New Triterpenoids from the Fruiting Bodies of *Laetiporus sulphureus* and Their Anti-Inflammatory Activity

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ABSTRACT: *Laetiporus sulphureus* is a popular medicinal mushroom with diverse pharmacological activities in many Asian countries. Four new triterpenoids, named sulphurenoids A–D (1−4), along with 12 known analogues, were isolated from the fruits of *L. sulphureus*. Nuclear magnetic resonance, infrared spectroscopy, and high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) techniques were used for the investigation of the chemical structure of isolated compounds. In addition, the anti-inflammatory activity of three new compounds (2−4) was tested for NO production in lipopolysaccharide-induced RAW 264.7 cells. The IC$_{50}$ values of isolated triterpenoids ranged from 14.3 to 42.3 μM, which were more effective than the positive control (IC$_{50}$ for minocycline was 73.0 μM). The experimentally obtained anti-inflammatory activity data of *L. sulphureus* are in agreement with its traditional use.

1. INTRODUCTION

*Laetiporus sulphureus* (Bull.) Murill belongs to Fomitopsidaceae family; it is a medicinal and edible mushroom distributed worldwide. The analysis of literature reports about the phytochemistry of *L. sulphureus* indicated the presence of lectins, polysaccharides, polyenelactiporic acids, triterpenoids, and volatile metabolites. Biological investigations on the compounds isolated from *L. sulphureus* demonstrated that they exhibited antitumor, antioxidant, antimicrobial, anti-inflammatory activities, and so on. Lanostane triterpenoids are a group of triterpenoids derived from lanosterol (the precursor of all natural steroids). Further chemical investigations of lanostane triterpenoids, namely, officimalonic acids, and their inhibitory activity against nitric oxide were performed in lipopolysaccharide (LPS)-induced RAW 264.7 cells. Our previous investigation of *Piptoporus betulinus* resulted in the discovery of several lanostane-type triterpenoids, namely, piptonic acids, with known analogues. 24-Methyl-lanostane triterpenes along with some known lanostane-type triterpenes were investigated by our research group.

The present work was performed for the isolation and identification of biologically active compounds from the medicinal mushroom *L. sulphureus*. In this study, four new lanostane triterpenoids (1−4) were evaluated for the first time, and 13 analogues (5−16) were found from the fruits of *L. sulphureus*. The anti-inflammatory activity of three novel compounds (2−4) against nitric oxide release in the LPS-induced RAW 264.7 cell line demonstrated significant inhibitory effects, with IC$_{50}$ ranging between 14.3 and 42.3 μM.

2. EXPERIMENTAL SECTION

2.1. Common Experimental Procedures. An Autopol VI automatic polarimeter (Rudolph Research Analytical) was used for the measurement of optical rotations at 20 °C. IR- and UV spectra were recorded on a Nicolet 6700 (Thermo Fisher Scientific) and a Shimadzu UV-2550 UV−vis spectrometer.
respectively. NMR of 400 and 100 MHz were used for $^1$H and $^{13}$C for recording 1D and 2D NMR spectra on a Varian 400MR spectrometer. A microTOF-Q II mass spectrometer (Bruker) was used for the recording of HR-ESI-MS data. Preparative HPLC (Hitachi Chromaster) was performed on a Phenomenex Luna C$_{18}$ column for the separation of extracts of L. sulphureus. ACS- and HPLC-grade solvents were received from Sigma-Aldrich and Tianjin Zhiyuan Chemicals.

### 2.2. L. sulphureus Materials

L. sulphureus fruits were collected from Xijin Yangyuh Medical Hospital in Xinjiang, China. The voucher specimen is deposited in Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, with the documented number LS-201611.

