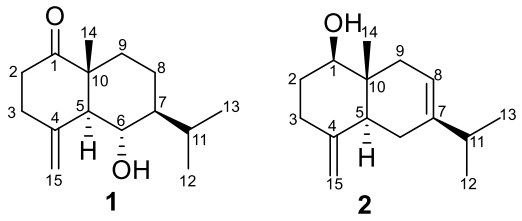

Figure 1. Compounds **1**-**2**

Table 1.^{1}H-NMR (175 MHz) and ^{13}C-NMR (700 MHz) of compound **1** in $CDCl_3$

Position of carbon	Compound 1		6α-hydroxy-eudesm-4(15)-en-1-one[47]	
	δ_C/ ppm	δ_H/ppm (ΣH, mult, *J*=Hz)	δ_C/ ppm	δ_H/ppm (ΣH, mult, *J*=Hz)
1	213.4	-	213.5	-
2	38.3	2.41 (1H, m)	38.3	2.39- 2.42(1H, m)
3	35.5	2.37 (1H, m)	35.4	2.35- 2.38 (1H, m)
		2.69 (1H, m)		2.58- 2.63 (1H, m)
4	144.3	-	144.4	-
5	55.6	2.14 (1H, d, 9.8)	55.5	2.14 (1H, d, 9.7)
6	67.1	3.81 (1H, t, 9.7)	67.1	3.38 (1H, dd, 9.8; 9.8)
7	49.0	1.25 (1H, m)	49.1	1.25- 1.30 (1H, m)
8	17.9	1.18 (1H, m)	17.9	1.25- 1.30 (1H, m)
9	31.5	1.56 (1H, m)	31.5	1.55- 1.58 (1H, m)
		1.80 (1H, m)		1.78- 1.82 (1H, m)
10	50.2	-	50.1	-
11	26.0	2.23 (1H, m)	2.21- 2.26 (1H, m)	26.0
12	21.1	0.95 (3H, d, 7.0)	21.0	0.96 (3H, d, 7.0)
13	16.2	0.86 (3H, d, 7.0)	16.2	0.88 (3H, d, 7.0)
14	18.0	0.98 (3H, s)	17.9	1.00 (3H, s)
15	110.2	4.99 (1H, d, 0.8)	110.1	5.00 (1H, d, 0.8)
		5.25 (1H, d, 0.8)		5.26 (1H, d, 0.8)

