



ORIGINAL ARTICLE

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Discovery of structurally diverse polyprenylated acylphloroglucinols with quorum sensing inhibitory activity from *Hypericum seniawinii* Maxim.

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Abstract

Four previously undescribed polyprenylated acylphloroglucinols, hyperisenins A–D (**1–4**), along with two known analogues (**5** and **6**), were obtained from the aerial part of *Hypericum seniawinii* Maxim. Compounds **1** and **2** were two highly degraded polyprenylated acylphloroglucinols with a cyclohexanone-monocyclic skeleton, while compound **3** was the first example of *O*-prenylated acylphloroglucinols with a 6/6/6 ring system. Their structures were identified by analyzing NMR, HRESIMS data, and quantum chemical calculations. The biosynthetic pathway of **1** and **2** might originate from bicyclic polyprenylated acylphloroglucinols via a series of complex retro-Claisen, keto–enol tautomerism, and intramolecular cyclization. The bioassay results showed that **4** exhibited quorum sensing inhibitory activity against *Pseudomonas aeruginosa*, which could decrease the activation of the *rhl* system, and significantly reduce rhamnolipid levels at a concentration of 100 μ M, and the mechanism might be the ability to bind **4** to lasR and pqsR.

Keywords Polyprenylated Acylphloroglucinols, *Hypericum seniawinii* Maxim., Quorum sensing inhibitory, *Pseudomonas aeruginosa*

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Hypericum seniawinii Maxim.

Chemical structures: 1, 2, 3, 4

Quorum sensing inhibitory activity against *Pseudomonas aeruginosa*

Graph 1: PAO1-*rhlA*-gfp

Y-axis: RFU₆₀₀ / OD₆₀₀

X-axis: Time (h)

Legend: 200 μM, 100 μM, 50 μM, 25 μM, 12.5 μM, 6.25 μM, 3.125 μM, 0 μM

Graph 2: OD₆₀₀

Y-axis: OD₆₀₀

X-axis: Time (h)

Legend: 200 μM, 100 μM, 50 μM, 25 μM, 12.5 μM, 6.25 μM, 3.125 μM, 0 μM

Graph 3: Rhamnolipid production (%)

Y-axis: Rhamnolipid production (%)

X-axis: Concentration (μM)

Legend: DMSO, 100, 50, 25, 12.5, 6.25, 3.125, 0 μM

Signaling pathway diagram:

3-oxo-C12-HSL, C4-HSL, PQS, LasI, LasR, RhlI, RhlR, PqsA, PqsR, RhlA, RhlB, RhlC, RhlD, RhlE, RhlF, RhlG, RhlH, RhlI, RhlJ, RhlK, RhlL, RhlM, RhlN, RhlO, RhlP, RhlQ, RhlR, RhlS, RhlT, RhlU, RhlV, RhlW, RhlX, RhlY, RhlZ, RhlAA, RhlAB, RhlAC, RhlAD, RhlAE, RhlAF, RhlAG, RhlAH, RhlAI, RhlAJ, RhlAK, RhlAL, RhlAM, RhlAN, RhlAO, RhlAP, RhlAQ, RhlAR, RhlAS, RhlAT, RhlAU, RhlAV, RhlAW, RhlAX, RhlAY, RhlAZ, RhlBA, RhlBB, RhlBC, RhlBD, RhlBE, RhlBF, RhlBG, RhlBH, RhlBI, RhlBJ, RhlBK, RhlBL, RhlBM, RhlBN, RhlBO, RhlBP, RhlBQ, RhlBR, RhlBS, RhlBT, RhlBU, RhlBV, RhlBW, RhlBX, RhlBY, RhlBZ, RhlCA, RhlCB, RhlCC, RhlCD, RhlCE, RhlCF, RhlCG, RhlCH, RhlCI, RhlCJ, RhlCK, RhlCL, RhlCM, RhlCN, RhlCO, RhlCP, RhlCQ, RhlCR, RhlCS, RhlCT, RhlCU, RhlCV, RhlCW, RhlCX, RhlCY, RhlCZ, RhlDA, RhlDB, RhlDC, RhlDD, RhlDE, RhlDF, RhlDG, RhlDH, RhlDI, RhlDJ, RhlDK, RhlDL, RhlDM, RhlDN, RhlDO, RhlDP, RhlDQ, RhlDR, RhlDS, RhlDT, RhlDU, RhlDV, RhlDW, RhlDX, RhlDY, RhlDZ, RhlEA, RhlEB, RhlEC, RhlED, RhlEE, RhlEF, RhlEG, RhlEH, RhlEI, RhlEJ, RhlEK, RhlEL, RhlEM, RhlEN, RhlEO, RhlEP, RhlEQ, RhlER, RhlES, RhlET, RhlEU, RhlEV, RhlEW, RhlEX, RhlEY, RhlEZ, RhlFA, RhlFB, RhlFC, RhlFD, RhlFE, RhlFF, RhlFG, RhlFH, RhlFI, RhlFJ, RhlFK, RhlFL, RhlFM, RhlFN, RhlFO, RhlFP, RhlFQ, RhlFR, RhlFS, RhlFT, RhlFU, RhlFV, RhlFW, RhlFX, RhlFY, RhlFZ, RhlGA, RhlGB, RhlGC, RhlGD, RhlGE, RhlGF, RhlGG, RhlGH, RhlGI, RhlGJ, RhlGK, RhlGL, RhlGM, RhlGN, RhlGO, RhlGP