Xanthanolides, Germacranolides, and Other Constituents from *Carpesium longifolium*

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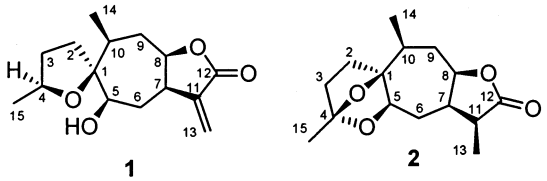
Three new xanthanolides, **1**−**3**, along with nine known compounds, were isolated from the aerial parts of *Carpesium longifolium*. The structures of the new compounds were elucidated as 1*β*,4*β*-epoxy-5*β*-hydroxy-10αH-xantha-11(13)-en-12,8*β*-olide (**1**), 1*β*,4*β*,4α,5*β*-diepoxy-10αH,11αH-xantha-12,8*β*-olide (**2**), and 4-acetoxy-1*β*,5*β*-epoxy-10αH-xantha-11(13)-en-12,8*β*-olide (**3**) by spectroscopic methods including IR, EIMS, HRESIMS, and 1D and 2D NMR experiments. Parthenolide and michelenolide exhibited significant cytotoxic activity against cultured SMMC-7721 (human hepatoma) and HO-8910 (human ovarian carcinoma) cells.

The genus *Carpesium* (Compositae) with only 21 species is widely distributed in Asia, mainly in the southwestern mountainous regions of China. The seeds, roots, leaves, and stems of some *Carpesium* species have long been used as Chinese traditional medicine for their hemostatic, vermifuge, antiinflammatory, and detoxication properties.[1,2] Sesquiterpene lactones are the most widespread secondary metabolites in the genus as reported, mainly eudesmanolides, germacranolides, and carabranolides.[3−10] In our previous work on three species of *Capesium* (*C. macrocephalum*, *C. lipskyi*, *C. cernuum*) in northwestern China, a number of sesquiterpene lactones were isolated. Some of them showed appreciable cytotoxic activity.[11−13]

We now report the first phytochemical investigation of *Carpesium longifolium* Chen et C. M. Hu (Compositae), which has led to the isolation and structural elucidation of three new sesquiterpene lactones, **1**−**3**, and nine known compounds. The cytotoxic activity test results of four compounds, parthenolide, 11*β*,13-dihydroparthenolide, michelenolide, and 5-hydroxy-4′,7-dimethoxydihydroflavone, are also reported.



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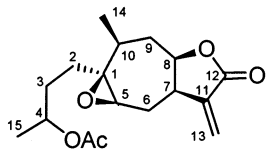

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Results and Discussion

The petroleum ether/Et_2O/MeOH (1:1:1) extract of the aerial parts of *C. longifolium* was subjected to CC over silica gel and fractioned further by repeated CC and preparative TLC to yield three new xanthanolides (**1**−**3**), along with nine known compounds: dihydroparthenolide diol,[14] parthenolide, 11*β*,13-dihydroparthenolide, michelenolide,[15] isoalantolactone,[16] 11α,13-dihydroisoalantolactone,[17] 5-hydroxy-4′,7-dimethoxydihydroflavone,[18] *β*-sitosterol, and sitogluside. This is the first report of dihydroparthenolide diol as a natural product. Rugutt, J. K. et al. previously reported that this compound had been synthesized from dihydroparthenolide, and the structure was determined by X-ray crystallographic analysis. The known compounds parthenolide, 11*β*,13-dihydroparthenolide, michelenolide, isoalantolactone, 11α,13-dihydroisoalantolactone, and 5-hydroxy-4′,7-dimethoxydihydroflavone were identified by comparison of their spectral data (MS, ^{1}H NMR, ^{13}C NMR) with those reported in the literature, and the known compounds *β*-sitosterol and sitogluside were identified on the basis of spectral data and direct comparison (TLC) with authentic samples.