Based on the result, compound **2** was isolated as a colorless oil. The HR-TOF-MS analysis showed a molecular ion peak at 221.1904 $[M+H]^+$ and a calculated mass of $C_{15}H_{24}O$ at *m/z* 220.1827, indicating four degrees of unsaturation. The IR spectra showed absorption peaks at 3364 cm^{-1} (-OH), 2955 cm^{-1} (C-H sp^3), 1645 cm^{-1} (olefinic bond), and 1464 and 1379 cm^{-1} (*gem*-dimethyl). The ^{1}H-NMR ($CDCl_3$ 700 MHz) analysis showed one tertiary methyl δ_H 0.63 (3H, s, 0.63, CH_3-14), two secondary methyls δ_H 0.98 (3H, d, *J*=6.8, CH_3-12) and δ_H 0.99 (3H, d, *J*=6.8, CH_3-13), two non-oxygenated methine δ_H 1.72 (1H, m, H-5), 2.16 (1H, m, H-11), one olefinic methine δ_H 5.31(1H, dd, *J*=5.5, 2.1 Hz, H-8) and one oxygenated methine δ_H 3.62 (1H, t, *J*=11.7, H-1). Based on ^{13}C-NMR and DEPT spectra showed the existence of 15 carbon atoms (**Table 2**), comprising three methyls [δ_C 21.7 (C-12), 21.2 (C-13), 10.3 (C-14)] five methylenes [δ_C 31.5 (C-2), 34.2 (C-3), 25.6 (C-6), 38.4 (C-9), 107.7 (C-15)] four methines [δ_C 79.5 (C-1), 42.9 (C-5), 115.8 (C-8), 35.1 (C-11)] three quaternary carbons (one olefinic group) [δ_C 148.3 (C-4), 141.7 (C-7), 38.8 (C-10)]. Compound 2 was identified to possess a fused bicyclic sesquiterpenoid backbone. This structural feature was confirmed by the detection of a non-protonated sp^3 quaternary carbon at C-10, which is typically located at the A/B-ring junction of the decalin system. The presence of this diagnostic carbon strongly supports the assignment of a sesquiterpenoid skeleton, in which the fused bicyclic framework constitutes the core structural motif. According to the NMR data (**Table 2**), compound **2** shares a similar skeleton with 1, classified as an eudesmane-type sesquiterpenoid. Comparison of the NMR spectroscopic data between **2** and **1** demonstrated that the ketonic moiety in **1** was substituted by hydroxyl [δ_H 3.62 (1H, t, *J*=11.7, H-1); δ_C 79.5 (C-1)]. Notably, the NMR spectra of **2** exhibited diagnostic resonances for a disubstituted double bond [δ_H 5.31 (1H, dd, *J*=5.4, 2.1 Hz, H-7); δ_C 115.8 (C-8) replacing those of one non sp^3 hybridized methylene (CH-7 and CH_2-8) in 1. The above elucidation was further verified through consistency in coupling constants and experimental NMR spectra of 2 (**Figure 2**). Therefore, a comparison of 1D NMR data between 2 and the related literature showed high similarity with the known compound eudesm-4(15), 7-dien-1β-ol. Thus, compound 2 was identified as being the same as reported in previous literature [48].

Table 2. H-NMR (175 MHz) and ^{13}C-NMR (700 MHz) of compound **2** in $CDCl_3$

Position of carbon	Compound 2		Eusdesm-4 (15), 7-dien-1β-ol[48]	
	δC/ ppm	δH/ppm (ΣH, mult, *J*=Hz)	δC/ ppm	δH/ppm (ΣH, mult, *J*=Hz)
1	79.5	3.62 (1H, t, 11.7)	79.6	3.62 (1H, t, 11.7)
2	31.5	1.85 (2H, m)	31.5	1.85 (2H, m)
3	34.2	2.35 (2H, m)	34.3	2.35 (2H, m)
4	148.3	-	148.4	-
5	42.9	1.72 (1H, m)	43.0	1.72 (1H, m)
6	25.6	1.95 (2H, m)	25.6	1.95 (2H, m)
7	141.7	-	141.7	-
8	115.8	5.31 (1H, dd, 5.4; 2.1)	115.8	5.31 (1H, dd, 5.4; 2.1)
9	38.4	1.90 (2H, m)	38.4	1.90 (2H, m)
10	38.8	-	38.9	-
11	35.1	2.16 (1H, m)	35.1	2.16 (1H, m)
12	21.7	0.98 (3H, d, 6.8)	21.7	0.99 (3H, d, 6.8)
13	21.2	0.99 (3H, d, 6.8)	21.3	0.99 (3H, d, 6.8)
14	10.3	0.63 (3H, s)	10.4	0.63 (3H, s)
15	107.7	4.62 (1H, d, 1.5) 4.83 (1H, d, 1.5)	107.8	4.62 (1H, d, 1.5) 4.83 (1H, d, 1.5)

Table 3. Cytotoxic activities of compounds **1**-**2** against HeLa cancer lines

Compounds	IC_{50} (μM)
6*α*-hydroxy-eudesm-4(15)-en-1-one (**1**)	28.04
Eusdesm-4 (15), 7-dien-1*β*-ol (**2**)	58.37
Cisplatin (positive control)	16.00

