Two New Naphthoquinone Derivatives from *Lysionotus pauciflorus*

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Two new naphthoquinones, (2*R*)-6,8-dihydroxy-α-dunnione (**1**), 6,8-dihydroxy-2,7-dimethoxy-3-(1,1-dimethylprop-2-enyl)-1,4-naphthoquinone (**2**), together with three known compounds, (2*R*)-6,8-dihydroxy-7-methoxy-α-dunnione (**3**), nevadensin (**4**), and lysioside C (**5**), were isolated from the whole plant of *Lysionotus pauciflorus*. Their structures were established by spectroscopic methods. Hydroxylated naphthoquinones are reported to occur in a *Lysionotus* species for the first time. The cytotoxic activities of compounds **1**–**3** were evaluated *in vitro* against a panel of tumor cell lines.

Introduction. – *Lysionotus pauciflorus* MAXIM (Gesneriaceae) is widespread around south China and was used as a traditional Chinese medicine (Chinese name '*Shi Diao Lan*') for the treatment of lymph node tuberculosis, cough with tachypnoea, rheumatic pains, and cancer [1]. Several compound classes, such as flavonoids, phenolic derivatives, β-sitosterol, and daucosterol, as well as ursolic acid [2–5], were detected in this plant. One of the major flavones, nevadensin, was reported to possess antituberculosis, anti-inflammatory, and antitussive activities [6–9]. Therefore, as part of our ongoing search for new anticancer and antimicrobial drugs or leads from traditional Chinese medicines, we investigated the whole plant of *L. pauciflorus*, and the results are presented herein.

Results and Discussion. – The dried plant material of *L. pauciflorus* was extracted with EtOH. After removing the organic solvent, the resulting extract was subjected to a series of separation steps, including liquid–liquid partition, and a number of normal- and reversed-phase chromatographic techniques. Two new naphthoquinones, 6,8-dihydroxy-α-dunnione (**1**) and 6,8-dihydroxy-2,7-dimethoxy-3-(1,1-dimethylprop-2-enyl)-1,4-naphthoquinone (**2**), were isolated and identified, along with the known compounds, α-dunnione (**3**), nevadensin (**4**), and lysioside C (**5**). Structures of the isolated compounds are presented in *Fig. 1*. The structures of the new compounds were elucidated by using a range of spectroscopic techniques, including 1D- and 2D-NMR spectroscopy and high-resolution time-of-flight mass spectrometry (HR-TOF-MS). In the case of the known compounds, their structures were identified by comparison of their spectroscopic data with those in the literature. This is the first time that hydroxylated naphthoquinones were found in *Lysionotus* species. The cytotoxic activities of compounds **1**–**3** against seven tumor cell lines were also evaluated.

Compound **1** was obtained as a purple, amorphous solid. Its positive-ion HR-TOF-MS exhibited a quasi-molecular-ion peak at *m*/*z* 297.0736 ($[M + Na]^+$; calc. 297.0739),