### 2.3. Extraction and Isolation

L. sulphureus fruits were dried at room temperature. Two kilograms of the powder of L. sulphureus fruits was extracted with methanol ($3 \times 20$ L) by the maceration method, and 226.4 g crude extract was obtained. Then, L. sulphureus methanol extract was mixed in 500 mL of distilled water ($30^\circ$C) and partitioned with petroleum ether (PE, 21.1 g), ethyl acetate (EtOAc, 23.0 g), and n-butanol (n-BuOH, 28.2 g). By using silica gel (300–400 mesh) column chromatography, the ethyl acetate fraction was separated into four fractions A–D with dichloromethane/methanol (100:1 to 0:1, v/v) gradient.

Fraction A ($1.1$ g) was subjected to column chromatography (Sephadex LH-20), eluting with absolute methanol, to afford four subfractions A1–A4. Subfraction A2 (485.4 mg) was again separated by column chromatography (silica gel) using the solvent system petroleum ether/ethyl acetate (100:1–1:1) gradient to obtain five subfractions (A2a–A2e). Subfractions A2c–A2d were mixed and subjected to ODS C$_{18}$ column chromatography, eluting with methanol/water (80:20–100:0) gradient, to obtain three subfractions (A2cd1–A2cd3). Purification of the subfraction A2cd3 (40.7 mg) by preparative HPLC (methanol/water, 95:5 to 100 at 0 in 20 min, flow rate is 3 mL/min) yields a new individual compound 4 at $R_f = 13$ min (5.1 mg) and known compounds $S$ at $R_f = 15$ min (11 mg) and $T$ at $R_f = 17$ min (9.4 mg).

Subfraction A3 (306.4 mg) is subjected to column chromatography (silica gel), eluting with dichloromethane/methanol (180:1–0:1) gradient, to afford four subfractions

Table 1. $^1$H and $^{13}$C NMR Data for Compounds 1–3 (in CD$_3$OD) and 4 (in CD$_3$N)

| position | $\delta_H$ (J in Hz) | $\delta_C$ | $\delta_H$ (J in Hz) | $\delta_C$ | $\delta_H$ (J in Hz) | $\delta_C$ | $\delta_H$ (J in Hz) | $\delta_C$ |
|----------|----------------------|------------|----------------------|------------|----------------------|------------|----------------------|------------|
| 1        | 1.99, m              | 37.3       | 1.88, m              | 38.0       | 1.71, m              | 37.1       | 1.62, m              | 36.9       |
| 2        | 1.65, m (2H)         | 28.6       | 1.56, m              | 23.1       | 1.24, m (2H)         | 28.6       | 1.24, m              | 35.3       |
| 3        | 3.15, dd (10.5, 5.3) | 79.7       | 3.42, dd (9.1, 7.2)  | 79.8       | 3.13, dd (9.1, 7.2)  | 79.8       | 3.13, dd (9.1, 7.2)  | 79.8       |
| 4        | 1.65, m (2H)         | 28.6       | 1.56, m              | 23.1       | 1.24, m              | 28.6       | 1.24, m              | 35.3       |
| 5        | 1.05, m              | 50.7       | 1.51, m              | 52.3       | 1.01, dd (12.7, 1.7) | 52.0       | 1.01, dd (12.7, 1.7) | 52.0       |
| 6        | 2.09, m (2H)         | 24.2       | 2.20, m              | 24.8       | 1.72, m              | 19.6       | 1.72, m              | 24.3       |
| 7        | 5.91, d (6.5)        | 123.0      | 5.95, d (6.6)        | 122.6      | 2.18, m (2H)         | 28.3       | 2.18, m (2H)         | 122.1      |
| 8        | 142.4                |            | 142.6                |            | 135.5                |            | 135.5                |            |
| 9        | 147.8                |            | 146.4                |            | 136.3                |            | 136.3                |            |
| 10       | 38.8                 |            | 38.7                 |            | 38.5                 |            | 38.5                 |            |
| 11       | 5.32, d (6.3)        | 117.1      | 5.43, d (6.4)        | 118.2      | 1.98, m (2H)         | 21.8       | 1.98, m (2H)         | 117.7      |
| 12       | 2.21, m              | 37.5       | 2.20, m              | 37.5       | 3.74, m              | 30.8       | 3.74, m              | 30.8       |
| 13       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 1.37, m              | 1.80       | 1.37, m              | 1.80       |
| 14       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 46.1                 |            | 46.1                 |            |
| 15       | 5.32, d (6.3)        | 117.1      | 5.43, d (6.4)        | 118.2      | 5.36, t (6.9)        |            | 5.36, t (6.9)        |            |
| 16       | 2.21, m              | 37.5       | 2.20, m              | 37.5       | 3.74, m              | 30.8       | 3.74, m              | 30.8       |
| 17       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 1.37, m              | 1.80       | 1.37, m              | 1.80       |
| 18       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 46.1                 |            | 46.1                 |            |
| 19       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 20       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 21       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 22       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 23       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 24       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 25       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 26       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 27       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 28       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 29       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
| 30       | 1.80, m              | 37.5       | 1.80, m              | 37.5       | 52.7                 |            | 52.7                 |            |
A3a–A3d. Subfraction A3b (187.4 mg) was purified via ODS C18 column chromatography, eluting with methanol/water (80:20–100:0) gradient, obtaining five subfractions A3b1–A3b5. Next, purification of mixed subfractions A3b2/A3b3 (107.8 mg) by preparative HPLC (methanol/water, 80:20 to 82:18 in 30 min; flow rate is 3 mL/min) yields three individual compounds 7 at Rf = 14 min (7.4 mg), 8 at Rf = 18 min (19.8 mg), and 9 at Rf = 23 min (12.2 mg), respectively.

