Electronic supplementary information (ESI)

Eremophilane and cadinane sesquiterpenoids from the fruits of *Alpinia oxyphylla* and their anti-inflammatory activities

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S1. Physical constants and spectral data of 1-6, 23-24, 26-29

alpinoxyphllaone C (**1**): yellow oil; $[\alpha]_D^{27}$ +18.8 (0.5, CHCl₃); HR-ESI-MS (positive) *m/z* 237.1855 [M + H]⁺ (calcd for C₁₅H₂₅O₂⁺, 237.1855); UV (MeOH) λ_{max} (log ε): 201 (3.26) nm; IR (KBr) v_{max} 3438, 2934, 1716, 1643, 1401, 1385, 1073, 890 cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 1**.

(3S,4S,5R,7R)-eremophila-3,4-epoxy-1(10),11-dien-2-one (**2**): colorless crystals; $[\alpha]_D^{27}$ -124.1 (0.5, CHCl₃); HR-ESI-MS (positive) *m/z* 233.1540 [M + H]⁺ (calcd for C₁₅H₂₁O₂⁺, 233.1542); UV (MeOH) λ_{max} (log ε): 245 (3.69) nm; IR (KBr) v_{max} 2961, 2931, 1671, 1641, 1626, 1451, 1401, 1384, 1314, 1107, 905, 875, 828, 664, 547, 481 cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 1**.

Crystal Data for **2**. $C_{15}H_{20}O_2$ (M = 232.31 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.12559(16) Å, b = 9.43073(17) Å, c = 14.8426(3) Å, V = 1277.37(4) Å³, Z = 4, T = 170.0(2) K, μ (CuK α) = 0.617 mm⁻¹, *Dcalc* = 1.208 g/cm³, 10537 reflections measured (11.116° $\leq 2\Theta$ $\leq 147.726^{\circ}$), 2556 unique ($R_{int} = 0.0442$, $R_{sigma} = 0.0279$) which were used in all calculations. The

final $R_1 = 0.0323$ (I > 2 σ (I)), $wR_2 = 0.0872$ (all data), CCDC number: 2217170.

(3R,4R,5R,7R)-eremophila-3,4-epoxy-1(10),11-dien-2-one (**3**): colorless oil; $[\alpha]_D^{27}$ +105.8 (0.5, CHCl₃); HR-ESI-MS (positive) m/z 233.1540 [M + H]⁺ (calcd for C₁₅H₂₁O₂⁺, 233.1542); UV (MeOH) λ_{max} (log ε): 202 (3.69), 242 (3.71) nm; IR (KBr) ν_{max} 2935, 1673, 1437, 1400, 1385, 1302, 1206, 1073, 890, 538 cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 1**.

(4R,5S,7S,9R)-eremophila-1(10),11-dien-9-ol (4): colorless oil; $[\alpha]_D^{27}$ +53.0 (0.5, CHCl₃); HR-ESI-MS (positive) *m/z* 203.1810 [M + H - H₂O]⁺ (calcd for C₁₅H₂₃⁺, 203.1800); UV (MeOH) λ_{max} (log ε): 203 (3.52) nm; IR (KBr) v_{max} 3424, 2927, 2363, 1642, 1441, 1400, 1384, 1051, 887, 472 cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 1**.

(2R,4R,5S,7S,9R)-eremophila-1(10),11-dien-2,9-diol (**5**): colorless crystals; $[\alpha]_{D}^{21}$ +115.2 (0.5, CHCl₃); HR-ESI-MS (positive) *m/z* 237.1859 [M + H]⁺ (calcd for C₁₅H₂₅O₂⁺, 237.1855); UV (MeOH)

 λ_{max} nm (log ε): 204 (2.46), 234 (1.45); IR (KBr) v_{max} 3323, 2928, 1647, 1441, 1375, 1284, 1052, 1007, 885, 682 cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 1**.

Crystal Data for **5**. $C_{15}H_{24}O_2$ (*M* =236.34 g/mol): orthorhombic, space group P2₁2₁2₁ (no. 19), *a* = 8.155(1) Å, *b* = 20.429(2) Å, *c* = 27.192(3) Å, *V* = 4530.3(7) Å³, *Z* = 4, *T* = 149.99(10) K, μ (Cu K α) = 1.54184 mm⁻¹, *Dcalc* = 1.087 g/cm³, 12357 reflections measured (5.41° ≤ 2 Θ ≤ 147.374°), 7861 unique (R_{int} = 0.0727, R_{sigma} = 0.1223) which were used in all calculations. The final R_1 = 0.0731 (I > 2 σ (I)) and wR_2 = 0.1626 (all data), CCDC number: 2221275.