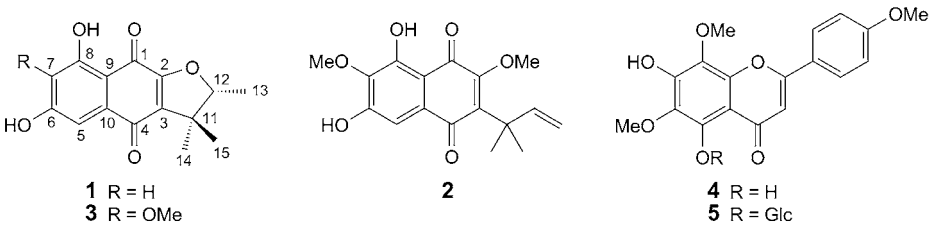

Fig. 1. *Chemical structures of compounds* **1**–**5**

indicating the molecular formula $C_{15}H_{14}O_5$, which corresponded to nine double bond (or ring) equivalents. The ^{1}H-NMR spectrum exhibited three Me signals at δ(H) 1.25 (*s*), 1.41 (*d*, $J = 6.8$), and 1.43 (*s*) (indicative of an α-dunnione derivative) [10]. In the aromatic region of the ^{1}H-NMR spectrum, only two aromatic signals were observed. Both of them resonated as *meta*-coupled *doublet*s (δ(H) 6.51 (*d*, $J = 2.4$) and 7.05 (*d*, $J = 2.4$)), suggesting a disubstituted derivative. The upfield shift of both of the aromatic C–H signals supported the presence of two oxygenated substituents on the aromatic ring. Analysis of the ^{13}C-NMR spectrum showed compound **1** to contain 15 C-atoms (*Table 1*), indicating the presence of the two C=O and the two aromatic OH groups. From further HMBC experiments, not only the quinone moiety was established, but also the presence of a furan ring was confirmed (*Fig. 1*).

HMB Correlations from two Me signals at δ(H) 1.43 (Me(14)) and 1.25 (Me(15)) to those of C(12) (δ(C) 91.4) and C(11) (δ(C) 44.8), and to each other's C-atom resonance established dimethyl substitution at C(11) (*Fig. 2*). These Me group signals also showed correlations to that of a quaternary C-atom (δ(C) 130.2), which could be assigned as C(3), thereby defining the furan ring system. The H-atom signal at δ(H) 7.05 correlated directly with that of the C-atom at δ(C) 106.0, and it further showed a strong correlation with the C(4)=O signal (δ(C) 181.0) in the HMBC spectrum, facilitating to locate this H-atom at C(5) in the molecule. This H-atom also showed connectivity to a quaternary C-atom with the signal at δ(C) 136.1, allowing this C-atom to be assigned as C(10). An additional HMBC from this H-atom signal to an oxygenated C-atom signal at δ(C) 166.0 was also observed, evidencing the presence of one OH group at C(6) of the aromatic ring. Furthermore, since the H-atom (δ(H) 6.51 (d, $J = 2.4$) at C(7) is *meta*-coupled, another OH group could be assigned to C(8). All of the above evidences identified the isolate as 6,8-dihydroxy-α-dunnione (**1**). Full

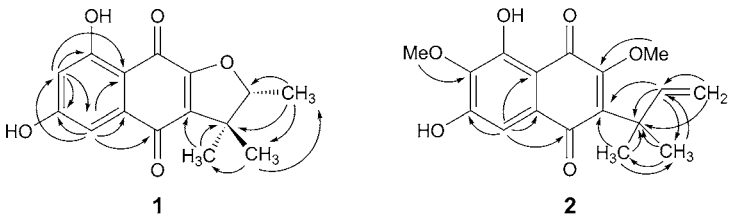

Fig. 2. *Key HMBCs* (H → C) *of compounds* **1** *and* **2**

Table 1. *^{1}H- and ^{13}C-NMR* (at 400 and 100 MHz, resp., in $(CD_3)_2CO$) *Data of Compounds* **1** *and* **2**. δ in ppm, J in Hz.

Position	**1**			**2**			
	δ(H)	δ(C)	HMBC	δ(H)	δ(C)	HMBC	NOESY
1		180.8			184.7		
2		159.3			157.7		
3		130.2			142.0		
4		181.0			184.8		
5	7.05 (d, J = 2.4)	108.8	4, 6, 7, 9, 10	7.01 (s)	108.8	4,6,7, 9,10	
6		166.0			158.0		
7	6.51 (d, J = 2.4)	106.0	1, 5, 6, 8		138.0		
8		164.5			154.3		
9		108.3			108.7		
10		136.1			129.0		
11		44.8			40.9		
12	4.61 (q, J = 6.8)	91.4	14, 15	6.21 (dd, J = 7.6, 11.6)	148.7	3,11,14,15	14, 15, 13a
13	1.41 (d, J = 6.8)	13.6	11, 12, 15	4.92 (d, J = 11.6, H_a), 4.84 (d, J = 7.6, H_b)	107.6	11, 12	11, 12
14	1.43 (s)	25.1	3, 11, 12, 15	1.48 (s)	27.7	3, 11, 12, 15	2-MeO, 12, 13b
15	1.25 (s)	19.7	3, 11, 12, 14, 15	1.48 (s)	27.7	3, 11, 12, 14	2-MeO, 12, 13b
7-MeO				3.91 (s)	59.8	7	
2-MeO				3.95 (s)	60.8	2	