Fraction B (17.59 g) was subjected to ODS C-18 column chromatography with methanol/water (60:40–100:0) gradient to afford six subfractions B1–B6. Subfraction B2 (1.15 g) was subjected to silica gel column chromatography, eluted with dichloromethane/methanol (80:1–0:1) gradient, affording nine subfractions B2a–B2i. Purification of subfraction B2g (171 mg) by preparative HPLC (methanol/water, 55:45 to 70:30 in 30 min, 3 mL/min) resulted in the isolation of three pure novel compounds 1 at Rf = 12 min (5.9 mg), 2 at Rf = 18 min (5.1 mg), and 3 at Rf = 23 min (9.6 mg).

Fraction C (368.5 mg) was subjected to column chromatography (ODS), eluting with methanol/water (70:30–100:0) gradient, to obtain six subfractions C1–C6. Subfraction C2 (98.3 mg) was subjected to column chromatography (silica gel), eluting with the gradient solvent system dichloromethane/methanol (60:1–0:1), to yield seven subfractions C2a–C2g. Subfraction C2a (25.0 mg) was purified by preparative HPLC (methanol/water, 80:20–82:18 in 30 min; flow rate is 3 mL/min) to yield pure compound 14 at Rf = 22 min (4.2 mg). Subfractions C2b/C2c were mixed and purified by preparative HPLC (methanol/water, 75:25–80:20 in 30 min, 3 mL/min) to afford pure compound 15 at Rf = 21 min (3.2 mg). Subfraction C6 (134.8 mg) was purified by preparative HPLC (methanol/water, 88:12–92:8 in 34 min, 3 mL/min), yielding substance 16 at Rf = 18 min (12.5 mg).

Further separation of fraction D (3.8088 g) was done with column chromatography (ODS C18), eluting with methanol/water solvent (70:30–100:0) gradient, to afford six subfractions D1–D6. Subfraction D1 (170.4 mg) was purified with column chromatography (silica gel), eluting with dichloromethane/methanol (80:1–0:1) gradient, to obtain eight subfractions D1a–D1h. Subfraction D1f (24.6 mg) was purified by preparative HPLC in an isocratic system (methanol/water, 65:35–65:35 in 40 min, 3 mL/min), to give compound 10 at Rf = 17 min (5.5 mg) and 11 at Rf = 31 min (3.7 mg). Further purification of subfraction D4 (481.4 mg) by preparative HPLC (methanol/water, 85:15–100:0 in 25 min, 3 mL/min) afforded compound 12 at Rf = 11 min (16.7 mg) and 13 at Rf = 19 min (18.8 mg).

