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# SECALONIC ACIDS J–M, FOUR NEW SECONDARY METABOLITES FROM THE MARINE-DERIVED FUNGUS *PENICILLIUM OXALICUM*

**Li Chen,[a] Zhi-Hao Lu,[a] Qin-Ying Liu,[b]* Qiu-Hong Zheng,[b] Lin Du,[c] and Qi-Qing Zhang[a]***

[a] Institute of Biomedical and Pharmaceutical Technology, Fuzhou University, Fuzhou, 350002, P. R. China. [b] Fujian Provincial Key Laboratory of Tumor Biotherapy, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital, Fuzhou 350014, P. R. China. [c] Institute for Natural Products Applications and Research Technologies, Department of Chemistry and Biochemistry, University of Oklahoma, Norman 73019–5251, United States. E-mail: liuqy@fjmu.edu.cn; zhangqiq@126.com.

**Abstract** – Four new secalonic acid derivatives, secalonic acids J–M (**1**–**4**), were isolated from the marine-derived fungus *Penicillum oxalicum*. The planar structures of these compounds were elucidated by NMR and high-resolution mass spectrometric analyses. The absolute configurations were established by comparison of their experimental and calculated electronic circular dichroism spectra. Finally, these compounds were further evaluated for cytotoxic activities against the selected cancer cell lines in *vitro*. The results of flow cytometry demonstrated that compound **1** owned moderate activity of inducing apoptosis against HeLa cell.

The secalonic acids bearing a xanthone dimers skeleton (ergochrome)[1] have been isolated from various fungal genera (e.g. *Penicillium oxalicum* and *Aspergillus ochraceus*).[2] Since Stoll et al.[3] discovered secalonic acid A from a fungus in 1952, totally nine secalonic acid analogues have been reported, namely secalonic acids A–I.[4] Naturally occurring secalonic acids have attracted a great deal of attention for their unusual structural features and broad spectrum of biological activities.

Comparing with the land, ocean has a quite different environment, which has made the marine-derived fungi evolve highly adapted metabolic systems in the natural selection process.[5] Therefore, the emergence of an increasing number of candidates for the development of new therapy drugs becomes possible. Till

2011, fungi from the marine environment have provided more than 1000 new natural products with surprisingly vast number of rare structures and well biological activities.[6] Marine-derived fungi, hence, are recognized as a fruitful source of antitumor drugs. So we selected the marine-derived fungi as the target strains to study the second metabolites.

In this study, an isolated fungal strain *Penicillium oxalicum*, obtained from southeast coast of China, was cultured in a nutrient-rich medium. Its mycelia extract displayed significant antitumor activity in *vitro*. During our previous study,[4] two new secalonic acid derivatives, secalonic acids H and I, and the known secalonic acid D have been reported. Further chemical study of this fungus led to the isolation of another four novel secalonic acid derivatives, secalonic acids J–M (**1**–**4**). In this paper, the isolation, structural elucidation and bioactivities of these new compounds are reported.