assignments of ^{1}H- and ^{13}C-NMR of **1** were thus obtained by the 2D-NMR spectra (*Table 1*).

Compound **2** was obtained as a purple, amorphous solid, whose molecular formula was deduced as $C_{17}H_{18}O_6$ by HR-TOF-MS (*m/z* 317.1024 ($[M-H]^-$; calc. 317.1025) with nine degrees of unsaturation. The ^{13}C-NMR spectrum of **2** showed 17 resonances, two belong to Me, one to CH_2, two to MeO, and two to CH groups, and ten to quaternary C-atoms from its DEPT data. Two signals, at δ(C) 184.8 and 184.7, were assigned to aromatic C=O groups, and four of the C-atoms in the molecule were bound to O-atoms because of the upfield shift of signals. The UV spectrum of **2** and the presence of the signals of two C=O groups (δ(C) 184.7, 184.8) in its ^{13}C-NMR spectrum accounted for its naphthoquinone structure, while two MeO signals (δ(H) 3.91, 3.95) and those of a *C*-linked α,α-dimethylallyl chain (δ(H) 1.48 (*s*, 6 H), 6.21 (*dd*, $J = 7.6$, 11.6, 1 H), 4.92 (*d*, $J = 11.6$, 1 H), and 4.84 (*d*, $J = 7.6$, 1 H)) were also evident in the ^{1}H-NMR spectrum. The aromatic region of the ^{1}H-NMR spectrum exhibited one aromatic H-atom signal at δ(H) 7.01 as a *singlet*, suggesting a trisubstituted aromatic system. The positions of two MeO substituents were determined by the HMBC experiment. In the HMBC spectra, the correlations between the signals at δ(H) 3.95 and δ(C) 157.7 (C(2)), and δ(H) 3.91 and δ(C) 138.0 (C(7)) located the MeO groups at C(2) and C(7), respectively. The H-atom with the signal at δ(H) 7.01 was found to be attached to the C-atom with the signal at δ(C) 108.8 from the HSQC spectrum; this C-atom signal had been shifted upfield in the ^{13}C-NMR spectrum, suggesting this H-atom to be adjacent to the oxygenated substituent. The H-atom also showed a significant correlation with the C=O group (δ(C) 184.8) in the HMBC spectrum, locating the uncoupled H-atom at C(5) beside the C(4)=O. This H–C(5) showed also a correlation to a quaternary C-atom with the signal at δ(C) 129.0, which was assigned as C(10). A weak correlation was also observed between H–C(5) and the oxygenated C-atom resonating at δ(C) 154.3, which was assigned to C(6). The ^{13}C-NMR of **2** contained signals of 17 C-atoms, including two Me signals at δ(C) 27.7, and two upfield-shifted Me signals at δ(C) 59.8 and 60.8, which were attributed to two MeO substituents. Furthermore, the attachment of the side chain to the naphthoquinone ring system was established by HMBCs from Me(14,15) (δ(H) 1.48) to both C(11) (δ(C) 40.9) and a quaternary C-atom, C(3) (δ(C) 142.0), furthermore confirmed by NOE correlations from Me(14,15) (δ(H) 1.48), H–C(12) (δ(H) 6.21) with the signal at δ(H) 3.95 (MeO–C(2)) observed in a complementary NOESY experiment.