The molecular formula of compound **1**, $C_{15}H_{22}O_4$, was deduced from its HRESIMS quasi-molecular ion peak at m/z = 267.1590 $[M + H]^+$ (calc 267.1591). Its IR spectrum indicated the presence of hydroxyl (3400 cm^{-1}) and α-methylene-*γ*-lactone (1759 cm^{-1}) groups. The ^{1}H and ^{13}C NMR (DEPT) spectra (Tables 1 and 2) indicated that **1** was a sesquiterpene with an α-unsaturated-*γ*-lactone [*δ* 6.28, 5.59 (d, J = 2.9 Hz, CH_2-13) and 169.6 (C-12)], one oxygenated quaternary carbon [*δ* 91.0 (C-1)], two *O*-methine units [*δ* 3.59 (brd, J = 10 Hz, H-5) and 4.18 (ddq, J = 5.8 Hz, H-4)], and two secondary methyl groups [*δ* 1.29 (d, J = 5.8 Hz) and 1.03 (d, J = 6.7 Hz)]. The ^{1}H−^{1}H COSY spectra revealed two partial structures of **1**: CH_3(15)CH(4)CH_2-(3)CH_2(2) and CH_3(14)CH(10)CH_2(9)CH(8)CH(7)CH_2(6)CH-(5). The C−C interconnectivity of all the fragments was established through response in HMBC spectra, e.g., C-1/H-3, C-2/H-5, and C-5/H-10, etc. The above information suggested that the basic structure of **1** was a xantha-11(13)-en-12,8-olide. A bridging oxygen was required for the molecular formula $C_{15}H_{22}O_4$, and the typical furanidine ring chemical shift of C-1 at *δ* 91.0, C-4 at *δ* 78.0, and H-4 at *δ* 4.18 indicated the oxygen bridge was between C-1 and C-4;[19] thus the hydroxyl was located at C-5. The stereochemistry of **1** was deduced from ^{1}H−^{1}H NOESY spectra, along with inspection of the molecular model. Clear NOE correlations (Figure 1) observed between H-7 and H-5, H-5 and H-10, and H-10 and H-8 indicated that these protons were all oriented on the bottom face of the molecule and were assigned as the α-protons, *β*-configurations of 14-CH_3,

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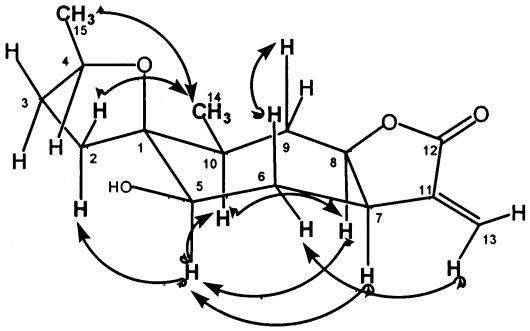

Figure 1. Key NOEs observed for compound **1**.

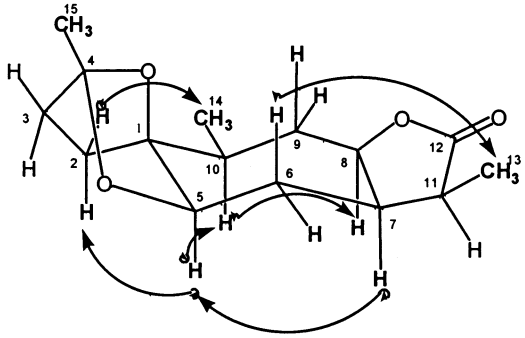

Figure 2. Key NOEs observed for compound **2**.

and the hydroxy at C-5 was also indicated. Key NOESY correlations between H-2a and H-5, and H-2b and H-14, demonstrated that the oxygen link at C-1 is β-oriented on the top face of the molecule. Likewise, correlation between H-14 and H-15 required the illustrated configuration at C-4. Hence, compound **1** was identified as 1β,4β-epoxy-5β-hydroxy-10αH-xantha-11(13)-en-12,8β-olide.

Compound **2** possessed the same molecular formula ($C_{15}H_{22}O_4$) as that of compound **1** (HRESIMS). Its ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) were similar to those of **1** and suggested that **2** was also a xanthanolide. Key evidence for the structure of **2** obtained from the HMBC experiment further confirmed this suggestion. However, the typical signals of an exocyclic methylene at C-11 were replaced by the signals of a methyl [δ 1.23 (d, J = 7.5 Hz), 11.9 (CH_3-13)] and a methine [δ 2.84 (dq, J = 7.5 Hz), 38.3 (CH-11)], and the γ-lactone carbonyl signal appeared at lower field, δ 178.6 (C-12), than that of **1**. Furthermore, a characteristic ketal signal at δ 109.8 (C-4) in **2** replaced the *O*-methine signal at δ_C 78.0 of C-4 in **1**, and the *O*-methine signal of C-5 in **2** shifted downfield to δ 85.9. The accumulated data indicated the presence of another oxygen bridge between C-4 and C-5,[18] which was also required for the molecular formula $C_{15}H_{22}O_4$.

