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Monoindole Alkaloids from a Marine Sponge *Spongosorites* sp.

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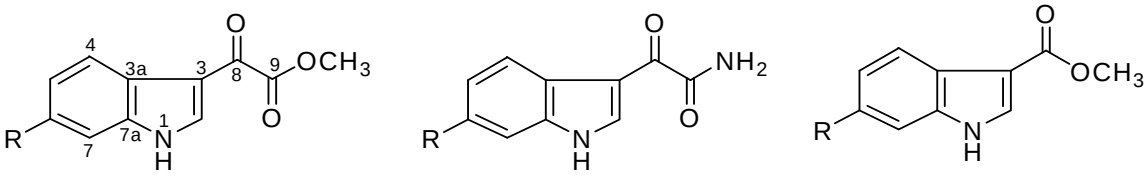
Abstract: Seven (**1**–**7**) monoindole derivatives were isolated from the MeOH extract of a marine sponge *Spongosorites* sp. by bioactivity-guided fractionation. The planar structures were established on the basis of NMR and MS spectroscopic analyses. Compounds **1**–**5** are unique indole pyruvic acid derivatives. Compounds **1**–**2** and **4**–**6** are isolated for the first time from a natural source although they were previously reported as synthetic intermediates. Compound **3** was defined as a new compound. Co-occurring bisindoles such as hamacanthins and topsentins might be biosynthesized by condensation of two units of these compounds. The compounds were tested for cytotoxicity against a panel of five human solid tumor cell lines, and compound **7** displayed weak activity.

Keywords: Marine sponge; *Spongosorites*; monoindole alkaloids; cytotoxicity.

Introduction

To date, dozens of simple monoindole derivatives were reported from marine sources, such as sponges [1–5], ascidians [6], bryozoans [7], bacteria [8], and fungi [9]. Some of these metabolites were reported to exhibit antibacterial [2,10], antifungal [3], and auxin [4] activities.

In our previous study on cytotoxic compounds from the marine sponge *Spongosorites* sp., we isolated a series of bisindole alkaloids [11,12]. In our continuing search for cytotoxic metabolites from the same sponge, seven monoindole alkaloids were isolated. Compounds **1**–**2** and **4**–**6** were isolated for the first time from a natural source although they were previously reported as synthetic intermediates (Figure 1). Compound **3** was defined as a new compound. Herein we describe the structure elucidation and the biological evaluation of these compounds.



1 R = Br
2 R = H
3 R = OH

4 R = H
5 R = Br

6 R = OH
7 R = H

Figure 1. Seven (**1**–**7**) monoindole derivatives were isolated from the MeOH extract of a marine sponge *Spongosorites* sp.

Result and discussion

Compound **1** was isolated as a yellow, amorphous powder. The molecular formula was established as $C_{11}H_8BrNO_3$ on the basis of the EIMS and NMR data. In the LREIMS of **1**, a $(M)^+$ ion cluster was observed at *m/z* 281/283 in the ratio of 1:1 that is characteristic of a monobrominated compound. The NMR spectrum of **1** were reminiscent of reported indole alkaloids.[11,12] Analysis of the ^{1}H, ^{13}C, COSY, HMBC, and HSQC data, along with comparison of chemical shift values with those of known indole alkaloids, allowed us to establish a 6-bromoindol-3-yl residue as a partial structure of **1**. The singlet at δ_H 8.45 (H-2), and a spin system comprised of signals at δ_H 8.07 (1H, d, *J*=8.0 Hz, H-4), 7.40 (1H, dd, *J*=8.0, 2.0 Hz, H-5), and 7.73 (1H, d, *J*=2.0, H-7) indicated the presence of a 6-bromoindol-3-yl moiety (Table 1). Long-range correlations from H-4 (δ_H 8.07) to C-3 (δ_C 112.5) and C-6 (δ_C 116.2), along with the COSY correlation between H-4 and H-5, and the long-range correlations from H-5 (δ_H 7.40) to C-3a (δ_C 124.8) and C-7 (115.5) strongly suggested the presence of a 6-bromoindol-3-yl moiety. The NMR signals at δ_C 178.2 (C-8), δ_C 164.0 (C-9), and δ_H 3.89 (-OCH_3, 3H), along with the HMBC correlations of -OCH_3/C-9, suggested an oxoacetic acid methyl ester moiety. The EIMS fragments at *m/z* 194/196, corresponding to C_8H_5BrN, corroborated the presence of a bromoindole group. These fragments, along with the fragments at *m/z* 222/224 revealed the presence of a 3-carbonyl-bromoindole group, and established the connectivity between the 6-bromoindole moiety and the oxoacetic acid methyl ester moiety (Figure 2). Therefore, compound **1** was defined as (6-bromo-1*H*-indol-3-yl) oxoacetic acid methyl ester. Compound **1** was known as an intermediate in the synthesis of some marine natural products, such as didemnimides A and B [13], whereas it has not been reported from a natural source. Pyruvic acid derivatives are unusual natural products, and most of indole pyruvic acid derivatives were isolated from marine sponges [14–16] and ascidians [6].