, RhlGQ, RhlGR, RhlGS, RhlGT, RhlGU, RhlGV, RhlGW, RhlGX, RhlGY, RhlGZ, RhlHA, RhlHB, RhlHC, RhlHD, RhlHE, RhlHF, RhlHG, RhlHH, RhlHI, RhlHJ, RhlHK, RhlHL, RhlHM, RhlHN, RhlHO, RhlHP, RhlHQ, RhlHR, RhlHS, RhlHT, RhlHU, RhlHV, RhlHW, RhlHX, RhlHY, RhlHZ, RhlIA, RhlIB, RhlIC, RhlID, RhlIE, RhlIF, RhlIG, RhlIH, RhlII, RhlIJ, RhlIK, RhlIL, RhlIM, RhlIN, RhlIO, RhlIP, RhlIQ, RhlIR, RhlIS, RhlIT, RhlIU, RhlIV, RhlIW, RhlIX, RhlIY, RhlIZ, RhlJA, RhlJB, RhlJC, RhlJD, RhlJE, RhlJF, RhlJG, RhlJH, RhlJI, RhlJJ, RhlJK, RhlJL, RhlJM, RhlJN, RhlJO, RhlJP, RhlJQ, RhlJR, RhlJS, RhlJT, RhlJU, RhlJV, RhlJW, RhlJX, RhlJY, RhlJZ, RhlKA, RhlKB, RhlKC, RhlKD, RhlKE, RhlKF, RhlKG, RhlKH, RhlKI, RhlKJ, RhlKK, RhlKL, RhlKM, RhlKN, RhlKO, RhlKP, RhlKQ, RhlKR, RhlKS, RhlKT, RhlKU, RhlKV, RhlKW, RhlKX, RhlKY, RhlKZ, RhlLA, RhlLB, RhlLC, RhlLD, RhlLE, RhlLF, RhlLG, RhlLH, RhlLI, RhlLJ, RhlLK, RhlLL, RhlLM, RhlLN, RhlLO, RhlLP, RhlLQ, RhlLR, RhlLS, RhlLT, RhlLU, RhlLV, RhlLW, RhlLX, RhlLY, RhlLZ, RhlMA, RhlMB, RhlMC, RhlMD, RhlME, RhlMF, RhlMG, RhlMH, RhlMI, RhlMJ, RhlMK, RhlML, RhlMM, RhlMN, RhlMO, RhlMP, RhlMQ, RhlMR, RhlMS, RhlMT, RhlMU, RhlMV, RhlMW, RhlMX, RhlMY, RhlMZ, RhlNA, RhlNB, RhlNC, RhlND, RhlNE, RhlNF, RhlNG, RhlNH, RhlNI, RhlNJ, RhlNK, RhlNL, RhlNM, RhlNN, RhlNO, RhlNP, RhlNQ, RhlNR, RhlNS, RhlNT, RhlNU, RhlNV, RhlNW, RhlNX, RhlNY, RhlNZ, RhlOA, RhlOB, RhlOC, RhlOD, RhlOE, RhlOF, RhlOG, RhlOH, RhlOI, RhlOJ, RhlOK, RhlOL, RhlOM, RhlON, RhlOO, RhlOP, RhlOQ, RhlOR, RhlOS, RhlOT, RhlOU, RhlOV, RhlOW, RhlOX, RhlOY, RhlOZ, RhlPA, RhlPB, RhlPC, RhlPD, RhlPE, RhlPF, RhlPG, RhlPH, RhlPI, RhlPJ, RhlPK, RhlPL, RhlPM, RhlPN, RhlPO, RhlPP, RhlPQ, RhlPR, RhlPS, RhlPT, RhlPU, RhlPV, RhlPW, RhlPX, RhlPY, RhlPZ, RhlQA, RhlQB, RhlQC, RhlQD, RhlQE, RhlQF, RhlQG, RhlQH, RhlQI, RhlQJ, RhlQK, RhlQL, RhlQM, RhlQN, RhlQO, RhlQP, RhlQQ, RhlQR, RhlQS, RhlQT, RhlQU, RhlQV, RhlQW, RhlQX, RhlQY, RhlQZ, RhlRA, RhlRB, RhlRC, RhlRD, RhlRE, RhlRF, RhlRG, RhlRH, RhlRI, RhlRJ, RhlRK, RhlRL, RhlRM, RhlRN, RhlRO, RhlRP, RhlRQ, RhlRR, RhlRS, RhlRT, RhlRU, RhlRV, RhlRW, RhlRX, RhlRY, RhlRZ, RhlSA, RhlSB, RhlSC, RhlSD, RhlSE, RhlSF, RhlSG, RhlSH, RhlSI, RhlSJ, RhlSK, RhlSL, RhlSM, RhlSN, RhlSO, RhlSP, RhlSQ, RhlSR, RhlSS, RhlST, RhlSU, RhlSV, RhlSW, RhlSX, RhlSY, RhlSZ, RhlTA, RhlTB, RhlTC, RhlTD, RhlTE, RhlTF, RhlTG, RhlTH, RhlTI, RhlTJ, RhlTK, RhlTL, RhlTM, RhlTN, RhlTO, RhlTP, RhlTQ, RhlTR, RhlTS, RhlTT, RhlTU, RhlTV, RhlTW, RhlTX, RhlTY, RhlTZ, RhlUA, RhlUB, RhlUC, RhlUD, RhlUE, RhlUF, RhlUG, RhlUH, RhlUI, RhlUJ, RhlUK, RhlUL, RhlUM, RhlUN, RhlUO, RhlUP, RhlUQ, RhlUR, RhlUS, RhlUT, RhlUU, RhlUV, RhlUW, RhlUX, RhlUY, RhlUZ, RhlVA, RhlVB, RhlVC, RhlVD, RhlVE, RhlVF, RhlVG, RhlVH, RhlVI, RhlVJ, RhlVK, RhlVL, RhlVM, RhlVN, RhlVO, RhlVP, RhlVQ, RhlVR, RhlVS, RhlVT, RhlVU, RhlVV, RhlVW, RhlVX, RhlVY, RhlVZ, RhlWA, RhlWB, RhlWC, RhlWD, RhlWE, RhlWF, RhlWG, RhlWH, RhlWI, RhlWJ, RhlWK, RhlWL, RhlWM, RhlWN, RhlWO, RhlWP, RhlWQ, RhlWR, RhlWS, RhlWT, RhlWU, RhlWV, RhlWW, RhlWX, RhlWY, RhlWZ, RhlXA, RhlXB, RhlXC, RhlXD, RhlXE, RhlXF, RhlXG, RhlXH, RhlXI, RhlXJ, RhlXK, RhlXL, RhlXM, RhlXN, RhlXO, RhlXP, RhlXQ, RhlXR, RhlXS, RhlXT, RhlXU, RhlXV, RhlXW, RhlXX, RhlXY, RhlXZ, RhlYA, RhlYB, RhlYC, RhlYD, RhlYE, RhlYF, RhlYG, RhlYH, RhlYI, RhlYJ, RhlYK, RhlYL, RhlYM, RhlYN, RhlYO, RhlYP, RhlYQ, RhlYR, RhlYS, RhlYT, RhlYU, RhlYV, RhlYW, RhlYX, RhlYY, RhlYZ, RhlZA, RhlZB, RhlZC, RhlZD, RhlZE, RhlZF, RhlZG, RhlZH, RhlZI, RhlZJ, RhlZK, RhlZL, RhlZM, RhlZN, RhlZO, RhlZP, RhlZQ, RhlZR, RhlZS, RhlZT, RhlZU, RhlZV, RhlZW, RhlZX, RhlZY, RhlZZ