From the similar ^{1}H and ^{13}C NMR data, the relative stereochemistry of the remaining chiral centers was assumed to be the same as that of **1**. This was confirmed by the ^{1}H$-^1$H NOESY experiments. Strong NOE cross-peaks observed between H-7 and H-5, H-5 and H-10, and H-10 and H-8 disclosed their α-configuration, and NOEs between H-14 and H-9α,9β confirmed the β-configuration of CH_3-14. The β-orientation of CH_3-13 deduced from the coupling constant $J_{7,11}$ = 7.5 Hz[20] was further confirmed by the correlation points between H-13 and H-6α,6β. Finally, together with inspection of the molecular model, the relative stereochemistry of C-1 and C-4 was also evidenced from the key NOESY correlations between H-2a and H-5, and H-2b and H-14 (Figure 2), namely, the oxygen bridge between C-1 and C-4 was β-orientated. Thus compound **2** was characterized as 1β,4β,4α,5β-diepoxy-10α,11αH-xantha-12,8β-olide.

The molecular formula of compound **3** was established as $C_{17}H_{24}O_5$ by HRESIMS. Its IR spectrum showed absorptions at 1762, 1732, 1246, 1024, and 816 cm^{-1}, and the ^{1}H and ^{13}C NMR spectra of **3** were typical for an α-methylene-γ-lactone, acetate, and epoxide ring. Comparison of the ^{1}H and ^{13}C NMR spectra of **3** with **1** and **2** suggested that **3** was another xantha-11(13)-en-12,8-olide with oxygen functions at C-1, C-4, and C-5. This was again supported by an HMBC experiment. Additional acetyl side chain signals were observed at δ 2.02 (3H, s), 21.2 (CH_3-2′), and 170.6 (C-1′). The obvious downfield chemical shift of H-4 at δ 4.88 (ddq, J = 6.4 Hz) suggested that the acetoxy group was located at the C-4, which was confirmed by long-range coupling between H-4 and C-1. As the molecular formula $C_{17}H_{24}O_5$ required, the fifth oxygen of compound **3** was assigned as the epoxy bridge between C-1 and C-5.

The relative stereochemistry of **3** was established as shown in structure **3** on the basis of ^{1}H$-^1$H NOESY spectra, along with analysis of ^{1}H NMR J data. The noticeably small couplings of $J_{7,13a}$ (2.2 Hz), $J_{7,13b}$ (1.6 Hz), and $J_{7,8}$ (7.5 Hz) were in good agreement with the 7β,8β-*cis*-lactone.[21] Likewise, NOESY correlations between H-5 and H-7, H-8 and H-10, and H-9α,9β and H-14 provided evidence that H-5, H-7, H-8, and H-10 were on the same α-face of the molecule, while CH_3-14 and the epoxy bridge between C-1 and C-5 were β-orientated. Consequently, compound **3** was determined to be 4-acetoxy-1β,5β-epoxy-10αH-xantha-11(13)-en-12,8β-olide.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Nicolet AVATAR 360 FT-IR spectrophotometer. All NMR spectra were recorded on a Bruker AM-400 FT-NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C NMR using TMS as internal standard. HRESIMS were obtained on a Bruker Daltonics APEX II, and EIMS data on a HP 5988A MS spectrometer. Silica gel (200−300 mesh) used for column chromatography (CC) and silica gel GF_{254} used for thin-layer chromatography (TLC) were supplied by the Qingdao Marine Chemical Factory in China. Spots were visualized on TLC plates under UV or by heating silica gel plates sprayed with 5% H_2SO_4 in C_2H_5OH. Melting points were uncorrected.

