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Hippotulosas A-D: four new sesterterpenes from marine sponge *Hippospongia fistulosa* Lendenfeld, 1889

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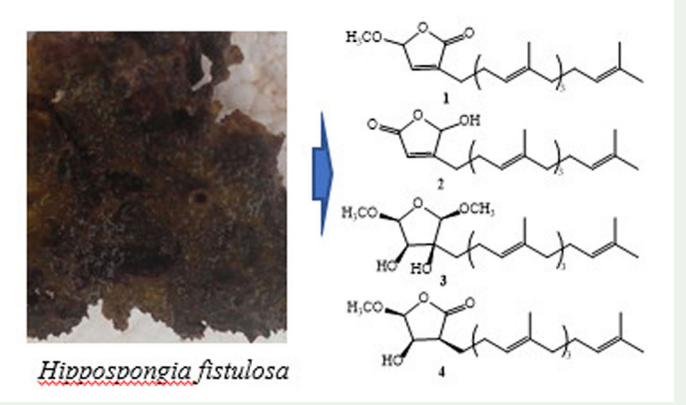
ABSTRACT

Four new sesterterpenes, named as hippotulosas A-D (**1–4**), and a known sesterterpene furospinulosin-1 (**5**) were isolated from the marine sponge *Hippospongia fistulosa* by various chromatographic methods. Their structures were established by extensive spectroscopic analyses (IR, HR-ESI-MS, 1D and 2D NMR) and by comparison of the spectral data with those reported in the literature.



List of abbreviations: COSY: Correlation Spectroscopy; HR-ESI-MS: high-resolution electrospray ionization mass spectrometry; HMBC: Heteronuclear Multiple Bond Correlation; HSQC: Heteronuclear Single Quantum Coherence; SK-LU-1: Human lung carcinoma; MCF-7: Human breast carcinoma; HepG2: Human hepatocellular carcinoma; SK-Mel-2: human melanoma cell; HL-60: human acute leukemia

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Marine sponge; *Hippospongia fistulosa*; Spongiidae; hippotulosa; sesterterpene

1. Introduction

Marine sponges of the genus *Hippospongia* belong to the family Spongiidae, order Dictyoceratida, which usually live in the South Pacific. The previous investigation of

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the chemical constituents of the sponge *Hippospongia* sp. showed that they contain the diversity of the bioactive compounds including sesquiterpenes (Jiao et al. 2012; Kobayashi et al. 1992; Shen et al. 2001; Oda et al. 2007), sesterterpenes and sesterterpene sulfates (Ishibashi et al. 1988; Musman et al. 2001; Lee et al. 2007; Chang et al. 2012; Zhou et al. 2020), furanoterpenes (Umeyama et al. 1989; Piao et al. 2011), triterpenoic acids (Rochfort et al. 1996), polyketides (Craig et al. 2002), hippolide derivatives (Piao et al. 2014). Many of these compounds have been reported to have significant antitumor activity (Ishibashi et al. 1988; Kobayashi et al. 1992; Chang et al. 2012; Zhou et al. 2020). However, up to now, there have been no studies on chemical constituents and bioactivity of marine sponge *Hippospongia fistulosa* Lendenfeld, 1889. During our continuing studies on bioactive substances from the Vietnam marine organisms (Kiem et al. 2019), the sponge *H. fistulosa* has attracted our special attention. Interestingly, studied on the methanol extract of the sponge *H. fistulosa* resulted in the isolation of five sesterterpenes (**1–5**), including four new compounds (**1–4**). This paper reports the isolation, structural elucidations, and the cytotoxic activities of these compounds on some cancer cell lines.

