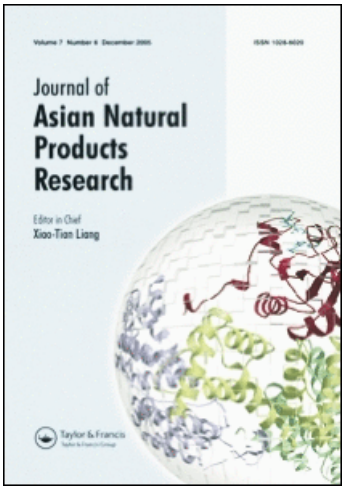

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Chemical constituents from *Cimicifuga foetida*

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From the rhizoma of *Cimicifuga foetida* L. (Ranunculaceae) a new chromone, 6′-hydroxylangelicain **(18)**, has been isolated together with 20 known compounds. The structure of **18** has been elucidated on the basis of spectroscopic and chemical evidence.

Keywords: *Cimicifuga foetida*; Ranunculaceae; Chromone; 6′-Hydroxylangelicain

1. Introduction

"Shengma", the rhizoma of *Cimicifuga* species belonging to the ranunculaceae family, is an important constituent of traditional Chinese medicines. Three *Cimicifuga* species (*C. heracleifolia*, *C. dahurica*, and *C. foetida*) are officially listed in the Chinese Pharmacopoeia for the treatment of anti-inflammatory, antipyretic and analgesic remedy [1]. Moreover, it has been used in combination with other herbs in the ancient Kampo medicine in Japan in anti-inflammatory drugs [2]. The effects of extracts from *C. racemosa* on gonadotropin release in menopausal women and ovariectomized rats have been tested [3]. During a series of chemical investigations of *Cimicifuga* species, some cyclolanostanol glycosides, fukiic acid esters, piscidic acid esters, caffeic acid derivatives, phenolic acid derivatives and chromones have been isolated [4].

We report here the isolation and structure elucidation of a new chromone, 6′-hydroxylangelicain **(18)**, from the rhizoma of *C. foetida*, together with 20 known compounds, identified as angelicain (norcimifugin) **(1)** [5], actein **(2)** [6], cimigenol-3-*O*-*β*-D-xylopyranoside (23*R*,24*S*) **(3)** [7], 12*β*-hydroxycimigenol-3-*O*-*β*-D-xylopyranoside (23*R*,24*S*) **(4a)** [7], 12*β*-hydroxycimigenol-3-*O*-α-L-arabinopyranoside (23*R*,24*S*) **(4b)** [8], daucosterol **(5)** [9], cimicidnol-3-*O*-α-L-arabinoside **(6)** [2], *β*-sitosterol **(7)** [9], 25-*O*-acetylcimigenol **(8)** [10], cimigenol **(9)** [7], cimigenol-3-one **(10)** [11], norkhellol **(11)** [12], 5,7-dihydroxy-2-methylchromen-4-one **(12)** [13], 3-methoxyisoferulic acid **(13)** [10], isoferulic acid **(14)** [10], 25-*O*-acetylcimigenol-3-*O*-*β*-D-xylopyranoside (23*R*,24*S*) **(15)**

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[7], cimicifugoside H-2 **(16)** [2], bergenin **(17)** [14], cimifugin **(19)** [15] and prim-*O*-glucosylangelicain **(20)** [16]. Among them, **8**–**13**, **17** and **20** have been isolated from the title plant for the first time.

2. Results and discussion

Compound **18** was obtained as colorless needles, giving a blue color with Gibbs reagent and a dark violet color with ferric chloride. Its molecular formula, $C_{15}H_{16}O_7$, was deduced from HRESI-MS (*m/z*: 331.0793 $[M + Na]^+$, calcd 331.0794). The UV spectrum shows absorption maxima at 215, 233, 251 and 300 nm. The IR spectrum indicates the presence of an hydroxyl group (3380 cm^{-1}), a carbonyl group (1670 cm^{-1}) and aromatic rings (1634, 1588, 1575 cm^{-1}). Thus, **18** appears to be a 5-hydroxychromone. Compared with the signals of one hydroxymethyl observed at δ_C 60.7 (t) and δ_H 4.66 (2H, br.s) and two methyl signals (δ_C 26.0, 26.4, q; δ_H 1.25, 6H, s) in the NMR spectra of **1** [4], **18** exhibits signals attributable to two hydroxymethyl groups (δ_C 67.5, 60.5, t; δ_H 4.66, 2H, br.s; 4.32, 4.10 each 1H, d, $J = \mathbf{10.5}$, 10.5 Hz) and one methyl group (δ_C 21.1, q; δ_H 1.54, 3H, s). Other carbon signals are quite coincident with those of **1**, except for the C-4′ and C-2′ carbon (β- and γ-positions relative to 6′-OH), which appear downfield, by 3.1 ppm, and upfield, by 3.9 ppm, respectively, in the NMR spectra of **18**. The absolute configuration of the asymmetric C-2′ can be reasonably deduced as an *S*-configuration from biogenesis of a series of chromones derived from **1**, which have been isolated from *Cimicifuga* species and determined by comparison of the molecular rotation [17] and ORD curve [5,16] with those of known absolute configuration. Furthermore, $NaIO_4$ acid oxidation of **18** gave an amorphous white powder **18a** (4′-carbonylangelicain) with a positive molecular rotation $[\alpha]_D^{25}$ +71, which is approximately the opposite value of that for 4′-carbonylcnidimol B (which has an R-configuration at C-2′) [5]. HMBC correlations (figure 1) confirm that **18** is 6′-hydroxylangelicain.