Table 1. ^{1}H NMR Data of Compounds **1**–**6** (in DMSO-d_6, 500 MHz, δ_{ppm}).

position	**1**	**2**	**3**	**4**	**5**	**6**
1				12.19		11.52
				(br s)		(br s)
2	8.45	8.44	8.22	8.69	8.68	7.86
	(d, *J*=2.0 Hz)	(s)	(s)	(s)	(s)	(s)
4	8.07	8.16	7.82	8.22	8.12	7.74
	(d, *J*=8.0 Hz)	(d, *J*=7.0 Hz)	(d, *J*=8.0 Hz)	(d, *J*=6.0 Hz)	(d, *J*=8.5 Hz)	(d, *J*=8.5 Hz)
5	7.40	7.27	6.74	7.25	7.36	6.68
	(dd, *J*=8.0, 2.0 Hz)	(t, *J*=7.0 Hz)	(dd, *J*=8.0, 2.0 Hz)	(t, *J*=6.0 Hz)	(dd, *J*=8.5, 2.0 Hz)	(dd, *J*=8.5, 2.0 Hz)
6		7.30		7.25		
		(t, *J*=7.0 Hz)		(t, *J*=6.0 Hz)		
7	7.73	7.55	6.87	7.52	7.70	6.81
	(d, *J*=2.0 Hz)	(d, *J*=7.0 Hz)	(d, *J*=2.0 Hz)	(d, *J*=6.0 Hz)	(d, *J*=2.0 Hz)	(d, *J*=2.0 Hz)
-OCH_3	3.89	3.90 (s)	3.87			3.76
	(s)		(s)			(s)
-NH_2				8.06	8.05	
				(br s)	(br s)	
				7.69	7.67	
				(br s)	(br s)	
-OH						9.17
						(br s)