Hyperisenin A (**1**) was obtained as a colorless oil, and the molecular formula was defined as $C_{30}H_{40}O_4$ based on its HRESIMS data (m/z $[M+Na]^+$: 487.2802, calcd 487.2819), which possessed eleven degrees of unsaturation. The 1H NMR data showed five aromatic protons [δ_H 8.01 (2H, dd, $J=8.5, 1.4$ Hz), 7.47 (1H, tt, $J=7.3, 1.4$ Hz),

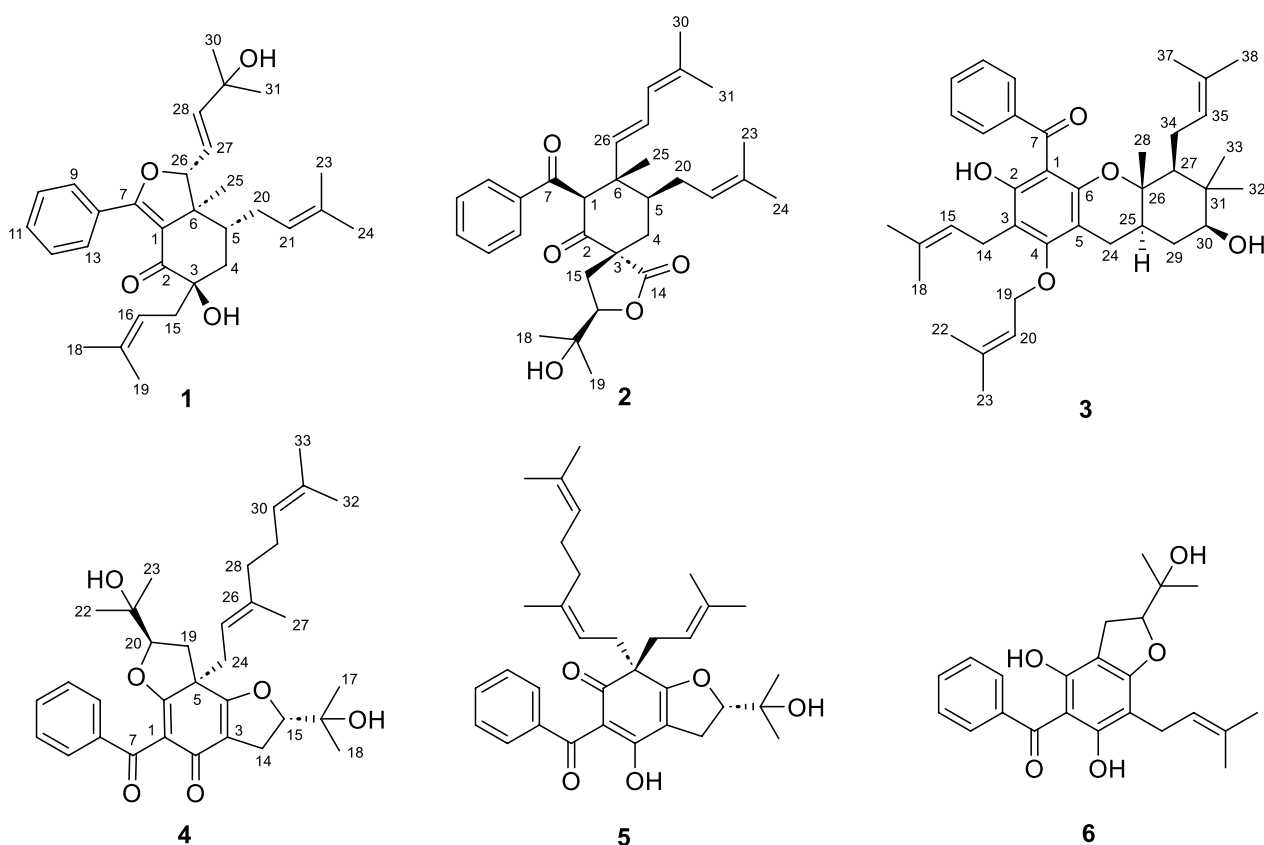


Fig. 1 Chemical structures of compounds 1–6

7.41 (2H, tt, $J=7.4, 1.4$ Hz)], four olefinic protons [δ_{H} 6.15 (1H, d, $J=15.5$ Hz), 5.98 (1H, dd, $J=15.5, 7.7$ Hz), 5.15 (1H, m), 5.13 (1H, m)], and seven methyls [δ_{H} 1.74 (3H, s), 1.71 (3H, s), 1.66 (3H, s), 1.60 (3H, s), 1.38 (3H, s), 1.37 (3H, s), 1.07 (3H, s)] (Table 1). The ^{13}C NMR spectrum showed 30 carbon signals (Table 1), which could be assigned to one ketone carbonyl (δ_{C} 196.0), one monosubstituted phenyl ring [δ_{C} 132.0, 130.5 ($\times 2$), 129.4, 127.8 ($\times 2$)], eight olefinic carbons (δ_{C} 166.8, 144.8, 135.6, 133.4, 122.3, 121.9, 119.0, 117.6), and three quaternary carbons including two oxygenated carbons (δ_{C} 76.3, 71.0), two methines, three methylenes and seven methyls. By analyzing the 1D NMR data and unsaturation, combined with the data reported in the literature [28–30], it is inferred that **1** was a polyprenylated acylphloroglucinol with a bicyclic system.

Its gross structure was confirmed by analyzing its 1D and 2D NMR data (Fig. 2). The HMBC correlations from $\text{H}_2\text{-4}$ to C-2, C-3, and C-6, from $\text{H}_3\text{-25}$ to C-1, C-5, and C-6, from H-13 to C-7, the $^1\text{H}\text{-}^1\text{H}$ COSY cross-peaks of $\text{H}_2\text{-4}/\text{H-5}$ and H-9/H-10/H-11/H-12/H-13, combined with chemical shifts of C-1 (δ_{C} 117.6) and C-7 (δ_{C} 166.8), indicated that the cyclohexanone system existed, and a benzoyl group converted into enol form was attached

at C-1. Then, the HMBC correlations from $\text{H}_2\text{-15}$ to C-2, C-3, and C-4, from $\text{H}_3\text{-18}$ to C-16, C-17, and C-19, from $\text{H}_3\text{-24}$ to C-21, C-22, and C-23, from $\text{H}_3\text{-25}$ to C-6, from $\text{H}_3\text{-30}$ to C-28 and C-29, combined with the $^1\text{H}\text{-}^1\text{H}$ COSY cross-peaks of $\text{H}_2\text{-15}/\text{H-16}$, H-5/ $\text{H}_2\text{-20}/\text{H-21}$, and H-26/H-27/H-28, revealed the existence of three side chains at C-3, C-5, and C-6. Further analysis of the downfield chemical shifts of C-3 (δ_{C} 76.3) and C-26 (δ_{C} 94.0) indicated that hydroxyl groups were attached to C-3 and C-26, respectively. The above-mentioned groups accounted for ten degrees of unsaturation. The remaining degree of unsaturation was attributed to a furan ring formed between C-7 and C-26, which was consistent with both the downfield chemical shift of C-26 (δ_{C} 94.0) and the HRESIMS data. Accordingly, the planar structure, featuring a cyclohexanone-monocyclic skeleton, was confirmed.

The relative configurations of C-5, C-6, and C-26 in **1** were assigned by the NOESY spectrum, in which the cross-peaks of H-5/H-26 and $\text{H}_3\text{-25}/\text{H-27}$ indicated that $\text{H}_3\text{-25}$ was α -oriented, while H-5 and H-26 were on the same side with the β -orientations. The large coupling constant between H-27 and H-28 ($J=15.5$ Hz) confirmed the *E* configuration. In order to determine

Table 1 The ^1H and ^{13}C NMR data of compounds **1–4** (δ in ppm, J in Hz)

No	1^a		2^b		3^b		4^c	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1		117.6	5.48 s	63.4		111.2		114.7
2		196.0		202.1		158.8		182.3
3		76.3		61.1		116.0		113.3
4	1.97 dd (15.0, 3.5) 1.73 ^d	36.3	a 2.46 dd (14.4, 4.4) b 1.73 ^d	40.2		161.4		170.0
5	2.08 m	41.4	2.67 m	44.8		109.2		50.5
6		50.9		50.5		153.4		175.7
7		166.8		197.2		200.8		193.9
8		129.4		139.8		142.0		138.0
9	8.01 dd (8.5, 1.4)	130.5	7.69 dd (8.5, 1.4)	128.7	7.57 dd (8.2, 1.1)	130.0	7.85 dd (8.5, 1.3)	129.6
10	7.41 tt (7.4, 1.4)	127.8	7.44 tt (7.8, 1.7)	129.8	7.37 t (7.8)	129.3	7.54 tt (7.4, 1.4)	128.5
11	7.47 tt (7.3, 1.4)	132.0	7.55 tt (7.4, 1.3)	134.3	7.52 tt (7.5, 1.3)	133.2	7.42 t (7.7)	133.5
12	7.41 tt (7.4, 1.4)	127.8	7.44 tt (7.8, 1.7)	129.8	7.37 t (7.8)	129.3	7.54 tt (7.4, 1.4)	128.5
13	8.01 dd (8.5, 1.4)	130.5	7.69 dd (8.5, 1.4)	128.7	7.57 dd (8.2, 1.1)	130.0	7.85 dd (8.5, 1.3)	129.6
14				176.7	3.35 m 3.31 ^d	23.8	a 2.75 dd (14.9, 8.6) b 2.89 dd (15.1, 10.7)	28.0
15	2.49 dd (13.9, 6.8) 2.41 dd (13.9, 8.4)	39.3	a 2.91 dd (13.0, 7.0) b 1.95 dd (13.1, 9.3)	32.5	5.22 m	124.8	4.70 dd (10.7, 8.6)	93.0
16	5.15 m	119.0	4.24 dd (9.3, 7.0)	86.0		131.8		72.2
17		135.6		70.9	1.76 s	18.1	1.22 s	23.8
18	1.66 s	18.3	1.28 s	26.5	1.68 s	25.9	1.28 s	25.5
19	1.74 s	26.0	1.14 s	24.8	4.47 dd (11.4, 7.0), 4.38 dd (11.4, 7.2)	71.1	a 2.23 dd (12.1, 5.8) b 2.32 dd (12.1, 9.3)	31.6
20	2.14 m 1.69 ^d	28.3	2.15 m 1.69 ^d	29.4	5.56 m	121.6	4.61 dd (9.3, 5.7)	90.8
21	5.13 m	122.3	5.14 m	123.9		138.9		71.2
22		133.4		134.1	1.70 s	18.2	1.09 s	23.4
23	1.60 s	18.1	1.59 s	18.0	1.81 s	26.0	1.28 s	27.6
24	1.71 s	26.2	1.70 s	26.0	2.64 dd (16.1, 4.7), 2.31 dd (16.2, 12.8)	25.1	2.71 dd (13.8, 8.4) 2.59 dd (13.8, 7.4)	36.3
25	1.07 s	16.2	1.30 s	13.9	1.58 ^d	40.7	5.12 m	116.7
26	4.86 d (7.7)	94.0	5.46 d (15.4)	137.7		82.3		141.4
27	5.98 dd (15.5, 7.7)	121.9	6.25 dd (15.4, 10.7)	127.9	1.15 dd (8.1, 1.9)	56.4	1.61 s	16.4
28	6.15 d (15.5)	144.8	5.64 d (10.6)	125.7	0.96 s	14.4	2.07 m	40.1
29		71.0		135.9	1.77 ^d , 1.38 m	35.2	2.08 m	26.8
30	1.37 s	29.7	1.66 s	18.3	3.27 dd (11.7, 4.3)	78.3	5.08 m	123.8
31	1.38 s	30.0	1.68 s	26.0		41.9		132.1
32					0.76 s	16.1	1.60 s	17.9
33					0.81 s	28.8	1.68 s	25.9
34					1.70 ^d , 0.90 m	24.1		
35					4.52 m	129.9		
36						128.0		
37					1.48 s	18.1		
38					1.59 s	25.8		