2. Results and discussion

Compound **1** was obtained as a colorless oil and the presence of C = O, C-O-C, and C = C groups at ν_{max} 1741.9, 1128.6, 1648.9 cm^{-1}, respectively, which were indicated by its IR spectrum. Its molecular formula was deduced to be $C_{26}H_{40}O_3$ based on the cluster of *quasi*-molecular ion peak in the high resolution electron spray ionization mass spectrum (HR-ESI-MS) at *m/z* 401.3063 $[M + H]^+$ (Calcd. for $[C_{26}H_{41}O_3]^+$, 401.3050, $\Delta = +3.2$ ppm), indicating 7 degrees of unsaturation. The ^{1}H NMR spectrum of **1** exhibited five methyl singlet signals at δ_H 1.53 (12H) and 1.61 (3H), five olefinic protons at δ_H 5.03 (4H, m) and 6.68 (1H, d, $J = 1.0$ Hz), one methine carbinol proton at δ_H 5.65 (1H, d, $J = 1.0$ Hz), one methoxy group at δ_H 3.48 (3H, s), and eight methylene groups at δ_H 1.91–2.20. The ^{13}C NMR spectrum of **1** showed twenty-six carbons including one carbonyl, one methoxy, one oxygenated methine, five methyl groups, five double bonds, and eight methylene carbons, which were identified by HSQC spectrum. Except one methoxy carbon, the twenty-five carbons were suggested to belong to a sesterterpene (Nakamura et al. 1986). A comparison made between the NMR data of **1** and **5** (furospinulosin-1, a compound has also been isolated from *Hippospongia sp*) indicated that they shared the same structure of the long side chain, and their differences in the additional one methoxy group of the furano ring of **1** (Nakamura et al. 1986). The above suggestions were confirmed by the HSQC and HMBC spectra. The HMBC correlations from H-5 (δ_H 2.20) to C-3 (δ_C 138.3), from H-4 (δ_H 2.28) to C-2 (δ_C 142.0)/C-3 (δ_C 138.3)/C-25 (δ_C 171.4) indicated that the side chain linked to C-3. Similarly, the analysis results of the HMBC correlations from H-2 (δ_H 6.68) to C-1 (δ_C 102.4), and from methoxy protons (δ_H 3.48) to C-1, as well as the interaction coupling constants of H-1 and H-2 ($J = 1.0$ Hz) confirmed that the methoxy group attached to C-1. The above NMR results were completely accurate with the HR-ESI-MS data of **1** and its planar structure was determined as shown in the Figure 1. The optical rotation

