Actaticas A–G, Cycloartane Triterpenes From Actaea asiatica With Their Antiproliferative Activity

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Phytochemical studies on the rhizomes of Actaea asiatica led to the isolation of seven new cycloartane triterpenes, actaticas A–G (1–7). Their structures were determined by NMR, HRESIMS, and chemical analysis. All the isolates were evaluated for their antiproliferative activity against HT-29 and MCF-7 cell lines. The results showed that all the compounds displayed cytotoxicity. All compounds showed significant inhibitory effects with IC50 values of 9.2–26.4 μM.

Keywords: Actaea asiatica, cycloartane triterpenes, antiproliferative activity, HT-29 cell lines, MCF-7 cell lines

INTRODUCTION

Actaea asiatica H. Hara, a perennial herb belonging to the family Ranunculaceae, is mainly distributed in the southwest and northwest of China. Its roots have been traditionally used among the Tujia folk in Hubei Province for treating headache, sore throat, rheumatic pain, rubella, measles, pertussis, uterine prolapse, and dog bites (Gao et al., 2006a; Gao et al., 2006b; Fan et al., 2007; Gao et al., 2007). Phytochemical studies indicated that the genus Actaea contained cycloartane triterpene glycosides with cytotoxic activities (Kusano et al., 1998; Kusano et al., 1999; Gao et al., 2006b). However, little systematic chemical work on A. asiatica has been carried out so far.

In order to find the bioactive constituents from A. asiatica, chemical research were carried out, resulting in the isolation of seven new cycloartane triterpene glycosides, namely, actaticas A–G (1–7) (Figure 1). Their structures were determined by spectroscopic analysis and chemical methods. Herein, structural elucidation of compounds 1–7 was reported as well as their cytotoxic activities.

MATERIALS AND METHODS

General Experimental Procedures

Optical rotations were obtained on a PerkinElmer 341 digital polarimeter. IR spectra were recorded on Shimadzu FTIR-8400S spectrometers. NMR spectra were obtained with a Bruker AV III 600 NMR spectrometer (chemical shift values are presented as δ values with TMS as the internal standard). HR-ESIMS spectra were performed on a LTQ-Obitrap XL spectrometer. Preparative HPLC was performed on a Lumtech K-1001 analytic LC equipped with two pumps of K-501, a UV
detector of K-2600, and an YMC Pack C18 column (250 × 10 mm, i.d., 5 μm, YMC Co. Ltd., Japan) eluted with CH₃OH-H₂O at a flow rate of 2 ml/min. C18 reversed–phase silica gel (40–63 μm, Merk, Darmstadt, Germany), MCI gel (CHP 20P, 75–150 μm, Mitsubishi Chemical Corporation, Tokyo, Japan), and silica gel (100–200 mesh, Qingdao Marine Chemical plant, Qingdao, the People’s Republic of China) were used for column chromatography. Pre-coated silica gel GF254 plates (Zhi Fu Huang Wu Pilot Plant of Silica Gel Development, Yantai, the People’s Republic of China) were used for TLC. All solvents used were of analytical grade (Beijing Chemical Works).

**Plant Material**
The plants of *A. asiatica* were collected at Jinfuo Mountain in Chongqing province, the People’s Republic of China, in November 2016, and were authenticated by Professor Sirong Yi. The voucher specimen (CS161108) has been deposited at the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences.

