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Cyclic dipeptide, furan, furanone, and butenolide derivatives from marine-derived fungus *Aspergillus* sp. HL24

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ABSTRACT

Using various chromatographic experiments, one cyclic dipeptide (1), one furan (2), one pyranone (3) and two butenolide (4 and 5) derivatives were isolated from the marine-derived fungus *Aspergillus* sp. HL24. Their chemical structures were elucidated on the basis of detailed analysis of the 1D (^{1}H NMR and ^{13}C NMR) and 2D (HSQC and HMBC) NMR spectroscopic data in comparison with the literature values. The cytotoxic activities of compounds 1–5 were evaluated on two human cancer cell lines as Hep-G2 (liver) and A549 (lung). However, these compounds did not show significant cytotoxicity (IC_{50} > 100 µM) against both cell lines.

Keywords: *Aspergillus*, marine-derived fungus, cytotoxic activity.

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Introduction

Bioactive compounds derived from marine microorganisms, especially those belonging to the genus *Aspergillus*, have attracted significant scientific interest in recent years [1, 2]. Marine-derived *Aspergillus* fungal strains have been found to produce a wide variety of metabolites, including polyketides, sterols, alkaloids, terpenoids, peptides, and butenolides, exhibiting notable biological activities such as antimicrobial, cytotoxic, insecticidal, neuroprotective, and antioxidant effects [3].

Within the framework of the authors' studies on the chemical composition and biological activities of marine-derived fungal strains belonging to the genus *Aspergillus* [4, 5], we have reported the isolation, structural elucidation, and cytotoxic evaluation of three new and five known compounds from the soft coral-derived fungus *Aspergillus* sp. HL24 [6]. Previously, the cytotoxic aromatic butenolide aspernolide A and lipodepsipeptide scopularide I have been isolated from the soft coral-derived fungi *Aspergillus terreus* [7] and *A. sclerotiorum* [8], respectively. In the current paper, the authors report one cyclo dipeptide, one furan, one pyranone, and two butenolide derivatives from the fungus *Aspergillus* sp. HL24. In addition, their cytotoxic effect on two human cancer cell lines as Hep-G2 (liver) and A549 (lung) was also evaluated.

Materials and methods

Fungal material

The fungal strain HL24 was isolated from an unidentified soft coral collected in Halong Bay, Quang Ninh, Vietnam. It was taxonomically identified as *Aspergillus* sp. (GenBank accession number: PV206771) and its preserved at the Institute of Chemistry (code: *Aspergillus* sp. IMBC.HL24.1), Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam.

General experiment procedures

Optical rotations were determined on a JASCO P-2000 polarimeter (Jasco Inc., Japan). Thin-layer chromatography (TLC) was performed using precoated silica gel 60 F_{254} (Merck) and RP-18 F_{254S} plates (Merck). Compounds were detected by spraying with aqueous 10% H_2SO_4, followed by heating for 3–5 minutes. Column chromatography (CC) was carried out using silica gel (Kieselgel 60, 70–230 mesh and 230–400 mesh, Merck) and reversed-phase silica gel (ODS-A, 12 nm, S-150 μm, YMC Co., Ltd.). An Agilent 1260 infinity II system (Agilent Tech., USA) equipped with a diode array detector (G7115A) and a YMC J'sphere ODS-H18 column (250 × 20 mm, S-04 μm, 8 nm) was used for preparative HPLC to isolate and purify compounds.

Fermentation, extraction and isolation

The EtOAc extract (20g) was obtained from the fermentation of the fungal strain *Aspergillus* sp. HL24, following the procedure outlined in the previous article [5]. This extract was separated on an RP-18 CC using a MeOH/H_2O gradient elution system (from 20% to 100% MeOH), yielding six fractions (E1–E6). Fraction E2 (1.2 g) was subjected to RP-18 CC with a MeOH/H_2O (2:1, v/v) eluent to obtain four subfractions, E2A–E2D. Subfraction E2D (400 mg) was further separated on a silica gel CC with CH_2Cl_2/MeOH (40:1, v/v) as the eluent, producing seven subfractions (E2D1–E2D7). Subfraction E2D1 (150 mg) was purified by HPLC using ACN/H_2O (30:70, v/v) as the eluent to afford compound **1** (8 mg). Similarly, subfraction E2D3 (48 mg) was purified by HPLC using an ACN/H_2O (30:70, v/v) eluent to yield compound **3** (20 mg). Fraction E2D5 (55 mg) was purified by HPLC with ACN/H_2O (25:75, v/v) to obtain compound **2** (8 mg).