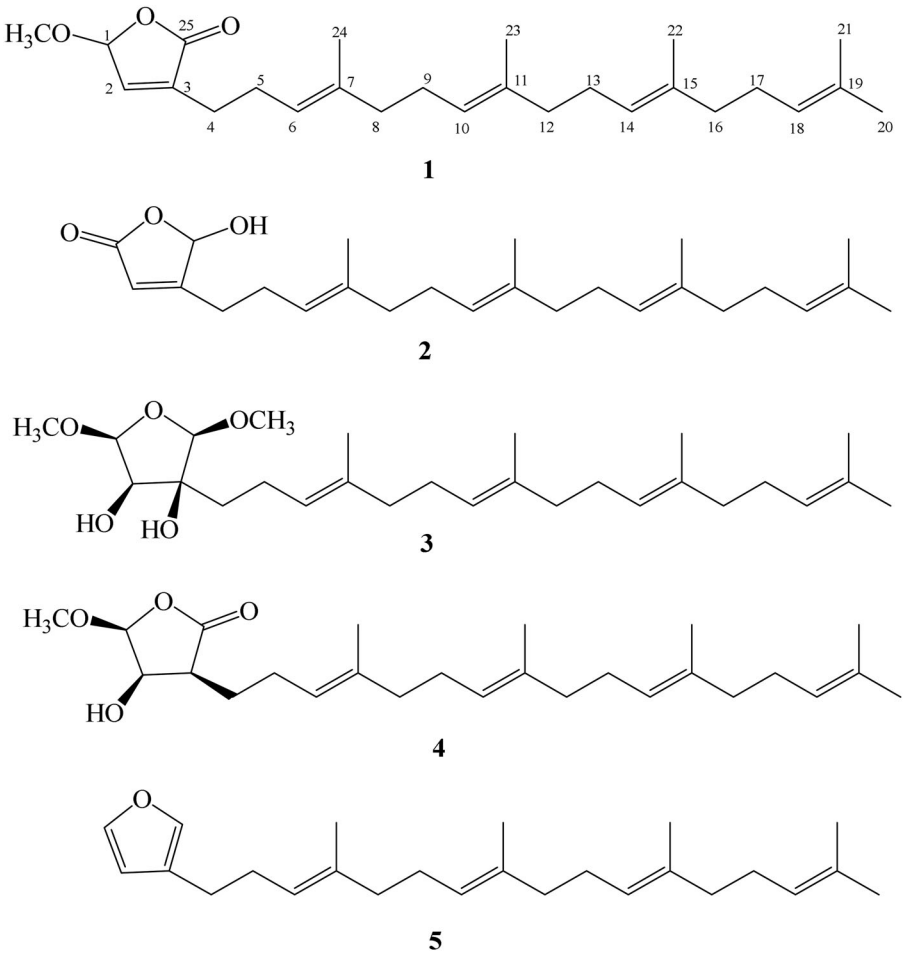

Figure 1. Chemical structures of compounds **1–5** from the marine sponge *Hippospongia fistulosa*.

of **1** was zero suggesting that **1** was a racemic. Consequently, the chemical structure of **1** was determined and named as hippotulosa A.

Compound **2** was obtained as a colorless oil and its molecular formula was established as $C_{25}H_{38}O_3$ by the HR-ESI-MS quasi-molecular ion peak at *m/z* 387.2881 $[M+H]^+$ (Calcd. for $[C_{25}H_{39}O_3]^+$, 387.2894, $\Delta = -3.4$ ppm). The IR spectrum of **2** exhibited the presence of hydroxyl (3463.9 cm^{-1}), carbonyl (1769.2 cm^{-1}), C=C (1449.8 cm^{-1}), and C-O-C (1083.9 and 1026.3 cm^{-1}) groups. The NMR spectra of **2** were similar to the corresponding spectra of **1** suggesting that **2** was a derivative of **1** with the same side chain, and their differences in the data of the furano ring. In the HSQC spectra, protons H-2 (δ_H 5.86) and H-25 (δ_H 5.98) had cross peaks with carbons at δ_C 117.9 and 98.6, respectively, confirming the quite differences of the furano ring between compounds **2** and **1**. Furthermore, the methoxy group in **1** was absent in **2** indicated by NMR and HR-ESI-MS spectra. A set of carbon chemical shifts of the furano ring [δ_C 168.8 (C), 98.6 (CH), 170.7 (C), 117.9 (CH)] was similar to that of compounds luffariellolide (Albizati et al. 1987), hydroxymokupalide (Wilson and Whitesides 1978), and other sesterterpenes (Jimenez et al. 1991), previously isolated from marine

sponges. In addition, HMBC correlations from H-4 (δ_H 2.52/2.41) to C-2 (δ_C 117.9)/C-3 (δ_C 168.8)/C-25 (δ_C 98.6) and from H-5 (δ_H 2.33) to C-3 were observed confirming the chemical structure of the lactone ring as shown in the Figure 1. The optical rotation of **2** was zero suggesting that **2** was a racemic. Consequently, the chemical structure of **2** was determined and named as hippotulosa B.