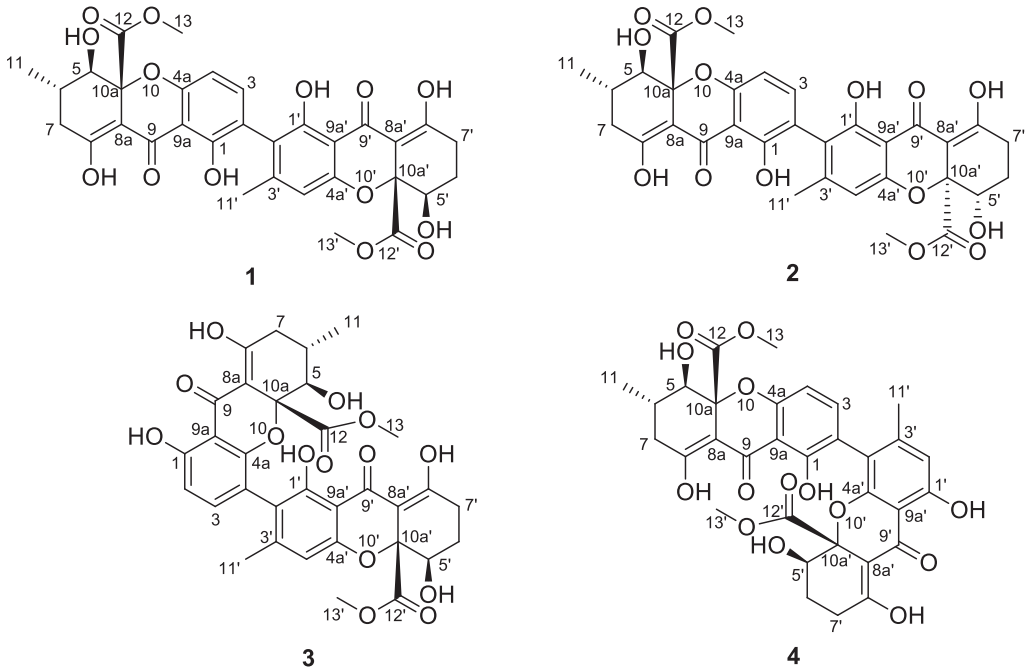


**Figure 1.** Structures of compounds **1**–**4** isolated from *P. oxalicum*

Secalonic acid J (**1**) was obtained as yellow gum. The molecular formula was determined to be $C_{32}H_{30}O_{14}$ on the basis of HRESIMS (*m/z*: 639.1712 $[M + H]^+$, calcd for $C_{32}H_{31}O_{14}$, 639.1714). Its NMR data (Tables 1 and 2), combined with DEPT and HMQC spectrum analyses, revealed the presence of thirty-two carbons, including nineteen quaternary carbons, six methines, three methylenes, and four methyls. Compared to sixteen carbon signals observed for the symmetrical structure of secalonic acid D,[7] thirty-two carbon signals were detected in the $^{13}C$ NMR spectrum of **1** indicating the structure of **1** is asymmetrical. All the sixteen carbon signals of secalonic acid D were identified in the thirty-two signals of **1**, which was further confirmed by COSY and HMBC spectrum analyses. Thus, it was suggested that a half structure of secalonic acid D was retained in **1**.

**Table 1.** $^{13}$C NMR Data (125 MHz, $\delta$ in ppm) of compounds **1**–**4** in DMSO-$d_6$

| No. | **1** | **2** | **3** | **4** |
|---|---|---|---|---|
| 1 | 158.7, C | 158.6, C | 160.5, C | 158.5, C |
| 2 | 116.2, C | 116.0, C | 109.3, CH | 116.3, C |
| 3 | 140.9, CH | 140.7, CH | 140.9, CH | 141.2, CH |
| 4 | 107.8, CH | 107.7, CH | 114.9, C | 107.8, CH |
| 4a | 159.0, C | 159.1, C | 157.3, C | 158.9, C |
| 5 | 75.4, CH | 75.2, CH | 75.0, CH | 75.3, CH |
| 6 | 29.9, CH | 29.9, CH | 30.4, CH | 29.9, CH |
| 7 | 35.8, $CH_2$ | 35.8, $CH_2$ | 35.9, $CH_2$ | 35.8, $CH_2$ |
| 8 | 178.2, C | 178.2, C | 178.6, C | 178.0, C |
| 8a | 101.6, C | 101.8, C | 101.9, C | 101.7, C |
| 9 | 186.5, C | 186.6, C | 186.4, C | 186.7, C |
| 9a | 106.4, C | 106.4, C | 106.7, C | 106.4, C |
| 10a | 85.2, C | 85.2, C | 84.7, C | 85.1, C |
| 11 | 17.8, Me | 17.7, Me | 17.7, Me | 17.7, Me |
| 12 | 170.04, C | 170.2, C | 169.9, C | 170.4, C |
| 13 | 52.9, Me | 52.7, Me | 52.7, Me | 52.7, Me |
| 1' | 158.8, C | 158.9, C | 159.2, C | 159.8, C |
| 2' | 117.6, C | 117.4, C | 118.2, C | 110.8, CH |
| 3' | 149.5, C | 149.5, C | 149.4, C | 149.5, C |
| 4' | 109.0, CH | 108.8, CH | 108.8, CH | 116.0, C |
| 4a' | 158.3, C | 158.3, C | 158.0, C | 156.8, C |
| 5' | 70.3, CH | 70.2, CH | 70.3, CH | 70.0, CH |
| 6' | 25.4, $CH_2$ | 25.4, $CH_2$ | 25.3, $CH_2$ | 25.9, $CH_2$ |
| 7' | 27.5, $CH_2$ | 27.5, $CH_2$ | 27.5, $CH_2$ | 27.5, $CH_2$ |
| 8' | 178.7, C | 178.7, C | 178.5, C | 179.1, C |
| 8a' | 101.3, C | 101.3, C | 101.4, C | 101.6, C |
| 9' | 186.2, C | 186.2, C | 186.1, C | 185.9, C |
| 9a' | 104.3, C | 104.4, C | 104.2, C | 104.8, C |
| 10a' | 84.7, C | 84.7, C | 84.4, C | 84.7, C |
| 11' | 21.0, Me | 20.8, Me | 21.4, Me | 20.7, Me |
| 12' | 169.95, C | 170.0, C | 170.4, C | 169.9, C |
| 13' | 52.9, Me | 52.8, Me | 52.8, Me | 52.8, Me |

For the other half of the structure, two methine groups (C-3, 140.9; H-3, 7.29; C-6, 29.9; H-6, 2.31) were replaced by a quaternary carbon (C-3', 149.5) and a methylene group (C-6', 25.4; H-6', 2.09, 1.91) respectively, and the obviously downfield shift of H-11' (from 1.04 d to 2.03 s) suggested that Me-11' was moved from C-6' to C-3'. The COSY correlation of H-6' with H-5' and H-7' and the key HMBC correlation from H-11' to C-2', C-3' and C-4' and from H-4' to C-11' further supported this deduction. Finally, the key COSY correlation of H-3 with H-4 and HMBC correlation from H-3 to C-2' revealed that

the two independent segments were linked through C-2 and C-2'. Until now, the planar structure of **1** was established (Figure 1).