Fraction E3 (1.7 g) was further separated on an RP-18 CC with MeOH/H_2O (2:1, v/v) as the eluent, resulting in two subfractions, E3A and E3B. Subfraction E3A (400 mg) was further subjected to silica gel CC with CH_2Cl_2/MeOH (20:1, v/v) to yield three subfractions, E3A1–E3A3. Subfraction E3A3 (150 mg) was purified by HPLC using ACN/H_2O (45:55, v/v) as the eluent to afford compound **5** (12 mg). Fraction E3B (730 mg) was further separated on a silica gel CC with CH_2Cl_2/MeOH (20:1, v/v) as the eluent to give five subfractions, E3B1–E3B5. Subfraction E3B3 (350 mg) was purified by

HPLC with ACN/H_2O (30:70, v/v) to obtain compound **4** (14 mg).

Cyclo-(S-Pro-R-Leu) (**1**): White powder; $C_{11}H_{18}N_2O_2$, M= 210; $[\alpha]_D^{25}$-65.1 (*c* 0,1, MeOH); ^{1}H-NMR (600 MHz, CD_3OD): δ_H 3.53 (2H, m, H-3), 1.96 (1H, m, H_a-4), 2.05 (1H, m, H_b-4), 2.05 (1H, m, H_a-5), 2.32 (1H, m, H_b-5), 4.27 (1H, m, H-6), 4.14 (1H, m, H-9), 1.55 (1H, m, H_a-10), 1.95 (1H, m, H_b-10), 1.90 (1H, m, H-11), 0.99 (3H, d, *J* = 6.6 Hz, H-12), and 0.98 (3H, d, *J* = 6,6 Hz, H-13); ^{13}C-NMR (150 MHz, CD_3OD) see Table 1.

Acetyl Sumiki's acid (2): White powder; $C_8H_8O_5$, M= 184; ^{1}H-NMR (600 MHz, CD_3OD): δ_H 7.10 (1H, d, *J* = 3.0 Hz, H-3), 6.57 (1H, d, *J* = 3.0 Hz, H-4), 5.12 (2H, s, H-6) và 2.08 (3H, s, H-8); ^{13}C-NMR (150 MHz, CD_3OD) see Table 1.

(7*R*)-(hydroxy(phenyl)methyl)-4H-pyran-4-one (3): White powder; $C_{12}H_{10}O_3$, M= 202; $[\alpha]_D^{25}$ +60.3 (*c* 0,1, MeOH); ^{1}H-NMR (600 MHz, CD_3OD): δ_H 6.64 (1H, d, *J* = 2.4 Hz, H-3), 6.31 (1H, dd, *J* = 2.4, 6.0 Hz, H-5), 7.95 (1H, d, *J* = 6.0 Hz, H-6), 5.55 (1H, s, H-7), 7.45 (2H, br d, *J* = 7.8 Hz, H-9 and H-13), 7.39 (2H, br t, *J* = 7.8 Hz, H-10 and H-12) and 7.34 (1H, br t, *J* = 7.8 Hz, H-11); ^{13}C-NMR (150 MHz, CD_3OD) see Table 1.

Eutypoid B (4): White powder; $C_{17}H_{14}O_4$, M= 282; ^{1}H-NMR (600 MHz, CD_3OD): δ_H 4.72 (2H, s, H-5), 3.87 (2H, br s, H-6), 7.00 (2H, br d, *J* = 8.4 Hz, H-8 and H-12), 6.74 (2H, br d, *J* = 8.4 Hz, H-9 and H-11), 7.36 (2H, br d, *J* = 8.4 Hz, H-14 and H-18) and 6.89 (2H, br d, *J* = 8,4 Hz, H-15 and H-17); ^{13}C-NMR (150 MHz, CD_3OD) see Table 1.

