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# Norditerpenoids from *Salvia castanea* Diels f. *pubescens*

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ABSTRACT

Three new norditerpenoids, castanol A–C (**1**–**3**), along with eighteen known diterpenoids, were isolated from *Salvia castanea* Diels f. *pubescens*. Their structures were elucidated by extensive spectroscopic analysis. All compounds were evaluated for their cytotoxic activities against five human cancer cell lines. The known compounds neo-tanshinlactone (**12**) and methyltanshinoate (**17**) exhibited significant cytotoxic activities against some cells.



## 1. Introduction

The genus *Salvia* (Labiatae), comprising about 900 species worldwide, has been used in folk medicine all around the world owing to the wide spectrum of biological activities, such as antibacterial, antioxidant, antitumor, cardioactive, antidiabetic, and anti-inflammatory activities [1]. The plants belonging to *Salvia* are particularly rich in abietanoids and diterpene quinine pigments with different oxygenations and cleavage patterns [2], which have attracted considerable interest within the chemical and biological research fields.

*Salvia castanea* Diels f. *pubescens* Stib., an herb with castaneous flowers, is distributed in the southwest of China [3]. In our prior paper, we reported two novel diterpenoids (castanolide and *epi*-castanolide) from this plant [4]. As a continuous search for the active diterpenoids from *S. castanea* Diels f. *pubescens* Stib., our further investigation yielded three other new abietane diterpenes, castanol A–C (**1**–**3**), together with eighteen known diterpenoids. In the present study, we report the isolation and structure elucidation of these compounds, as well as their cytotoxicity.

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## 2. Experimental procedure

### 2.1. General

Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained on a Shimadzu UV-2401A spectrophotometer. IR spectroscopy was measured in a Bio-Rad FTS-135 spectrometer with KBr pellets. EI-MS and HREI-MS were performed on a VG Autospec-3000 spectrometer. ESI-MS and HRESI-MS were recorded on an API QSTAR Pulsar 1 spectrometer. The NMR spectra were recorded on Bruker AM-400 and DRX-500 spectrometers with TMS as internal standard, and chemical shifts ($\delta$) were expressed in ppm with reference to the solvent signals. Silica gel (200 − 300 mesh; Qingdao Marine Chemical Inc., Qingdao, China), RP-18 gel (40 − 63 μm; Merck, Darmstadt, Germany), and MCI gel (75 − 150 μm, Mitsubinhi Chemical Corporation, Japan) were used for column chromatography. Fractions were monitored by TLC and spots were visualized by heating silica gel plates sprayed with 10% $H_2SO_4$ in EtOH. Solvents were distilled before use. Semipreparative HPLC was performed on an Agilent 1100 liquid chromatography with a Zorbax SB-C18 (5 μm, 9.4 × 250 mm) column.

### 2.2. Plant material

The whole plant of *S. castanea* Diels f. *pubescens* Stib. was collected from Zhongdian of Yunnan, China, in July 2005, and identified by Prof. Xi-Wen Li, Kunming Institute of Botany. The voucher specimen (No. 200501) was deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, CAS.