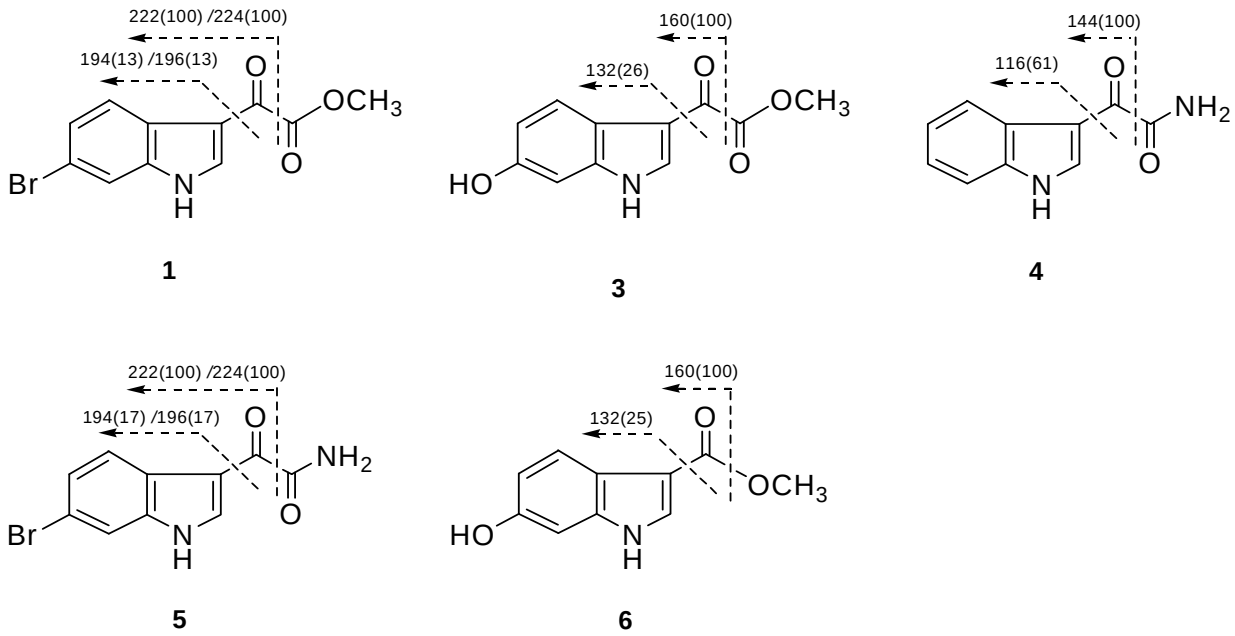


Figure 2. Key fragmentations of $[M]^+$ ions of **1** and **3**–**6** in LREIMS (relative intensity in parentheses).

Compound **2** was isolated as a yellow, amorphous powder. The molecular formula was established as $C_{11}H_9NO_3$ on the basis of the FABMS and NMR data. In the LRFABMS of **2**, a $(M + H)^+$ ion was observed at *m/z* 204. The main difference from compound **1** was lack of bromine atom on the indole ring. Therefore, compound **2** was defined as (1*H*-indol-3-yl) oxoacetic acid methyl ester. Compound **2** was known as an intermediate in the synthesis of natural products, such as didemnimides A and B [13], rebeccamycin, and 11-dechlororebeccamycin [17], whereas it has not been reported as a natural product.

Compound **3** was isolated as a yellow, amorphous powder. The molecular formula was established as $C_{11}H_9NO_4$ on the basis of the EIMS and NMR data. In the LREIMS of **1**, a $(M)^+$ ion was observed at *m/z* 219. The main difference from compound **2** was an additional hydroxyl group on the indole ring. A singlet at δ_H 8.22 (1H, s, H-2), and a spin system comprised of signals at δ_H 7.82 (1H, d, *J*=8.0, H-4), 6.74 (1H, dd, *J*=8.0, 2.0, H-5), and 6.87 (1H, d, *J*=2.0, H-7), were observed in ^{1}H NMR spectrum. The HMBC correlations from H-2 (δ_H 8.22), H-5 (δ_H 6.74), and H-7 (δ_H 6.87) to C-3a (δ_C 118.5), from H-2 to C-3 (δ_C 112.5) and C-7a (δ_C 138.5), and from H-5 (δ_H 6.74) to C-6 (δ_C 154.4), indicated the presence of a 6-hydroxyindol-3-yl moiety. The EIMS fragments at *m/z* 132 and 160 corroborated the proposed structure (Figure 2). Therefore, compound **3** was defined as (6-hydroxy-1*H*-indol-3-yl) oxoacetic acid methyl ester. To the best of our knowledge, compound **3** has not been reported previously either from a natural source or as a synthetic product.

Compound **4** was isolated as a white, amorphous powder. The molecular formula was established as $C_{10}H_8N_2O_2$ on the basis of the EIMS and NMR data. In the LREIMS of **3**, a $(M)^+$ ion was observed at *m/z* 188. The main difference from compound **2** was the presence of an oxoacetamide moiety instead of the oxoacetic acid methyl ester moiety. The ^{13}C signals at δ_C 182.9 (C-8) and δ_C 165.9 (C-9), the ^{1}H singlets at δ_H 8.06 and δ_H 7.69 (each 1H, $-NH_2$) (Tables 1 and 2), along with the long-range correlation between $-NH_2$ (δ_H 7.69) and C-8 (δ_C 182.9), established an oxoacetamide moiety. The EIMS fragments at *m/z* 116 and 144 revealed the presence of a 3-carbonylindole group, and established the connectivity between the oxoacetamide moiety and the indole moiety (Figure 2). Thus, compound **4** was defined as (1*H*-indol-3-yl) oxoacetamide, which was also known as an intermediate in the synthesis of some marine natural products, such as arborescidines [18] and dihydrohamacanthins [19], but has not been isolated previously from a natural source.

