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Three Minor Diterpenoids with Three Carbon Skeletons from *Euphorbia peplus*

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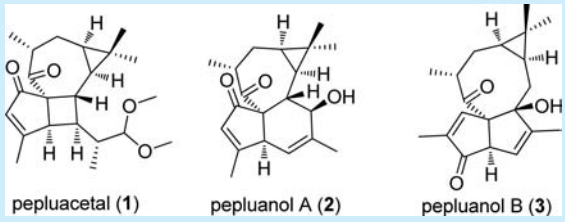
Supporting Information

ABSTRACT: *Euphorbia peplus* has been used in traditional medicine to treat asthma and psoriasis. Three highly modified diterpenoids, namely, pepluacetal (**1**) and pepluanol A–B (**2**–**3**), have been isolated and identified from this plant. Compounds **1**–**3** exhibit unprecedented 5/4/7/3, 5/6/7/3, and 5/5/8/3 ring systems, respectively. Their structures with absolute configurations were determined by spectroscopic analyses, X-ray crystallography, and electronic circular dichroism calculations. Since Kv1.3 is a validated target for the treatment of autoimmune diseases, such as multiple sclerosis, type-1 diabetes, asthma, and psoriasis, Kv1.3 was studied in terms of its response to the new compounds. All three compounds inhibit Kv1.3, with compound **3** being the most effective with an IC_{50} value of 9.50 μM.



Many species of the genus *Euphorbia* are well-known medicinal plants, and their characteristic chemical constituents, "Euphorbia diterpenoids", have been the focus of natural product drug discovery due to their structural diversity and broad spectrum of biological activities.[1] There have also been intense efforts toward developing the total synthesis of the diterpenoids.[2] One of the diterpenoids, ingenol mebutate (PEP005, Picato, LEO Pharma) from *E. peplus*, has been recently approved in the United States and the European Union for the treatment of actinic keratosis.[3]

The voltage-gated Kv1.3 potassium channel is important for T-cell activation, proliferation, and cytokine secretion.[4,5] In the activated effector memory T (T_{EM}) cells, Kv1.3 is the predominant K^+ channel, and since channel activity is required for T_{EM} cell proliferation and cytokine production,[6,7] Kv1.3 blockers have been proposed as T_{EM}-cell-specific immunosuppressants for autoimmune disorders, such as multiple sclerosis, type-1 diabetes, asthma, and psoriasis without suppressing native immune response.[8−11] Since *E. peplus* has been traditionally used to treat asthma and psoriasis,[12] we examined whether diterpenoids isolated from this plant can block Kv1.3. Consequently, we have isolated and identified three highly modified and biogenetical related diterpenoids: pepluacetal (**1**) and pepluanol A–B (**2**–**3**) (Figure 1). The three compounds each separately has a novel 5/4/7/3, 5/6/7/3, and 5/5/8/3 fused-ring skeletons. Further biological studies showed that all three compounds blocked Kv1.3. Compound **3** inhibits on Kv1.3 with an IC_{50} value of 9.50 μM, while compounds **1** and **2** have IC_{50} values beyond 30 μM, respectively.

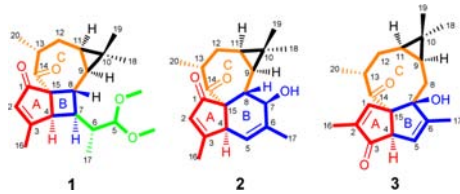


Figure 1. Structures of **1**–**3**.

