SUPPLEMENTARY MATERIAL

First report of two antioxidative meroterpeno 2H-pyrans from short-necked yellow-foot clam *Paphia malabarica* (Family: Veneridae) with bioactivity against pro-inflammatory cyclooxygenases and lipoxygenase

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ABSTRACT

Two new meroterpeno 2H-pyrans were isolated from the EtOAc:MeOH extract of yellow-foot clam *Paphia malabarica*. The structures of these newly reported compounds were elucidated based on spectroscopic interpretations. This is the first report of biogenic 2H-pyrans bearing decadienyl and allyloxy-(isopentanyl)-cyclohexene skeletons from marine biota. The extended C₁₈ sesquiterpenoid with prenylated irregular farnesene framework was characterized as 2-((E)-deca-1,8-dien-10-yl)-11,12-dihydro-13-propyl-2H-pyran (**1**). The compound **2**, 1'-((10E)-10-(10-(pentan-4-yl)-cyclohex-4-enyl)-allyloxy)-tetrahydro-2',2'-dimethyl-2H-pyran represents the first example of naturally occurring C₂₁ prenylated bisabolene type meroterpenoid, whereas tetrahydro-2',2'-dimethyl-2H-pyran remains attached at C-2' position of rearranged bisabolene framework formed by allyloxy linkage. The antioxidant activities (DPPH/ABTS⁺) of **1** and **2** were comparable (IC₅₀<1.0 mg/mL) with α-tocopherol. In addition, these compounds exhibited greater activity against cyclooxygenase-2 (COX-2) than COX-1, and the selectivity indices were significantly lesser (~1.1). No significant differences in anti-5-lipoxygenase (5-LOX) activity of **1** and **2** (IC₅₀ 1.02-1.06 mg/mL) than ibuprofen (IC₅₀ 0.93 mg/mL) indicated the potential anti-inflammatory properties of title compounds.

Keywords: *Paphia malabarica*; meroterpeno 2*H*-pyranoids; antioxidative, anti-inflammatory, cyclooxygenases, lipoxygenase

Supplemental file Legends

- Table S1.** NMR spectroscopic data of **1** and **2** in CDCl₃
- Figure S1.** ¹H NMR spectrum of **1**(500 MHz, CDCl₃)
- Figure S2.** ¹³C NMR spectrum of **1** (125 MHz, CDCl₃)
- Figure S3.** DEPT NMR spectrum of **1**
- Figure S4.** ¹H-¹H COSY spectrum of **1** (Couplings are represented by bold face bonds)
- Figure S5.** HSQC spectrum of **1**
- Figure S6.** HMBC spectrum of **1** (couplings are indicated by single barbed arrow)
- Figure S7.** NOESY spectrum of **1** (couplings are indicated by single barbed arrow)
- Figure S8.** GCMS spectrum and mass fragmentation pattern of **1**
- Figure S9.** ¹H NMR spectrum of **2** (500 MHz, CDCl₃)
- Figure S10.** ¹³C NMR spectrum of **2** (125 MHz, CDCl₃)
- Figure S11.** DEPT NMR spectrum of **2**
- Figure S12.** ¹H-¹H COSY spectrum of **2** (couplings are represented by bold face bonds)
- Figure S13.** HSQC spectrum of **2**
- Figure S14.** HMBC spectrum of **2** (couplings are indicated by single barbed arrow)
- Figure S15.** NOESY spectrum of **2** (couplings are indicated by single barbed arrow)
- Figure S16.** GCMS spectrum and mass fragmentation pattern of **2**
- Figure S17.** 2D NMR correlations observed in **1** and **2**. (A) Key ¹H-¹H COSY couplings (bold face bonds); HMBC couplings (C-H couplings are indicated as double barbed arrows) of **1**. (B) Key NOESY correlations (long range H-H couplings are indicated as double barbed arrow) of **1**. (C) Key ¹H-¹H COSY couplings (bold face bonds); HMBC couplings (double barbed arrows) of **2**. (D) Key NOESY correlations (double barbed arrow) of **2**.