^a ^1H NMR 400 MHz, ^{13}C NMR 100 MHz, in CDCl_3 ^b ^1H NMR 600 MHz, ^{13}C NMR 150 MHz, in CD_3OD ^c ^1H NMR 600 MHz, ^{13}C NMR 150 MHz, in CDCl_3 ^d Overlapped signal

Table 1 (continued)

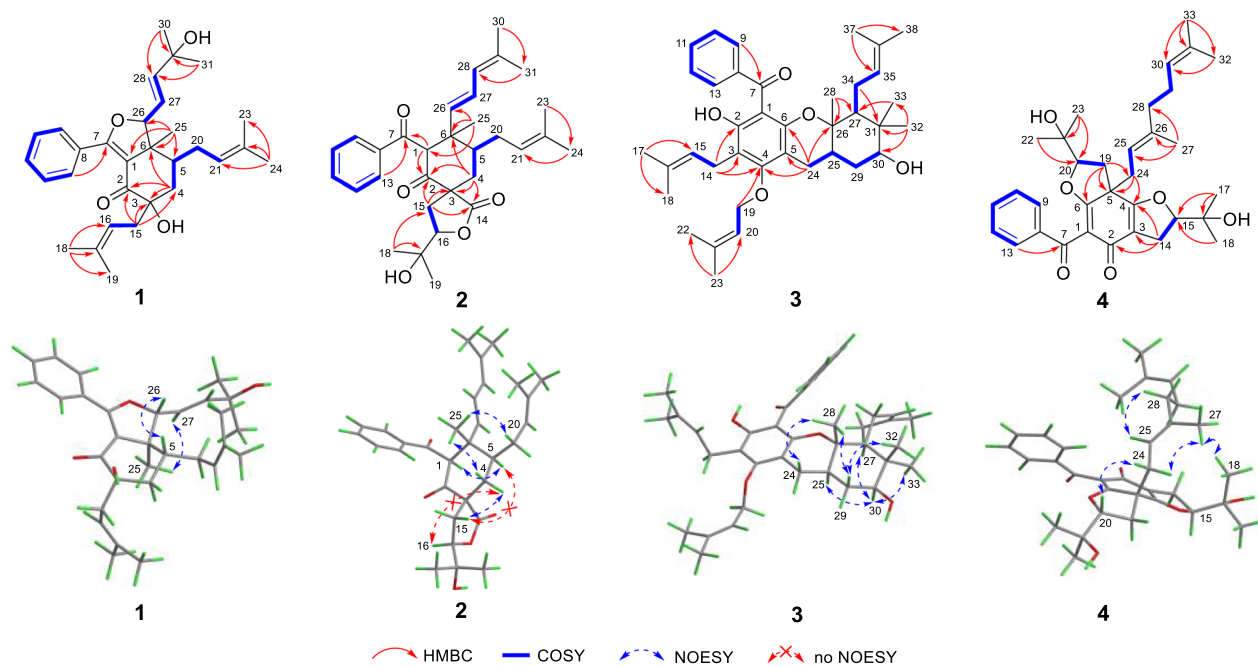


Fig. 2 Key 2D NMR correlations of compounds 1–4

the relative configuration of C-3, the calculated ^{13}C NMR data with DP4+ analysis of two configurations ($3R^*,5R^*,6S^*,26R^*$)-1 and ($3S^*,5R^*,6S^*,26R^*$)-1 were applied at the mPW1PW91/6–311+G** level. The results showed that ($3R^*,5R^*,6S^*,26R^*$)-1 had a better linear correlation with 100% DP4+ probability ($R^2=0.9990$) (Fig. 3A), suggesting that the relative configuration of **1** was defined as $3R^*,5R^*,6S^*,26R^*$. The absolute configuration of **1** was identified by ECD calculation at the PBE0/def2-TZVP level, the result showed that the calculated ECD ($3R,5R,6S,26R$)-1 curve matched well with the experimental one, allowing to assign its absolute configuration as $3R,5R,6S,26R$ (Fig. 4). Thus, the structure of **1** was elucidated.

Hyperisenin B (**2**), a colorless oil, possesses the molecular formula $\text{C}_{31}\text{H}_{40}\text{O}_5$ on the basis of the HRESIMS data (m/z $[\text{M}+\text{Na}]^+$: 515.2753, calcd 515.2768). Its ^1H and ^{13}C NMR spectra showed the presence of a monosubstituted benzene ring, two ketone carbonyls, one ester carbonyl, six olefin carbons, and seven methyl groups, which were similar to those of spirohypolactone B [31]. Further comparison of NMR data between **2** and spirohypolactone B revealed that they possessed the same skeleton, except for the acyl substituent and the number of the double bond [31]. The presence of a phenyl group at C-7 was

verified by the ^1H - ^1H COSY cross-peaks of H-9/H-10/H-11/H-12/H-13 and the HMBC cross-peak from H-13 to C-7, which was consistent with its 1D NMR data (Fig. 2). Furthermore, the 4-methylpenta-1,3-diene group was attached at C-6, deduced from the HMBC correlations from H_3 -25 to C-6 and C-26, from H_3 -30 to C-31, from H_3 -31 to C-28, and the ^1H - ^1H COSY cross-peaks of H-26/H-27/H-28. The relative configurations was the same as that of spirohypolactone B and norhyperpalum H assigned as $1R^*,3R^*,5S^*,6S^*,16R^*$ via the similar the NOESY cross-peaks of H-1/H-5, H_2 -20/ H_3 -25, H_2 -4a/ H_2 -15b, and H_2 -4b/ H_3 -25, and along with the crucial absence of the NOESY cross-peaks of H_2 -4/H-16 and H-5/ H_2 -15 (Fig. 2). To further confirm the relative configurations of C-3 and C-16, a DP4+ probability analysis of four isomers [A: ($3R^*,16R^*$), B: ($3R^*,16S^*$), C: ($3S^*,16R^*$), D: ($3S^*,16S^*$)] was conducted, and the calculated data of ($1R^*,3R^*,5S^*,6S^*,16R^*$)-2 has good linear correlations with the experimental data with 100% DP4+ probability (all data) (Fig. 3B and S40). This deduction was further supported by a critical 1D NMR comparison in the same solvent of **2** with similar compounds, spirohypolactones A and B, and norhyperpalum H [31, 32] (Figure S41). The $\Delta^{26(27)}$ double bond was assigned as *E* configuration based on the coupling constant ($J_{\text{H-26}, \text{H-27}}=15.4$ Hz). Finally, the ECD