Plant Material. *C. longifolium* was collected from Shennongjia, Hubei Province, People's Republic of China, in August 1999. It was identified by Prof. Guoliang Zhang, Department of Biology, Lanzhou University. A voucher specimen (No. 9908) was deposited in the Institute of Organic Chemistry, Lanzhou University.

Extraction and Isolation. The air-dried aerial parts of *C. longifolium* (990 g) were pulverized and then extracted with petroleum ether/Et_2O/MeOH (1:1:1) (7 days × 3 times) at room temperature. After concentration of the combined extracts under reduced pressure, the residue (36 g) was chromatographed over a silica gel column (6.0 × 40 cm, 200−300 mesh, 400 g) with a gradient of petroleum ether (60−90 °C)/EtOAc (15:1, 8:1, 5:1, 2.5:1, and 1:1) and Me_2CO as the eluent, respectively. Six fractions, A−F, were collected according to TLC analysis. Isoalantolactone (15 mg) was obtained from fraction A (15:1, 6000 mL) after CC (45 g) with petroleum ether/Me_2CO (30:1−10:1) and repeated recrystallization from EtOAc. Fraction B (8:1, 6500 mL) gave β-sitosterol (36 mg) by repeated recrystallization, then the mother liquid yielded 11α,13-dihydroisoalantolactone (10 mg) after further silica gel (45 g) CC with petroleum ether/EtOEt (10:1−5:1) and repeated recrystallization from EtOAc. Fractions C (5:1, 7800 mL) and

Table 1. ^{1}H NMR (400 MHz) of **1**, **2**, and **3** ($CDCl_3$, TMS, δ, ppm)[a,b]

no.	1	2	3
1			
2	2.11 (brdd, 12.2, 8.6)	1.92* (m)	1.98* (m)
	1.71 (brdd, 12.2, 4)	1.80 (m)	
3	2.01 (m)	1.90* (m)	1.57* (m)
	1.47* (m)	1.74* (m)	
4	4.18 (ddq, 5.8)		4.88 (ddq, 6.4)
5	3.59 (brd, 10)	3.55 (brd, 11.5)	3.05 (dd, 8, 5.4)
6	2.03 (dd, 15, 5.6)	1.97 (dd, 14, 4.5)	2.17 (dd, 15, 8, 3.2)
	1.65 (ddd, 15, 12, 10)	1.60 (ddd, 14, 12, 11.5)	1.95* (ddd, 15, 13, 5.4)
7	3.34 (dddt, 12, 9, 5.6, 3.2)	2.74 (dddd, 12, 7.5, 7, 4.5)	3.28 (dddd, 13, 7.5, 3.2, 2)
8	4.64 (ddd, 12, 9, 3.3)	4.62 (ddd, 11, 7.0, 6.0)	4.60 (ddd, 11.5, 7.5, 3.5)
9	1.79 (brdd, 14, 3.3)	2.04* (brdd, 14, 6.0)	1.77 (ddd, 14, 3.5, 3.5)
	1.50* (ddd, 14, 12, 11)	1.58 (ddd, 14, 12, 11)	1.50* (ddd, 14, 11.5, 11)
10	1.58* (brdq, 11, 6.7)	2.02* (dq, 12, 7.0)	1.58* (brdq, 11, 7, 3.5)
11		2.84 (dq, 7.5)	
12			
13	6.28 (d, 3.2)	1.23 (d, 7.5)	6.28 (d, 2.2)
	5.59 (d, 2.9)		5.65 (d, 1.6)
14	1.03 (d, 6.7)	1.13 (d, 7.0)	1.15 (d, 7)
15	1.29 (d, 5.8)	1.59 (s)	1.22 (d, 6.4)
1′			
2′			2.02 (s)

[a] Signal multiplicity and coupling constants (Hz) are in parentheses. [b] *Overlapping signals.