Pepluacetal (**1**) formed colorless crystals and has a molecular formula of $C_{22}H_{32}O_4$ with seven double-bond equivalents as established by the HRESIMS ion peak at m/z 383.2193 $[M + Na]^+$ (calcd 383.2198). Its ^{13}C DEPT spectra exhibited 22 carbon signals (Table 1), attributed to two methoxys, five methyls, a methylene, nine methines [one olefinic at δ_C 133.2 (C-2) and one acetal at δ_C 107.1 (C-5)], and five quaternary carbons [two carbonyls at δ_C 203.7 (C-1) and 205.3 (C-14), and one olefinic at δ_C 176.5 (C-3)]. In ^1H spectra, two methoxys (δ_H 3.32 and 3.34), five methyls (δ_H 0.99–2.17), one olefinic signal (δ_H 5.99), and one acetal signal (δ_H 3.93) were observed, consistent

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Table 1. NMR Data for 1−3 in $CDCl_3$, Obtained at 600 and 150 MHz for ^1H and ^{13}C, Respectively (J in Hz)

	1		2		3	
	δ_H	δ_C, type	δ_H	δ_C, type	δ_H	δ_C, type
1		203.7, C		203.5, C	7.20 brs	152.6, CH
2	5.99 brs	133.2, CH	5.66 brs	125.1, CH		140.1, C
3		176.5, C		181.8, C		209.2, C
4	3.96 d (10.1)	45.9, CH	3.95 brs	46.5, CH	4.03 m	56.7, CH
5	3.93 d (3.2)	107.1, CH	5.71 brd	122.7, CH	5.64 m	125.3, CH
6	1.65 m	38.6, CH		134.5, C		142.3, C
7	2.45 m	46.5, CH	3.89 brs	73.5, CH		88.3, C
8	2.17 m	41.9, CH	2.95 dd (11.8, 2.2)	41.7, CH	2.24 dd (14.9, 0.9) 1.72 dd (14.9, 12.8)	33.0, CH_2
9	0.57 dd (8.7, 5.5)	28.5, CH	0.35 dd (11.8, 9.4)	28.3, CH	−0.03 m	21.9, CH
10		18.2, C		18.7, C		20.5, C
11	0.79 m	22.8, CH	0.61 td (9.4, 5.2)	22.2, CH	0.67 brq	26.6, CH
12	2.22 m; 1.81 brd	26.9, CH_2	1.96 m; 1.70 m	29.2, CH_2	1.85 m; 1.79 m	28.2,CH_2
13	3.06 m	45.8, CH	3.49 m	39.3, CH	3.55 m	40.6, CH
14		205.3, C		207.4, C		211.5, C
15		66.6, C		71.6, C		74.2, C
16	2.17 brs	20.1, CH_3	2.24 brs	18.3, CH_3	1.75 brs	10.5, CH_3
17	1.00 d (6.5)	12.8, CH_3	1.82 brs	22.5, CH_3	1.66 brs	11.9, CH_3
18	1.03 s	28.6, CH_3	0.97 s	28.8, CH_3	0.95 s	28.5, CH_3
19	0.99 s	15.5, CH_3	1.17 s	14.9, CH_3	1.01 s	15.2, CH_3
20	1.15 d (6.9)	14.0, CH_3	0.94 d (6.4)	17.6, CH_3	1.11 d (6.6)	19.4, CH_3
OCH_3	3.34 s	56.1, CH_3				
OCH_3	3.32 s	55.2, CH_3				

with the functional units in the ^{13}C and DEPT spectroscopic data. The aforementioned functionalities accounted for three degrees of unsaturation, and the remaining double-bond equivalents thus required the existence of four additional rings in the molecule.

The planar structure of **1** was determined by interpretation of 2D NMR spectra, especially HMBC spectrum (Figure 2). In the

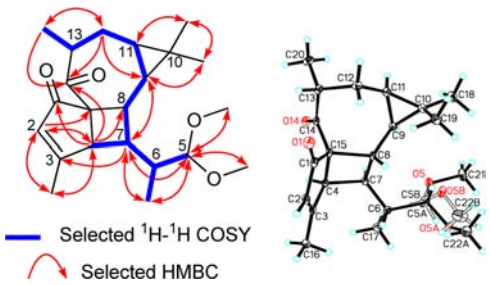

Figure 2. Key 2D correlations and X-ray structure of **1**.