**Extraction and Isolation**
The air-dried powdered rhizomes *A. asiatica* (6.8 kg) was extracted with 95% EtOH (20 L) three times (each time for 2 h). Removal of the EtOH under reduced pressure yielded the extract (879 g). The residue was suspended in H₂O (1.5 L) and partitioned with petroleum ether (3 × 1 L), EtOAc (3 × 1 L), acetone (3 × 1 L), and n-BuOH (3 × 1 L) successively. The EtOAc fraction (510 g) was subjected to CC over silica gel (100–200 mesh, 8 × 100 cm) eluting with a stepwise gradient of CH₂Cl₂-MeOH (from 1:0 to 0:1) to afford six fractions A–F. Fraction B (29.4 g) was subjected to MCI column chromatography (4 × 80 cm) elution with MeOH-H₂O (40:60; 60:40; 70:30; 80:20; 100:0, v/v) giving five subfractions (Fr. B1–B5). Subfraction B3 (911 mg) was chromatographed by semi-preparative HPLC using acetonitrile–H₂O (75:25, v/v) to yield compound 1 (9.4 mg, tᵣ = 26.3 min) and 7 (7.2 mg, tᵣ = 29.5 min). Subfraction B4 (503 mg) was purified through preparative HPLC elution using an acetonitrile–H₂O (65:35, v/v) system to give compound 2 (12.1 mg, tᵣ = 23.0 min).
Fraction D (5.8 g) was loaded on an ODS C18 column (2 × 80 cm) eluted with MeOH–H2O (40:60; 60:40; 70:30; 80:20; 100:0, v/v) to give five subfractions (Fr. D1–D5). Subfraction D3 (503 mg) was chromatographed by semi-preparative HPLC using acetonitrile–H2O (70:30, v/v) to yield compounds 3 (6.1 mg, tR = 18.5 min), 4 (8.7 mg, tR = 21.4 min), and 5 (7.0 mg, tR = 28.3 min). Fraction F (6.7 g) was fractionated on an MCI-gel column chromatography eluted with MeOH–H2O (40:60; 60:40; 70:30; 80:20; 100:0, v/v) to give five subfractions (Fr. F1–F5). Subfraction F3 (223 mg) was chromatographed by preparative HPLC using acetonitrile–H2O (75:25, v/v) to yield compounds 6 (5.8 mg, tR = 22.7 min).

**Actatica A (1):** C39H62O11, white amorphous powder; [α]20 D + 19.0 (c = 0.15, MeOH); IR (KBr) νmax max: 3,736, 2,957, 1,738, 1,373, 1,032 cm−1; UV (MeOH) λmax (log e): 201 nm; for 1H NMR (600 MHz, pyridine-d5) and 13C-APT (150 MHz, pyridine-d5) spectroscopic data, see Tables 1, 2; HR-ESIMS m/z: 729.4233 (calcld for C39H62O11Na [M + Na]+, 729.4184).

**Actatica B (2):** C32H50O6, white amorphous powder; [α]20 D + 35.1 (c = 0.31, MeOH); IR (KBr) νmax max: 3,376, 2,957, 1,738, 1,373, 1,032 cm−1; UV (MeOH) λmax (log e): 201 nm; for 1H NMR (600 MHz, pyridine-d5) and 13C-APT (150 MHz, pyridine-d5) spectroscopic data, see Tables 1, 2; HR-ESIMS m/z: 553.3533 (calcld for C32H50O6Na, 553.3500).

**Actatica C (3):** C39H62O11, white amorphous powder; [α]20 D + 35.1 (c = 0.31, MeOH); IR (KBr) νmax max: 3,493, 2,928, 1,730, 1,375, 1,044, 3,436, 3,374, 3,272 cm−1; UV (MeOH) λmax (log e): 201 nm; for 1H NMR (600 MHz, pyridine-d5) and 13C-APT (150 MHz, pyridine-d5) spectroscopic data, see Tables 1, 2; HR-ESIMS m/z: 727.4100 (calcld for C39H62O11Na [M + Na]+, 727.4088).