3. Experimental

3.1 General experimental procedures

All melting points were measured on a XRC-1 melting point apparatus and are uncorrected. UV spectra were taken on a Perkin-Elmer Lambda 35 spectrometer, IR spectra were recorded

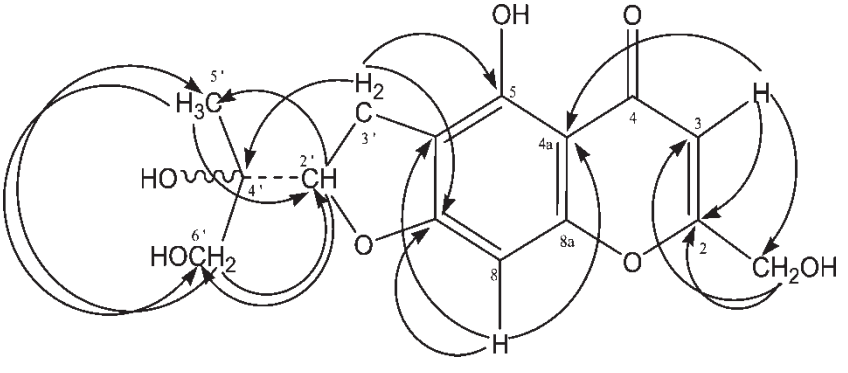


Figure 1. Key HMBC correlations for **18**.

on a Perkin-Elmer FT-IR spectrometer, and optical rotations on a PE-341 polarimeter. NMR spectra were run on an Avance-600 spectrometer using TMS as internal standard. ESI-MS spectra were obtained on a Finnigan LCQ^{DECA} and HR-ESIMS spectra on API GSTAR PULSARI spectrometers. Preparative TLC was conducted on silica gel GF254 plates (Marine Chemical Factory, Qingdao, China) and reversed-phase TLC on RP-18 F254 plates (Merck). Column chromatography was performed on silica gel (Marine Chemical Factory, Qingdao, China); ODS (Cosmosil 75 C_{18}-OPN) (Nacalai Tesque), Lobar LiChroprep Rp-8 (Merck), Sephadex LH-20 (Pharmacia) and Macroporous Resin HPD100 (Bao-En Chemical Company, China).

3.2 Plant material

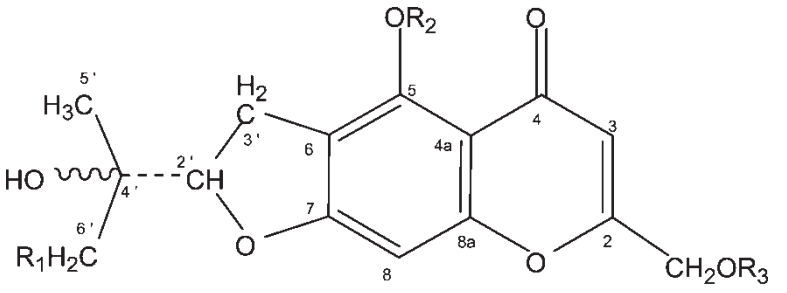
Ethanol extracts of rhizoma of *Cimicifuga foetida* were provided by En-Wei Pharmaceutical Co., Ltd., and a voucher specimen (no. 2002191) identified by Xu-feng Pu of the Chengdu Institute for Drug Control has been deposited in the Herbarium of the Chengdu Institute of Biology, Chinese Academy of Sciences.

3.3 Extraction and isolation

Dried, powdered rhizoma of *Cimicifuga foetida* were extracted with warm ethanol (3×) to give a residue that was then dissolved in warm water (50–60°C) and filtered. The water-insoluble material (400 g) was subsequently suspended in water, and was then successively partitioned with light petroleum, EtOAc and n-BuOH. The EtOAc and n-BuOH extracts were mixed and subjected to repeated chromatography on normal and reversed-phase silica gel columns to yield compounds **1** (1.0 g), **2** (79 mg), **3** (450 mg), **4a** + **4b** (65 mg), **5** (25 mg) and **6** (80 mg). The water-soluble fraction was absorbed on macroporous resin HPD100, and then eluted with 95% ethanol. The evaporated elution was then suspended in water, and partitioned with light petroleum, EtOAc and n-BuOH successively. The light petroleum extracts were chromatographed on a silica-gel column, eluting with light petroleum–EtOAc–acetone to provide compounds **7** (636 mg), **8** (100 mg), **9** (468 mg), **10** (80 mg) and **11** (31 mg). The EtOAc extracts were then fractionized by repeated chromatography on normal and reversed-phase silica gel and Sephadex LH-20 column to yield compounds **12** (10 mg), **13** (99 mg), **14** (173 mg), **15** (515 mg) and **16** (23 mg). The n-BuOH extracts were subsequently subjected to normal silica-gel column chromatography and preparative TLC to yield compounds **17** (168 mg) and **18** (3.4 mg). Compounds **19** (1.2 g) and **20** (1.5 g) were isolated from the water extracts by repeated chromatography on normal silica gel (scheme 1).