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78 **Table S1.** NMR spectroscopic data of **1** and **2** in CDCl₃^a

C. No.	¹³ C	¹ H (int., mult., J in Hz) ^b	¹ H- ¹ H COSY	HMBC (¹ H- ¹³ C)	C. No.	¹³ C	¹ H (int., mult., J in Hz) ^b	¹ H- ¹ H COSY	HMBC (¹ H- ¹³ C)
1	114.06	5.01 (1H ^β , m, J=14.5)	-	C-2	1	14.15	0.87 (3H, t)	2-H	C-2, 3
-	-	4.94 (1H ^α , m, J=10.2)	-	C-3,2	2	22.69	1.42 (2H, m)	3-H	C-3, 4
2	139.27	5.81 (1H ^α , m, J=10.2, 6.9)	1-H ^α , 1-H ^β	C-3	3	34.37	2.31 (2H, m)	13-H	-
3	33.83	2.06 (2H, t)	2-H	C-2,1	4	143.18	-	-	-
4	29.37	1.36 (2H, m)	3-H	-	5	31.93	2.02 (2H, d)	6-H	-
5	29.52	1.26 (2H, m)	4-H	C-3,4,11	6	32.84	2.35 (1H ^α , t)	7-H, 10-H	C-7
6	28.97	1.30 (2H, m)	5-H	-	7	29.37	1.57 (1H, m)	8-H	-
7	31.94	1.97 (2H, t)	6-H	C-9,8,2	-	-	1.59 (1H, m)	-	-
8	130.38	5.35 (1H ^α , t, J=10.6, 5.5)	7-H	-	8	27.23	1.99 (1H ^β , t)	9-H	-
9	129.91	-	-	-	-	-	2.00 (1H ^α , t)	-	-
10	108.3	4.68 (1H ^α , t)	11-H	C-13,9	9	124.47	5.34 (1H, t, J=9.2)	-	-
11	26.72	1.58 (1H ^β , m)	12-H	C-12	10	139.27	5.38 (1H, d, J=8.5)	-	C-5
-	-	1.60 (1H ^α , m)	-	-	11	127.67	5.35 (1H, t, J=9.2)	12-H	-
12	29.71	2.02 (1H ^β , t)	-	C-15,16,10	12	65.05	4.12 (1H ^α , d)	-	C-11, 2'
-	-	2.00 (1H ^α , t)	-	-	-	-	4.14 (1H ^β , d)	-	C-1'
13	112.37	-	-	-	13	22.69	1.43 (2H, m)	14-H	C-3,4,5
14	123.34	6.96 (1H ^β , s)	-	C-15,13,10	14	14.15	0.89 (3H, t)	-	C-13,3
15	37.11	2.03 (2H, t)	16-H	-	1'	68.39	4.59 (1H ^α , s)	-	C-4',12,2',2'a,2'b
16	22.70	1.37 (2H, m)	17-H	C-12	2'	39.07	-	-	-
17	14.12	0.88 (3H, t)	-	C-16	2'a	30.25	1.48 (3H ^α , s)	-	C-5',2'
18	30.41	1.44 (3H ^β , s)	-	C-9,10,8,7	2'b	30.09	1.46 (3H ^β , s)	-	C-5',3'
-	-	-	-	-	3'	29.62	1.63 (1H ^α , m)	4'-H	-
-	-	-	-	-	-	-	1.66 (1H ^β , m)	-	-
-	-	-	-	-	4'	25.74	1.55 (1H ^α , m)	5'-H	C-3',2'a,2'b
-	-	-	-	-	-	-	1.56 (1H ^β , m)	-	-
-	-	-	-	-	5'	63.11	3.64 (2H, t)	-	C-4'

79 ^aNMR spectra recorded using Bruker AVANCE III 500 MHz (AV 500) spectrometer (Bruker, Karlsruhe, Germany) in CDCl₃ as aprotic solvent at ambient temperature
80 with TMS as the internal standard (δ 0 ppm). The ¹H NMR spectra were recorded at 500 MHz, while the ¹³C NMR spectra were recorded at 125 MHz.81 ^b Values in ppm, multiplicity and coupling constants (J = Hz) are indicated in parentheses. The assignments were made with the aid of the ¹H-¹H COSY, HSQC,
82 HMBC and NOESY experiments.
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84 **Figure S1.**

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