Secalonic acid K (**2**) was obtained as yellow gum. The molecular formula was determined to be $C_{32}H_{30}O_{14}$ on the basis of HRESIMS (*m/z*: 639.1714 $[M + H]^+$, calcd for $C_{32}H_{31}O_{14}$, 639.1714). After careful comparison the 1D-NMR data of **2** and **1** (Tables 1 and 2) and further analysis the COSY and HMBC correlations of **2** (Figure 2), compound **2** was deduced to own the same planar structure as **1**.

**Table 2.** $^1$H NMR Data (500 MHz, *J* in Hz and $\delta$ in ppm) of compounds **1**–**4** in DMSO-$d_6$

| No. | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 2 | | | 6.53, d (8.4) | |
| 3 | 7.29, d (8.1) | 7.31, d (8.4) | 7.18, d (8.4) | 7.65, d (8.5) |
| 4 | 6.64, d (8.1) | 6.63, d (8.4) | | 6.65, d (8.5) |
| 5 | 3.81, d (11.0) | 3.82, d (11.0) | 3.67, d (10.9) | 3.81, d (11.1) |
| 6 | 2.31, m | 2.31, m | 2.28, m | 2.30, m |
| 7a | 2.66, dd (19.4, 5.1) | 2.65, dd (19.3, 5.9) | 2.61, dd (19.3, 6.2) | 2.65, dd (19.2, 6.0) |
| 7b | 2.46, dd (19.4, 8.4) | 2.47, dd (19.3, 10.5) | 2.46, dd (19.3, 10.8) | 2.46, dd (19.2, 10.9) |
| 11 | 1.04, d (5.6) | 1.04, d (6.4) | 0.97, d (6.5) | 1.03, d (6.4) |
| 13 | 3.63, s | 3.59, s | 3.55, s | 3.59, s |
| 1-OH | 11.51, s | 11.41, s | 11.25, brs | 11.42, s |
| 5-OH | 6.00[b], brs | | | |
| 8-OH | 13.74[a], brs | 13.72[a], brs | 13.90[a], brs | 13.96[a], brs |
| 2' | | | | 6.48, s |
| 4' | 6.56, s | 6.56, s | 6.54, s | |
| 5' | 4.19, dd (11.2, 3.7) | 4.20, dd (12.0, 5.0) | 4.18, dd (12.1, 4.9) | 4.02, dd (11.7, 4.8) |
| 6'a | 2.09, m | 2.09, m | 2.09, m | 2.04, m |
| 6'b | 1.91, m | 1.91, m | 1.91, m | 1.83, m |
| 7'a | 2.80, m | 2.80, m | 2.80, m | 2.73, m |
| 7'b | 2.54, m | 2.52, m | 2.53, m | 2.52, m |
| 11' | 2.03, s | 2.05, s | 2.19, s | 1.99, s |
| 13' | 3.64, s | 3.62, s | 3.62, s | 3.64, s |
| 1'-OH | 11.41, s | 11.36, s | 11.30, s | 11.12, s |
| 5'-OH | 5.75[b], s | | | |
| 8'-OH | 13.60[a], s | 13.62[a], brs | 13.83[a], brs | 13.66[a], brs |

[a,b] exchangeable signals

Secalonic acid L (**3**) was obtained as yellow gum. The molecular formula was determined to be $C_{32}H_{30}O_{14}$ on the basis of HRESIMS (*m/z*: 661.1537 $[M + Na]^+$, calcd for $C_{32}H_{30}NaO_{14}$, 661.1533). The same molecular formula and similar NMR data implied that the structure of **3** was similar to those of **1** and **2**. After careful analysis the COSY and HMBC correlations of **3**, the two independent segments of **1** were reserved in **3** respectively. However, their binding site was changed from 2-2' in **1** to 4-2' in **3**,

considering the key COSY correlation of H-2 with H-3 and HMBC correlation from H-3 to C-2'. Thus, the planar structure of **3** was established (Figure 1).

Secalonic acid M (**4**) was obtained as yellow gum. The molecular formula was determined to be $C_{32}H_{30}O_{14}$ on the basis of HRESIMS (*m/z*: 661.1535 $[M + Na]^+$, calcd for $C_{32}H_{30}NaO_{14}$, 661.1533). After careful comparison the 1D-NMR data of **4** and **1** (Tables 1 and 2) and further analysis the COSY and HMBC correlations of **4** (Figure 2), the two independent segments of **1** were also reserved in **4**. However, the key COSY correlation of H-3 with H-4 and HMBC correlation from H-3 to C-4' revealed that the two independent segments were linked through C-2 and C-4'. Until now, the planar structure of **4** was determined (Figure 1).