3.4 Identification

3.4.1 Compound 18. Colorless needle crystals (3.4 mg), mp 196–198°C (CH_3OH); $[\alpha]_D^{25}$ +83 (*c* 0.045, CH_3OH); UV (CH_3OH) λ_{max} (nm) (log ϵ): 215 (3.76), 233 (2.67), 251 (2.36), 300 (1.78); IR (KBr) ν_{max} (cm^{-1}): 3380, 1670, 1634, 1588, 1575; ^{1}H NMR (pyridine-d_5) δ (ppm): 4.66 (2H, br.s, 2-CH_2—), 6.76 (1H, s, 3-H), 6.43 (1H, s, 8-H), 5.44 (1H, t, J = **8.4 Hz**, 2′-H), 3.70 (1H, dd, J = **8.4**, 15.2 Hz, 3′-H), 3.33 (1H, dd, J = **9.6**, 15.2 Hz, 3′-H), 1.54 (3H, s, 5′-H), 4.32 (1H, d, J = **10.5 Hz**, 6′-H), 4.10 (1H, d, J = **10.5 Hz**, 6′-H), ^{13}C NMR see



	R_1	R_2	R_3
1:	H	H	H
18:	OH	H	H
19:	H	CH_3	H
20:	H	H	glc

Scheme 1.

table I; ESI-MS (positive) *m/z*: 309 $[M + H]^+$, 639 $[2M + Na]^+$; ESI-MS (negative) *m/z*: 307 $[M - H]^-$, 615 $[2M - H]^-$; HR-ESIMS *m/z* 331.0793 $[M + Na]^+$ (calcd. for $C_{15}H_{16}O_7Na$, 331.0794).

3.4.2 $NaIO_4$ acid oxidation of 18 to 18a. $NaIO_4$ (2 mg) was added to **18** (2 mg) dissolved in CH_3OH—H_2O (1:1, 1.5 ml). The resultant solution was then stirred at room temperature for 4 h until an amorphous solid residue was produced, and the solution was then diluted with H_2O (3 ml). The amorphous solid residue was filtered off, washed with water and dried to yield **18a** as a white powder (1.2 mg). **18a**: $[\alpha]_D^{25}$ +71 (*c* 0.06, CH_3OH); ^1H NMR ($CDCl_3$) δ (ppm): 4.59 (2H, d, $J = 5.7$ **Hz**, 2-CH_2—), 2.19 (1H, br. s, 2-CH_2-O*H*), 6.44 (1H, s, 3-H),

Table 1. ^{13}C NMR data of compounds **1**, **11**, **12** and **18**–**20** (**1**, **11** and **18** measured in pyridine-d_5 and **12**, **19** and **20** in DMSO-d_6).

Carbon	***1***	***11***	***12***	***18***	***19***	***20***
2	171.1(s)	172.6	168.3	170.9(s)	167.0	167.3(s)
3	106.2(d)	106.5	108.6	106.1(d)	109.1	109.9(d)
4	183.2(s)	184.8	182.4	183.0(s)	176.1	182.7(s)
4a	107.4(s)	104.6	104.1	105.9(s)	112.0	105.5(s)
5	167.1(s)	159.2	164.7	167.1(s)	165.2	167.0(s)
6	109.9(s)	105.5	99.4	110.9(s)	118.1	107.7(s)
7	158.4(s)	155.8	162.2	158.2(s)	159.5	158.1(s)
8	90.2(d)	91.1	94.4	89.5(d)	93.9	92.2(d)
8a	157.3(s)	154.6	158.5	157.1(s)	155.8	156.4(s)
2-CH_2	60.7(t)	60.8	20.6	60.5(t)	61.0	65.9(t)
2′	92.8(d)	145.9		88.9(d)	91.7	89.5(d)
3′	27.2(t)	113.3		26.4(t)	27.6	26.5(t)
4′	70.8(s)			73.9(s)	70.7	70.7(s)
5′	26.0(q)			21.1(q)	25.5	25.5(q)
6′	26.4(q)			67.5(t)	26.4	26.4(q)
—OCH_3					60.1	*

* glc: 103.1, 74.0, 77.7, 70.7, 77.2, 61.7.

12.90 (1H, s, 5-OH), 6.36 (1H, s, 8-H), 5.23 (1H, dd, $J = \mathbf{6.0}$, 10.8 Hz, 2′-H), 3.50 (1H, dd, $J = \mathbf{10.8}$, 16.0 Hz, 3′-H), 3.29 (1H, dd, $J = \mathbf{6.0}$, 16.0 Hz, 3′-H), 2.31 (3H, s, 5′-H); ESI-MS (positive) *m/z*: 277 $[M + H]^+$; ESI-MS (negative) *m/z*: 275 $[M - H]^-$.

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