To date, only five 1,4-naphthoquinone derivatives bearing a 1,1-dimethylprop-2-enyl moiety have been reported. Two of them were obtained from slipper plant, *Calceolaria andina,* by *Chamy et al.* [11]. The others are synthetic products [12][13]. This is the first report of a hydroxylated 1,4-naphthoquinone derivative with a 1,1-dimethylprop-2-enyl side chain from *Lysionotus* species.

Compound **3** possessed the molecular formula $C_{16}H_{16}O_6$ according to its HR-TOF-MS (*m/z* 327.0850 ($[M + Na]^+$; calc. 327.0845)). The ^{1}H- and ^{13}C-NMR spectra of **3** showed the characteristics of those of **1** with the exception of an additional MeO group. The structure of compound **3** was elucidated as 6,8-dihydroxy-7-methoxy-α-dunnione by comparison of its ^{1}H- and ^{13}C-NMR data with those in the literature [14].

The specific optical rotation value of **1** was $+136.9°$, which further suggested the absolute configuration (2*R*) of **1** according to the X-ray-diffraction analysis of the (4-

bromophenyl)hydrazone derivative of (2*R*)-α-dunnione [15]. The optical rotation values of **1** and **3** were $+136.9°$ and $+287.3°$, respectively, indicating that they had the same configuration. Thus isolates **1** and **3** were defined as (2*R*)-6,8-dihydroxy-α-dunnione and (2*R*)-6,8-dihydroxy-7-methoxy-α-dunnione, respectively.

On the other hand, the structures of compounds **4** and **5** were identified by spectroscopic methods and comparison with literature data as 5,7-hydroxy-4′,6,8-trimethoxyflavone (nevadensin) [5a] and 7-hydroxy-4′,6,8-trimethoxyflavone-5-*O*-β-D-glucopyranoside (lysioside C) [3a][5a], respectively.

Compound **1** and **2** are new naphthoquinone derivatives determined in this study. This is also the first report on the isolation of hydroxylated naphthoquinone derivatives from *Lysionotus* species. It is interesting to note that three of the isolates, **1**–**3**, are prenylated 1,4-naphthoquinone derivatives: the result of our investigation is thus in entire consistency with their biosynthetic pathway [16].

Cytotoxic activities of **1**–**3** were evaluated *in vitro* against seven human cancer cell lines (A549, lung cancer; MCF-7, breast cancer; BEL-7402, hepatoma; HeLa, cervix adenocarcinoma; COLO205, colon cancer; BGC-823, gastric cancer; SK-OV-3, ovarian adenocarcinoma). The results (*Table 2*) indicated that compound **3** showed a weak inhibitory effect on all of the cell lines tested, while compound **1** exhibited slight cytotoxicities against A549, MCF-7, HeLa, and no activity toward the others.

Table 2. *Inhibition Rate of Compounds* **1**–**3** *against Cell Lines*[a])

Cell line	Final concentration [M]	**1**	**2**	**3**	Adriamycin[b])
A549	0.001	91.79 ± 0.41	88.82 ± 0.05	89.29 ± 0.001	0.66
	0.0001	64.06 ± 1.51	5.43 ± 3.00	75.36 ± 0.76	
	0.00001	0	0	0	
MCF-7	0.001	96.26 ± 0.04	91.12 ± 0.37	95.36 ± 0.08	0.45
	0.0001	57.70 ± 1.08	5.16 ± 0.22	95.43 ± 0.20	
	0.00001	0	0	8.64 ± 1.29	
BEL-7402	0.001	85.95 ± 0.31	86.41 ± 0.23	80.24 ± 0.11	0.26
	0.0001	9.49 ± 0.90	61.30 ± 0.19	68.40 ± 0.78	
	0.00001	0	0	1.02 ± 1.00	
HeLa	0.001	94.74 ± 1.45	96.12 ± 3.48	96.96 ± 1.18	0.66
	0.0001	25.28 ± 8.72	59.93 ± 12.90	45.19 ± 17.53	
	0.00001	0	0	0	
COLO205	0.001	90.76 ± 0.18	60.17 ± 7.86	78.12 ± 0.20	1.67
	0.0001	5.83	0	62.15 ± 6.58	
	0.00001	0.275	0	0	
BGC-823	0.001	93.86 ± 4.98	95.96 ± 3.10	94.86 ± 2.70	0.58
	0.0001	52.64 ± 6.62	54.42 ± 2.09	73.34 ± 0.48	
	0.00001	8.60 ± 3.58	7.95 ± 5.33	9.90 ± 2.78	
SK-OV-3	0.001	79.05 ± 15.30	96.64 ± 1.27	94.00 ± 3.40	0.62
	0.0001	15.95 ± 11.13	27.66 ± 16.41	20.84 ± 10.24	
	0.00001	0	0	0	