Table 2. ^{13}C NMR (100 MHz) and DEPT Data of **1**, **2**, and **3** ($CDCl_3$, TMS, δ, ppm)

no.	1	2	3
1	91.0 s	91.0 s	63.3 s
2	24.9 t	21.6 t	32.3 t
3	35.5 t	37.1 t	31.9 t
4	78.0 d	109.8 s	70.1 d
5	77.5 d	85.9 d	61.7 d
6	33.3 t	24.1 t	30.8 t
7	38.8 d	39.4 d	39.2 d
8	80.5 d	80.7 d	79.4 d
9	35.3 t	35.8 t	32.8 t
10	37.3 d	30.6 d	30.7 d
11	138.9 s	38.3 d	138.9 s
12	169.6 s	178.6 s	169.2 s
13	122.8 t	11.9 q	122.8 t
14	18.4 q	16.3 q	17.6 q
15	20.5 q	18.8 q	19.6 q
1′			170.6 s
2′			21.2 q

D (2.5:1, 8600 mL) were decolorized with activated charcoal. Fraction C afforded parthenolide (12 mg) by CC (60 g) with $CHCl_3$/EtOAc (30:1−20:1) and recrystallization from Me_2CO. Further purified by preparative TLC, the residues gave 11β,13-dihydroparthenolide (7 mg, $R_f = 0.32$) with petroleum ether/EtOAc (2:1) and gave michelenolide (10 mg, $R_f = 0.36$) and 5-hydroxy-4′,7-dimethoxydihydroflavone (8 mg, $R_f = 0.27$) with $CHCl_3$/Me_2CO (10:1). Compounds **2** (3 mg, $R_f = 0.29$), **3** (7 mg, $R_f = 0.40$), and **1** (9 mg, $R_f = 0.32$) were isolated from fraction D by CC (45 g) with $CHCl_3$/MeOH (30:1) and purified by preparative TLC developed with cyclohexane/Et_2O (1:4), $CHCl_3$/EtOAc (3:1), and cyclohexane/Me_2CO (2:1). After CC with $CHCl_3$/MeOH (20:1−10:1) and preparative TLC with petroleum ether/Me_2CO (1:1), fraction E (1:1, 5200 mL) gave dihydroparthenolide diol (7 mg, $R_f = 0.25$). Crystals of sitogluside deposited from fraction F (Me_2CO).

1β,4β-Epoxy-5β-hydroxy-10αH-xantha-11(13)-en-12,8β-olide (1): colorless gum; $[\alpha]^{20}_D$ +23.0° (*c* 0.71, $CHCl_3$); IR (KBr) ν_{max} 3400, 2961, 2889, 1759, 1659, 1272, 1128, 1086, 1015, 880, 753 cm^{-1}; ^{1}H and ^{13}C NMR (DEPT) data, see Tables 1 and 2; EIMS *m*/*z* 266 $[M]^+$ (3), 248 $[M - H_2O]^+$ (1), 125 (100), 111 (78), 69 (31), 55 (27); HRESIMS *m*/*z* 267.1590 $[M + H]^+$ (calcd for $C_{15}H_{23}O_4$, 267.1591).

1β,4β,4α,5β-Diepoxy-10α,11αH-xantha-12,8β-olide (2): colorless gum; $[\alpha]^{20}_D$ −16.0° (*c* 0.22, $CHCl_3$); IR (KBr) ν_{max} 2934, 2859, 2388, 1769, 1458, 1382, 1195, 1093, 1028, 919, 838, 801 cm^{-1}; ^{1}H and ^{13}C NMR (DEPT) data, see Tables 1 and 2; EIMS *m*/*z* 266 $[M]^+$ (4), 251 $[M - CH_3]^+$ (2), 248 $[M - H_2O]^+$ (1), 237 (10), 224 (13), 206 (20), 196 (15), 178 (12), 43 (100); HRESIMS *m*/*z* 267.1594 $[M + H]^+$ (calcd for $C_{15}H_{23}O_4$, 267.1591).

4-Acetoxy-1β,5β-epoxy-10αH-xantha-11(13)-en-12,8β-olide (3): colorless gum; $[\alpha]^{20}_D$ +26.2° (*c* 0.68, $CHCl_3$); IR (KBr) ν_{max} 2931, 2889, 1762, 1732, 1652, 1456, 1376, 1246, 1124, 1067, 1024, 839, 816 cm^{-1}; ^{1}H and ^{13}C NMR (DEPT) data, see Tables 1 and 2; EIMS *m*/*z* 308 $[M]^+$ (0), 232 $[M - AcOH - O]^+$ (4), 203 (2), 187 (8), 131 (16), 93 (46), 79 (46), 55 (27), 43 (100); HRESIMS *m*/*z* 331.1511 $[M + Na]^+$ (calcd for $C_{17}H_{24}NaO_4$, 331.1516).