Compound **5** was isolated as a yellow, amorphous powder. The molecular formula was established as $C_{10}H_7BrN_2O_2$ on the basis of the EIMS and NMR data. In the EIMS data of **5**, a $(M)^+$ ion cluster was observed at *m/z* 266/268. The main difference from compound **4** was an additional bromine atom on the indole ring. The fragments at *m/z* 194/196 and 222/224 revealed the presence of 3-carbonyl-bromoindole group (Figure 2). Therefore, compound **5** was defined as (6-bromo-1*H*-indol-3-yl) oxoacetamide, which was also reported as an intermediate in the synthesis of some natural products, such as arborescidines [18], dihydrohamacanthins [19], but has not been isolated from a natural source.

Compound **6** was isolated as colorless oil. The molecular formula was established as $C_{10}H_9NO_3$ on the basis of the EIMS and NMR data. In the LREIMS of **6**, a $[M]^+$ ion was observed at *m/z* 191. Analysis of the ^{1}H, ^{13}C, COSY, HMBC, and HSQC data, allowed us to establish a 6-hydroxyindol residue as a partial structure of **6**. The long-range correlation from H-2 (δ_H 7.86, 1H, s) and $-OCH_3$ (δ_H 3.76, 3H, s) to C-8 (δ_C 164.8) established the presence of a formic acid methyl ester and the connectivity between the 6-hydroxyindol moiety and the carboxylic acid methyl ester. The EIMS

fragments at *m/z* 132 and 160 corroborated the proposed structure (Figure 1). Therefore, compound **6** was defined as (6-hydroxy-1*H*-indol-3-yl) carboxylic acid methyl ester, which was known as an intermediate in the organic synthesis of a 5-HT_4 receptor antagonist [20], but has not been reported from a natural source.

Compound **7** was also isolated as a yellow, amorphous powder. According to the MS and NMR data of **7**, the main difference from **6** was lack of a hydroxyl group in the indole moiety. The MS and NMR data of **7** matched well with reported data [8], and was identified as (1*H*-indol-3-yl) carboxylic acid methyl ester which was previously reported from marine-derived bacteria [8] and fungi [21], and red alga [22], with cytotoxicity against K562 human chronic leukemia (MIC s 14.0 μg/mL) [21].

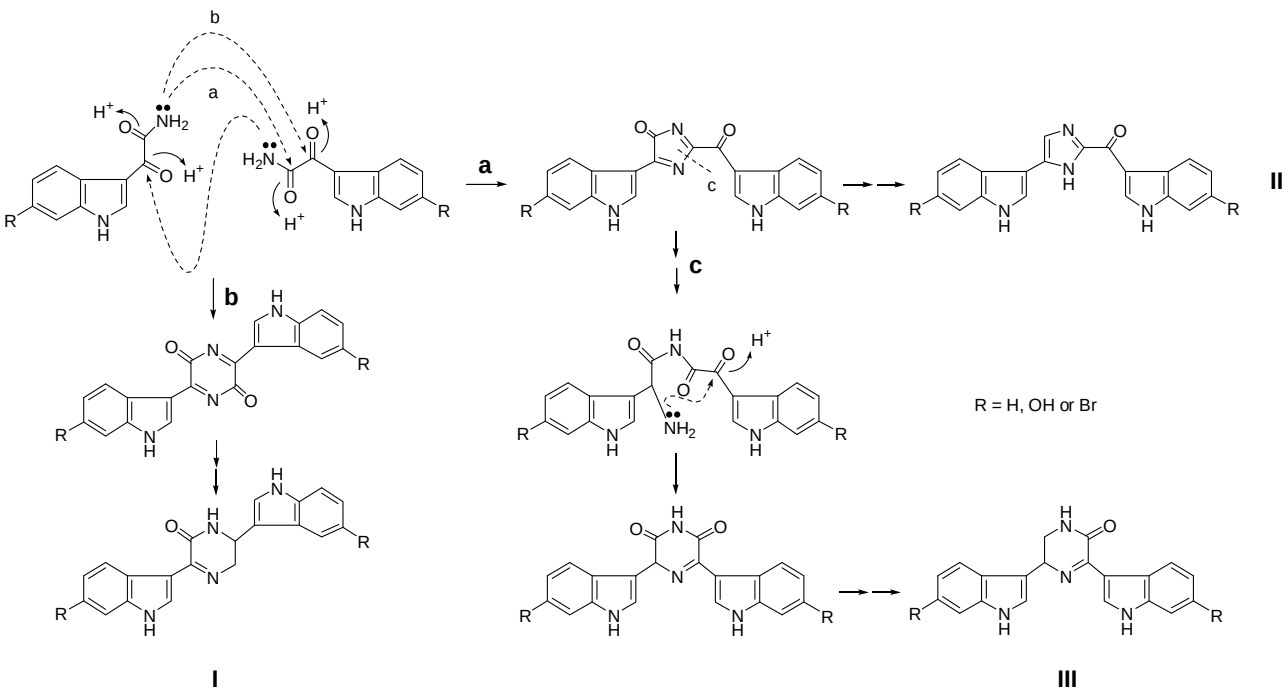
Table 2. ^{13}C NMR Data of Compounds **1**–**6** (in DMSO-d_6, 75 MHz, δ_{ppm}).