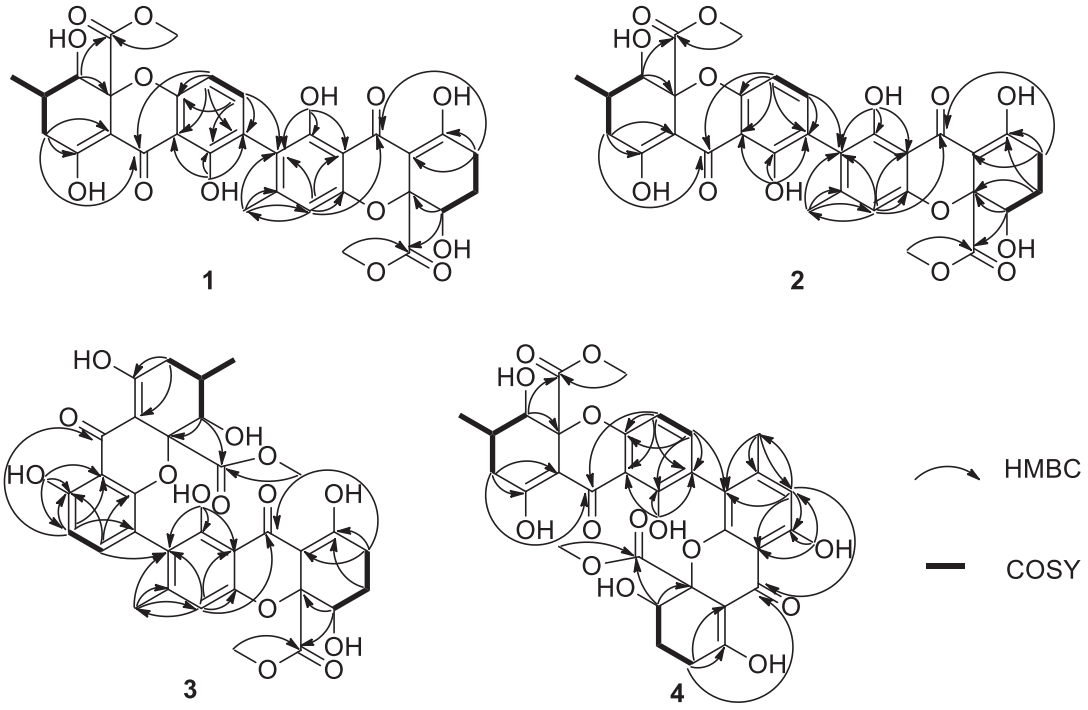


**Figure 2.** COSY and HMBC correlations for compounds **1**–**4**

The relative configurations of **1**–**4** were proposed by selected NOE experiments. In the NOE spectrum (Figure 3) of **1**, correlations of H-5 with Me-11, H-6 with Me-13, H-6'b with H-5' and H-6'a with Me-13' help to determine the configurations of two cyclohexene rings, which were further supported by these coupling constants ($J_{5,6}$ = 11.0 Hz, $J_{5',6'a}$ = 11.2 Hz, and $J_{5',6'b}$ = 3.7 Hz). The similar phenomena and coupling constants were also observed in **2**–**4**, suggesting the relative configurations of compounds **1**–**4** were the same.