D-H	d (D-H)	d (HA)	<dha< th=""><th>d (DA)</th><th>Α</th></dha<>	d (DA)	Α
O1C-H1C	0.99(8)	1.74(8)	174(9)	2.732(5)	O2C [x-1, y, z]
O1A-H1A	0.97(5)	1.75(5)	174(10)	2.711(5)	O2A [x-1, y, z]
O2A-H2A	0.91(10)	1.87(11)	152(10)	2.706(6)	O1B
O2C-H2C	0.91(10)	1.89(10)	174(11)	2.799(6)	O2B [-x+2, y+1/2, -z+3/2]
O1B-H1B	1.03(12)	1.71(13)	171(11)	2.727(6)	O1C
O2B-H2B	1.04(11)	1.70(11)	176(10)	2.735(7)	O1M [-x+1, y-1/2, -z+3/2]
O1M-H1M	0.96(6)	1.75(5)	161(11)	2.676(7)	O1A

Table S1 Hydrogen Bond Interactions in Compound 5

(1R,2R,4R,5S,7R)-eremophila-9,11-dien-1,2-diol (6): yellow amorphous solid; $[\alpha]_D^{26}$ -46.4 (0.5, CHCl₃); HR-ESI-MS (positive) *m/z* 259.1677 [M + Na]⁺ (calcd for C₁₅H₂₄O₂Na ⁺, 259.1674); UV (MeOH) λ_{max} nm (log ε): 204 (3.01); IR (KBr) ν_{max} 3339, 2962, 2925, 1639, 1447, 1374, 1071, 1006, 889cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 1**.

oxyphyllone J (23): yellow oil; $[\alpha]_{D}^{27}$ +16.8 (0.5, CHCl₃)_o HR-ESI-MS (positive) *m/z* 235.1338

 $[M+H]^+$ (calcd for C₁₄H₁₉O₃, 235.1334); UV (MeOH) λ_{max} (log ε): 208 (4.08), 237 (3.90), 274 (3.90)

nm; IR (KBr) *v*_{max} 2961, 2872, 1636, 1470, 1385, 1354, 1259, 1218, 1185, 1124, 1058, 1008, 938, 907,

872, 846, 810, 616, 549 cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 2**.

oxyphyllone H (**24**): yellow oil; $[\alpha]_D^{30}$ +197.5 (0.5, CHCl₃); HR-ESI-MS (positive) *m/z* 237.1499 [M+H]⁺ (calcd for C₁₄H₂₁O₃⁺, 237.1491); UV (MeOH) λ_{max} nm (log ε): 202 (3.64), 265 (4.07); IR

(KBr) *v*_{max} 3498, 2963, 2872, 1680, 1457, 1372, 1158, 979, 856cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 2**.

oxyphyllone K (**26**): yellow oil; HR-ESI-MS (positive) m/z 237.0883 [M+Na]⁺ (calcd for C₁₄H₁₄O₂Na, 237.0891); UV (MeOH) λ_{max} (log ε): 207 (4.33), 230 (4.12), 256 (4.23) nm; IR (KBr) ν_{max} 3438, 2967, 2929, 1694, 1655, 1605, 1590, 1560, 1465, 1400, 1384, 1286, 1255, 1082, 880, 799, 519 cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 2**.

oxyphyllone I (**27**): brown gelatinous; $[\alpha]_D^{26}$ -8.2 (0.5, CHCl₃); HR-ESI-MS (positive) *m/z* 233.1540 [M+H]⁺ (calcd for C₁₅H₂₁O₂⁺, 233.1542); UV (MeOH) λ_{max} nm (log ε): 208 (4.04), 260 (3.84); IR (KBr) ν_{max} 2930, 1676, 1606, 1450, 1386, 1283, 1053, 824cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 2**.

oxyspirone A (**28**): light yellow colloid; $[\alpha]_D^{25}$ -12.0 (0.35, CHCl₃); HR-ESI-MS (positive) *m/z* 259.1660 [M+Na]⁺ (calcd for C₁₅H₂₄O₂Na⁺, 259.1674); UV (MeOH) λ_{max} nm (log ε): 203 (2.14),237 (2.24); IR (KBr) ν_{max} 3436, 2928, 2862, 1699, 1456, 1381, 1041cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 2**.

oxyspirone B (**29**): light yellow oil; $[\alpha]_D^{25}$ +6.5 (0.7, CHCl₃); HR-ESI-MS (positive) *m/z* 261.1790 [M+Na]⁺ (calcd for C₁₅H₂₆O₂Na ⁺, 261.1831); UV (MeOH) λ_{max} nm (log ε): 204 (3.39); IR (KBr) v_{max} 3470, 2943, 2873, 1641, 1455, 1377, 1055, 887, 541cm⁻¹; ¹H and ¹³C-NMR spectroscopic data, see **Table 2**.