Figure 1. (a) Key 1H−1H COSY (—) and selected HMBC correlations (H → C) of 1; (b) selected NOESY correlations (H ↔ H) of 1.

3. RESULTS AND DISCUSSION

Compound 1 was a colorless, amorphous solid. Its molecular formula was determined as C27H34O7 by the basis of HR-ESI-MS at m/z 445.2964 [M − H]− (calcd. For C27H34O7 445.2954).

2.3.1. Sulphurenoid A (1). Colorless amorphous solid; [α]D20 + 79 (c 0.110, methanol); UV (methanol) λmax 244 nm; IR νmax 3432, 2930, 1717, 1684, 1457, 1204, 1049 cm−1; 1H and 13C NMR spectroscopic data are presented in Table 1; HR-ESI-MS at m/z 445.2964 [M − H]− (calcd. For C27H34O7 445.2954).

2.3.2. Sulphurenoid B (2). Colorless amorphous solid; [α]D20 + 85 (c 0.200, methanol); UV (methanol) λmax 243 nm; IR νmax 3447, 2935, 1700, 1559, 1457, 1379, 1204, 1051, 799 cm−1; 1H and 13C NMR spectroscopic data are represented in Table 1; HR-ESI-MS at m/z 447.3123 [M − H]− (calcd. For C27H34O7 447.3110).

2.3.3. Sulphurenoid C (3). Colorless amorphous solid; [α]D20 + 30 (c 0.200, methanol); UV (methanol) λmax 203 nm; IR νmax 3421, 2940, 1717, 1684, 1437, 1204, 1142 cm−1; 1H and 13C NMR spectroscopic data are presented in Table 1; HR-ESI-MS at m/z 447.3123 [M − H]− (calcd. For C27H34O7 447.3110).

2.3.4. Sulphurenoid D (4). Colorless amorphous solid; [α]D20 + 46 (c 0.200, methanol); UV (methanol) λmax 243 nm; IR νmax 1705, 1682, 1602, 1449, 1381, 1354, 862 cm−1; 1H and 13C NMR spectroscopic data are presented in Table 1; HR-ESI-MS at m/z 447.3123 [M − H]− (calcd. For C27H34O7 447.3110).

The 1H NMR data (Table 1) showed the signals of five tertiary methyl groups at δH 0.68 (H1–18), 0.87 (H2–29), 0.93 (H3–30), 0.98 (H4–28), and 0.99 (H5–19); two oxygenated methines (δH 3.15, dd, J = 10.5, 5.3 Hz, H-13 and 4.24, dd, J = 9.6, 5.7 Hz, H-15); and an oxygenated methylene (δH 3.52, t, J = 5.9 Hz, H-24), as well as two olefinic protons (δH 5.32, d, J = 6.3 Hz, H-11 and 5.91, d, J = 6.5 Hz, H-7). The 13C NMR spectrum of I exhibited signals for 27 carbons, ascribed to five methyls, eight methylenes, seven methines, and seven quaternary carbons (one of which is carbonyl). There are two protonated carbon signals at δC 123.0 (C-7) and 117.1 (C-11) besides two quaternary carbon signals at δC 142.4 (C-8) and 147.8 (C-9), which were set by the HSQC experiment. These data show the existence of two double bonds in the molecules of 1. In a more high-field region of the spectrum, three oxygenated carbon signals at δC 79.7 (C-3), 74.6 (C-15), and 62.7 (C-24) show up. The above-stated data implied that substance 1 is probably a nortriterpenoid. Further investigation
of 1D and 2D NMR data of 1 revealed that it has a similar structure with that of 15, the difference being the C-17 side chain. A 5-hydroxy-valeric acid moiety was settled by the 1H-1H COSY correlations (Figure 1) of H-20/H-22, H-22/H-23, H-23/H-24 and the HMBC (Figure 1) correlations from H-24 to C-22 (δC 31.5) and C-23 (δC 29.9), based on the HMBC correlation between H-17 and C-20 (δC 49.0).

