A Guaianolide Sesquiterpene, a Chromenone, and a Flavanone from *Ligularia macrophylla*

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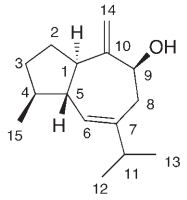
Three new compounds, (5*β*,9*β*)-guaia-6,10(14)-dien-9-ol (= rel-(1*R*,3a*S*,5*R*,8a*R*)-1,2,3,3a,4,5,6,8a-octahydro-1-methyl-4-methylene-7-(1-methylethyl)azulen-5-ol; **1**), 6-acetyl-8-methoxy-2,3-dimethylchromen-4-one (=6-acetyl-8-methoxy-2,3-dimethyl-4*H*-1-benzopyran-4-one; **2**), and (2*S*)-3′-hydroxy-5′,7-dimethoxyflavanone (=(2*S*)-2,3-dihydro-2-(3-hydroxy-5-methoxyphenyl)-7-methoxy-4*H*-1-benzopyran-4-one; **3**) were isolated from the roots and rhizomes of *Ligularia macrophylla*, together with seven known compounds. Their structures and configurations were elucidated by spectroscopic methods, including 2D-NMR techniques.

Introduction. – Much attention has been focused on the *Ligularia* (Asteraceae) plants for the long history of use as folk remedies and the abundant sesquiterpenes distributed in this genus. The roots and rhizomes of *Ligularia macrophylla* (LEDEB.) DC. are used as a Chinese folk medicine for the treatment of tracheitis, phthisis, hemoptysis, cough, and asthma [1]. In the previous reports, fatty acids, polyenes, pyrrolizidine alkaloids, and eremophilane sesquiterpenes have been isolated [2–4]. Our preliminary study showed that the AcOEt-soluble fraction from an EtOH extract of the roots and rhizomes of *L. macrophylla*, a plant growing in the Tianshan mountains of China, exhibited cytotoxic activity against human breast adenocarcinoma cells (MCF-7) *in vitro*. This prompted us to investigate its chemical constituents. The phytochemical study led to the isolation and characterization of three new compounds **1**–**3**, together with seven known ones; however, no isolate showed cytotoxicity (EC_{50} > 20 μg/ml). This paper deals with the isolation and structural elucidation of the three new compounds **1**–**3**.



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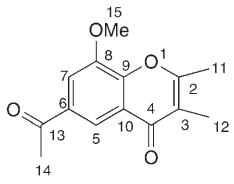

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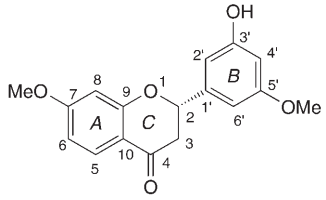

3[1])

[1]) Trivial or arbitrary numbering; for systematic names, see *Exper. Part.*

Results and Discussion. – Repeated column chromatography of the AcOEt extract of the roots and rhizomes of *Ligularia macrophylla* yielded compounds **1**–**3** and seven known compounds.

Compound **1** was obtained as a colorless gum. It had the molecular formula $C_{15}H_{24}O$ with four degrees of unsaturation, as determined by HR-EI-MS (*m*/*z* 220.1833). The structure of **1** was established by the ^{1}H- and ^{13}C-NMR (*Table*), ^{1}H,^{1}H-COSY and HMBC (*Fig. 1*), and ROESY data (*Fig. 2*) (5*β*,9*β*)-guaia-6,10(14)-dien-9-ol[1]).