S2. Selected spectra for compounds 1-6, 23-24, 26-29



Fig. S1 HR-ESI-MS spectrum of compound 1





Fig. S2¹H NMR (600 MHz, CDCl₃) spectrum of compound 1



Fig. S4 DEPT (150 MHz, CDCl₃) and ¹³C NMR spectra of compound 1









Fig. S6 HMBC spectrum of compound 1

Fig. S7 ¹H-¹H COSY spectrum of compound 1



Fig. S8 NOESY spectrum of compound 1



Fig. S9 UV spectrum of compound 1



Fig. S10 IR spectrum of compound 1

Page 1

Single Mass Analysis Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 36 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass) Elements Used: C: 0-100 H: 0-200 O: 0-200 A04E4I2 20220111-24 202 (1.634) 1: TOF MS ES+ 7.46e+004 187,1119 100-233.1540 159.1177 187.1488 215.1433 % 205.1591 234.1573 145.1015 160.1208 341.6478 368.2009 377.1871 315.1580 0-44-140 180 160 200 220 -1.5 50.0 Minimum: Maximum: 5.0 10.0 Calc. Mass mDa 233.1542 -0.2 PPM -0.9 i-FIT 199.3 Conf (%) Formula n/a C15 H21 02 Mass 233.1540 DBE Norm 5.5 n/a







Fig. S12 ¹H NMR (600 MHz, CDCl₃) spectrum of compound 2



Fig. S13 ¹³C NMR (150 MHz, CDCl₃) spectrum of compound 2





Fig. S14 DEPT (150 MHz, CDCl₃) and ¹³C NMR spectra of compound 2

Fig. S15 HSQC spectrum of compound 2



Fig. S16 HMBC spectrum of compound 2



Fig. S17 ¹H-¹H COSY spectrum of compound 2



Fig. S18 NOESY spectrum of compound 2



Fig. S19 UV spectrum of compound 2



Fig. S20 IR spectrum of compound 2

Page 1

Single Mass Analysis Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 36 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass) Elements Used: C: 0-100 H: 0-200 O: 0-200 A04E41 20220111-22 212 (1.709)



Fig. S21 HR-ESI-MS spectrum of compound 3

5.72 5.72 5.71	-4.77		255 255 255 255 255 255 255 255 255 255	-1.33
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Fig. S22 ¹H NMR (600 MHz, CDCl₃) spectrum of compound 3





Fig. S24 DEPT (150 MHz, CDCl₃) and 13 C NMR spectra of compound 3







Fig. S27 ¹H-¹H COSY spectrum of compound 3



Fig. S28 NOESY spectrum of compound 3



Fig. S29 UV spectrum of compound 3



Fig. S30 IR spectrum of compound 3

Page 1



Fig. S31 HR-ESI-MS spectrum of compound 4



Fig. S32 ¹H NMR (600 MHz, DMSO-d₆) spectrum of compound 4



Fig. S33 ¹³C NMR (150 MHz, DMSO-*d*₆) spectrum of compound 4



220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1 fl (ppm)

Fig. S34 DEPT (150 MHz, DMSO-d₆) and ¹³C NMR spectra of compound 4



Fig. S35 HSQC spectrum of compound 4







Fig. S37 ¹H-¹H COSY spectrum of compound 4



Fig. S38 NOESY spectrum of compound 4



Fig. S39 UV spectrum of compound 4



Fig. S40 IR spectrum of compound 4

Page 1

1: TOF MS ES+



Monoisotopic Mass, Even Electron Ions 65 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass) Elements Used: C: 0-500 H: 0-1000 O: 0-200 Na: 0-1 A03F5E1 20210913-23 141 (1.145)