Compound **3** was obtained as a colorless oil and its IR spectrum exhibited the presence of hydroxyl (3407.0 cm^{-1}), C = C (1449.7 cm^{-1}), and C-O-C (1099.8 and 1026.3 cm^{-1}) groups. The molecular formula of **3** was deduced to be $C_{27}H_{46}O_5$ based on the cluster of *quasi*-molecular ion peak in the HR-ESI-MS at *m/z* 473.3238 $[M + Na]^+$ (Calcd. for $[C_{27}H_{46}O_5Na]^+$, 473.3237, $\Delta = +0.2$ ppm), indicating 5 degrees of unsaturation. The NMR spectra of **3** were similar to those of **1** and **2**, suggesting that they shared similar structure. The NMR data of the side chains of **3** were compared with the corresponding data of **1** and **2** and found to match well. The remaining NMR signals of **3** were identified as two methoxy [δ_H 3.40 (3H, s)/δ_C 55.2 and δ_H 3.47 (3H, s)/δ_C 56.4], three oxygenated methine groups [(δ_H 4.73/δ_C 109.1), (δ_H 3.94/δ_C 80.1), and (δ_H 4.89/δ_C 110.7)], and one oxygenated quaternary carbon (δ_C 81.2), which were indicated by HSQC spectrum. The above HR-ESI-MS and NMR data suggested that there were two methoxy and two hydroxy groups attaching to the furano ring. In the COSY spectrum of **3**, H-5 (δ_H 2.11/2.22) had the cross peaks with H-4 (δ_H 1.71/1.80) and H-6 (δ_H 5.19), H-2 (δ_H 3.94) had a cross peak with H-1 (δ_H 4.89). In addition, HMBC correlations from H-5 to C-3 (δ_C 81.2), from H-4 to C-25 (δ_C 109.1)/C-3/C-2 (δ_C 80.1), from H-25 (δ_H 4.73) to C-2/C-1 (δ_C 110.7), from H-2 to C-1, from $OC\underline{H}_3$ (3.40) to C-25, and from $OC\underline{H}_3$ (3.47) to C-1 were observed. The above evidence confirmed that two methoxy groups were attached to C-1 and C-25, two hydroxy groups linked to C-2 and C-3, and the side chain attached to C-3. In the NOESY spectrum of **3**, H-25 (δ_H 4.73) had cross peaks with H-1 (δ_H 4.89)/H_a-4 (δ_H 1.80)/H_a-5 (δ_H 2.11), while H_b-4 (δ_H 1.70) had cross peak with H-2 (δ_H 3.94), indicating all these protons were in the same side and the two methoxy and two hydroxy groups were in the other side of the molecule. Consequently, the relative structure of **3** was determined as shown in the Figure 1, which was named as hippotulosa C.

Compound **4** was obtained as a colorless oil and its molecular formula was established as $C_{26}H_{42}O_4$ by the HR-ESI-MS quasi-molecular ion peak at *m/z* 419.3155 $[M + H]^+$ (Calcd. for $[C_{26}H_{43}O_4]^+$, 419.3156, $\Delta = -0.2$ ppm), indicating 6 degrees of unsaturation. The IR spectrum of **4** indicated the presence of hydroxyl (3418.2 cm^{-1}), carbonyl (177.8 cm^{-1}), C = C (1451.9 cm^{-1}), and C-O-C (1119.7 cm^{-1}) groups. A comparing NMR spectra of **4** with the corresponding spectra of compounds **1**-**3** showed that they had the same side chain and differences in the furano ring as shown in the Figure 1. Focus on the furano ring, one carbonyl (δ_C 177.3), one methoxy (δ_H 3.49/δ_C 56.6), one methine carbinol (δ_H 4.24/δ_C 72.8), and one methine (δ_H 2.69/δ_C 42.9) groups were identified. In addition, the HMBC correlations from H-5 (δ_H 2.15/2.18) to C-3 (δ_C 42.9), from H-4 (δ_H 1.90/1.70) to C-25 (δ_C 177.3), C-3, and C-2 (δ_C 72.8), and from methoxy protons (δ_H 3.49) to C-1 (δ_C 107.5) indicated the carbonyl group was at C-25, the methoxy and hydroxy groups linked to C-1 and C-2, respectively. In the NOESY spectrum of **4**, H-3 (δ_H 2.69) had cross peak with H-2 (δ_H 4.24) and H-2 had cross peak with H-1 (δ_H 5.17). This evidence indicated that H-1, H-2, H-3 were in the

same side and CH_2-1, the methoxy, and the hydroxy groups were in the other side of the molecule. Therefore, the relative structure of **4** was determined as shown in the Figure 1, which was named as hippotulosa D.