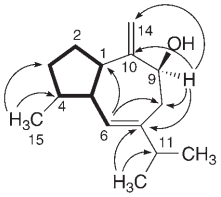

Fig. 1. *Key ^{1}H,^{1}H-COSY* (▬) *and HMBC* (H → C) *correlations in* **1**[1])

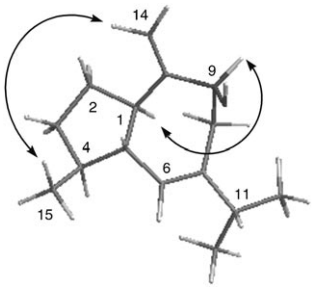

Fig. 2. *Key ROESY correlations in* **1**[1])

Table. *^{1}H- and ^{13}C-NMR Data* (400 and 100 MHz, resp., $CDCl_3$, 27°) *of* **1** *and* **2**[1]). *δ* in ppm, *J* in Hz.

	1		**2**	
	δ(H)	*δ*(C)	*δ*(H)	*δ*(C)
H–C(1)	2.55 (*ddd, J* = 8.6, 8.6, 15.3)	42.2 (*d*)	–	–
CH_2(2) or C(2)	1.69–1.72, 1.82–1.87 (2*m*[a]))	27.4 (*t*)	–	145.5 (*s*)
CH_2(3) or C(3)	1.30–1.35, 1.88–1.92 (2*m*[a]))	32.5 (*t*)	–	135.1 (*s*)
H–C(4) or C(4)	2.22–2.26 (*m*[a]))	36.7 (*d*)	–	183.0 (*s*)
H–C(5)	2.21–2.25 (*m*[a]))	48.2 (*d*)	7.92 (*d*, *J* = 1.5 Hz)	117.6 (*d*)
H–C(6) or C(6)	5.70 (*d, J* = 1.1)	125.5 (*d*)	–	132.5 (*s*)
C(7) or H–C(7)	–	142.7 (*s*)	7.78 (*d*, *J* = 1.5 Hz)	115.4 (*d*)
CH_2(8) or C(8)	2.27, 2.60 (*dd, J* = 8.6, 15.3)	37.8 (*t*)	–	146.1 (*s*)
H–C(9) or C(9)	4.40 (*d, J* = 8.6)	73.0 (*d*)	–	157.3 (*s*)
C(10)	–	155.7 (*s*)	–	124.3 (*s*)
H–C(11) or Me(11)	2.26 (*q, J* = 7.0)	37.5 (*d*)	2.40 (*s*)	17.7 (*q*)
Me(12)	1.01 (*d, J* = 7.0)	21.4 (*q*)	2.18 (*s*)	20.4 (*q*)
Me(13) or C(13)	1.01 (*d, J* = 7.0)	21.4 (*q*)	–	196.5 (*s*)
CH_2(14) or Me(14)	4.82, 4.95 (2 br. *s*)	107.1 (*t*)	2.63 (*s*)	26.4 (*q*)
Me(15)	0.94 (*d, J* = 7.0)	17.2 (*q*)	4.02 (*s*)	56.3 (*q*)

[a]) Overlapped signals, assigned by HMBC and HMQC.

The ^{1}H- and ^{13}C-NMR (DEPT) spectra of **1** contained signals for a trisubstituted C=C bond (δ(H) 5.70 (*d*, *J* = 1.1, 1 H); δ(C) 142.7 (*s*) and 125.5 (*d*)), an exocyclic C=C bond (δ(H) 4.82 and 4.95 (each br. *s*, 1 H); δ(C) 155.7 (*s*) and 107.1 (*t*)), an ^{i}Pr group (δ(H) 1.01 (*d*, *J* = 7.0 Hz, 6 H) and 2.26 (*q*, *J* = 7.0 Hz, 1 H); δ(C) 21.4 (*q*), 21.4 (*q*) and 37.5 (*d*)), and a secondary Me group (δ(H) 0.94 (*d*, *J* = 7.0 Hz); δ(C) 17.2 (*q*)). The locations of these groups were confirmed by the HMBC (*Fig. 1*) H–C(6) (δ 5.70)/C(1), C(8), and C(11), Me(12) (δ 1.01)/C(7), and Me(15) (δ 0.94)/C(3), C(4) and C(5)[1]). The ^{1}H,^{1}H-COSY of **1** (*Fig. 1*) implied the connectivities H–C(1)/CH$_2$(2), CH$_2$(2)/CH$_2$(3), CH$_2$(3)/H–C(4), H–C(4)/H–C(5), H–C(1)/H–C(5) and H–C(5)/H–C(6). These evidences indicated that **1** was a guaian-type sesquiterpene [5]. The NMR signals at δ(H) 4.40 (*d*, *J* = 8.6 Hz, 1 H) and δ(C) 73.0 suggested the presence of an OH group, which was confirmed by the IR absorption at 3423 cm^{-1}. The location of the OH group at C(9) was deduced from the HMBC H–C(9) (δ 4.40)/C(7), C(8), C(10), and C(14) (*Fig. 1*). The relative configuration of **1** was deduced from the ^{1}H,^{1}H coupling constants and the ROESY data. Since H–C(5) was supposed to be β-oriented [6], H–C(1) should be α-oriented from the coupling constant between H–C(1) and H–C(5) (*J* = 15.3 Hz). The ROESY cross-peaks H–C(1)/H–C(9) and H$_{trans}$–C(14) (*trans* to C(9))/Me(15) indicated that H–C(9) was α-oriented, while Me(15) was β-oriented (*Fig. 2*).