**Actatica D (4):** C32H42O13, white amorphous powder; [α]20 D + 22.4 (c = 0.22, MeOH); IR (KBr) νmax max: 3,493, 2,934, 1,734, 1,264, 1,033, 1,033, 962 cm−1; λmax (log e): 201 nm; for 1H NMR spectroscopic data, see Tables 1, 2.
### Table 2

| Position | Compounds | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------|------------|---|---|---|---|---|---|---|
| 1        |            | 32.6 | 33.0 | 32.6 | 32.6 | 32.8 | 32.9 | 32.8 |
| 2        |            | 30.9 | 31.7 | 30.9 | 32.3 | 30.1 | 31.1 | 32.3 |
| 3        |            | 88.8 | 82.8 | 86.7 | 88.8 | 88.7 | 88.8 | 88.7 |
| 4        |            | 41.7 | 40.5 | 40.5 | 41.7 | 41.7 | 41.7 | 41.7 |
| 5        |            | 47.7 | 47.8 | 47.8 | 47.7 | 47.6 | 47.7 | 47.7 |
| 6        |            | 21.2 | 21.7 | 21.4 | 21.1 | 21.4 | 21.1 | 21.4 |
| 7        |            | 26.5 | 26.5 | 26.4 | 26.5 | 26.1 | 26.7 | 26.5 |
| 8        |            | 48.3 | 48.3 | 48.2 | 48.5 | 48.0 | 50.3 | 49.0 |
| 9        |            | 19.9 | 20.1 | 20.1 | 20.2 | 19.8 | 20.7 | 20.2 |
| 10       |            | 26.7 | 27.1 | 26.7 | 26.9 | 27.1 | 26.9 | 26.9 |
| 11       |            | 26.3 | 26.6 | 26.5 | 31.2 | 27.0 | 31.9 | 31.2 |
| 12       |            | 37.5 | 25.9 | 26.4 | 216.6 | 216.6 | 216.6 | 216.6 |
| 13       |            | 48.6 | 50.3 | 50.3 | 59.5 | 48.3 | 59.0 | 59.1 |
| 14       |            | 47.6 | 47.0 | 47.0 | 42.4 | 46.4 | 42.7 | 42.4 |
| 15       |            | 86.4 | 80.3 | 76.7 | 86.1 | 85.7 | 42.7 | 82.4 |
| 16       |            | 79.8 | 78.3 | 80.3 | 80.1 | 79.8 | 77.3 | 79.1 |
| 17       |            | 56.1 | 51.6 | 51.6 | 52.7 | 59.0 | 53.2 | 56.5 |
| 18       |            | 21.7 | 14.1 | 33.5 | 64.4 | 26.1 | 64.5 | 64.7 |
| 19       |            | 30.5 | 31.2 | 30.4 | 30.5 | 30.6 | 26.2 | 26.5 |
| 20       |            | 85.2 | 86.7 | 82.9 | 86.6 | 87.3 | 86.6 | 87.2 |
| 21       |            | 27.6 | 25.1 | 25.1 | 27.7 | 22.3 | 24.4 | 24.7 |
| 22       |            | 33.7 | 41.5 | 41.4 | 39.0 | 39.1 | 39.1 | 32.3 |
| 23       |            | 27.0 | 29.0 | 29.0 | 29.7 | 30.5 | 31.2 | 30.9 |
| 24       |            | 83.8 | 111.2 | 111.2 | 81.7 | 115.2 | 81.6 | 114.7 |
| 25       |            | 70.9 | 72.4 | 72.4 | 71.2 | 72.8 | 71.7 | 71.7 |
| 26       |            | 27.6 | 25.9 | 25.8 | 26.1 | 30.3 | 26.1 | 26.4 |
| 27       |            | 27.6 | 26.5 | 25.9 | 21.7 | 22.3 | 21.5 | 26.3 |
| 28       |            | 26.1 | 25.7 | 25.6 | 21.7 | 26.1 | 21.5 | 26.3 |
| 29       |            | 15.8 | 15.3 | 15.6 | 14.5 | 15.7 | 15.8 | 15.7 |
| 30       |            | 13.8 | 14.1 | 14.1 | 13.7 | 13.9 | 14.5 | 15.2 |
| 15-Ac    |            | 170.9 | 170.7 | 170.6 | 171.5 | 171.2 | 171.5 |
| 16-Ac    |            | 171.2 | 22.0 | 171.2 | 170.2 | 171.8 | 171.1 |
| 3-Ac     |            | 22.0 | 22.0 | 21.6 | 21.8 | 24.4 | 21.4 |
| 26r      |            | 170.6 | 21.9 | 30.3 | 27.4 |
| 27r      |            | 21.9 | 30.3 | 27.4 |
The 1H-1H COSY spectrum also showed two oxygenated proton signals at δH 5.49 (d, J = 4.8 Hz) and δH 5.82 (d, J = 4.8 Hz), indicating two acetyl groups at C-15 and C-16. Except for sugar carbons, the 13C-NMR spectrum (Table 2) of 1 displayed 39 carbon resonances including methylene carbon of cyclopropane ring at δC 30.5 (C-19), an oxymethine carbon at δC 88.8 (C-3), an oxygenated quaternary carbon at δC 85.2 (C-20), and an anomic carbon at δC 108.1, together with acetyl signals at δC 170.9, 171.2, 21.2, and 22.0. The 1H and 13C NMR spectroscopic data of 1 confirmed that the compound was a cycloartane triterpene glycoside (Jung et al., 2002; Wu et al., 2017; Wu et al., 2017).