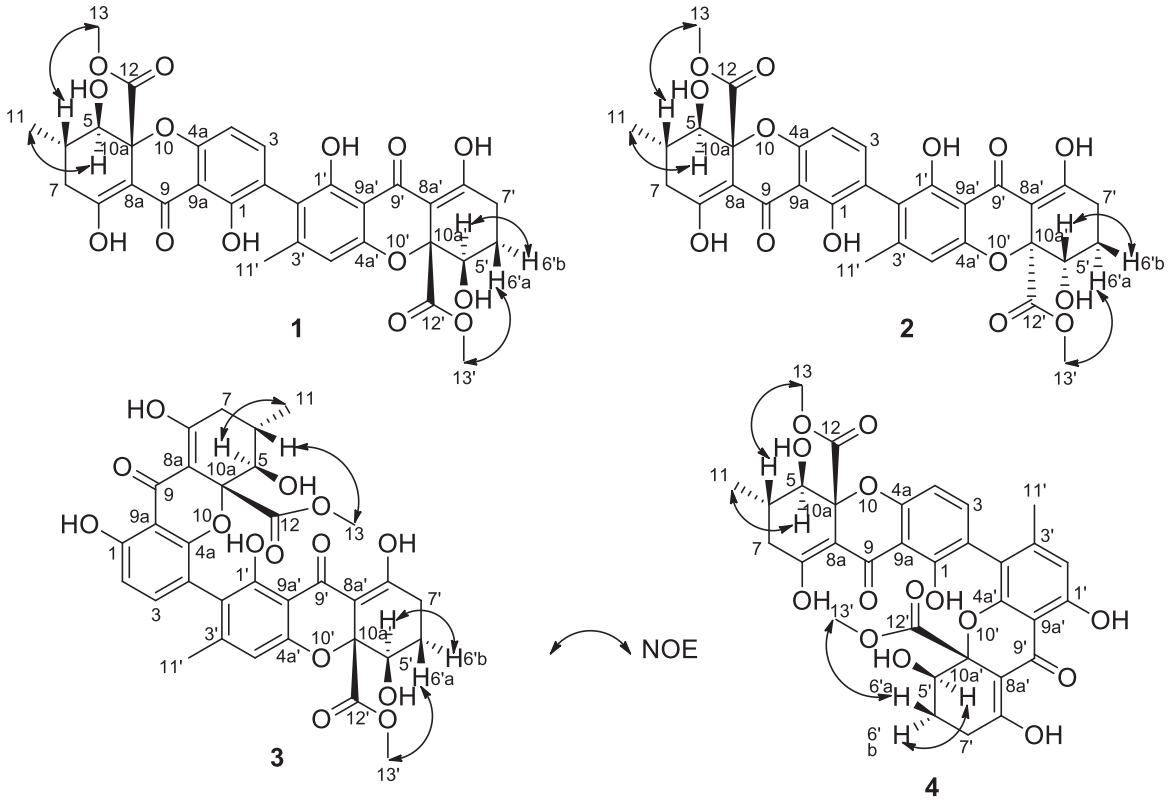


**Figure 3.** NOE correlations for compounds **1**–**4**

The absolute configurations of compounds **1**–**4** were further determined by comparison their experimental CD spectra with the computed spectra. Considering **1** and **2** owned the same planar structures and similar relative configurations, there were four possible assemblies for two compounds. After careful comparison the experimental CD spectra of **1** and **2**, **2** was excluded to be the enantiomer of **1**. Furthermore, the CD spectra of these four possible assemblies were calculated, respectively. Finally, the experimental CD spectra of **1** and **2** matched well with two among them. Thus, the absolute configurations of **1** and **2** were determined to be 5*R*, 6*S*, 10a*R*, 5'*R*, 10a'*R* and 5*R*, 6*S*, 10a*R*, 5'*S*, 10a'*S* (Figures 4 and 5). In addition, the similar CD spectra of **1** and secalonic acid D[2] and the reverse CD spectra of **1** and secalonic acid A[8] further confirmed this conclusion. The experimental CD spectra of **3** and **4** agreed well with the experimental spectra of **1** and secalonic acid D[2] suggesting that the absolute configurations of **3** and **4** were similar to **1** and secalonic acid D, which were also fully supported by quantum chemical ECD calculation (Figures 4 and 5).

These new compounds were further tested for cytotoxic effects on five different cell lines by MTT method (Table 3). Compounds **1**–**4** showed different levels of cytotoxic effects against these cell lines. Moreover, we adopted Annexin V-FITC/PI double staining to explore whether these compounds could induce cancer cell apoptosis or not. As shown in Figure 6, the apoptotic rates of HeLa cell increased from 2.8% to 18.8%, 53.4% and 58.4% when treated with 2.5, 5, and 10 μM of compound **1**, respectively.