position	**1**	**2**	**3**	**4**	**5**	**6**
2	139.5	136.8	134.5	138.1	140.2	130.6
3	112.5	112.7	112.5	112.0	112.0	106.3
3a	124.8	125.5	118.5	126.1	125.6	118.7
4	122.5	121.1	121.4	121.2	122.8	120.8
5	125.3	122.8	112.2	122.4	125.0	111.6
6	116.2	123.8	154.4	123.3	115.6	153.7
7	115.5	112.4	97.7	112.4	115.6	97.2
7a	138.6	138.4	138.5	136.2	140.0	137.4
8	178.2	178.6	[a]	182.9	180.0	164.8
9	164.0	164.9	164.4	165.9	165.9	
-OCH_3	52.4	52.5	51.9			50.4

[a] The carbonyl carbon signal was not detected due to low concentration of the NMR sample.

It is expected that (1*H*-indol-3-yl) oxoacetamide derivatives serve as intermediate for the biogenesis of co-occurring bisindole alkaloids, topsentins and hamacanthins [11,12] (Scheme 1). Schiff base formation between amino and carbonyl groups may (either via **a** or **b**) leads to the genesis of hamacanthin A (Ⅰ) and topsentin (Ⅱ) skeletons. Cleavage of the C–N bond (**c**) in the topsentin skeleton, and successive Schiff base formation between newly generated amino group and the intact carbonyl group may lead to a genesis of hamacanthin B skeleton (Ⅲ).

Compounds **1**, **2**, and **4**–**7** were evaluated for cytotoxicity against a panel of five human solid tumor cell lines. Compound **7** showed weak cytotoxicity to human lung cancer, human ovarian cancer, human skin cancer, human CNS cancer, and human colon cancer with ED_{50} values 24.1, 13.4, 15.2, 26.2, and 4.85μg/mL, respectively, while other compounds did not show significant activity (ED_{50}>30μg/mL). The ED_{50} values of doxorubicin against these tumor cell lines in the same experiment were 0.02, 0.14, 0.03, 0.04, and 0.10μg/mL, respectively.



Scheme 1. Hypothetical biogenesis of topsentins and hamacanthins.

Experimental

General Experimental Procedures

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 and Varian INOVA 500 instruments. Chemical shifts were reported with reference to the respective residual solvent or deuterated solvent peaks (δ_H 2.5 and δ_C 39.5 for DMSO-d_6). FABMS data were obtained on a JEOL JMS SX-102A; EIMS data were obtained on a Shimadzu QP5050. HPLC was performed with an YMC ODS-H80 column (250 × 10 mm i.d., 4 μm, 80 Å) and C18-5E Shodex packed column (250 × 10 mm i.d., 5 μm, 100 Å) using a Shodex RI-71 detector.