All proton signals were assigned to the corresponding carbons through direct 1H and 13C correlations in the HSQC spectrum. Inspection of the 1H-1H COSY spectrum showed fragments of C-1/C-2/C-3, C-5/C-6/C-7/C-8, C-11/C-12, C-15/C-16/C-17, and C-22/C-23/C-24. In the HMBC spectrum (Figure 2), the correlations were observed from H-28/29 to C-3 and C-5, H-19 to C-1, C-5, C-6, C-9, and C-11, and H-18 to C-12 and C-17, H-30 to C-8, C-14, C-16 and C-18, H-21 to C-22, H-22 to C-24, and H-24 to C-26 and C-2 fully confirmed the basic skeleton cycloartane triterpene of compound 1, which was consistent with the above deduction. The acetyl groups were connected with C-15 and C-16 supported by the correlations from H-15 to δC 170.9 (the carbonyl carbon of OAc) and H-16 to δC 171.2 (the carbonyl carbon of OAc). The sugar was connected with C-3 based on the key HMBC correlation between H-1′ (δH 4.86, d, J = 7.2 Hz) and C-3 (δC 88.8), which was identified as D-xylene by TLC in comparison with authentic monosaccharides (visualization with ethanol-5% H2SO4 spraying) followed by gas chromatography.

The NOESY experiment and coupling constants established the relative configuration of compound 1 (Figure 3), in which correlation of H-3/H-5 showed a-orientation of H-3. The larger coupling constants (JH1,2 > 7.0 Hz) of the anomic protons indicated the β configuration of the sugar unit. The significant cross peaks from H-15 to H2-18, H-17α to Me-21, H-16 to H2-30, and H-24 to Me-21 were observed, which enabled the establishment of OAc-15α and OAc-16β. Until now, all the isolated cycloartane triterpenes share the identical absolute configuration with trans A/B, B/C, C/D rings. Considering the same cycloartane skeleton and identical carbon signals at C-20/C-24, compound 1 was established as 20S and 24R configurations (Ju et al., 2002a). Therefore, the structure of the compound was identified as shown and given the trivial name actatica A.