The structure of 1 was determined as 25,26,27-trisnor-3,15,24-trihydroxy-lanost-7,9(11) -dien-21-oic acid. The correlations of H-3 to H-5 and H-22/H-24 suggested that they were co-facial and in an α-orientation. Based on the NOESY data, the absolute configuration of 1 was determined as depicted and given a trivial name sulphurenoid A. The structure of the new and known substances are displayed in Figure 2.

Compounds 2 has the molecular formula C_{27}H_{40}O_{5} determined by HR-ESI-MS at m/z 443.2793 [M − H]− (calcld for C_{27}H_{39}O_{5} 443.2797). Comparison of 1H and 13C NMR (Table 1) data of 2 with those of 1 revealed that their structure showed high similarity with that of 1, the main difference being the absence of oxygenated methane signal at C-3 but the existence of a carbonyl signal at δC 219.2 in 2. The above analysis suggested the existence of a hydroxyl group at C-3 in 2 instead of a hydroxyl group in 1. The HMBC correlations from H-28 (or H-29) to C-3 (δC 219.2), C-4 (δC 48.6), and C-5 (δC 52.3) supported the assignment. The NOESY correlations from H-18 to H-15 and H-19, from H-19 to H-28, from H-5 to H-29, and from H-17 to H-30 indicated that they had the same stereochemistry with those of 1. Therefore, the structure of substance 2 was named sulphurenoid B.

The molecular formula for substance 3 was found as C_{36}H_{44}O_{5} by HR-ESI-MS at m/z 474.3123 [M − H]− (calcld for C_{35}H_{43}O_{5} 474.3110). Five tertiary methyl signals at δH 0.80 (H-29), 0.82 (H-18), 0.93 (H-30), 0.98 (H-28), 1.0 (H-19), two oxygenated methine signals at δH 3.15 (dd, J = 9.1, 7.2 Hz, H-3) and 4.18 (J = 6.2 Hz, H-24) were readily observed in the 1H NMR spectrum of 3 (Table 1). The 13C NMR (Table 1) and HSQC data displayed 27 resonances attributed to five methyls, 10 methylenes, five methines (including two oxygenated ones), and seven quaternary carbons (including a double bond and a carbonyl). Comparison of 1H and 13C NMR data of compounds 3 and 1 indicated that they possessed similar structures, except for the number of double bonds. There is one double bond present in 3, which was then determined to locate between C-8 and C-9 by the HMBC correlations from H-19 to C-9 (δC 136.3) and from H-30 to C-8 (δC 135.5). The NOESY correlations of 3 were almost the same as those of 1, suggesting that they had the same stereochemistry. The structure of 3 was named sulphurenoid C.

The molecular formula of substance 4 was found as C_{33}H_{36}O_{5} by HR-ESI-MS at m/z 467.3167 [M − H]− (calcld for C_{32}H_{35}O_{4} 467.3161). Seven tertiary methyl signals at δH
1.06 (H-28), 1.12 (H-29), 1.14 (H-18), 1.16 (H-19), 1.41 (H-30), 1.62 (H-26), and 1.66 (H-27) were observed. One oxygenated methine signal at δH = 4.78 (dd, J = 9.6, 5.8 Hz, H-15) was readily observed in the 1H NMR spectrum of 4 (Table 1). The 13C NMR (Table 1) and HSQC data displayed 30 resonances attributed to seven methyls, seven methylenes, seven methines (including one oxygenated and a double bond), and nine quaternary carbons (including a double bond and a carbonyl). Comparison of the 1H and 13C NMR data of compounds 4 with 5 indicated that they possessed similar structures, except for the number of double bonds. There are two double bonds present in 5 while three double bonds in 4, which were then determined to be located at C-8 and C-9 by the HMBC correlations from H2-19 to C-9 (δC 145.7) and from H1-30 to C-8 (δC 142.4). The structure of compound 4 was named sulphurenoid D.