Helvafuranone (5): White powder; $C_{17}H_{14}O_5$, M= 298; $[\alpha]_D^{25}$ –5.7 (*c* 0,1, MeOH); ^{1}H-NMR (600 MHz, CD_3OD): δ_H 5.84 (1H, s, H-5), 3.67 (1H, br s, H_a-6), 3.97 (1H, br s, H_b-6), 7.02 (2H, br d, *J* = 8.4 Hz, H-8 and H-12), 6.74 (2H, br d, *J* = 8.4 Hz, H-9 and H-11), 7.36 (2H, br d, *J* = 8.4 Hz, H-14 and H-18) and 6.88 (2H, br d, *J* = 8.4 Hz, H-15 and H-17); ^{13}C-NMR (150 MHz, CD_3OD) see Table 1.

Table 1. ^{13}C NMR (150 MHz, CD_3OD) data of compounds **1**-**5**

C		1	2		3		4		5
	$^a\delta_C$	δ_C	δ_C	$^b\delta_C$	δ_C	$^c\delta_C$	δ_C	$^d\delta_C$	δ_C
1	172.9	168.9	*						
2			148.4	170.2	173.1	176.3	176.3	170.1	173.4
3	46.5	46.4	118.5	112.3	113.1	127.2	127.2	127.7	129.6
4	23.6	23.6	113.0	177.9	182.0	162.4	162.4	156.1	160.0
5	29.1	29.1	154.4	117.1	117.1	72.8	72.8	96.7	98.5
6	60.3	60.3	59.0	156.2	158.0	33.8	33.8	31.0	32.5
7	168.9	172.8	172.1	71.2	73.4	128.6	128.7	126.5	128.6
8			20.6	140.6	141.1	130.6	130.7	129.6	130.9
9	54.7	54.7		126.8	128.0	116.8	116.8	115.5	116.6
10	39.4	39.4		128.4	129.7	157.7	157.6	157.8	157.5
11	25.7	25.8		128.0	129.5	116.8	116.8	115.5	116.6
12	23.4	23.3		128.4	129.7	130.6	130.7	129.6	130.9
13	22.2	22.2		126.8	128.0	122.3	122.3	119.9	121.8
14						131.5	131.4	130.1	131.6
15						116.4	116.4	115.3	116.4
16						159.1	159.1	157.9	159.4
17						116.4	116.4	115.3	116.4
18						131.5	131.4	130.1	131.6

Notes: $^a\delta_C$ of cyclo-(*S*-Pro-*R*-Leu) in CD_3OD [9], $^b\delta_C$ of (7*R*)-(hydroxy(phenyl)methyl)-4*H*-pyran-4-one in DMSO-d_6 [10], $^c\delta_C$ of eutypoid B in CD_3OD [11], $^d\delta_C$ of helvafuranone in DMSO-d_6 [12], *signal not detected.

Cytotoxic assay

SRB (Sulforhodamine B) method [13] was used to evaluate the *in vitro* cytotoxic activity of isolated compounds against two human cancer cell lines as Hep-G2 (liver) and A549 (lung). The detailed procedures have been described in the reference [14].

Results and discussion

Using combined chromatographic methods, five compounds were isolated from the EtOAc extract of the marine fungal strain *Aspergillus* sp. HL24. Compound **1** was obtained as a white powder. Its ^{1}H and ^{13}C NMR spectra are characteristic of a cyclic dipeptide, a class of compounds commonly found in microorganisms, with the presence of two amide CO groups at δ_C 168.9 (C-1) and 172.1 (C-7) (Fig. 1).