Compound 2 was determined to have the molecular formula C31H48O11, by the observation of the ion peak at m/z 553.3533 (calcd for C31H48O11Na, 553.3500). The 1H-NMR spectrum (Tables 1, 2) displayed signals for seven tertiary methyls (δH 1.67, 1.62, 1.54, 1.54, 1.58, 1.08, and 1.25), two typical signals at 0.53 (1H, d, J = 4.2 Hz) ascribable to a cyclopropane moiety, indicating that 2 might be a cycloartane-type triterpenoid. The 13C NMR spectrum of 2 displayed 32 carbon signals, three signals attributable to oxygen-bearing quaternary carbons at δ 82.8, 111.2, and 72.4. The NMR data were similar to the reported one (20S, 24S)-16β, 20α, 24-3-deoxy-19-cycloeoxanostane-3β, 15α, 18, 25-tetraol-3-O-β-D-xlyopyranoside (Mu et al., 2014). The differences were the absence of the sugar at C-3, and the appearance of acetyl group at C-15 in compound 2. In the HMBC spectrum, the correlation observed from H-15 to OAc together with the molecular formula confirmed the deduction above. The a configurations of H-16 and H-17 were confirmed by the NOESY correlations between δH 1.86 (H-17) and δH 1.23 (H-30), δH 4.47 (H-16) and δH 2.00 (H-17). Taken together with the 2D-NMR spectra data, compound 2 was characterized and named actatica B.

Compound 3, which was isolated as a white amorphous powder, was assigned as C39H60O11Na, based on its positive HRESIMS ion at m/z 727.4100 (calcd for C39H60O11Na, [M + Na]+, 727.4088). The 1H NMR spectrum showed that 3 possesses a cyclopropane ring, seven methyl groups, and an AB-type hydroxymethyl group (H2-18). The NMR (Tables 1, 2) spectroscopic data for this compound were analogous to 2, except for the appearance of the anomeric proton at δH 4.81 (d, J = 7.8 Hz) and δC 105.1, 71.7, 76.0, 89.0, 67.6, 170.6, and 22.0. The
sugar was identified as a 4′-O-β-D-xylene after acid hydrolysis. Inspection of the 
$^1H$-$^1H$ COSY spectrum showed fragments of C-1/ 
C-2/C-3, C-5/C-6/C-7/C-8, C-11/C-12, C-15/C-16/C-17/C-18, and C-22/C-23. In the HMBC 
spectrum, the correlation from H-3 (3.36, dd, $J = 11.4, 3.0$ Hz) to the anomeric carbon signal at $\delta_C$ 
86.7 supported that the sugar unit was attached to C-3. Thus, the 
structure of 3 was determined as actatica C.

Compound 4 has a molecular formula of $C_{39}H_{60}O_{13}$ according to 
the HRESIMS (m/z 759.3974 [M + Na]$^+$, calcd for 
$C_{39}H_{60}O_{13}Na$, 759.3926). Its IR spectrum showed strong 
hydroxyl (3,439, 1,044 cm$^{-1}$) and carbonyl (1,730 cm$^{-1}$) 
asorptions. The $^1H$ and $^{13}C$ NMR spectra indicated that 4 
had two acetoxyl groups. Detailed NMR spectral analysis revealed that 4 
possessed a cyclopropane ring, six methyl groups, a 
hydroxymethyl group at C-18, and a D-xylosyl unit at C-3. The 
$^1H$ and $^{13}C$ NMR spectra of 4 were similar to those of beesioside J 
(Ju et al., 2002b), except for a carbonyl group (C=O) connected to 
C-12 of 4, which causes the downfield chemical shift of C-12 ($\delta_C$ 
216.6). The correlation from $\delta_H$ 4.54 (H-11) to $\delta_C$ 216.6 (C=O) 
according to the HMBC supported the above result. Therefore, 
compound 4 was tentatively determined and named actatica D.

Compound 5 has the molecular formula $C_{42}H_{66}O_{12}$ determined by 
HR-ESIMS (m/z 785.4301, calcd for $C_{42}H_{66}O_{12}Na$, 785.4341). In the $^1H$ NMR spectrum (Table 1) two 
cyclopropane-methylene protons as an AX system at $\delta_H$ 0.21 and 
0.59 (each 1H, $J = 4.0$ Hz, H$_2$-19) together with nine tertiary 
methyl groups indicated a cycloartane triterpenoid structure. The $^1H$ NMR and $^{13}C$ APT data for this compound were analogous to 1, except for the additional NMR signals at $\delta_C$ 30.3 and 27.4, and $\delta_H$ 1.31 (3H, s), and 1.45 (3H, s). The differences showed that 5 had one 
more hydroxysopropyl group connected at C-24. In the HMBC 
spectrum, the correlations from H-24 to C-26, C-27, and C- 
27$'$ confirmed the above deduction. Taken together with the NOESY 
spectra data, compound 5 was established as 24$'$- 
configured (Ju et al., 2016). As a result, the structure of 5 was 
8-established and named actatica E.