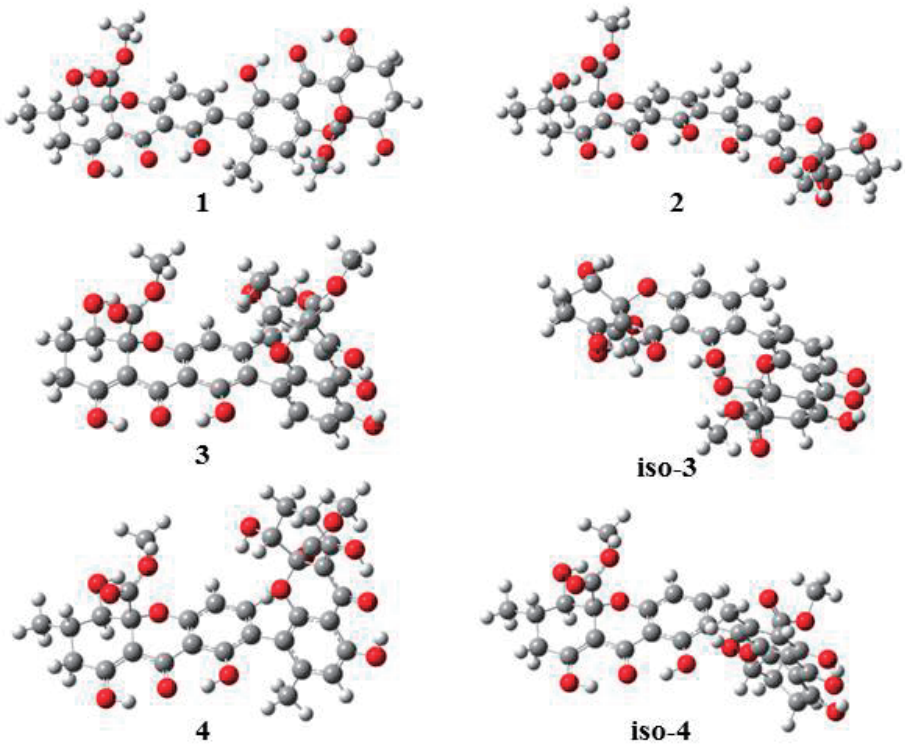


**Figure 4.** The lowest energy conformation of compounds **1**–**4** (the absolute configurations of **iso-3** and **iso-4:** 5*R*, 6*S*, 10a*R*, 5'*S*, 10a'*S*)

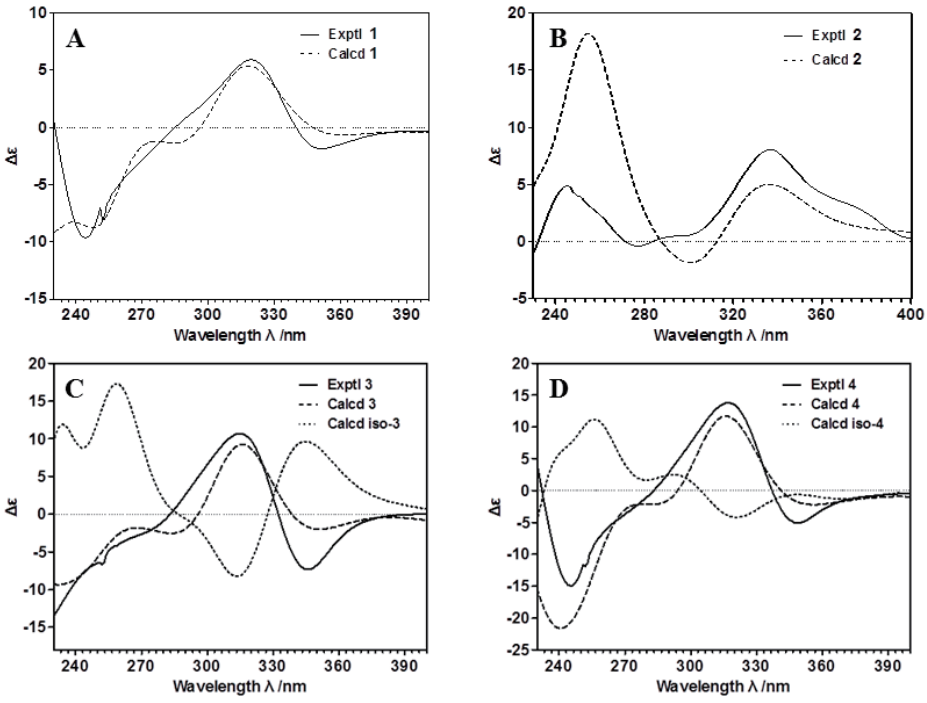


**Figure 5.** Comparison of experimental and calculated ECD spectra of compounds **1**–**4** (the absolute configurations of **iso-3** and **iso-4:** 5*R*, 6*S*, 10a*R*, 5'*S*, 10a'*S*)

**Table 3.** Cytotoxic effects of compounds **1**–**4** in the selected cancer cell lines ($IC_{50}$, μM)

| No. | HeLa | HCT116 | MCF-7 | Hep-3B | A549 |
|---|---|---|---|---|---|
| **1** | 3.2 | 6.1 | 9.2 | 19.3 | 36.7 |
| **2** | 4.5 | 5.4 | 4.5 | 12.1 | 6.3 |
| **3** | 7.4 | 19.7 | 16.9 | >100 | 76.8 |
| **4** | 16.3 | 4.4 | 5.7 | 5.5 | 7.9 |
| ADM[a] | 0.3 | 0.2 | 0.4 | 0.3 | 0.7 |

[a] ADM = doxorubicin (positive control)