Compound **5** was identified as furospinulosin-1 (Nakamura et al. 1986). The NMR spectral data this compound was consistent with those previously reported in the literature and further confirmed by 1D and 2D NMR spectra.

Compounds **1**-**5** were evaluated their cytotoxic effects on five human cancer cell lines including breast carcinoma (MCF-7), hepatocellular carcinoma (HepG2), lung carcinoma (SK-LU-1), and melanoma cell (SK-Mel-2), and human acute leukemia (HL-60). As shown in Table S1 (Supplementary material), at concentration of 100 μM, compounds **1**-**5** exhibited cytotoxic effects against MCF-7, HepG2, SK-LU-1, SK-Mel-2, and HL-60 cell lines with percentages of dead cells in the range from 19.0 ± 0.2% to 64.3 ± 1.2%. Compounds **1** and **5** exhibited cytotoxic effects against MCF-7 and HL-60 cell lines with IC_{50} values of 75.6 ± 6.5 and 81.3 ± 5.2 μM for **1**, and 86.9 ± 2.1 and 80.6 ± 2.3 μM for **5**, respectively. In overall, because of high IC_{50} values as above, compounds **1**-**5** were considered no cytotoxic activity on tested cell lines.

3. Experimental

3.1. General

Optical rotation was measured using Jasco P2000 polarimeter. HR-ESI-MS was obtained on an Agilent 6530 Accurate Mass Q-TOF LC/MS. NMR spectra were recorded on a Bruker AVANCE III 500 MHz spectrometer. Column chromatography was performed using silica gel (40-63 μm) or reversed phase C-18 resins (150 μm) as adsorbents. Thin layer chromatography (TLC) was carried out on pre-coated silica gel 60 F_{254} or RP-18 F_{254S} plates.

3.2. Animal material

The sponge samples were collected in Vanphong Bay, Nha Trang, Vietnam in May 2020 and identified as *Hippospongia fistulosa* Lendenfeld, 1889, by Prof. Do Cong Thung, the Institute of Marine Environment and Resources, Vietnam Academy of Science and Technology (VAST). A voucher specimen (NCCT-B63) was deposited at the Institute of Marine Biochemistry, VAST.

3.3. Extraction and isolation

The fresh sponge (*Hippospongia fistulosa*) samples (25 kg) were washed with water and then cut into small pieces. This sample was ultrasonically extracted in MeOH for three times (each 50 L, 2 hrs in room temperature). Extract solution was filtered through filter paper and removed the solvent under reduced pressure to yield 110 g of a solid residue. Methanol extract (105 g) was suspended in distilled water and partitioned with dichloromethane to give dichloromethane soluble fraction (30 g). The dichloromethane fraction (HFD, 29 g) was separated into seven smaller fractions HFD1-HFD5 by a silica gel column chromatography eluting with gradient solvent system of hexane/acetone

(40/1-0/1, v/v). Fraction HFD1 (6.8 g) was chromatographed on a reversed phase C-18 (RP-18) column eluting with methanol/water (7/2, v/v) to give three fractions, HFD1A – HFD1C. Compound **5** (10.2 mg) was isolated from the fraction HFD1B (2.0 g) by a silica gel column chromatography, eluting with dichloromethane/acetone (20/1, v/v). Fraction HFD4 (14.5 g) was chromatographed on a silica gel column and eluting by acetone/methanol/water (15/1/0.1, v/v/v) to give five smaller fractions (HFD4A-HFD4E). Fraction HFD4B (3.5 g) was chromatographed on a RP-18 column eluting with methanol/water (15/2, v/v) to give compounds **1** (15.0 mg) and **2** (18.1 mg). Fraction HFD4C (4.8 g) was chromatographed on a RP-18 column eluting with methanol/water (13/2, v/v) to give compounds **3** (23.2 mg) and **4** (31.4 mg).