Compound 6 was determined to have the molecular formula $C_{39}H_{60}O_{13}$ based on the $^{13}C$ APT data and by the HRESIMS ion peak at 
m/z 701.3904 ([M + Na]$^+$, calcd for $C_{39}H_{58}O_{13}Na$, 701.3926). The $^1H$-NMR spectrum (Table 1) displayed signals for seven tertiary 
methyls ($\delta_H$ 1.02, 1.22, 1.23, 1.30, 1.53, and 1.55), two typical signals at $\delta_H$ 0.12 (1H, $J = 4.2$ Hz) ascribable to a 
cyclopropane-methylene protons as an AX system at $\delta_H$ 0.21 and 
0.41 (each 1H, $J = 4.2$ Hz, H$_2$-19) together with nine tertiary 
methyl groups indicated a cycloartane triterpenoid structure. The $^1H$ NMR and $^{13}C$ APT data were closely related to those of 
beesioside I (Tables 1, 2) (Sakurai et al., 1990). The differences showed that 7 had a carbonyl group attached to C-12, which 
cause C-12 to move to a lower field, and the chemical shift is 
greatly increased to $\delta_C$ 216.6). The HMBC spectrum shows that 
$\delta_H$ 4.54 (H-11) is related to $\delta_C$ 216.6 (C = O), confirming the 
above inference. Moreover, in the NOESY spectrum, correlations were also detected between Me-21/H-22a/H- 
23a/H-24a, H-22a/H-22β, H-23a/H-23β, H-22β/H-23β, and 
H-24a/Me-26/Me-27. Considering the same cycloartane triterpene skeleton and identical carbon signals at C-20/C- 
24, compound 7 enabled a determination of a 20S$, 24R$ configuration (Ju et al., 2016). As a result, the structure of 7 
was established and named actatica G.

### Bioactive Activity

The cytotoxicity of all compounds 1–7 was tested for their inhibitory activity against human HT-29 and McF-7 cancer cell lines using MTT assay. All compounds showed significant 
inhibitory effects with IC$_{50}$ values of 9.2–26.4 μM (Table 3). Compound 7, with an oxygen bridge between C-18 and C-24, 
showed the best potency among the isolated constituents. With a 
tetrahydrofuran fragment connected by C-20 and C-24, 
compounds 1 and 4–7 showed better activity than 2 and 3.

Seven new 9,19-cycloartane glycosides were isolated from the 
rhizomes of *A. asiatica* H. Hara. Until now, nearly 200 naturally 
occurring triterpenes with a 9,19-cycloartane have been reported 
(Su et al., 2016; Hassan et al., 2020). However, compound 5 with 
one more hydroxy isopropyl group was first isolated from the 
genus *Actaea*. All compounds displayed inhibitory activity against 
human HT-29 and McF-7 cancer cell lines. Further analysis of the 
data showed that compounds 1 and 4–7 exhibited better protective 
effect than other compounds, which indicated that the 
tetrahydrofuran fragment connected by C-20 and C-24 may 
affect the inhibitory activity regarding HT-29 and McF-7.

### DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in 
the article/Supplementary Material; further inquiries can be 
directed to the corresponding authors.
AUTHOR CONTRIBUTIONS

HW and XC were responsible for study design. MH and DZ were responsible for compound isolation and cytotoxic activity testing. GM, XX, MH, and DZ were responsible for structure elucidation and validation of compound identities. All authors contributed equally to manuscript writing, review, and editing. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2021.695456/full#supplementary-material

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