### 2.3. Extraction and isolation

The whole plant of *S. castanea* Diels f. *pubescens* Stib. (11.5 kg) was extracted with acetone (3×15 L, each 24 h) at room temperature. After evaporation of the solvent under vacuum, the gummy residue (760 g) was partitioned between water and ethyl acetate (EtOAc). The EtOAc extract (580 g) was chromatographed on a silica gel column eluted with a system of petroleum ether–acetone to yield fractions A–G. Fraction B was subjected to silica gel column chromatography (petroleum ether–EtOAc, increasing polarity) to provide three subfractions $B_1$–$B_3$. Subfraction $B_1$ was further chromatographed over repeated silica gel CC combined with Sephadex LH-20 eluted with $CHCl_3$–MeOH (1:1) to afford **13** (53 mg) and **20** (5000 mg). Subfraction $B_2$ was further chromatographed over silica gel CC eluted with petroleum ether–EtOAc (9:1→0:1) and then separated by semipreparative HPLC (MeOH–$H_2O$, 85:15) to give **7** (5 mg), **8** (6 mg), **9** (4 mg), and **10** (4 mg). Subfraction $B_3$ was further chromatographed over MCI gel (MeOH–$H_2O$, 90:10, then 100% MeOH) and then further purified by Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) to yield **4** (11 mg), **11** (6.3 mg), and **12** (2 mg). Fraction C was further purified by silica gel column chromatography using petroleum ether–acetone (9:1→0:1) as eluents to provide subfractions $C_1$–$C_3$. Subfraction $C_1$ was subjected to Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) and applied to semipreparative HPLC (MeOH–$H_2O$, 78:22) to get compounds **14** (7 mg), **15** (7 mg), **16** (53 mg), and **21** (2500 mg). Subfraction $C_2$ was subjected to a RP-18 gel eluted with MeOH–$H_2O$ (1:1→1:0) followed by Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) to yield **2** (7.2 mg), **5** (60 mg), **6** (101 mg), and **17** (11 mg). Subfraction $C_3$ was applied to a RP-18 gel column with a gradient elution (MeOH–$H_2O$, 60:40), and further purified by Sephadex LH-20 (MeOH) to obtain compound **1** (40 mg) and **19** (29 mg). Subfraction D was applied to a RP-18 gel eluted with MeOH–$H_2O$ (50:50) followed by chromatography over repeated silica gel CC, and finally purified by Sephadex LH-20 (MeOH) to give **3** (3.5 mg) and **18** (22 mg).

Castanol A (**1**): red oil; [α]18.6 D −15.4 ($c$=0.14, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ nm ($\varepsilon$): 241 (4.13); IR (KBr) $\nu_{max}$ $cm^{-1}$: 3422, 2961, 2935, 2869, 1765, 1725; $^1H$ and $^{13}C$ NMR data, see Table 1; EI-MS *m/z*: 326 $[M]^+$; HREI-MS *m/z* 326.1146 $[M]^+$ (calcd. for $C_{19}H_{18}O_5$, 326.1154).

Castanol B (**2**): yellow oil; [α]18.6 D +48.0 ($c$=0.15, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ nm ($\varepsilon$): 280 (3.25), 240 (3.31); IR (KBr) $\nu_{max}$ $cm^{-1}$: 3420, 2960, 2927, 2869, 1618, 1418; $^1H$ and $^{13}C$ NMR data, see Table 1; EI-MS *m/z*: 270 $[M]^+$; HREI-MS *m/z* 270.1989 $[M]^+$ (calcd. for $C_{19}H_{26}O$, 270.1984).

Castanol C (**3**): colorless oil; [α]13.8 D −24.5 ($c$=0.18, $CH_3OH$); UV ($CHCl_3$) $\lambda_{max}$ (log$\varepsilon$) nm: 217 (4.02), 257 (4.09); IR (KBr) $\nu_{max}$ $cm^{-1}$: 3433, 2956, 2924, 1623, 1577, 1469, 1384, 1242, 1079, 1036, 796; $^1H$ and $^{13}C$ NMR data, see Table 1; ESI-MS (positive) *m/z*: 259 $[M+H]^+$; HRESI-MS (positive) *m/z* 259.1327 $[M+H]^+$ (calcd. for $C_{16}H_{19}O_3$, 259.1334).

### 2.4. Bioassay

The cytotoxicity of all the compounds against HL-60, SMMC-7721, A-549, MCF-7 and SW-480 cell lines was assessed using

**Table 1**
$^1H$ and $^{13}C$ NMR (500 and 125 MHz, respectively) data for **1**−**3** in $CDCl_3$ ($\delta$ in ppm and *J* in Hz).