Compound **2**, obtained as colorless needles (acetone), had the molecular formula $C_{14}H_{14}O_4$, according to the HR-EI-MS (*m*/*z* 246.0895). The IR spectrum suggested the presence of a vinylogous ester C=O (1649 cm^{-1}) and a ketone C=O group (1730 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra (*Table*) indicated that **2** has a chromenone skeleton [7]. The HMBC data (*Fig. 3*) allowed to establish the structure of **2** as 6-acetyl-8-methoxy-2,3-dimethylchromen-4-one[1]).

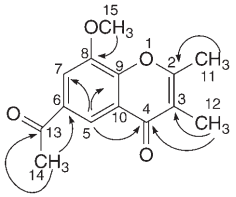

Fig. 3. *Key HMBC correlations in* **2**[1])

The ^{13}C-NMR spectrum of **2** confirmed the presence of a vinylogous ester carbonyl moiety conjugated with an aromatic ring (δ(C) 145.5, 135.1, 157.3, 124.3, and 183.0). The ^{1}H-NMR spectrum of **2** showed the signals of two Me groups at δ(H) 2.40 (*s*) and 2.18 (*s*), which were attached to C(2) (δ 145.5) and C(3) (δ 135.1), respectively, as shown by the HMBC Me(11) (δ 2.40)/C(2) and Me(12) (δ 2.18)/C(3) and C(4) (*Fig. 3*). In the ^{1}H- and ^{13}C-NMR spectra (*Table*), there were signals for a methyl ketone at (δ(H) 2.63 (*s*, 3 H) and δ(C) 26.4 (Me) and 196.5 (C=O), as well as a MeO group at δ(H) 4.02 (*s*) and δ(C) 56.3 [8]. Besides these signals, one pair of coupled protons appearing each as *d* at δ(H) 7.92 (*J* = 1.5 Hz) and 7.78 (*J* = 1.5 Hz) indicated that **2** has a tetrasubstituted benzene ring with two protons in *meta* position [9]. The specially low-field shifted proton signal at δ(H) 7.92 (H–C(5)) suggested that this proton should be deshielded by C(4)=O and the acetyl C=O group, while the substituent effects on the δ(C) of the C-atoms of the benzene moiety allowed to locate the methyl ketone moiety at C(6) and the MeO group at C(8) [10]. These conclusions were supported by the HMBC H–C(5) (δ 7.92)/C(4), C(7), and C(9), Me(14) (δ 2.63)/Me*C*=O and C(6), and Me(15) (δ 4.02)/C(8) (*Fig. 3*).