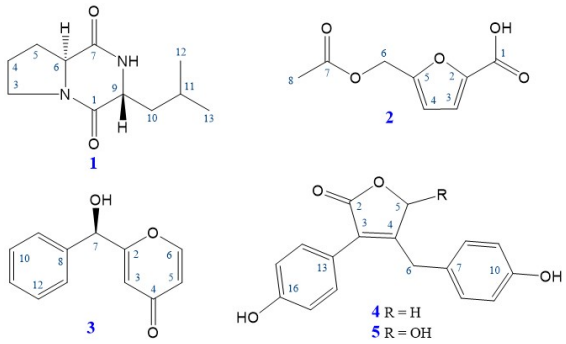

Figure 1. Secondary metabolites **1**-**5** from *Aspergillus* sp. HL24

In addition, signals for a nitrogen-bearing methylene group [δ_C 46.5 (C-3)/δ_H 3.53 (2H, m, H-3)], two nitrogen-bearing methine groups [δ_C 60.3 (C-6) and 54.7 (C-9)/δ_H 4.27 (1H, m, H-6) and 4.14 (1H, m, H-9)] and two doublet methyls [δ_C 23.3 (C-12) and 22.2 (C-13)/δ_H 0.99 (3H, d, J = 6.6 Hz, H-12) and 0.98 (3H, d, J = 6.6 Hz, H-13)] were also observed. Based on the obtained data, the ^{13}C NMR data of **1** matched those reported for cyclo-(*S*-Pro-*R*-Leu) [9]. However, the long-range J_3 HMBC correlations (Fig. 2) of H-3 (δ_H 3.53) and H-10 (δ_H 1.55 and 1.95) with C-1 (δ_C 168.9) and between H-5 (δ_H 2,05 and 2,32) and C-7 (δ_C 172.1) precisely confirm the chemical shifts of the two amide CO positions. Therefore, compound **1** was identified as cyclo-(*S*-Pro-*R*-Leu) [11] and the chemical shift values at C-1 and C-17 must be reassigned as shown in Table 1. The stereochemistry of compound **1** was determined based on the agreement of its optical rotation with previously reported data.

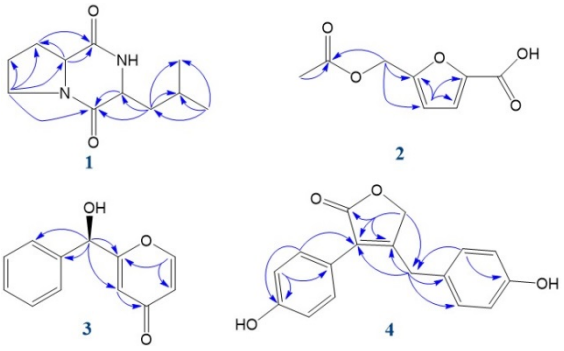

Figure 2. Key HMBC correlations of compounds **1**-**4**

Compound **2** was also isolated as a white powder. In its ^{1}H NMR spectrum, characteristic signals of two olefinic protons at δ_H 7,10 (1H, d, J = 3,0 Hz, H-3) and 6,57 (1H, d, J = 3,0 Hz, H-4) and one oxymethylene at δ_H 5,12 (2H, s, H-6) were observed, indicating the presence of a Sumiki's acid unit [15]. The ^{1}H NMR spectrum also revealed signal of an acetoxy-methyl at δ_H 2.08 (3H, s, H-8). Based on the obtained data, the ^{1}H NMR spectral data of compound **1** showed complete agreement with the corresponding data of acetyl Sumiki's acid [16]. Furthermore, detailed analysis of the signals in the ^{13}C NMR, HSQC, and HMBC spectra (Fig. 2) confirmed that this compound is acetyl Sumiki's acid.

In the ^{1}H NMR spectrum of compound **3**, signals corresponding to an ABX proton system (with coupling constants differing from those of aromatic protons) could be assigned to three pyrone protons at δ_H 6.64 (1H, d, J = 2.4 Hz, H-3), 6.31 (1H, dd, J = 2.4, 6.0 Hz, H-5) and 7,95 (1H, d, J = 6.0 Hz, H-6); one oxymethine δ_H 5.55 (1H, s, H-7) and five protons belonging to a phenyl group at δ_H 7.45 (2H, br d, J = 7.8 Hz, H-9 and H-13), 7.39 (2H, br t, J = 7.8 Hz, H-10 and H-12) and 7.34 (1H, br t, J = 7.8 Hz, H-11). The ^{13}C NMR signals further confirmed the presence of pyran-4-one [δ_C 173.1 (C-2), 113.1 (C-3), 182.0 (C-4), 117.1 (C-5) and 158.0 (C-6)],