| No. | **1** | | **2** | | **3** | |
|---|---|---|---|---|---|---|
| | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ |
| 1 | 77.6 (d) | 5.20 (dd, 11.5, 5.1) | 33.6 (t) | 2.17 (overlap)<br>1.59 (m) | 122.5 (d) | 8.33 (d, 8.2) |
| 2 | 26.1 (t) | 2.38 ($H_\beta$, dd, 8.8, 5.1)<br>1.60 ($H_\alpha$, ddd, 12.5, 11.5, 8.8) | 23.2 (t) | 2.18 (m) | 125.6 (d) | 7.42 (t, 8.2) |
| 3 | 36.8 (t) | 1.86 ($H_\beta$, t, 12.5, 12.1)<br>1.93 ($H_\alpha$, dd, 10.5, 3.9) | 121.2 (d) | 5.42 (br s) | 130.9 (d) | 7.46 (d, 8.2) |
| 4 | 34.6 (s) | | 134.8 (s) | | 134.0 (s) | |
| 5 | 143.8 (s) | | 43.9 (d) | 2.28 (d, 16.5) | 136.4 (s) | |
| 6 | 130.1 (d) | 7.50 (d, 7.8) | 20.7 (t) | 2.08 (m)<br>1.64 (m) | 114.7 (d) | 7.39 (d, 9.1) |
| 7 | 131.1 (d) | 7.63 (d, 7.8) | 28.6 (t) | 2.87 (m) | 124.2 (d) | 7.73 (d, 9.1) |
| 8 | 126.4 (s) | | 127.4 (s) | | 112.8 (s) | |
| 9 | 122.2 (s) | | 145.8 (s) | | 163.0 (s) | |
| 10 | 148.1 (s) | | 35.7 (s) | | 125.4 (s) | |
| 11 | 168.7 (s) | | 110.9 (d) | 6.71 (s) | 206.4 (s) | |
| 12 | 168.8 (s) | | 150.4 (s) | | 42.3 (t) | 2.89 (dd, 15.8, 7.1)<br>3.25 (dd, 15.8, 6.1) |
| 13 | 117.1 (s) | | 131.4 (s) | | 32.8 (d) | 2.42 (m) |
| 14 | 153.6 (s) | | 126.9 (d) | 6.89 (s) | 67.6 (t) | 3.53 (dd, 10.5, 7.0)<br>3.66 (dd, 10.5, 5.0) |
| 15 | 122.8 (s) | | 26.7 (d) | 3.15 (m) | 17.0 (q) | 1.05 (d, 6.8) |
| 16 | 140.4 (d) | 7.30 (s) | 22.6 (q) | 1.28 (d, 6.0) | 19.5 (q) | 2.66 (s) |
| 17 | 9.9 (q) | 2.15 (s) | 22.7 (q) | 1.28 (d, 6.0) | | |
| 18 | 31.6 (q) | 1.09 (s) | 21.5 (q) | 1.71 (s) | | |
| 19 | 30.8 (q) | 1.42 (s) | 22.1 (q) | 1.03 (s) | | |

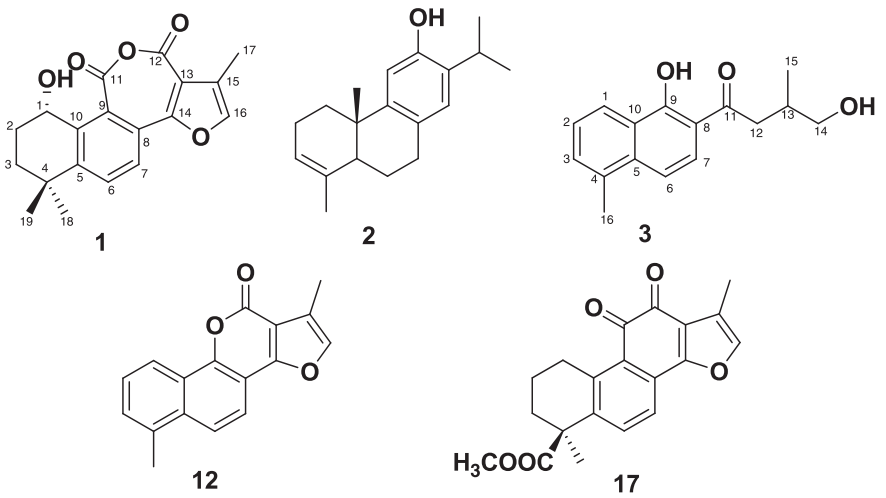


**Fig. 1.** Structures of compounds **1**−**3**, **12** and **17**.

the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method [5]. Cells were plated in 96-well plates 12 h before treatment and continuously exposed to different concentrations of compounds. After 48 h, 20 μL of MTT solution was added to each well, which was incubated for a further 4 h. Then 20% SDS (100 μL) was added to each well. After 12 h at room temperature, the OD value of each well was recorded at 595 nm. The $IC_{50}$ value of each compound was calculated by the Reed and Muench method [6].