Compound **3**, obtained as a yellow oil, had the molecular formula $C_{17}H_{16}O_5$ with ten degrees of unsaturation, according to the HR-EI-MS (*m*/*z* 300.0996). The IR spectrum showed absorption bands for an OH (3424 cm^{-1}) and conjugated C=O group

(1674 cm^{-1}), and for an aromatic ring (1574 and 1519 cm^{-1}). The UV spectrum exhibiting a maximum at 274 nm with a shoulder at 310 nm was consistent with a flavanone chromophor [11]. With the aid of HMBC (*Fig. 4*) and HMQC experiments, all ^{1}H- and ^{13}C-NMR signals were fully assigned. The absolute configuration at C(2) of **3** was determined as (*S*) from the CD spectrum, which showed a positive *Cotton* effect at 335 nm and a negative one at 296 nm [12][13]. Thus, **3** was characterized as (2*S*)-3′-hydroxy-5′,7-dimethoxyflavanone.

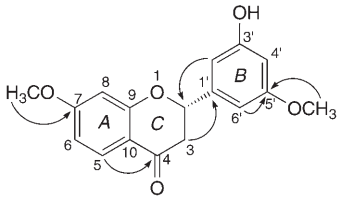

Fig. 4. *Key HMBC correlations in* **3**[1])

The ^{13}C-NMR signals of **3** at δ(C) 190.8 for a C=O group and at δ(C) 80.1 and 44.3 for two aliphatic C-atoms, together with the special *ABX* signals at δ(H) 5.39 (*dd*, *J* = 13.3, 2.7 Hz, 1 H), 3.08 (*dd*, *J* = 16.8, 13.3 Hz, 1 H), and 2.80 (*dd*, *J* = 16.8, 2.7 Hz, 1 H)) in the ^{1}H-NMR spectrum confirmed the presence of a flavanone skeleton [14]. The EI-MS showed the M^+ ion at *m*/*z* 300 ($C_{17}H_{16}O_5$) and fragment ions at *m*/*z* 151 ($[A_1+1]^+$, $C_8H_7O_3^+$) and 150 (B_3^+, $C_9H_{10}O_2^+$), indicating that ring *B* contained an OH and a MeO substituent, while ring *A* had a MeO substituent only [15]. The ^{1}H-NMR spectrum showed a set of signals (δ(H) 6.49 (*d*, *J* = 2.4 Hz, 1 H), 6.62 (*dd*, *J* = 8.8, 2.4 Hz, 1 H), and 7.87 (*d*, *J* = 8.8 Hz, 1 H)) for a 1,3,4-substituted benzene ring [16]. The MeO group in ring *A* was determined to be bound to C(7) by the HMBC H–C(5) (δ 7.87)/C(4) and MeO–C(7) (δ 3.84)/C(7) (*Fig. 4*). In the ^{1}H-NMR spectrum of **3**, there were three *meta*-coupled aromatic protons at δ(H) 6.99 (br. *s*, 1 H) and 6.96 (*d*, *J* = 1.1 Hz, 2 H) [14], indicating the location of the OH and MeO groups at C(3′) or C(5′) in ring *B*, respectively. This was confirmed by the HMBC H–C(6′) (δ 6.96)/C(5′) and MeO–C(5′) (δ 3.94)/C(5′) (*Fig. 4*).

The known compounds were identified as 6-acetyl-1,10-epoxyeuryopsin [17], (10α)-10-hydroxy-1-oxoeremophila-7(11),8(9)-dieno-8(12)-lactone [18], (6β,10α)-6,10-dihydroxy-1-oxoeremophila-7(11),8(9)-dieno-8(12)-lactone [18], 2-hydroxyplatyphyllid [4], kaempferol [19], 2,4′-dihydroxy-5′-methoxychalcone [12] and 6-acetyl-2-isopropenyl-8-methoxy-1,3-benzodioxin-4-one [10] by comparing their UV, IR, ORD and NMR data with those reported. The 2-hydroxyplatyphyllid has been previously isolated from *Ligularia macrophylla* [4] and compounds (10α)-10-hydroxy-1-oxoeremophila-7(11),8(9)-dieno-8(12)-lactone, (6β,10α)-6,10-dihydroxy-1-oxoeremophila-7(11),8(9)-dieno-8(12)-lactone, and 6-acetyl-2-isopropenyl-8-methoxy-1,3-benzodioxin-4-one have been previously isolated from genus *Ligularia* [10][18].