Animal Material

The sponges were collected by hand using SCUBA (20 m depth) in October 2002, off the coast of Jeju Island, Korea. The collected sample was a loose association of two sponges *Spongosorites* sp. and *Halichondria* sp. The two sponges were separated and only *Spongosorites* sp. was subjected to chemical analysis. The morphology of the sponge was described elsewhere [11]. A voucher specimen (registry No. Spo. 44) is deposited at the Natural History Museum, Hannam University. Korea.

Extraction and Isolation

Evaluation was performed at Korea Research Institute of Chemical Technology. The frozen sponge (0.8 kg) was chopped into small pieces and extracted with MeOH at room temperature. The MeOH extract showed significant toxicity to brine shrimp larvae (LD_{50} 23.7 μg/mL). The MeOH extract was

partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was further partitioned between aqueous MeOH and *n*-hexane. Aqueous MeOH fraction was subjected to a reversed-phase flash column chromatography (YMC Gel ODS-A, 60 Å, 230 mesh) with a stepped gradient solvent system of 60 to 100% MeOH/H_2O to afford 16 fractions. Fraction 2 (0.80 g), one of the bioactive fractions (LD_{50} 33.9 μg/mL), was subjected to a reversed-phase HPLC (YMC ODS-H80 column) eluting with 75% MeOH to afford 13 sub-fractions. Compound **1** (0.95 mg) was obtained by separation of the sub-fraction 2-8 on a reversed-phase HPLC eluting with 58% MeCN. Compound **2** (2.2 mg) was obtained by separation of the sub-fraction 2-2 on a reversed-phase HPLC eluting with 35% MeCN. The sub-fraction 2-1 was subjected to successive reversed-phase HPLC (YMC ODS-H80 column) eluting with 38% MeCN, and further purification with 43% MeCN (C18-5E Shodex packed column) to afford compounds **3** (0.4 mg), **4** (0.78 mg) and **6** (0.62 mg). Compounds **5** (1.2 mg) and **7** (3.3 mg) were obtained by separation of sub-fractions 2-5 and 2-4, respectively, on a reversed-phase HPLC (Shodex C18 M10E column) eluting with 42% MeCN.

(6-Bromo-1*H*-indol-3-yl) oxoacetic acid methyl ester (**1**): yellow amorphous powder; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; LREIMS *m/z* 281/283 $(M)^+$.

(1*H*-Indol-3-yl)oxoacetic acid methyl ester (**2**): yellow amorphous powder; IR (film) ν_{max} 3206 (br), 1727, 1615 cm^{-1}; UV (MeOH) λ_{max} (log $\in$) 362 (3.11), 262 (3.03) nm; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; LRFABMS *m/z* 204 $(M + H)^+$.

(6-Hydroxy-1*H*-indol-3-yl) oxoacetic acid methyl ester (**3**): yellow amorphous powder; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; LREIMS *m/z* 219 $(M)^+$.

(1*H*-Indol-3-yl) oxoacetamide (**4**): white amorphous powder; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; LREIMS *m/z* 188 $(M)^+$.

(6-Bromo-1*H*-indol-3-yl) oxoacetamide (**5**): yellow amorphous powder; IR (film) ν_{max} 3386, 3211, 1663, 1591, 1572, 1407 cm^{-1}; UV (MeOH) λ_{max} (log $\in$) 320 (2.61), 275 (2.75), 258 (2.73), 212 (3.21) nm; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; LREIMS *m/z* 266/268 $(M)^+$.

(6-Hydroxy-1*H*-indol-3-yl) carboxylic acid methyl ester (**6**): colorless oil; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; LREIMS *m/z* 191 $(M)^+$.

(1*H*-Indol-3-yl) carboxylic acid methyl ester (**7**): yellow amorphous powder; IR (film) ν_{max} 3255 (br), 1693, 1620, 1591, 1531, 1444, 1197 cm^{-1}; UV (MeOH) λ_{max} (log $\in$) 349 (2.62), 240 (2.75); LREIMS *m/z* 175 $(M)^+$.

Evaluation of Cytotoxicity

A panel of five human solid tumor cell lines, human lung cancer, human ovarian cancer, human skin cancer, human CNS cancer, and human colon cancer, were used to screen cytotoxicity of the compounds based on an established protocol [11,12].

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Sample Availability: Not available.