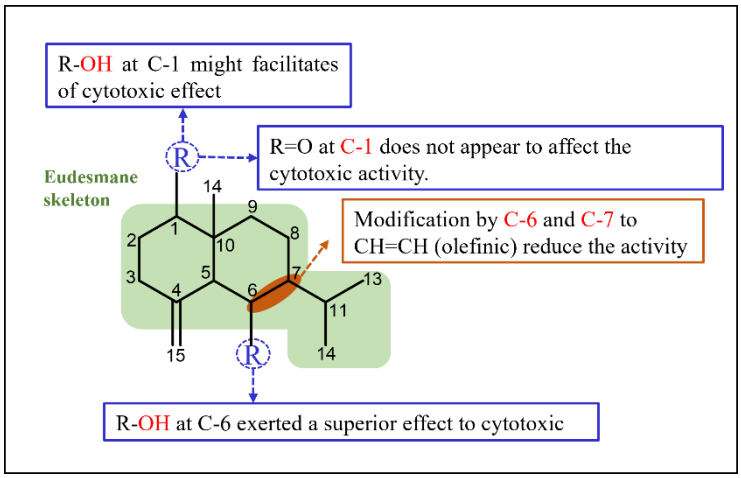

Figure 2. Structure-activity relationship of eudesmane-type sesquiterpenoids **1** and **2**

The in vitro cytotoxic activities of the isolated compounds **1** and **2** were evaluated against human cervical cancer (HeLa) cells. As summarized in Table 3, compound 1 exhibited a markedly higher cytotoxic effect than compound **2**. Nevertheless, its IC_{50} value (28.04 μM) was higher than that of the reference drug cisplatin (**Table 3**), indicating a moderate level of cytotoxic potency [49]. The cytotoxicity data obtained for all compounds allowed for elucidation of structure-activity relationships (SAR). Since all compounds shared the same eudesmane-type sesquiterpenoid skeleton, a concise structure–activity relationship (SAR) analysis was conducted (**Figure 2**). The results indicated that the hydroxyl group at C-6 contributed to the cytotoxic activity of compound **1** compared to compound **2**. In contrast, the presence of a hydroxyl group at C-1 in compound **2** did not significantly enhance cytotoxicity, likely due to the presence of an olefinic group at C-7 within its framework.

4. CONCLUSIONS

In summary, phytochemical investigation of *Dysoxylum gaudichaudianum* (Meliaceae) from Indonesia resulted in the isolation of two previously reported eudesmane-type sesquiterpenoids: 6α-hydroxy-eudesm-4(15)-en-1-one (**1**) and eudesm-4(15),7-dien-1β-ol (**2**). Structural elucidation was achieved through comprehensive spectroscopic analyses, including ^{1}H-NMR and ^{13}C-NMR experiments. All of compound was identified for the

first time within the genus *Dysoxylum*. Biological evaluation revealed that compound **1** exhibited the highest cytotoxic activity against HeLa cervical cancer cells using the PrestoBlue method, with an IC_{50} value of 28.04 μM, which was more potent than the reference control, cisplatin. Structure–activity relationship analysis indicated that the substituent at the C-6 position plays an important role in modulating biological activity. Compound **1**, bearing a hydroxyl group instead of a carbonyl at C-6, exhibited higher cytotoxic potency than compound **2**. This observation can be attributed to the increased polarity and hydrogen-bonding ability of the hydroxyl group, which facilitates interactions with nucleophilic or hydrogen-bond-accepting sites in biomolecules or enzyme active sites, thereby enhancing the compound's reactivity toward biological targets. The hydroxyl group at the C-6 position on the eudesmane skeleton has also been reported to influence other biological properties, such as immunomodulatory effects51. In contrast, the presence of an olefinic (C=C) moiety at C-6/C-7 appears to enhance the biological potency, possibly by increasing molecular rigidity and facilitating π–π or hydrophobic interactions with the target site, thereby resulting in a lower IC_{50} value. Similar structure–activity tendencies have also been reported for other eudesmane-type compounds.

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