Dihydroparthenolide diol: $[\alpha]^{20}_D$ +14.6° (*c* 0.75, $CHCl_3$); IR (KBr) ν_{max} 3402, 3020, 1778, 1419, 1387, 1216, 1095, 909, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.97 (1H, dd, $J = 10.0$, 5.8 Hz, H-1), 1.83 (1H, dddd, $J = 12$, 12, 10, 6.5 Hz, H-2), 1.99 (1H, brddd, $J = 12$, 6.8, 5.8 Hz, H-2), 2.20 (1H, ddd, $J = 12.5$, 12, 6.8 Hz, H-3), 1.74 (1H, ddd, $J = 12.5$, 12, 6.8 Hz, H-3), 3.67 (1H, d, $J = 7.5$ Hz, H-5), 4.18 (1H, dd, $J = 9$, 7.5 Hz, H-6), 2.20 (1H, dddd, $J = 9$, 7 Hz, H-7), 1.80 (1H, dddd, $J = 12$, 5, 4, 2.5 Hz, H-8), 1.64 (1H, dddd, $J = 12$, 12 Hz, H-8), 1.69 (1H, ddd, $J = 12$, 12, 5 Hz, H-9), 1.65 (1H, brdd, $J = 12$, 5 or 7 Hz, H-9), 2.25 (1H, dq, $J = 7.0$ Hz, H-11), 1.26 (1H, d, $J = 7.0$ Hz, H-13), 1.38 (1H, s, H-14), 1.31 (1H, s, H-15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 86.5 (C, C-1), 26.8 (CH_2, C-2), 36.4 (CH_2, C-3), 84.7 (C, C-4), 77.0 (CH, C-5), 82.5 (CH, C-6), 55.6 (CH, C-7), 25.3 (CH_2, C-8), 36.9 (CH_2, C-9), 74.0 (C, C-10), 42.8 (CH, C-11), 177.2 (C, C-12), 12.8 (CH_3, C-13), 27.9 (CH_3, C-14), 20.9 (CH_3, C-15); EIMS *m*/*z* 284 $[M]^+$ (1.5), 269 $[M - CH_3]^+$ (4), 266 $[M - H_2O]^+$ (2.7), 251 $[M - CH_3 - H_2O]^+$ (7), 248 $[M - 2H_2O]^+$ (5), 233 $[M - 2H_2O - CH_3]^+$ (3.2), 205 (18), 85 (48), 71 (30), 43 (100); HRESIMS *m*/*z* 307.1516 $[M + Na]^+$ (calcd for $C_{15}H_{24}NaO_4$, 307.1521). The spectral data of this compound were not reported in the literature.[14]

Cytotoxic Activity Assays. Parthenolide, 11β,13-dihydroparthenolide, michelenolide, and 5-hydroxy-4′,7-dimethoxydihydroflavone, due to their abundance in the plant, were evaluated for their cytotoxic activity against cultured SMMC-7721 (human hepatoma), HO-8910 (human ovarian carcinoma), and LO2 (human hepatocytes) cells using the MTT method.[21] IC_{50} (half inhibition concentration) values are summarized in Table 3. From cytotoxic activity data, it was found that parthenolide and michelenolide both showed significant cytotoxic activity against SMMC-7721 and HO-8910 cells. The

Table 3. Cytotoxic Activity Evaluation of Parthenolide, 11β,13-Dihydroparthenolide, Michelenolide, and 5-Hydroxy-4′,7-dimethoxydihydroflavone

	$IC_{50}/\mu g\ mL^{-1}$	
compound	SMMC-7721	HO-8910
parthenolide	4.20 ± 0.59	1.37 ± 0.21
11β,13-dihydroparthenolide	>200	157.93 ± 9.78
michelenolide	7.13 ± 1.66	2.32 ± 0.67
5-hydroxy-4′,7-dimethoxy-dihydroflavone	>200	>200
vincristine	30.35 ± 2.23	20.74 ± 1.91

α,β-unsaturated lactone is apparently the key active center in these compounds.

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