Fig. S41 HR-ESI-MS spectrum of compound 5





Fig. S42 ¹H NMR (400 MHz, CDCl₃) spectrum of compound 5



Fig. S43 ¹³C NMR (100 MHz, CDCl₃) spectrum of compound 5





Fig. S44 DEPT (100 MHz, CDCl₃) and $^{13}\mathrm{C}$ NMR spectra of compound 5



Fig. S47 ¹H-¹H COSY spectrum of compound 5






Fig. S49 UV spectrum of compound 5



Fig. S51 HR-ESI-MS spectrum of compound 6





Fig. S53 ¹³C NMR (100 MHz, CDCl₃) spectrum of compound 6



Fig. S55 HSQC spectrum of compound 6



Fig. S56 HMBC spectrum of compound 6



Fig. S57 ¹H-¹H COSY spectrum of compound 6







Fig. S59 UV spectrum of compound 6



Fig. S61 HR-ESI-MS spectrum of compound 23





Fig. S63 ¹³C NMR (150 MHz, CDCl₃) spectrum of compound 23





Fig. S64 DEPT (150 MHz, CDCl₃) and ¹³C NMR spectra of compound 23







Fig. S66 HMBC spectrum of compound 23



Fig. S67 ¹H-¹H COSY spectrum of compound 23







Fig. S70 HR-ESI-MS spectrum of compound 24



Fig. S72 ¹³C NMR (150 MHz, CDCl₃) spectrum of compound 24





Fig. S75 ¹H-¹H COSY spectrum of compound 24











Elemental Composition Report

Single Mass Analysis Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 65 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass) Elements Used: C: 0-100 H: 0-200 O: 0-200 Na: 0-1

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Maximu	m:			5.0	10). ()	50.0															
Mass 237.08	83	Calc. Ma 237.0891 237.0916	ass I S	mDa -0.8 -3.3	PI -:	PM 3.4 13.9	DBE 7.5 10.5	i-FI 156. 160.	Г 7 2	Norm 0.028 3.602	Conf (97.27 2.73	%) Fo C1 C1	rmula 4 H14 6 H13	02 Na 02								

Fig. S79 HR-ESI-MS spectrum of compound 25



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Fig. S82 DEPT (150 MHz, CDCl₃) and ¹³C NMR spectra of compound 25



Fig. S83 HSQC spectrum of compound 25





Fig. S85 ¹H-¹H COSY spectrum of compound 25









Elemental Composition Report

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Fig. S88 HR-ESI-MS spectrum of compound 27



Fig. S90 ¹³C NMR (150 MHz, CDCl₃) spectrum of compound 27



Fig. S91 DEPT (150 MHz, CDCl₃) and ¹³C NMR spectra of compound 27



Fig. S94 ¹H-¹H COSY spectrum of compound 27







Fig. S96 IR spectrum of compound 27

Elemental Composition Report

Single Mass Analysis DBE: min = -1.5, max = 50.0 Tolerance = 5.0 mDa / Element prediction: Off Number of isotope peaks used for i-FIT = 3 Monoisotopic Mass, Even Electron Ions 81 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass) Elements Used: C: 0-500 H: 0-1000 O: 0-200 Na: 0-1 AO3D3G8D2 20210712018 188 (1.519) 1: TOF MS ES+ 4.52e+004 219.1750 100-237.1854 135.0815 220.1778 238.1885 191.1809 201.1647 121.0660 259.1660 163.1123 93.0712 107.0871 239.1911 275.1300.293.1035 275.1300.293.1035 280 300 79.0546 160 0-100 180 60 240 80 120 140 200 220 260 Minimum: Maximum: -1.5 50.0 5.0 10.0 DBE Mass Calc. Mass mDa PPM i-FIT Formula. 259.1660 259.1674 -1.4 3.5 63.6 C15 H24 O2 Na -5.4

Fig. S97 HR-ESI-MS spectrum of compound 28



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Fig. S99 ¹³C NMR (150 MHz, CDCl₃) spectrum of compound 28



Fig. S100 DEPT (150 MHz, CDCl₃) and ¹³C NMR spectra of compound 28



Fig. S101 HSQC spectrum of compound 28



Fig. S102 HMBC spectrum of compound 28



Fig. S103 ¹H-¹H COSY spectrum of compound 28



Fig. S104 NOESY spectrum of compound 28







Fig. S106 IR spectrum of compound 28



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Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 77 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass) Elements Used: C: 0-500 H: 0-1000 O: 0-200 Na: 0-1 AO3D3G9D4 20210712020 190 (1.533)