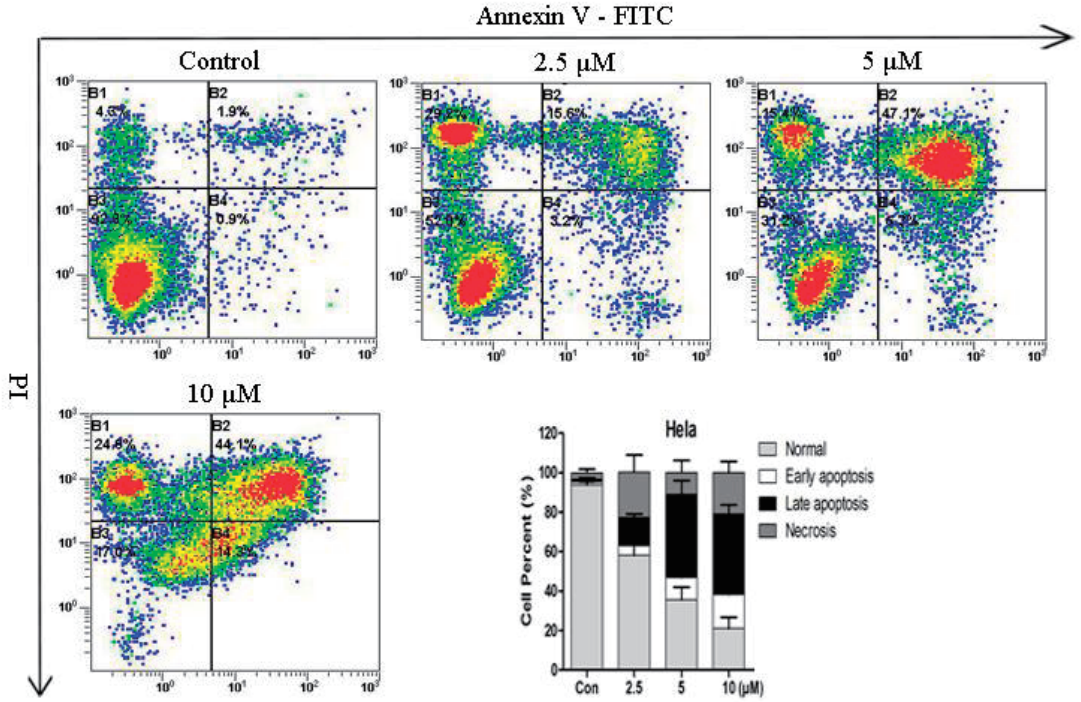


**Figure 6.** Annexin V/PI test of HeLa cell treated with compound **1** (0, 2.5, 5, and 10 μM) for 48 h

## EXPERIMENTAL

**General Experimental Procedures.** Optical rotations were obtained from an Anton Paar MCP 200 digital polarimeter. UV spectra were recorded on a Shimadzu UV-2450 spectrophotometer, while CD spectra were measured on a Jasco J-715 spectra polarimeter. IR spectra were recorded on a Nicolet 670 spectrophotometer. $^{1}$H NMR, $^{13}$C NMR, DEPT spectra and 2D NMR were recorded on a Bruker Biospin Avance III spectrometer using TMS as the internal standard. HRESIMS were obtained by an Agilent Q-TOF 6520 LC mass spectrometer. Semipreparative HPLC was performed using an ODS column (ODS-A, 10×250 mm, 5 μm) at 5 mL/min. Apoptosis and necrosis cells were detected with the Annexin

V FLUOS staining kit (Roche, Mannheim, Germany) and recorded on a Beckman Coulter FC500 flow cytometer.

**Fungal Material.** The fungus *P. oxalicum* was isolated from marine sediments collected from Langqi Island, Fujian, China. It was identified according to its morphological characteristics and ITS by Beijing Sunbiotech Co. Ltd, and preserved in our laboratory at –80 ˚C. The producing strain was prepared on Martin medium and stored at 4 ˚C.

**Fermentation and Extraction.** The fungus was cultured under static conditions at 28 ˚C for 30 days in 150×1000 mL conical flasks containing 400 mL liquid medium, composed of glucose (10 g/L), maltose (20 g/L), mannitol (20 g/L), monosodium glutamate (10 g/L), $KH_2PO_4$ (0.5 g/L), $MgSO_4$•$7H_2O$ (0.3 g/L), yeast extract (3 g/L), NaCl (15 g/L) and water. The fermented whole broth (60 L) was filtered through cheese cloth to separate supernatant from mycelia. The mycelia were extracted three times with acetone. The acetone solution was concentrated under reduced pressure to afford an aqueous solution. The aqueous solution was extracted three times with EtOAc and concentrated in vacuo to give mycelia extract (36.5 g).

**Purification.** The mycelia extract (36.5 g) was separated into five fractions on a silica gel column using a step gradient elution of petroleum ether, $CH_2Cl_2$, and MeOH. Fraction D (5.9 g) eluted with $CH_2Cl_2$/MeOH (100:1) was separated into five subfractions (D1 to D5) on a silica gel column again, using a step gradient elution of $CH_2Cl_2$ and MeOH. Subfraction D3 (1.1 g) was further purified on a reversed-phase column (MeOH:$H_2O$) to obtain four subfractions (D3-1 to D3-4). Subfraction D3-2 (168 mg) was purified by semipreparative HPLC (50% MeCN with 0.1% TFA), yielding compounds **1** (2.8 mg), **2** (2.3 mg), **3** (2.1 mg), and **4** (2.6 mg).