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Experimental Part

General. Anal. TLC: silica-gel plates (GF_{254}, 10–40 μm; *Yantai,* China), detection by UV light (254 nm) and visualization by spraying with 10% aq. H_2SO_4 soln., followed by heating. Column

chromatography (CC): silica gel (200–300 or 300–400 mesh; *Qingdao*, China). M.p.: *XT-4* micro-melting-point apparatus; uncorrected. Optical rotations (ORD): *Jasco P-1020* spectropolarimeter. UV Spectra: *Shimadzu UV-260* spectrophotometer; λ_{max} (log ε) in nm. CD Spectra: *Jasco J-715* spectropolarimeter; $\lambda([\theta])$ in nm. IR Spectra: *Avatar-360-E.S.P.* spectrophotometer (*Thermo Nicolet*); as KBr pellets or CH_2Cl_2 films; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker DRX-400* spectrometer; ^{1}H at 400 MHz, ^{13}C at 100 MHz; in $CDCl_3$; δ in ppm, J in Hz. EI-MS: *HP 5989A* mass spectrometer; in m/z. HR-EI-MS: *Waters Micromass-GCT* mass spectrometer.

Plant Material. The roots and rhizomes of *Ligularia macrophylla* were collected in August, 2005, in the Tianshan mountains (altitude 2100 m) in Xinjiang, China. The identity of the plant material was verified by Prof. *Ping Yan*, Shihezi University, and a voucher specimen (WQ-LM-05-1) has been deposited in the Herbarium of Materia Medica, Department of Pharmacognosy, School of Pharmacy, Fudan University, Shanghai, People's Republic of China.

Extraction and Isolation. The air-dried roots and rhizomes (5.1 kg) of *L. macrophylla* were ground and extracted (3 × 7 days) with 95% aq. EtOH (3 × 20 l) at r.t. The EtOH extract was concentrated to give a residue (600 g). A portion of the latter (550 g) was suspended in H_2O (1.2 l) and partitioned successively with petroleum ether, AcOEt, and BuOH (each 3 × 1 l). The AcOEt extract (180 g) was subjected to CC (10 × 120 cm column, SiO_2 (2 kg), petroleum ether/Me_2CO 30:1, 15:1, 9:1, 7:1, 5:1, 3:1, 2:1, and 1:1, then Me_2CO): *Fractions 1–8*. *Fr. 3* (eluted with petroleum ether/Me_2CO 9:1) was subjected to CC (SiO_2, petroleum ether/Me_2CO 20:1): 6-acetyl-1,10-epoxyeuryopsin (68 mg). *Fr. 4* (eluted with petroleum ether/Me_2CO 7:1) was subjected to CC (SiO_2, petroleum ether/Me_2CO 12:1): **1** (66 mg). *Fr. 5* (eluted with petroleum ether/Me_2CO 5:1) was subjected to CC (SiO_2, petroleum ether/AcOEt 10:1): **2** (5 mg), (10α)-10-hydroxy-1-oxoeremophila-7(11),8(9)-dieno-8(12)-lactone (6 mg), and (6β,10α)-6,10-dihydroxy-1-oxoeremophila-7(11),8(9)-dieno-8(12)-lactone (11 mg). *Fr. 6* (eluted with petroleum ether/Me_2CO 3:1) was subjected to CC (SiO_2, petroleum ether/AcOEt 7:1): **3** (3 mg), 2-hydroxyplatyphyllid (28 mg), and 6-acetyl-2-isopropenyl-8-methoxy-1,3-benzodioxin-4-one (5 mg). *Fr. 7* (eluted with petroleum ether/Me_2CO 2:1) was subjected to CC (SiO_2, petroleum ether/Me_2CO 5:1): kaempherol (55 mg) and 2,4′-dihydroxy-5′-methoxychalcone (36 mg).