oxymethine [δ_C 73.4 (C-7)] and phenyl [δ_C 141,1 (C-8), 128.0 (C-9 and C-13), 129.7 (C-10 and C-12) and 129.5 (C-1)] structural units. The oxymethine proton H-7 showed HMBC correlations with carbons C-2, C-3, C-8, and C-9, demonstrating its linkage to C-2 and C-8. Thus, compound **3** was identified as (7*R*)-(hydroxy(phenyl)methyl)-4*H*-pyran-4-one [10]. The 7*R* configuration was determined based on the agreement of its optical rotation value with previously reported data.

In the ^{1}H NMR spectrum of compound **4**, characteristic signals of two para-disubstituted benzene rings at δ_H 7.00 (2H, br d, *J* = 8.4 Hz, H-8 and H-12), 6.74 (2H, br d, *J* = 8.4 Hz, H-9 and H-11), 7.36 (2H, br d, *J* = 8.4 Hz, H-14 and H-18) and 6.89 (2H, br d, *J* = 8.4 Hz, H-15 and H-17) along with two methylene groups at δ_H 4.72 (2H, s, H-5) and 3.87 (2H, br s, H-6) were observed. The ^{13}C NMR spectrum also displayed signals indicating the presence of two para-disubstituted benzene rings and two methylene groups (Table 1). Additionally, signals of a lactone carbonyl group [δ_C 176.3 (C-2)] and a fully substituted double bond [δ_C 127.2 (C-3) and 162.4 (C-4)] were also observed. Based on the obtained data, the ^{13}C NMR signals of compound **4** matched perfectly at all positions with the published data for eutypoid B [11]. The HMBC correlation between H-5 and C-2 permitted the assignment of the lactone ring closure at C-2/C-5. Furthermore, HMBC correlations between H-5 and C-6, H-6 and C-8/C-12, and between H-14/H-18 and C-3 confirmed the attachment positions of the two para-disubstituted benzene rings.

The ^{1}H NMR and ^{13}C NMR spectral data of compound **5** were similar to those of **4** (Table 1), except for the presence of a dioxymethine group at δ_C 98.5 (C-5)/δ_H 5.84 (1H, s, H-5) in compound **5**, replacing the oxymethylene group found in **4**. The long-range HMBC correlations observed between proton H-5 and carbons C-2 and C-6 allowed for the assignment of the dioxymethine group at C-5. Thus, compound **5** was identified as helvafuranone. With a very small specific optical rotation value, **5** was determined to possibly exist as a racemic mixture [12].

Previous investigations of soft coral-derived *Aspergillus* fungi have resulted in the isolation of alkaloid, indole-diterpenoid, benzophenone, prenylated indole alkaloid, prenylated xanthone, benzodipyran, aromatic butenolide, cyclic peptide, ecdysteroid, sesquiterpene lactone, phenylalanine derivatives [7, 8, 17–24]. However, this is the first report of compounds **1**–**5** from an *Aspergillus* fungus derived from soft corals. The cytotoxic activities of compounds **1**–**5** were evaluated on two human cancer cell lines, Hep-G2 (liver) and A549 (lung), using the SRB method [13]. However, these compounds did not show significant cytotoxicity (IC_{50} > 100 µM) against both cell lines.

Conclusion

From the marine fungal strain *Aspergillus* sp. HL24, a cyclic dipeptide (**1**), a furan (**2**), a pyranone (3), and two butenolide derivatives (**4** and **5**) were isolated using chromatographic methods. Their chemical structures were determined by one-dimensional (^{1}H NMR and ^{13}C NMR) and two-dimensional (HSQC and HMBC) nuclear magnetic resonance spectroscopy. Compounds **1**-**5** did not show significant cytotoxicity (IC_{50} > 100 µM) against two human cancer cell lines as Hep-G2 (liver) and A549 (lung).

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