Other twelve (5-16) known compounds were identified as 1α-hydroxy-3-oxolanosta-8,24-dien-21-oic acid (5), 17 3-keto-dehydroasfuranic acid (6), 18 3β-hydroxylanosta-8,24-dien-21-oic acid (7), 19 eburicoic acid (8), 20 3-oxolanosta-8,24-dien-21-oic acid (9), 21 laricinolic acid (10), 22 3β,15α-dihydroxy-24-keto-double bond 8-lanostene-21-oic acid (11), 23 1α-hydroxytramenetic acid (12), 24 sulphurenic acid (13), 20 3-oxosulphurenic acid (14), 4 dehydroasfuranic acid (15), 26 and trametenelic acid (16). 25

Anti-inflammatory activities revealed that compounds 2–4 demonstrate significant anti-inflammatory activity in terms of inhibiting NO release in LPS-stimulated RAW 264.7 cell line, with IC50 values at 14.3–42.3 μM, compared to that of the positive control minocycline (IC50 = 73.0 μM) (Table 2). The accumulation of nitrates in the cells increased due to the treatment with LPS. To perform this experiment, cells were simultaneously treated with 1 μg/mL LPS and various concentrations of compounds. RAW 264.7 cells were activated by LPS, and NO release was measured as the concentration of nitrite in the culture medium. New isolated compounds 2, 3, and 4 showed a significant reduction of nitrite level of 14.3, 30.2, and 42.3 μM at a concentration of 50 μM, which is more effective than the positive control. Sulphurenoid B reduction of nitrite level with IC50 value of 14.3 μM is fivefold more effective than the positive control.

4. CONCLUSIONS

Our results provided new insights into the chemical composition and medicinal values of the fruiting bodies Laetiporus sulphureus. For the first time, four new lanostane triterpenoids, sulphurenoids A–D (1–4) were isolated from the fruiting bodies of Laetiporus sulphureus. The chemical structures of sulphurenoids A–D were characterized by different analytical techniques, including HR-ESI-MS and 1D and 2D NMR spectroscopies. Unusual 25,26,27-trisnortriterpenoid structures revealed compounds 1–3. In addition, compounds 2–4 demonstrated significant anti-inflammatory activity against NO release in LPS-induced RAW 264.7 cells. Their IC50 values ranged between 14.3 and 42.3 μM, while the IC50 value of the positive control was 73.0 μM. This research provided exciting evidence for the medicinal utility of L. sulphureus fruiting bodies and for seeking novel secondary metabolites that can be used for developing new anti-inflammatory phytomedicines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02165.

Chemical structures of all compounds; 1H, 13C, NMR, 1H-1H COSY, HSQC, HMBD, and NOESY spectra; and HR-ESI-MS and IR spectra for all four new compounds (PDF)

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Supporting Information

Table 2. Anti-Inflammatory Activities against NO Release in LPS-Induced RAW 264.7 Cells

| No. | name of compound | IC50 inhibition ratio (μM) |
|-----|------------------|---------------------------|
| 1   | sulphurenoid A (1)| no effect                  |
| 2   | sulphurenoid B (2)| 14.3 ± 0.9                |
| 3   | sulphurenoid C (3)| 30.2 ± 1.6                |
| 4   | sulphurenoid D (4)| 42.3 ± 4.0                |
|     | minocycline (positive control) | 73.0 ± 2.5 |
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Notes
The authors declare no competing financial interest.

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