**Secalonic acid J (1):** yellow gum ($CHCl_3$); $[\alpha]^{25}_D$ –34.3 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ (log $\varepsilon$) 263 (4.30), 336 (4.51) nm; CD ($CHCl_3$) $\lambda_{max}$ ($\Delta\varepsilon$) 243 (–9.4), 319 (+6.0), 350 (–1.7) nm; IR (KBr) $\nu_{max}$ 3469, 2962, 2925, 1740, 1618, 1430, 1238, 1062 $cm^{-1}$; $^1H$ and $^{13}C$ NMR see Tables 1 and 2; HRESIMS $[M + H]^+$ *m/z*: 639.1712 (calcd for $C_{32}H_{31}O_{14}$, 639.1714), $[M – H]^–$ *m/z*: 637.1567 (calcd for $C_{32}H_{29}O_{14}$, 637.1557).

**Secalonic acid K (2):** yellow gum ($CHCl_3$); $[\alpha]^{25}_D$ +17.4 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ (log $\varepsilon$) 262 (4.30), 336 (4.45) nm; CD ($CHCl_3$) $\lambda_{max}$ ($\Delta\varepsilon$) 244 (+4.87), 277 (–0.25), 336 (+8.20) nm; IR (KBr) $\nu_{max}$ 3436, 2966, 2929, 1730, 1630, 1454, 1240, 1042 $cm^{-1}$; $^1H$ and $^{13}C$ NMR see Tables 1 and 2; HRESIMS $[M + H]^+$ *m/z*: 639.1714 (calcd for $C_{32}H_{31}O_{14}$, 639.1714), $[M – H]^–$ *m/z*: 637.1560 (calcd for $C_{32}H_{29}O_{14}$, 637.1557).

**Secalonic acid L (3):** yellow gum ($CHCl_3$); $[\alpha]^{25}_D$ –385.0 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ (log $\varepsilon$) 264 (4.35), 336 (4.54) nm; CD ($CHCl_3$) $\lambda_{max}$ ($\Delta\varepsilon$) 315 (+10.9), 345 (–7.3) nm; IR (KBr) $\nu_{max}$ 3454, 2960, 2924, 1742, 1617, 1438, 1236, 1050 $cm^{-1}$; $^1H$ and $^{13}C$ NMR see Tables 1 and 2; HRESIMS $[M + Na]^+$ *m/z*: 661.1537 (calcd for $C_{32}H_{30}NaO_{14}$, 661.1533), $[M – H]^–$ *m/z*: 637.1568 (calcd for $C_{32}H_{29}O_{14}$, 637.1557).

**Secalonic acid M (4):** yellow gum ($CHCl_3$); $[\alpha]^{25}_D$ –272.3 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ (log $\varepsilon$) 263 (4.22), 337 (4.42) nm; CD ($CHCl_3$) $\lambda_{max}$ ($\Delta\varepsilon$) 244 (–14.6), 317 (+13.9), 348 (–4.8) nm; IR (KBr) $\nu_{max}$ 3455, 2958, 2926, 1735, 1628, 1437, 1245, 1061 $cm^{-1}$; $^1H$ and $^{13}C$ NMR see Tables 1 and 2; HRESIMS $[M + Na]^+$ *m/z*: 661.1535 (calcd for $C_{32}H_{30}NaO_{14}$, 661.1533).

**Quantum Chemical ECD Calculations.** A conformational search was carried out with ComputeVOA 0.1 software for the proposed absolute configuration as shown using GMMX method. Geometry and frequency calculations of the lowest-energy conformers resulted from the conformational search were carried out with Gaussian 09 (Gaussian Inc., Wallingford, CT)[9] at the DFT level (B3LYP functional/DGDZVP basis set) in $CHCl_3$ using the COSMO solvation model. TD-DFT calculations (B3LYP functional/DGDZVP basis set in $CHCl_3$ using the COSMO solvation model) provided the single UV and CD spectra of the optimized lowest-energy conformers, which were then added up after a Boltzmann statistical weighting using SpecDis 1.60 (by using a sigma value of 0.3 eV).[10] After applying a UV-shift correction of +10 nm, the computed CD spectra were compared with the CD curves experimentally obtained.

**Cytotoxicity Assay.** The cytotoxic activity for the tumor cell lines were evaluated by the MTT method as previous reported.[4]

**Annexin V-FITC/PI Double Staining.** Apoptosis and necrosis cells were detected with the Annexin V FLUOS staining kit as previously described.[11] In a typical procedure, cells were collected, washed, and incubated with Annexin V-EGFP buffer for 15 min. Furthermore, cells were resuspended in 200 μL mixed solution with PI and tested by flow cytometry. Data were analyzed by Flowjo software.

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