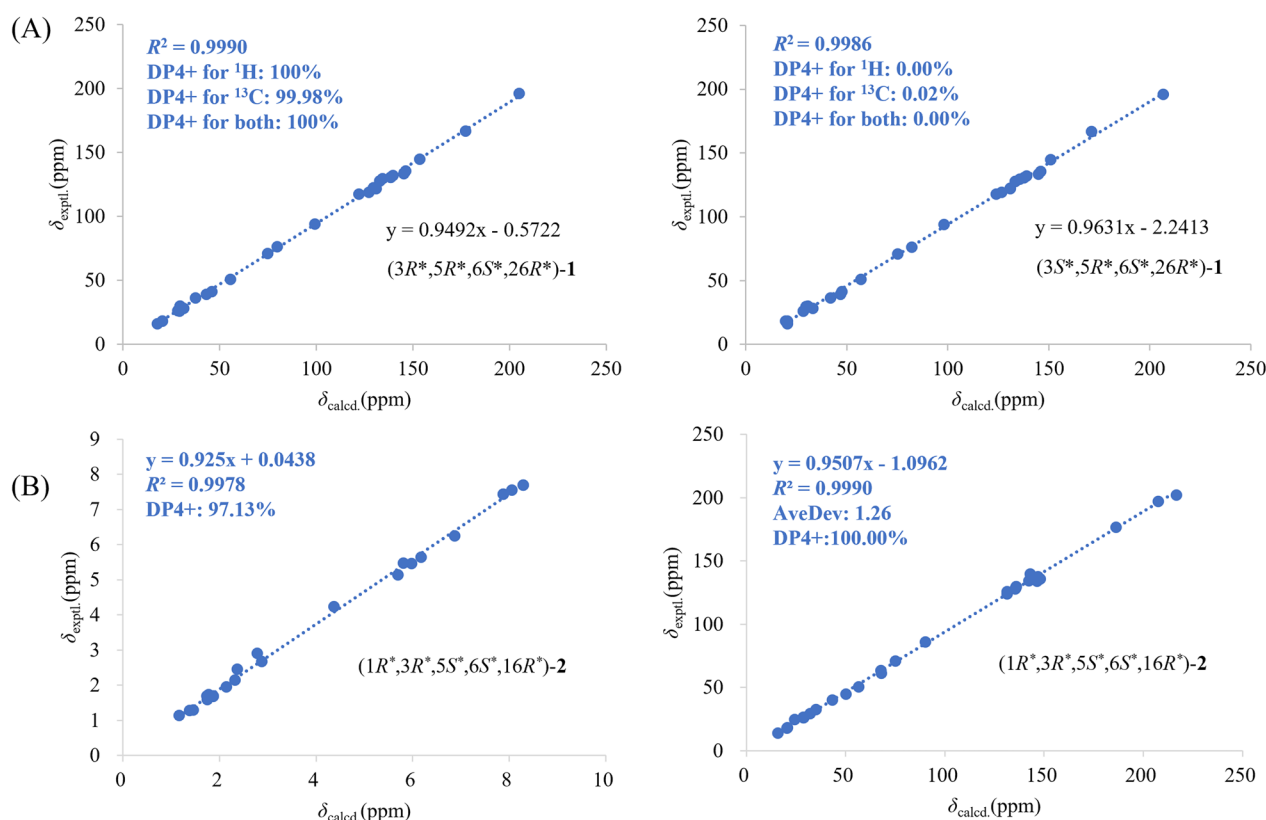


Fig. 3 (A) NMR calculations with a DP4+ probability analysis: $(3R^*,5R^*,6S^*,26R^*)-1$ and $(3S^*,5R^*,6S^*,26R^*)-1$. (B) Linear correlation between the experimental and calculated ^1H (left) and ^{13}C NMR (right) chemical shifts, and the results of a DP4+ probability analysis for $(1R^*,3R^*,5S^*,6S^*,16R^*)-2$

calculation of **2** was conducted at the PBE0/def2-TZVP level, and its absolute configuration was determined to be $1R,3R,5S,6S,16R$ (Fig. 4).

Hyperisenin C (**3**), obtained as a yellow oil, had the molecular formula $\text{C}_{38}\text{H}_{50}\text{O}_5$ based on its HRESIMS data (m/z $[\text{M} + \text{Na}]^+$: 609.3572, calcd 609.3550), suggesting fourteen indices of hydrogen deficiency. Its ^1H NMR spectrum showed the existence of five characteristic protons of the benzene ring [δ_{H} 7.57 (2H, dd, $J=8.2, 1.1$ Hz), 7.52 (1H, tt, $J=7.5, 1.3$ Hz), 7.37 (2H, t, $J=7.8$ Hz)], three olefinic protons [δ_{H} 5.56 (1H, m), 5.22 (1H, m), 4.52 (1H, m)], and nine methyl groups [δ_{H} 1.81 (3H, s), 1.76 (3H, s), 1.70 (3H, s), 1.68 (3H, s), 1.59 (3H, s), 1.48 (3H, s), 0.96 (3H, s), 0.81 (3H, s), 0.76 (3H, s)] (Table 1). Its ^{13}C NMR and DEPT data indicated 38 carbons (Table 1). The 1D NMR spectra characteristics of the above analysis indicated that **3** belonged to a polyprenylated acylphloroglucinol derivative.

Detailed analysis of its HSQC, HMBC, and $^1\text{H}-^1\text{H}$ COSY spectra indicated that **3** had the same skeleton as that of madeleinal A [33], and the main differences were acyl side chain and isopentenyl side chain (Fig. 2). The HMBC correlations from H_2-14 to C-2,

C-3, and C-4, from H_3-17 to C-15 and C-18, from H_3-32 to C-30, C-31, and C-33, from H_3-33 to C-27, from H_3-37 to C-35 and C-38, combined with the $^1\text{H}-^1\text{H}$ COSY correlations of $\text{H}-27/\text{H}_2-34/\text{H}-35$ and $\text{H}_2-14/\text{H}-15$, suggested the location of the *gem*-dimethyl group, and two isoprenyl groups located at C-3 and C-27, respectively. Furthermore, the *O*-isoprenyl side chain was attached at C-4, which was deduced from the HMBC correlations from H_2-19 to C-4, from H_3-23 to C-20 and C-22, along with the $^1\text{H}-^1\text{H}$ COSY cross-peaks of $\text{H}_2-19/\text{H}-20$, and the downfield chemical shift of C-19 (δ_{C} 71.1). In addition, the benzene ring was attached at C-7 by analysis of its 1D NMR data and the HMBC correlation from H-9 to C-7, and the $^1\text{H}-^1\text{H}$ COSY cross-peaks of H-9/10/H-11/H-12/H-13. In the NOESY spectrum (Fig. 2), the cross-peaks of H-25/H-30, H-27/H-30, and H-30/ H_3-33 indicated that these groups were cofacial, assigned as α -orientations, while H-24 β / H_3-28 , $\text{H}_3-28/\text{H}-29\beta$, and H-29 β / H_3-32 clarified that they were β -oriented. The calculated ECD method was applied to determine its absolute configuration as $25R,26S,27S,30S$ (Fig. 4).

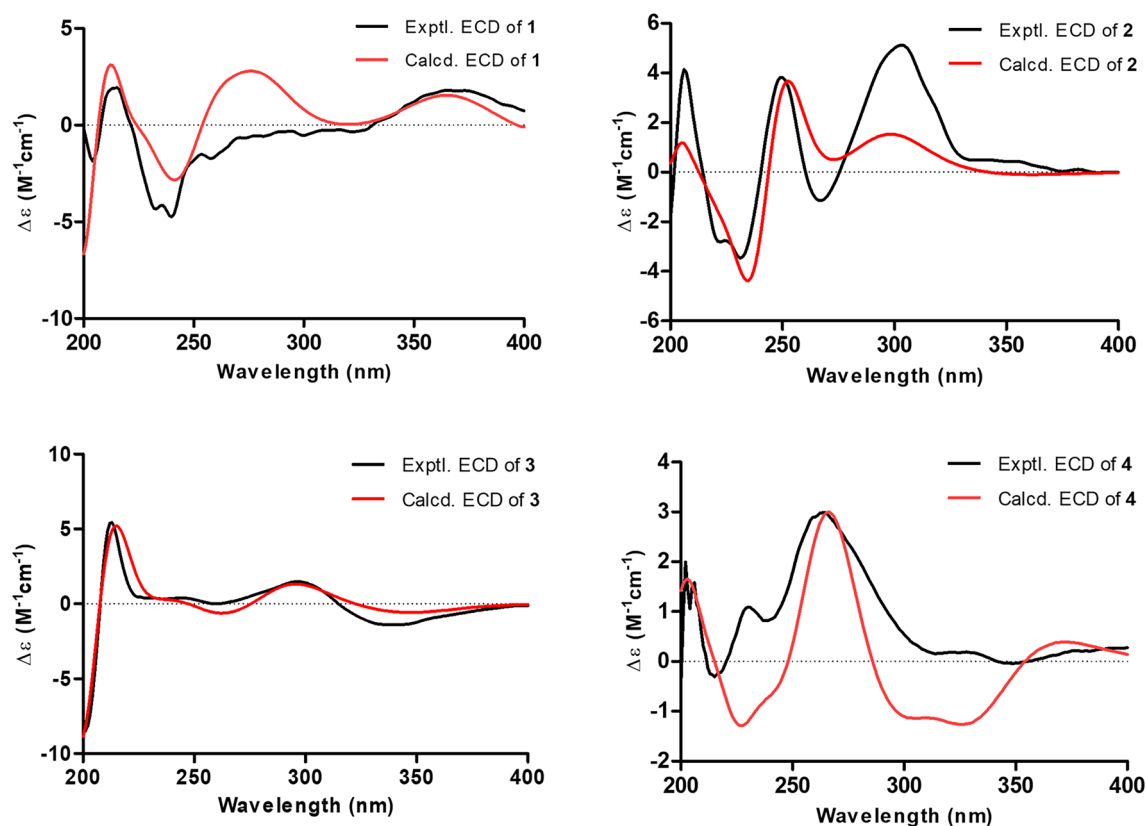


Fig. 4 Experimental and calculated ECD spectra of compounds 1–4

Thus, a unique *O*-prenylated acylphloroglucinol with a 6/6/6 ring system was established.