3.3.1. Hippotulosa A (1)

A colorless oil; $[\alpha]_D^{25}$: 0° (*c* 0.1, MeOH); IR (KBr) ν_{max}: 2928.4, 1741.9, 1648.9, 1451.9, 1128.6 cm^{-1}; HR-ESI-MS *m/z* 401.3063 $[M+H]^+$ (Calcd. for $[C_{26}H_{41}O_3]^+$, 401.3050). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.53 (12H, s, H-21, H-22, H-23, H-24), 1.61 (3H, s, H-20), 1.91 (6H, m, H-8, H-12, H-16), 2.20 (8H, m, H-5, H-9, H-13, H-17), 2.28 (2H, m, H-4), 3.48 (3H, s, OCH_3), 5.03 (4H, m, H-6, H-10, H-14, H-18), 5.65 (1H, d, $J = 1.0$ Hz, H-1), 6.68 (1H, d, $J = 1.0$ Hz, H-2). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 16.0 × 2, 16.2 (C-22, C-23, C-24), 17.7 (C-21), 25.4 (C-4), 25.5 (C-5), 25.7 (C-20), 26.6, 26.7, 26.8 (C-9, C-13, C-17), 39.7 (C-8, C-12, C-16), 56.7 (OCH_3), 102.4 (C-1), 122.3, 124.0, 124.2 (C-6, C-10, C-14), 124.4 (C-18), 131.3 (C-19), 135.0, 135.2, 137.0 (C-7, C-11, C-15), 138.3 (C-3), 142.0 (C-2), 171.4 (C-25).

3.3.2. Hippotulosa B (2)

A colorless oil; $[\alpha]_D^{25}$: 0° (*c* 0.1, MeOH); IR (KBr) ν_{max}: 3463.9, 2971.3, 2935.5, 1769.2, 1449.8, 1083.9, 1026.3 cm^{-1}; HR-ESI-MS *m/z* 387.2881 $[M+H]^+$ (Calcd. for $[C_{25}H_{39}O_3]^+$, 387.2894). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.60 (9H, s, H-21, H-22, H-23), 1.63 (3H, s, H-24), 1.68 (3H, s, H-20), 1.98 (6H, m, H-8, H-12, H-16), 2.04-2.10 (6H, m, H-9, H-13, H-17), 2.33 (2H, m, H-5), 2.41 (1H, m, H_a-4), 2.52 (1H, m, H_b-4), 5.09 (4H, m, H-6, H-10, H-14, H-18), 5.98 (1H, s, H-25), 5.86 (1H, s, H-2). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 16.0 × 2, 16.2 (C-22, C-23, C-24), 17.7 (C-21), 25.2 (C-5), 25.7 (C-20), 26.5, 26.7, 26.8 (C-9, C-13, C-17), 27.7 (C-4), 39.6, 39.7 × 2 (C-8, C-12, C-16), 98.6 (C-25), 117.9 (C-2), 121.9 (C-6), 123.9 (C-10), 124.2 (C-14), 124.4 (C-18), 131.3 (C-19), 135.0, 135.4, (C-11, C-15), 137.5 (C-7), 168.8 (C-3), 170.7 (C-1).

3.3.3. Hippotulosa C (3)

A colorless oil; $[\alpha]_D^{25}$: + 7.6° (*c* 0.1, MeOH); IR (KBr) ν_{max}: 3407.0, 2930.8, 1715.0, 1449.7, 1099.8 cm^{-1}; HR-ESI-MS *m/z* 473.3238 $[M+Na]^+$ (Calcd. for $[C_{22}H_{46}O_5Na]^+$, 437.3237); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.71 (1H, m, H_a-4), 1.80 (1H, m, H_b-4), 2.11 (1H, m, H_a-5), 2.22 (1H, m, H_b-5), 1.98 (6H, t, H-8, H-12, H-16), 2.04-2.10 (6H, m, H-9, H-13, H-17), 1.68 (3H, s, H-20), 1.60 (9H, s, H-21, H-22, H-23), 1.64 (3H, s, H-24), 3.40 (3H, s, 25-OCH_3), 3.47 (3H, s, 1-OCH_3), 3.94 (1H, d, $J = 3.5$ Hz, H-2), 4.73 (1H, s, H-25), 4.89 (1H, d, $J = 3.5$ Hz, H-1), 5.10 (3H, t, $J = 7.0$ Hz, H-10, H-14, H-18), 5.19 (1H, m, H-6). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 16.0 (C-22, C-23), 16.1 (C-24), 17.7 (C-21), 22.1 (C-5), 25.7 (C-20), 26.5, 26.7, 26.8 (C-9, C-13, C-17), 32.8 (C-4), 39.7 (C-8, C-12, C-16), 55.2 (25-OCH_3),