[a]) Samples dissolved in DMSO. [b]) Positive control; IC_{50} [μM].

Compound **2** showed weak inhibition only on BEL-7402 and HeLa cell lines with a comparatively low inhibition rate of *ca.* 60%.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 200–300 mesh; *Qingdao Marine Chemical Inc.*), *Sephadex LH-20* (25–100 μm; *Amersham Pharmacia, Sweden*), *Toyopearl HW-40F* gel (*TOSOH*, Japan), and *MCI* resin *CHP-20P* (*Mitisubishi Kasei Industry Co Ltd*, Japan). TLC: SiO_2 GF_{254} precoated plates (*Qingdao Marine Chemical Inc.*), UV detection at 254 and 365 nm, and spraying with 10% H_2SO_4 in EtOH, followed by heating. Optical rotations: *WZZ-3* polarimeter (*Shanghai Shenguang Co.*, Shanghai, China) at 25°. UV Spectra: *UV-2100* spectrophotometer (*Rayleigh Co.*, Beijing, China); λ_{max} (log ε) in nm. CD Spectra: *Chirascan* spectropolarimeter (*Applied Photophysics Limited Spectroscopic*, UK) in MeOH at 25°. NMR Spectra: *Bruker AM-400* spectrometers; in (D_6)acetone; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-TOF-MS: A *Q-Tof Premier* coupled with an ESI source (*Micromass*, *Simonsway*, Manchester, UK); in m/z.

Plant Material. The whole plants of *L. pauciflorus* were purchased in May 2010 from a local herbal medicine store (Chengdu, Sichuan Province, China) and identified by *Y.-F. L.* A voucher specimen (D201002) was deposited with the Department of Pharmaceutics and Bioengineering, Sichuan University, Chengdu, China.