HMBC spectrum, correlations from H-2 to C-1, C-3, C-4, C-15, and C-16; H-4 to C-1, C-2, C-3, and C-16; H_3-16 to C-2, C-3, and C-4 suggested the presence of a five-membered ring A (C-1−C-4 and C-15) with a methyl group (CH_3-16) at C-3. HMBC cross-peak from H-4 to C-15, combined with the $^1H-^1H$ COSY associations of H-4/H-7/H-8 and H-5/H-6/H-7 (and H_3-17) (Figure 2) revealed the presence of a four-membered ring B (fused to C-4 and C-15) with a side chain of C-5, C-6, and C-17 substituted at C-7. Furthermore, the $^1H-^1H$ COSY correlations of H-8/H-9/H-11/H_2-12/H-13/H_3-20 revealed a six-membered chain as shown (Figure 2). Besides, HMBC couplings of H-13 and H_3-20 to carbonyl carbon at δ_C 205.3 (C-14) indicated the connection between C-13 and C-14. Similarly, the correlation of H-4/C-14 in the HMBC spectrum indicated the linkage of C-14 and C-15. Thus, a seven-membered ring C integrated to ring B at C-8 and C-15 was established. Finally, the last double-bond equivalent was assigned to a cyclopropane ring (C-9/C-10/C-11) with two tertiary methyl groups (CH_3-18 and CH_3-19) substituted at C-10 by the HMBC associations of H_3-18/C-9, C-10, C-11, C-19 and H_3-19/C-9, C-10, C-11, C-18, respectively. Therefore, the deduced planar structure of **1** was shown in Figure 2.

X-ray diffraction analysis of **1** with Cu Kα radiation resulted in the Flack parameter of 0.14(19) and the Hooft parameter of 0.21(7) for 1166 Bijvoet pairs,[13] allowing an explicit assignment of the absolute configuration of **1** as shown in Figure 2, consistent with the sequential correlations of H-4/H-7/H-9/H_3-18/H-11/H_3-20 in the ROESY spectrum (Figure S1), respectively.

Pepluanol A (**2**) has a molecular formula of $C_{20}H_{26}O_3$ as determined by the HRESIMS ($[M + Na]^+$ m/z 337.1780, calcd 337.1780), requiring eight degrees of unsaturation. Two pairs of double bonds of C-2 (δ_C 125.1)/C-3 (δ_C 181.8) and C-5 (δ_C 122.7)/C-6 (δ_C 134.5), together with two carbonyl groups at δ_C 203.5 (C-1) and 207.4 (C-14), were observed in the ^{13}C spectrum, indicating that **2** had a tetracyclic skeleton (Table 1).

Based on the HMBC and $^1H-^1H$ COSY correlations (Figure S2), rings A and C along with a dimethyl (CH_3-18 and CH_3-19) substituted cyclopropane ring (C-9, C-10, and C-11), similar to those present in **1**, were determined in **2** as shown (Figure S2). Furthermore, $^1H-^1H$ COSY correlations of H-4/H-5 and H-7/H-8 together with HMBC couplings from H-4 and H-8 to C-6; H-5 and H-7 to C-15, revealed the presence of a six-membered ring B (C-4−C-8, and C-15). In addition, a methyl (CH_3-17) and a hydroxy group were assigned to C-6 and C-7, respectively, by the HMBC correlation of CH_3-17 (δ_H 1.82)/C-6 and the diagnostic chemical shift of C-7 at δ_C 73.5. Thus, the planar structure of **2** was elucidated as displayed (Figure S2).