Hyperisenin D (**4**) was also obtained as a yellow oil and had the molecular formula $C_{33}H_{42}O_6$ based on its HRESIMS at m/z 557.2876 $[M + Na]^+$ (calcd 557.2874), which possessed thirteen degrees of unsaturation. The 1D NMR and HSQC spectra revealed 33 carbons (Table 1), including a benzoyl group [δ_C 193.9, 138.0, 133.5, 129.6 ($\times 2$), 128.5 ($\times 2$)], a geranyl group (δ_C 141.4, 132.1, 123.8, 116.7, 40.1, 36.3, 26.8, 25.9, 17.9, 16.4), two oxidated quaternary carbon (δ_C 72.2, 71.2), two methines (δ_C 93.0, 90.8), two methylenes (δ_C 31.6, 28.0), and four methyl groups (δ_C 27.6, 25.5, 23.8, 23.4), and the remaining six carbons were characteristic of a dearomatized phloroglucinol core including an enolic 1,3-diketone moiety (δ_C 182.3, 175.7, 114.7), one oxygen-bearing ene (δ_C 170.0, 113.3), and one quaternary carbon (δ_C 50.5). The mentioned groups occupied eleven degrees of unsaturation. Two additional rings should be formed in the structure of **4**. Thus, the aforementioned evidence suggested that **4** should be a tricyclic dearomatized prenylated acylphloroglucinol derivative.

The planar structure was confirmed by analyzing its HSQC, HMBC, and 1H - 1H COSY spectra (Fig. 2), similar to that of hypermonin C (**5**) [34], and the main difference was the isoprenyl side chain at C-5. The HMBC correlations from H_2 -19 to C-5, C-6, and C-24, from H_3 -22 to C-20, from H_3 -23 to C-20 and C-21, combined with the 1H - 1H COSY cross-peaks of H_2 -19/ H -20, indicated that the oxidized isopentenyl side chain was located at C-5. Furthermore, the downfield chemical shift of C-20 (δ_C 90.8), combined with degrees of unsaturation, indicated that C-6 and C-20 were connected via an oxygen atom to form a furan ring. In the NOESY spectrum (Fig. 2), the cross-peaks of H_3 -18/ H_3 -27 and H -20/ H_2 -24 indicated that H -20 and the geranyl group at C-5 were on the same side, assigned as β -orientations, while H -15 was on the opposite side with α -orientation. Then, the NOESY cross-peaks of H -25/ H_2 -28 revealed the *E*-configuration of C-25/C-26 double bond. Thus, the relative configuration of **4** was determined to be $5S^*, 15S^*, 20R^*$. Finally, the absolute configuration of **4** was defined as $5S, 15S, 20R$ by ECD calculation (Fig. 4).

Two known compounds, hypermonin C (**5**) [34] and vismiaguanone B (**6**) [35], were obtained from this plant.

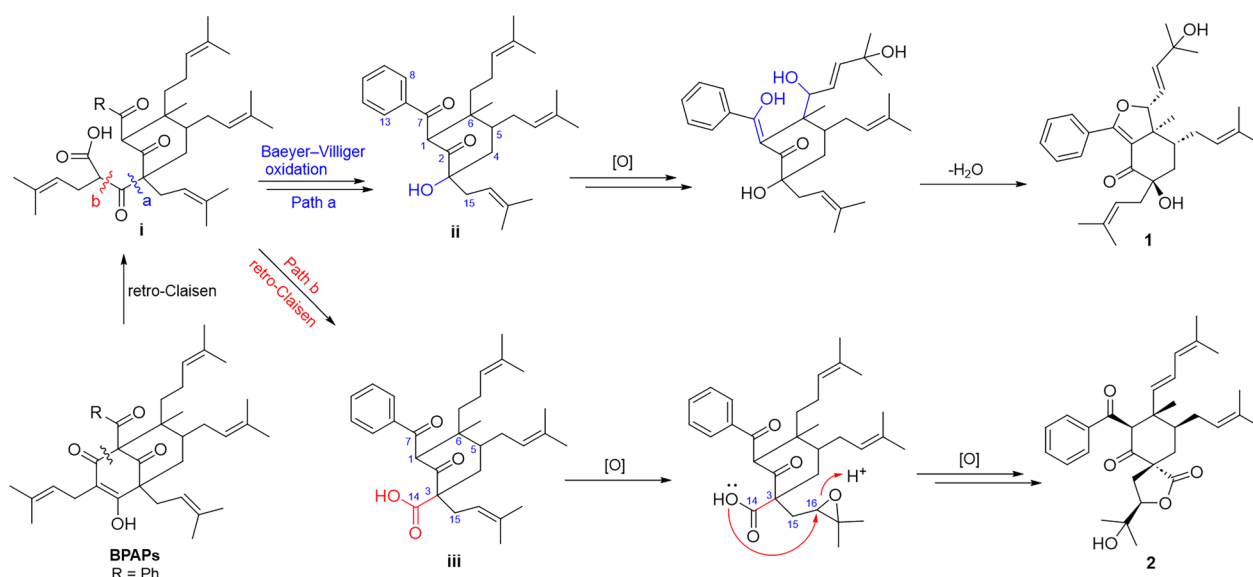


Fig. 5 Plausible biogenetic pathway of compounds **1** and **2**

Their structures were confirmed by comparing the 1D NMR data with those of the literature.

Hyperisensins A (**1**) and B (**2**), possessing a unique cyclohexanone-monocyclic system, were proposed to biogenetically originate from BPAPs (Fig. 5) [28, 36, 37]. It underwent a retro-Claisen reaction to yield the crucial intermediate **i**, followed by two distinct pathways to form intermediates **ii** and **iii**. Subsequently, compound **1** was constructed from **ii** via oxidation, keto–enol tautomerism, and intramolecular cyclization. On the other hand, **iii** underwent oxidation and intramolecular cyclization to obtain compound **2**.

Considering QS is the vital target for antimicrobial therapy [13, 14] and *Pseudomonas aeruginosa* is an opportunistic pathogen that is typically resistant to multiple clinically available antibiotics [38], compounds **1–6** were evaluated for the QS inhibitory activity against *P. aeruginosa* (Figure S46). The results showed that compound **4** was a potential QS inhibitor that decreased the activation of the *rhl* system, as evidenced by the reduced fluorescence density of the reporter strain PAO1-*rhlA-gfp* (Fig. 6A). As expected, compound **4** did not affect the growth of *P. aeruginosa*, consistent with its role as a QS inhibitor. We further examined the production of rhamnolipids, a virulence factor regulated by the *rhl* system, in a clinically isolated carbapenem-resistant *P. aeruginosa* (CRPA) strain. Compound **4** significantly reduced rhamnolipid levels at a concentration of 100 μ M (Fig. 6B). *P. aeruginosa*'s QS system includes two other well-defined pathways apart from the *rhl* system: the *las* and *pqs* systems [8]. Due to the limited yield of compound **4**, its

potential mechanism was explored through molecular docking with three QS receptors (*lasR*, *rhlR*, and *pqsR*).

Unexpectedly, compound **4** failed to dock with *rhlR* but successfully engaged with *lasR* and *pqsR*, demonstrating significant affinity within their ligand-binding pockets. For *lasR*, it is proposed that compound **4** forms two aromatic hydrogen bonds with Tyr47 and a combination of a hydrogen bond and an aromatic bond with Tyr56, yielding a docking score of -6.476 kcal/mol (Fig. 6C). Regarding *pqsR*, compound **4** appears to bind to the ligand-binding site, albeit slightly shifted towards the dimer interface, forming a hydrogen bond with Glu151 in chain A and both a hydrogen bond and an aromatic bond with Glu151 in chain B, resulting in a docking score of -6.217 kcal/mol (Fig. 6D). Given that both the *las* and *pqs* systems enhance the activation of the *rhl* system [8], we hypothesize that the binding of compound **4** to *lasR* and *pqsR* may competitively inhibit their contribution to the *rhl* system, thereby regulating rhamnolipid production (Fig. 6E).