(5β,9β)-Guaia-6,10(14)-dien-9-ol (= rel-*(1*R,*3a*S,*5*R,*8a*R*)-1,2,3,3a,4,5,6,8a-Octahydro-1-methyl-4-methylene-7-(1-methylethyl)azulen-5-ol*; **1**): Colorless gum. $[\alpha]_D^{25} = -49$ ($c = 0.1$, MeOH). IR (CH_2Cl_2): 3423, 2964, 2875, 1459, 1382, 1267, 1175, 1051, 736. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 220 (6), 202 (12), 187 (14), 177 (26), 159 (37), 149 (17), 131 (26), 117 (45), 107 (50), 91 (60), 41 (100). HR-EI-MS: 220.1833 ($C_{15}H_{24}O^+$; calc. 220.1827).

6-Acetyl-8-methoxy-2,3-dimethylchromen-4-one (=*6-Acetyl-8-methoxy-2,3-dimethyl-4*H*-1-benzopyran-4-one*; **2**): Colorless needles. M.p. 159–160°. UV ($CHCl_3$): 352 (sh, 3.12), 262 (4.62), 205 (4.51). IR (KBr): 2926, 1730, 1649, 907, 651. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 246 (7), 212 (7), 202 (19), 189 (11), 171 (8), 157 (17), 129 (43), 91 (100). HR-EI-MS: 246.0895 ($C_{14}H_{14}O_4^+$; calc. 246.0892).

*(2*S*)-3′-Hydroxy-5′,7-dimethoxyflavanone* (=*(2*S*)-2,3-Dihydro-2-(3-hydroxy-5-methoxyphenyl)-7-methoxy-4*H*-1-benzopyran-4-one*; **3**): Yellow oil. $[\alpha]_D^{25} = -12.6$ ($c = 0.03$, MeOH). UV (MeOH): 310 (sh, 3.42), 274 (4.28), 231 (sh, 4.31), 207 (4.56). CD ($c = 0.05$, MeOH): 335 (+9.13), 296 (−14.65), 244 (+7.85), 206 (−8.74). IR (CH_2Cl_2): 3424, 2921, 1674, 1574, 1519, 1444, 1259, 1201, 1159. ^{1}H-NMR (400 MHz, $CDCl_3$)[1]): 7.87 (*d*, $J = 8.8$, H−C(5)); 6.99 (br. *s*, H−C(4′)); 6.96 (*d*, $J = 1.1$, H−C(2′), H−C(6′)); 6.62 (*dd*, $J = 8.8$, 2.4, H−C(6)); 6.49 (*d*, $J = 2.4$, H−C(8)); 5.39 (*dd*, $J = 13.3$, 2.7, H−C(2)); 3.94 (*s*, MeO−C(5′)); 3.84 (*s*, MeO−C(7)); 3.08 (*dd*, $J = 16.8$, 13.3, H_α−C(3)); 2.80 (*dd*, $J = 16.8$, 2.7, H_β−C(3)). ^{13}C-NMR (100 MHz, $CDCl_3$)[1]): 190.8 (C(4)=O); 166.1 (C(7)); 163.5 (C(9)); 146.7 (C(5′)); 146.1 (C(3′)); 130.6 (C(1′)); 128.7 (C(5)); 119.6 (C(2′)); 114.7 (C(10)); 114.4 (C(6′)); 110.2 (C(6)); 108.7 (C(4′)); 100.8 (C(8)); 80.1 (C(2)); 55.9 (*Me*O−C(5′)); 55.6 (*Me*O−C(7)); 44.3 (C(3)). EI-MS: 300 (16), 151 (37), 150 (23), 135 (16), 105 (26), 55 (57), 43 (100). HR-EI-MS: 300.0996 ($C_{17}H_{16}O_5^+$; calc. 300.0998).

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