1: TOF MS ES+ 4.42e+003 219.1753 100-221.1903 % 222.1926 259.1680 243.1952 262.2166 233.1487 235.1691 239.6625 215.1821217.1599 223.1956 258.1165 245.1947 249.1705 +++++++++++ m/z 0-255.0 +111 230.0 225.0 235.0 245.0 1 240.0 **י**די 250.0 220.0 210.0 215.0 260.0 Minimum: Maximum: -1.5 50.0 5.0 10.0 mDa PPM DBE i-FIT Mass Calc. Mass Formula [Variable] 261.1790 261.1831 -4.1 -15.7 2.5 4.6 C15 H26 O2 Na

Fig. S107 HR-ESI-MS spectrum of compound 29



Fig. S109 ¹³C NMR (150 MHz, CDCl₃) spectrum of compound 29



Fig. S110 DEPT (150 MHz, CDCl₃) and ¹³C NMR spectra of compound 29



Fig. S111 HSQC spectrum of compound 29



Fig. S112 HMBC spectrum of compound 29



Fig. S113 ¹H-¹H COSY spectrum of compound 29


Fig. S114 NOESY spectrum of compound 29





Fig. S116 IR spectrum of compound 29



Fig. S117 Linear correlation plots of calculated and experimental 1C values of two plausible epimers 1A and 1B

NO.	exptl. δ_C	calcd. $\delta_C 1 \mathbf{A}$	deviation	calcd. $\delta_C 1B$	B deviation		
1	209.1	227.4	18.3 219.7		10.6		
2	73.8	78.2	4.4	77.7	3.9		
3	40.4	43.3	2.9	45.7	5.3		
4	41.7	46.5	4.8	46.0	4.3		
5	44.8	52.6	7.8	51.1	6.3		
6	45.7	48.3	2.6	39.1	-6.6		
7	40.1	45.5	5.4	46.4	6.3		
8	25.4	28.9	3.5	31.7	6.3		
9	22.7	25.9	3.2	27.3	4.6		
10	60.6	66.0	5.4	72.8	12.2		
11	149.6	163.4	13.8	163.6	14.0		
12	108.9	114.4	5.5	115.32	6.4		
13	21.1	23.0	1.9	22.61	1.5		
14	19.9	21.0	1.1	15.61	-4.3		
15	18.0	18.9	0.9	19.52	1.5		
		DP4+	100%	DP4+	0%		

Table S1. Experimental and Calculated ¹³C NMR Chemical Shifts of 1A and 1B



Fig. S118 Rh₂(OCOCF₃)₄-induced CD spectra of (4*R*,5*S*,7*S*,9*R*)-eremophila-1(10),11-dien-9-ol (4)



Fig. S119 CD spectra of *in situ* formed Mo-complexes of 6 recorded in DMSO after 0.5 h from dissolving in the 1:1 ligand-to-metal ratio



Fig. S120 CD spectra of compounds 28



Fig. S121 Chiral HPLC chromatogram of compound 27

Table S2	2. Prime	rs for ql	PCR
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Gene		Forward			Reverse			
TNF-α	CCCTCAC	ACTCAGAT	ГСАТСТТ	'CT	GCTACGA	CGTGGGG	CTACA	G
IL-6	TAGTCCT	TCCTACCC	CAATTT	CC T	TGGTCCT	TAGCCAG	CTCCT	ſC
Actin	GTCGTACC	ACAGGCA	TTGTGA	ГGG G	CAATGCC	TGGGTA	CATGG	ΤG
iNOS	CTGGC1	GCCTTGT	FCAGCT A	A A	AGTGTAG	CGTTTCG	GGATC	T
COX-2	TGCTGT	ACAAGCA	GTGGCA	A A	AGGTGCT	CGGCTTC	CAGTA	Т
		<u>ν</u> ⁵ 5 8 9 9 1 13(μM)	2 × ⁰ γ ⁰ κ ⁰ 17(μΜ)			- - - - - - - - - - - - - -	・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・	本日本日本日本日本日本日本日本日本日本日本日本日本日本日本日本日本日本日本日

Fig. S122 Effects of different concentrations of compounds (IC50) alone on cell viability



Fig. S123 NO inhibitions of all the isolated compounds at 50 Mm



Fig. S124 Effects of different fractionations of *A. oxyphylla* on cell viability. Data represent means ± SD, n=3.



Fig. S125 NO inhibitions of different fractionations. Data represent means ± SD, n=3; ###P < 0.001, *P < 0.05, **P< 0.01, vs LPS.