In summary, the phytochemical investigation of the dried aerial parts of *H. seniawinii* Maxim. resulted in the isolation of four undescribed polyprenylated acylphloroglucinols (**1–4**), as well as two known analogs (**5** and **6**). All isolates were obtained from this plant for the first time. Compounds **1** and **2** were two degraded polyprenylated acylphloroglucinols bearing the unique cyclohexanone-monocyclic system, and their plausible biosynthetic pathway was proposed. Furthermore, compound **4** was a potential QS inhibitor that decreased the activation of the *rhl* system and reduced rhamnolipid levels. Its mechanism might be the ability to bind between

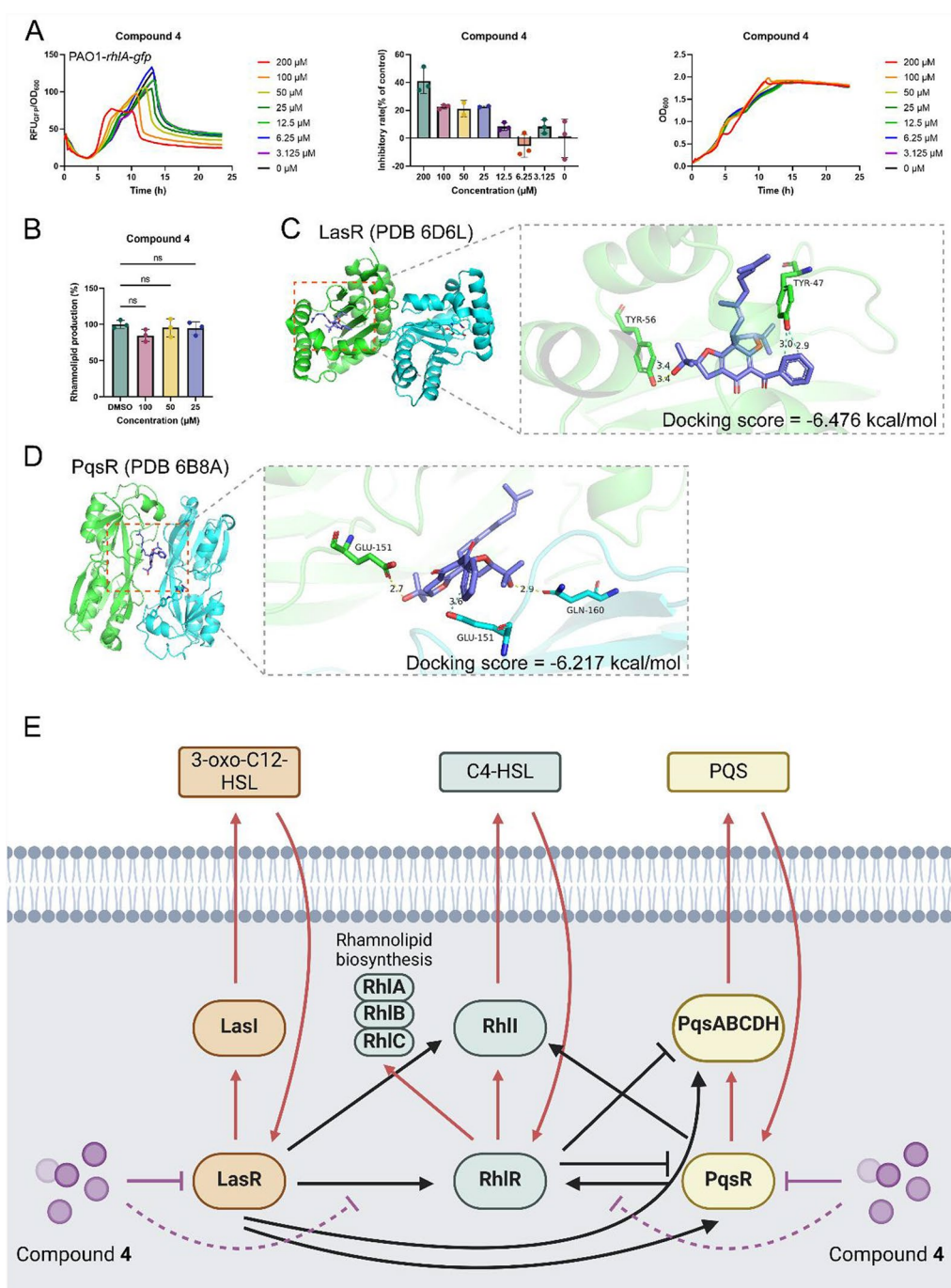


Fig. 6 Compound **4** as a quorum sensing inhibitor against *P. aeruginosa*. **A** Compound **4** inhibited the activation of the *rhl* pathway without affecting bacterial growth. **B** Compound **4** reduced the expression of the virulence factor rhamnolipid in CRPA. **C** Docking results of compound **4** with lasR (PDB 6D6L, colored by chain), depicted as slate sticks. **D** Docking results of compound **4** with pqsR (PDB 6B8A, colored by chain), shown as slate sticks. **E** Proposed mechanism of inhibition by compound **4** against rhamnolipid production, potentially through competitive inhibition of the lasR and pqsR receptors, both of which enhance the activation of the *rhl* system and rhamnolipid production. Data are presented as mean $\pm$ SD ($n=3$). Significance levels are indicated as * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$

4 lasR and pqsR. Our findings might provide a potential candidate as QS inhibitors to treat infectious diseases for further research.

3 Experimental section

3.1 General experimental procedures

Optical rotations were recorded with a PerkinElmer

341 polarimeter (PerkinElmer Inc., Fremont, California, USA). UV spectra were obtained in CH₃OH using a Lambda 35 instrument (PerkinElmer Inc., Fremont, California, USA). ECD spectra in CH₃OH were detected on a JASCO-810 spectrometer (JASCO, Tokyo, Japan). A Bruker Vertex 70 FT-IR spectrophotometer (Bruker, Karlsruhe, Germany) was used to acquire IR spectra. 1D and 2D NMR spectra were collected using Bruker AM-400 and AV-600 spectrometers. HRESIMS data were measured with a Bruker micrOTOF II and Solarix 7.0 spectrometer (Bruker, Karlsruhe, Germany). Analytical HPLC was performed on a Dionex HPLC system with a DAD detector, and semipreparative HPLC was performed on an Agilent 1200 system equipped with a reversed-phase (RP) C₁₈ column (5 μ m, 10 $\times$ 250 mm, Welch Ultimate XB-C₁₈). Column chromatography (CC) including Silica gel (100–200 and 200–300 mesh; Qingdao Marine Chemical Inc., China), ODS (50 μ m, YMC Co. Ltd., Japan), Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden), and MCI gel (75–150 μ m, Merck, Germany) was used to separation and purification of the sample.

3.2 Plant material

The aerial parts of *H. seniawinii* Maxim. were collected from the Shennongjia area in Hubei Province, People's Republic of China. The plants were identified by Prof. C. G. Zhang of Huazhong University of Science and Technology (HUST). A voucher specimen (no. HP20230824) was deposited in the herbarium of Tongji Medical College, HUST.

3.3 Extraction and isolation

The dried aerial parts of *H. seniawinii* Maxim. (20.0 kg) were powered and extracted with 95% EtOH (3 $\times$ 25 L) at room temperature, removing the solvents in *vacuo* to yield the crude extract (0.4 kg). The crude extract was then suspended in water and successively partitioned with CH₂Cl₂ and EtOAc. The CH₂Cl₂ extract was separated into seven fractions (A–G) by a silica gel CC (100–200 mesh), eluted with a gradient of petroleum ether–ethyl acetate (80:1–0:1). Fr. E was subsequently further chromatographed on an RP-C₁₈ column (CH₃OH–H₂O, 50:50 to 100:0) to yield eight subfractions, E3a–E3h. Fr. E3b (1.0 g) was applied to Sephadex LH-20 (CH₃OH), obtaining three subfractions, Fr. E3b1–E3b3. Fr. E3b2 (500 mg) was then purified on semipreparative HPLC to afford **2** (3.3 mg, t_R 19 min, CH₃OH–H₂O, 91:9, v/v, 2 mL/min), and **6** (3.6 mg, t_R 27 min, CH₃OH–H₂O, 80:20, v/v, 2 mL/min). Fr. E3c (1.2 g) was conducted

on Sephadex LH-20 (CH₃OH) and further purified by semi-preparative HPLC to afford **1** (7.5 mg, t_R 15 min, CH₃OH–H₂O, 88:12, v/v, 2 mL/min), **4** (1.7 mg, t_R 45 min, CH₃OH–H₂O, 77:23, v/v, 2 mL/min), and **5** (6.0 mg, t_R 12 min, CH₃OH–H₂O, 97:3, v/v, 2 mL/min). Compound **3** was isolated from Fr. E3e by silica gel CC (100–200 mesh), Sephadex LH-20 (CH₃OH), and HPLC (2.4 mg, t_R 32 min, CH₃OH–H₂O, 94:6, v/v, 2 mL/min).