## 3. Results and discussion

### 3.1. Chemistry

Compound **1** was obtained as red oil. Its molecular formula was established as $C_{19}H_{18}O_5$ by HREI-MS at *m/z* 326.1146 $[M]^+$ (calcd. 326.1154), indicating 11 degrees of unsaturation. The IR spectrum implied the presence of hydroxyl (3422 $cm^{-1}$) and carbonyl (1765 $cm^{-1}$ and 1725 $cm^{-1}$) groups. The $^{13}C$ and DEPT NMR spectra (Table 1) exhibited nineteen carbon signals due to three methyls, two methylenes, four methines (including one oxygenated and three olefinic), eight quaternary carbons (including seven olefinic ones) and two ester carbonyls. Two structural fragments, C-1/C-2/C-3 and C-6/C-7, were deduced from the $^1H$ $^1H$ COSY spectrum as shown in Fig. 2.

Comparison of the 1D NMR spectroscopic data (Table 1) of **1** with those of the known compound 6,7,8,9-tetrahydro-1,6,6-trimethylfuro[3,2-c]naphth-[2,1-e]oxepine-10,12-dione (**4**) [7] showed that the two compounds were very similar. The only differece was the replacement of a methylene at C-1 in **4** by a hydroxyl group in **1**. The HMBC correlations from H-1 ($\delta_H$ 4.65, dd, $J$ = 11.5, 5.1 Hz) to C-2 ($\delta_C$ 26.1, t), C-3 ($\delta_C$ 36.8, t), C-5 ($\delta_C$ 143.8, s), C-9 ($\delta_C$ 122.2, s) and C-10 ($\delta_C$ 148.1, s) further confirmed the presence of the hydroxyl group at C-1.

The configuration of **1** was deduced from the $^1H$ NMR splitting patterns and a comparison with the literature data for known related compounds. The hydroxyl group at C-1 in **1** was determined to be *S* on the basis of the $^1H$ NMR splitting patterns of H-1, which was found to be separated in a classic ABX system (dd, $J$ = 10.0, 5.0 Hz) [8], while in an *R* disposition, it would appear as a triplet with a $J$ value between 3.0 and 3.5 Hz [9]. Therefore, the structure of **1** was established as shown in Fig. 1, and named castanol A.

Compound **2**, yellow oil, showed a molecular ion peak at *m/z* 270.1989 $[M]^+$ (calcd. 270.1974), corresponding to the molecular formula $C_{19}H_{26}O$. The IR spectrum clearly exhibited absorptions of hydroxy (3561 $cm^{-1}$) group. The NMR data (Table 1) indicated that **2** contained an aromatic ring [$\delta_C$ 110.9 (d), 126.9 (d), 127.4 (s), 131.4 (s), 145.8 (s), 150.4 (s)], a trisubstituted double bond [$\delta_C$ 121.4 (d), 134.8 (d)], and an isopropyl unit [$\delta_C$ 26.7 (d), 22.6 (q), and 22.7 (q)]. These characteristic data, along with knowledge of the structural types of diterpenoids previously isolated from the genus *Salvia*, indicated that compound **2** was an abietane diterpenoid.

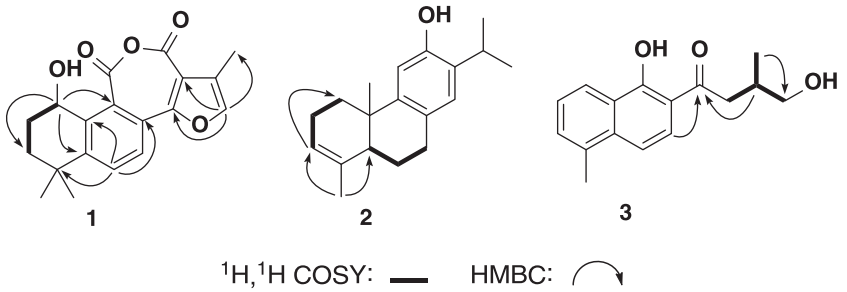


**Fig. 2.** $^1H$, $^1H$ COSY and key HMBC correlations of **1**−**3**.

The $^{1}H$ and $^{13}C$ NMR data (Table 1) of **2** were similar to those of ferruginol (**5**) [10]. The key difference was the presence of a trisubstituted olefin at the 3,4-position in **2**, as confirmed by the HMBC correlations from $H_3$-18 ($\delta_H$ 1.71) to C-3, C-4 and C-5 and the $^{1}H$ $^{1}H$ COSY spin system $H_2$-1/$H_2$-2/H-3. Consequently, the structure of castanol B was established as **2**.