X-ray diffraction analysis of **2** determined the relative configuration of **2** (Figure 3), consistent with correlations of H-8/H-13/H_3-19 and H-9/H_3-18/H-11 in the ROESY spectrum (Figure S2). Further, the absolute configuration was deduced by comparison of the experimental circular dichroism (CD)

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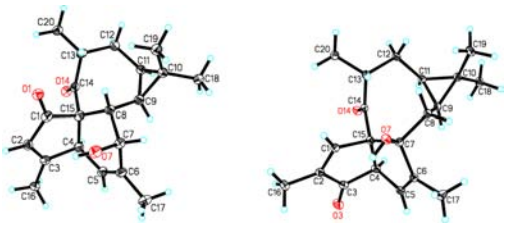


Figure 3. X-ray structure of **2** (left) and **3** (right).

spectrum with the electronic CD (ECD) spectrum calculated from quantum mechanical using a time-dependent density functional theory (TDDFT),[14] and the good agreement between the calculated ECD spectrum and the experimental CD spectrum allowed the assignment of **2** as 4*S*, 7*R*, 8*S*, 9*R*, 11*R*, 13*R*, and 15*R* (Figure 4).

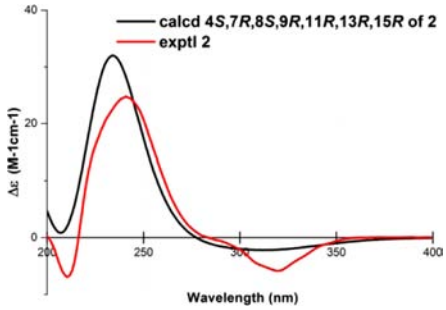


Figure 4. Experimental and calculated ECD spectra of **2**.

The molecular formula of pepluanol B (**3**) was determined as $C_{20}H_{26}O_3$ (*m*/*z* 314.1877 $[M]^+$, calcd 314.1882) by HREIMS, indicating eight degrees of unsaturation. Similar to that of **2**, five-membered rings A and B were established by analyses of HMBC and $^1H-^1H$ COSY correlations (Figure S3). In addition, $^1H-^1H$ COSY correlations of H-8/H9/H-11/H-12/H-13/H_3-20 (Figure S3) and HMBC correlations from H-1 and H-4 to C-14 (δ_C 211.5); H_2-8 to C-7 and C-15; and H-13 and H_3-20 to C-14 revealed the presence of an eight-membered ring C (Figure S3). Finally, a cyclopropane ring (C-9, C-10, and C-11) with CH_3-18 and CH_3-19 substituted at C-10 was determined by HMBC correlations similar to that of **1**. The planar structure of **3** was thereby depicted and shown in Figure S3.

The ROESY correlations of H-9/H-11/H_3-18 indicated that they were on the same orientation. Furthermore, X-ray diffraction analysis of **3** with Cu Kα radiation resulted in the Flack parameter of 0.16(17) and the Hooft parameter of 0.12(4),[13] allowing an explicit assignment of the absolute configuration of **3** (Figure 3).

Inspired by the traditional use of *E. peplus* for the treatment of asthma and psoriasis, where blockage of Kv1.3 in stimulated T_{EM} cells has selectively therapeutic effects,[6,7] we examined whether compounds **1**−**3** affect Kv1.3 activity. All three compounds exhibited inhibitory effects on this channel. Among them, compound **3** shows the strongest effect with an IC_{50} value of 9.50 μM (Figure 5). Compounds **1** and **2** inhibit Kv1.3 by 24.9 ± 8.6% and 46.0 ± 9.1%, respectively, at a concentration of 30 μM (Figure S4).