Extraction and Isolation. The air-dried whole plants (5.0 kg) of *L. pauciflorus* were ground and then extracted four times with 95% EtOH (25 l) at r.t. for 3 d. The combined extracts were concentrated under reduced pressure to afford a dark brown residue (387 g). This residue was suspended in dist. H_2O (2 l) and partitioned successively with petroleum ether (PE; 60–90°, 5 × 1.2 l), AcOEt (5 × 1.2 l), and BuOH (3 × 1.2 l). After evaporation, the AcOEt-soluble fraction (44 g) was subjected to CC (silica gel (160 g, 200–300 mesh, 50 × 470 mm); PE/acetone 100:1 → 1:5) to afford 10 fractions, *Frs. A–J*, on the basis of TLC analysis for further isolation. *Fr. B* (900 mg) was submitted to CC (*MCI* (18 × 320 mm); acetone/H_2O 1:1 → 1:0) and six fractions, *Frs. B1–B6*, were collected. *Fr. B3* (95 mg) was further purified by CC (*Toyopearl HW-40* (11 × 530 mm); CH_2Cl_2/MeOH 1:1); followed by prep. TLC to give **1** (9.9 mg) and **3** (6 mg). *Fr. B5* (98 mg) eluted with 70% acetone was subjected to CC (*Sephadex LH-20* (18 × 920 mm); CH_2Cl_2/MeOH 1:1) to afford three subfractions *Frs. B5a–B5c*. While *Fr. B5a* (138 mg) was further subjected to CC *Toyopearl HW-40F* (11 × 530 mm), CH_2Cl_2/MeOH 1:1) to provide **2** (19 mg), *Fr. C* (1.9 g) was purified by CC (MCI (18 × 320 mm); acetone/H_2O 1:1 → 1:0) to furnish five fractions, *Frs. C1–C5*). Petroleum ether (PE) was dropwise added after *Fr. C5* (1.2 g) was dissolved with a small amount of acetone for recrystallization; after *ca.* 2 d yellow crystals of **4** (20 mg) precipitated. *Fr. D* (7.4 g) was subjected to CC (SiO_2 (60 g, 200–300 mesh, 62 × 290 mm); CH_2Cl_2/MeOH 50:1 → 0:1) to afford eight fractions, *Frs. D1–D8*. *Fr. D3* (1.49 g) was further purified by CC (Sephadex LH-20 (18 × 920 mm); CH_2Cl_2/MeOH 5:1; then *MCI* (18 × 320 mm); acetone/H_2O 3:7 → 1:0) to afford **5** (555 mg).

*(2*R*)-6,8-Dihydroxy-α-dunnione* (=*(2*R*)-6,8-Dihydroxy-2,3,3-trimethyl-2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione*; **1**). Purple, amorphous solid. $[\alpha]_D^{20}$ +136.9 (c = 1.23, MeOH). UV (MeOH): 215 (3.74), 267 (3.44), 324 (3.39). CD (MeOH, c = 0.40): 213, 261, 320, 394 ($\Delta\varepsilon$ +4.56, −1.54, −4.09, +0.28). ^{1}H- and ^{13}C-NMR: see *Table 1*. HR-TOF-MS: 297.0736 ($[M+Na]^+$, $C_{15}H_{14}NaO_5^+$; calc. 297.0739).

6,8-Dihydroxy-2,7-dimethoxy-3-(1,1-dimethylprop-2-enyl)-1,4-naphthoquinone (=*5,7-Dihydroxy-3,6-dimethoxy-2-(1,1-dimethylprop-2-enyl)naphthalene-1,4-dione*; **2**). Purple, amorphous solid. UV (MeOH): 219 (3.77), 270 (3.63), 296 (3.39), 420 (2.95). ^{1}H- and ^{13}C-NMR: see *Table 1*. HR-TOF-MS: 317.1024 ($[M-H]^-$, $C_{17}H_{17}O_6^-$; calc. 317.1025).

Cytotoxicity Assay. The *in vitro* cytotoxicities of the three naphthoquinones against human cancer cell lines (BEL-7402, COLO-205, Hela, MCF-7, A549, BGC-823, and SK-OV-3) were determined by a sulforhodamine B (SRB) bioassay on 96-well microplates as described in [17]. Briefly, cells were plated

at 90 µl per well in 96-well microplates and incubated for 24 h. Different concentrations of the compounds were added at 10-µl per well, while to some wells only physiological saline at corresponding concentration as background wells was added. After incubating for 48 h, cells fixed by TCA were eluted with dist. H_2O (5 ×) before natural drying, then dyed by SRB, followed by eluting with AcOH. Finally, OD value was read on a *SYNERYTM 4* multi-mode microplate reader (*BioTek Instrument Inc.*, USA) at 570 nm. In the course of our work, adriamycin served as positive control, whose activity was expressed as IC_{50} values (50% inhibition of cell proliferation; mg/ml) calculated by SPSS 16.0. Inhibition rate of compounds **1**–**3** at different final concentrations were calculated according to the following formula.

Inhibition rate = [(OD of the control group) – (OD of the sample)]/(OD of the control group) × 100%

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