56.4 (1-OCH_3), 81.2 (C-3), 80.1 (C-2), 109.1 (C-25), 110.7 (C-1), 123.9 (C-6), 124.3 (C-10, C-14), 124.4 (C-18), 131.3 (C-19), 135.0, 135.4 (C-11, C-15), 136.7 (C-7).

3.3.4. Hippotulosa D (4)

A colorless oil; $[\alpha]_D^{25}$: + 11.2° (*c* 0.1, MeOH); IR (KBr) ν_{max}: 3418.2, 2932.3, 1777.8, 1714.9, 1645.9, 1119.7 cm^{-1}; ESI-HR-MS: m/z 419.3155 $[M+H]^+$ (calcd. for $[C_{26}H_{43}O_4]^+$, 419.3156); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.60 (9H, s, H-21, H-22, H-23), 1.68 (3H, s, H-20), 1.63 (3H, s, H-24), 1.70 (1H, m, H_a-4), 1.90 (1H, m, H_b-4), 1.98 (6H, t, H-8, H-12, H-16), 2.15 (1H, m, H_a-5), 2.18 (1H, m, H_b-5), 2.69 (1H, m, H-3), 2.04-2.10 (6H, m, H-9, H-13, H-17), 3.49 (3H, s, 1-OCH_3), 4.24 (1H, d, $J = 3.5$ Hz, H-2), 5.10 (3H, t, $J = 7.0$ Hz, H-10, H-14, H-18), 5.15 (1H, m, H-6), 5.17 (1H, d, $J = 3.5$ Hz, H-1). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 16.0 (C-22, C-23), 16.2 (C-24), 17.7 (C-21), 23.1 (C-4), 25.7 (C-20), 26.5, 26.7, 26.8 (C-9, C-13, C-17), 26.7 (C-5), 39.7 (C-8, C-12, C-16), 42.9 (C-3), 56.6 (1-OCH_3), 72.8 (C-2), 107.5 (C-1), 122.9 (C-6), 123.9 124.2, 124.4 (C-10), C-14, C-18), 131.3 (C-19), 135.0, 135.4 (C-11, C-15), 137.5 (C-7), 177.3 (C-25).

3.3.5. Cytotoxic assay

Refer to Supplemental material.

4. Conclusions

Phytochemical study on the Vietnamese sponge *Hippospongia fistulosa* resulted five sesterterpenes including four new compounds (named as hippotulosas A-D). Their structures were established by extensive spectroscopic analyses (IR, HR-ESI-MS, 1D and 2D NMR) and by comparison of the spectral data with those reported in the literature. At concentration of 100 μM, compounds **1**-**5** exhibited cytotoxic effects against MCF-7, HepG2, SK-LU-1, SK-Mel-2, and HL-60 cell lines with percentages of dead cells in the range from 19.0 ± 0.2% to 64.3 ± 1.2%. Compounds **1** and **5** exhibited cytotoxic effects against MCF-7 and SK-Mel-2 cell lines with IC_{50} values of 75.6 ± 6.5 and 81.3 ± 5.2 μM for **1**, and 86.9 ± 2.1 and 80.6 ± 2.3 μM for **5**, respectively. These results suggested that compounds **1**-**5** are inactivity on the cytotoxic assay against tested cell lines.

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Disclosure statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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