Hyperisenin A (**1**): Colorless oil; $[\alpha]_D^{29} +42.0$ (c 0.1, CH₃OH); UV (CH₃OH) λ_{max} (log ϵ) = 201 (4.40) nm, 231 (4.06), 321 (3.77); IR (KBr) ν_{max} 3424, 2973, 2929, 2873, 1721, 1634, 1603, 1553, 1490, 1449, 1382, 1363, 1328, 1233, 1180, 1148, 1066, 1027, 974, 838, 761, 694 cm^{−1}; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$) 215 (+1.95), 241 (−4.60), 365 (+1.81) nm. ¹H and ¹³C NMR data see Table 1; positive HRESIMS: m/z 487.2802 [M+Na]⁺ (calcd. for C₃₀H₄₀O₄Na⁺, 487.2819).

Hyperisenin B (**2**): Colorless oil; $[\alpha]_D^{29} +48.8$ (c 0.3, CH₃OH); UV (CH₃OH) λ_{max} (log ϵ) = 201 (4.49), 240 (4.28) nm; IR (KBr) ν_{max} 3458, 2972, 2928, 1756, 1715, 1597, 1447, 1383, 1226, 1180, 988, 690 cm^{−1}; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$) 206 (+4.15), 231 (−3.45), 249 (+3.83), 267 (−1.15), 303 (+5.13) nm. ¹H and ¹³C NMR data, see Table 1; positive HRESIMS: m/z 515.2753 [M+Na]⁺ (calcd for C₃₁H₄₀O₅Na⁺, 515.2768).

Hyperisenin C (**3**): Yellow oil; $[\alpha]_D^{29} +33.0$ (c 0.4, CH₃OH); UV (CH₃OH) λ_{max} (log ϵ) = 205 (4.29) nm; IR (KBr) ν_{max} 3409, 2970, 2927, 2874, 1722, 1666, 1603, 1449, 1418, 1382, 1326, 1292, 1219, 1123, 1106, 1074, 1019, 955 cm^{−1}; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$) 213 (+5.45), 260 (+0.02), 296 (+1.48), 340 (−1.39) nm. ¹H and ¹³C NMR data; positive HRESIMS: m/z 609.3572 [M+Na]⁺ (calcd. for C₃₈H₅₀O₅Na⁺, 609.3550).

Hyperisenin D (**4**): Yellow oil; $[\alpha]_D^{29} +22.1$ (c 0.1, CH₃OH); UV (CH₃OH) λ_{max} (log ϵ) = 202 (4.60) nm; IR (KBr) ν_{max} 3429, 2973, 2927, 2854, 1715, 1668, 1618, 1449, 1412, 1384, 1237, 1175, 1027, 961 cm^{−1}; ECD (CH₃OH) λ_{max} ($\Delta\epsilon$) 206 (+1.58), 215 (−0.31), 264 (+2.99), 349 (−0.04) nm. ¹H and ¹³C NMR data; positive HRESIMS: m/z 557.2876 [M+Na]⁺ (calcd. for C₃₃H₄₂O₆Na⁺, 557.2874).

3.4 NMR and ECD calculations

The details of NMR and ECD calculations were put in the Supporting Information (SI).

3.5 Strains and culture conditions

The GFP reporter strains were provided by Prof. Pinghua Sun from Jinan University and were cultured in Luria–Bertani (LB) medium (1% w/v NaCl, 1% w/v tryptone,

and 0.5% w/v yeast extract) supplemented with 100 µg/mL ampicillin and 20 µg/mL gentamicin at 37 °C. The CRPA strain was provided by Prof. Yan He from Tongji Hospital at Huazhong University of Science and Technology and cultured in LB medium at 37 °C.

3.6 Screening for QS inhibitors

GFP reporter strains were cultured overnight in LB medium supplemented with 100 µg/mL ampicillin and 20 µg/mL gentamicin at 37 °C. The cultures were then diluted 1:5 in ABTGC medium (2 g/L (NH₄)₂SO₄, 6 g/L Na₂HPO₄, 3 g/L NaCl, 1 mM MgCl₂, 0.1 mM CaCl₂, 0.01 mM FeCl₃, 0.025% thiamine, 0.5% glucose, 0.5% casamino acids). For the assay, 100 µL of either a 200 µM solution of the compound for high-throughput screening or gradient-diluted concentrations for secondary confirmation, or an equivalent volume of DMSO, was mixed with the diluted GFP reporter strain (100 µL). This mixture was transferred to a 96-well plate (200 µL per well) and incubated at 37 °C. A microplate reader continuously monitored bacterial growth at OD₆₀₀ and GFP fluorescence (excitation at 485 nm, emission at 535 nm) every 15 min for approximately 24 h.

3.7 Determination of virulence factor production

CRPA was cultured overnight in LB medium at 37 °C and then 1:10 in ABTGC medium successively. A 100 µL volume of either gradient-diluted compound or an equivalent volume of DMSO was combined with the diluted CRPA (100 µL). This mixture was incubated for 24 h at 37 °C with agitation at 200 rpm in a 96-well plate (200 µL per well). The OD₆₀₀ of the culture was measured to normalize the virulence factor content. Virulence factors were then extracted from the supernatant after centrifugation at 4000 rpm for 15 min. Rhamnolipids were extracted with a three-fold volume of ethyl acetate three times. The ethyl acetate fraction was evaporated and redissolved in a freshly prepared reagent (0.19% orcinol in 60% H₂SO₄, 900 µL), incubated at 80 °C for 30 min, and then the solution (200 µL) was used to quantify rhamnolipid levels at OD₄₂₁ after cooling to room temperature.

3.8 Molecular docking

Molecular docking was performed using Schrödinger Maestro (Schrödinger Release 2023–1: Maestro, Schrödinger, LLC, New York, NY, 2023). Protein models were sourced from the Protein Data Bank (PDB) and prepared via the Protein Preparation Workflow module. Compound structures were pre-processed using the Lig-Prep module. Interactions and alignments were visualized and analyzed using PyMOL software.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s13659-025-00520-z>.

Supplementary material 1.

Author contributions

Yonghui Zhang and Changxing Qi designed the experiments and revised the manuscript. Weiguang Sun and Guosheng Cao guided the experiments and wrote the manuscript. Yulin Duan contributed to the extraction, isolation, identification, and manuscript preparation. Xiaoxia Gu and Xincui Hao contributed to the bioactivity evaluation. All authors read and approved the final submission.

Funding

This work was financially supported by the National Key Research and Development Program of China (2021YFA0910500); National Natural Science Foundation of China (Nos. 32470422 and 32300335); the National Natural Science Foundation of Hubei Province (2023AFB791 and 2023AFB530); Knowledge Innovation Project of Wuhan Science and Technology Bureau (2023020201020534); Natural Science Foundation of Wuhan (2024040801020205); the Science and Technology Major Project of Hubei Province (2021ACA012); the National Key Research and Development Program (No.2023YFC2307004); the open foundation of Key Laboratory of Ethnomedicine (Minzu University of China), Ministry of Education (No. KLEM-KF202402); the open foundation of Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education (RDZH2024001); the open foundation of Hubei Key Laboratory of Wudang Local Chinese Medicine Research (Hubei University of Medicine) (WDCM2024002); the Fundamental Research Funds for the Central Universities (HUST: 2023JYCXJJ058).

Data availability

The data that support the findings of this study are openly available in the Science Data Bank at.

Declarations

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Received: 6 March 2025 Accepted: 13 May 2025

Published online: 19 June 2025

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