Compound **3** was isolated as colorless oil, and its molecular formula was found to be $C_{16}H_{18}O_3$ by HRESI-MS (positive) ($[M+H]^+$, *m/z* 259.1327, calcd. 259.1334), corresponding to 8 degrees of unsaturation. The IR spectrum exhibited hydroxyl absorption at 3433 $cm^{-1}$ and the other carbonyl group with intramolecular hydrogen bonding and conjugation to an aromatic ring at 1623 $cm^{-1}$. The $^{13}C$ and DEPT NMR spectra of **3** indicated the presence of 16 carbon signals (Table 1), which were assigned to two methyl, two methylene (one oxygenated), one saturated methine, one ketone ($\delta$ 206.4), and ten aromatic (five protonated and five quaternary) carbons. The connectivities of the $^{1}H$ and $^{13}C$ signals were determined by analysis of its HSQC spectrum. The NMR data were quite identical to those of the known compound salvianonol [11]. The only difference lies in that the acetyl group at C-14 of salvianonol was replaced by a hydroxyl group in **3**. The upfield shift of C-14 and the molecular formula of **3** also confirmed the above conclusion. Compound **3** was thus elucidated as 4-hydroxy-1-(1-hydroxy-5-methylnaphthalen-2-yl)-3-methylbutan-1-one, and named as castanol C.

The structures of other known compounds (**4—21**) were identified to be 6,7,8,9-tetrahydro-1,6,6-trimethylfuro[3,2-c]naphth-[2,1-e]oxepine-10,12-dione (**4**) [7], ferruginol (**5**) [10], przewalskin (**6**) [12], methylenetanshinquinone (**7**) [13], 1,2-dihydrotanshinone I (**8**) [13], danshenspiroketallactone (**9**) [14], epi-danshenspiroketallactone (**10**) [14], sibiriquinone B (**11**) [15], neo-tanshinlactone (**12**) [16], tanshinone I (**13**) [17], methylenedihydrotanshinquinone (**14**) [18], trijuganone B (**15**) [19], dihydrotanshinone I (**16**) [20], methyltanshinoate (**17**) [21], salvicanol (**18**) [22], tanshinone IIB (**19**) [23], tanshinone IIA (**20**) [17], and crypotanshinone (**21**) [20], respectively, by comparison of their spectroscopic data with those reported in the literature.

### 3.2. Biological activity

All the compounds were evaluated for cytotoxicity against five human cancer cell lines using the MTT method as reported previously [5], with DDP as positive control. The known compound methyltanshinoate (**17**) exhibited potent toxicity effects against SMMC-7721, A-549, MCF-7, and SW-480 cells, with $IC_{50}$ values of 4.07, 5.26, 3.44, and 6.35 μM, respectively, while neo-tanshinlactone (**12**) showed significant cytotoxicity against MCF-7 and SW-480 cell lines, with $IC_{50}$ values of 13.46 and 12.65 μM, respectively (Table 2). The other compounds were inactive in the tested system ($IC_{50} > 40$ μM).

**Table 2**
Cytotoxicity of compounds **12** and **17** against tumor cell lines with $IC_{50}$ (μM).

| Compound | HL-60 | SMMC-7721 | A-549 | MCF-7 | SW480 |
|---|---|---|---|---|---|
| **12** | >40 | 20.02 | 26.75 | 13.46 | 12.65 |
| **17** | 16.24 | 4.07 | 5.26 | 3.44 | 6.35 |
| Cisplatin[a] | 0.97 | 14.75 | 13.61 | 17.13 | 15.56 |

[a] Positive control.

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