Compounds **1**−**3** are characterized by the 5/4/7/3, 5/6/7/3, and 5/5/8/3 fused-ring carbon skeletons, respectively, which have never been identified in natural products. The plausible biosynthetic pathways starting from lathyrane-type diterpenoid

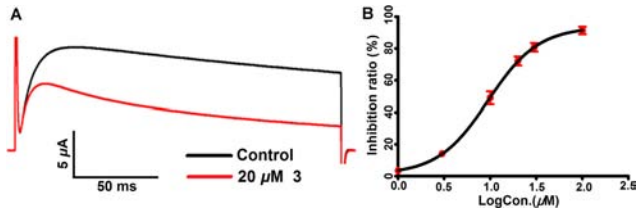
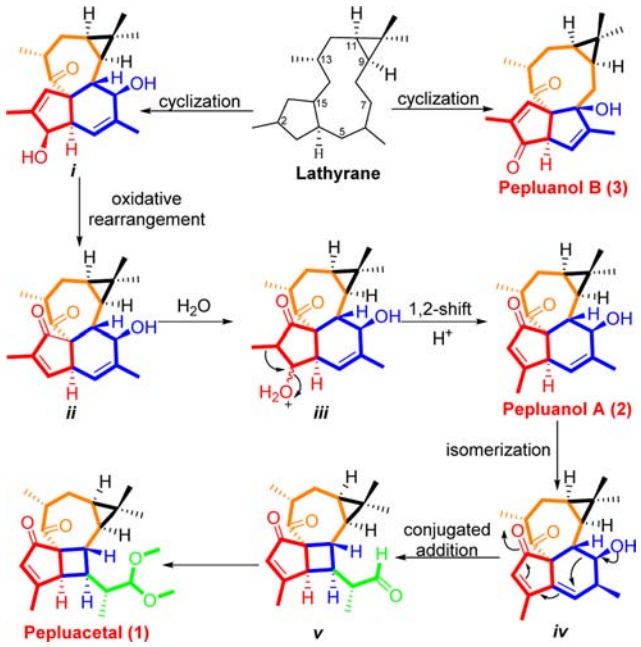


Figure 5. Inhibitory effect of compound **3** on Kv1.3. (A) Representative Kv1.3 current trace was evoked by 200 ms depolarization to +40 mV at 15 s intervals from a holding potential (HP) of −80 mV in the absence and presence of **3**. Kv1.3 was expressed in *Xenopus* oocytes. (B) Dose−response relationship of **3** for Kv1.3 at HP of −80 mV. Data points represent mean ± SEM of five measurements. Solid curve represents fit to the Hill equation. The IC_{50} value of **3** is 9.50 μM with the Hill coefficient of 1.6.

for compounds (**1**−**3**) were postulated in Scheme 1. For compounds **1** and **2**, a 8 → 15 cyclization of lathyrane would give

Scheme 1. Plausible Biosynthetic Pathway of 1−3



the intermediate ***i***, which could be further converted into another intermediate ***ii*** by oxidative rearrangement. Then ***ii*** could undergo Michael addition with H_2O to afford intermediate ***iii***, followed by acid-catalyzed 1,2-shift to produce **2**. Compound **2** would be further isomerized into intermediate ***iv***, a higher conjugated one, followed by a cascade of intramolecular conjugated addition and intermolecular aldol condensation with methanol to produce **1**; a 7 → 15 cyclization of lathyrane would give **3**.

To date, more than 750 "Euphorbia diterpenoids" with approximate 25 carbon skeletons have been reported.[1,15] Significantly, in the present study, pepluacetal (**1**) and pepluanol A−B (**2**−**3**), three new classes of diterpenoid derivatives, were isolated from *E. peplus*. In addition, a variety of therapeutically relevant bioactivities, such as antitumor, multidrug-resistance-reversing, antiviral, various vascular effects, and anti-inflammatory property, have been studied for "Euphorbia diterpenoids".[1] Here, we report for the first time that pepluanol B (**3**) is a potent Kv1.3 inhibitor. Altogether, our findings provide more skeletal

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types of diterpenoids for the genus *Euphorbia* and new structural classes for the exploration of immunosuppressive agents targeting on Kv1.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00787.

Experimental details and characterization data (PDF)
X-ray data of compound **1** (CIF)
X-ray data of compound **2** (CIF)
X-ray data of compound **3** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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