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Three new sulfur-containing alkaloids, polycarpaurines A, B, and C, from an Indonesian ascidian *Polycarpa aurata*

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Abstract—Three new sulfur-containing alkaloids, polycarpaurines A (**1**), B (**2**), and C (**3**) were isolated from the tropical ascidian *Polycarpa aurata* collected in Indonesia, together with six known compounds (**4**–**9**). The structures of new compounds were assigned on the basis of their spectral data. Compounds **1**, **3**, **4**, and **8** inhibited colony formation of Chinese hamster V79 cells with EC_{50} values of 6.8, 8.6, 3.8, and 10 μM, respectively. Compounds **2** and **7** showed modest activity against V79 cells (EC_{50}>10 μM).
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1. Introduction

Many interesting sulfur-containing alkaloids have been isolated from ascidians (tunicates). From ascidians of the genus *Polycarpa*, disulfide alkaloids, polycarpamines A–E,[1] a dimeric disulfide alkaloid, polycarpine (**4**),[2] and its derivatives[3,4] have been reported. These compounds presented various biological activities, such as antifungal activity,[1] cytotoxicity,[3] inhibition of inosine monophosphate dehydrogenase (IMPDH),[2] and induction of apoptosis in JB6 cells through p53- and caspase 3-dependent pathways.[5]

In the search for bioactive metabolites from marine organisms, we found that the ethanol extract of the ascidian *Polycarpa aurata*, collected in North Sulawesi, Indonesia, exhibited notable cytotoxicity against a murine leukemia cell line L1210 and inhibitory activity against the colony formation of Chinese hamster V79 cells. Bioassay-guided separation gave three new alkaloids, named polycarpaurines A (**1**), B (**2**), and C (**3**), together with six known compounds, which were assigned as polycarpine (**4**) and its presumed decomposed compound (**5**) and 2-(4-methoxyphenyl)-*N*-methyl-2-oxoacetamide (**6**), *N*-(4-methoxybenzoyl)-*N*′-methylguanidine (**7**), *N*,*N*-didesmethylgrossularine-1 (**8**), and *p*-methoxybenzoic acid (**9**).[1–4] In this paper we describe the isolation, structure elucidation, and bioactivity of three new compounds **1**–**3**.

2. Results and discussion

Polycarpaurine A (**1**) was obtained as a bis-TFA salt, because the purification was performed by HPLC using a solvent mixture containing 0.1% trifluoroacetic acid (TFA). HRFABMS of **1** showed a pseudomolecular ion $[M+H]^+$ at *m*/*z* 437.1727 and the molecular formula of **1** was deduced as $C_{22}H_{24}N_6O_2S$, which showed 14 degrees of unsaturation. The ^1H and ^{13}C NMR signals of **1** (Table 1) were assigned by HMQC and HMBC spectra. The ^1H NMR spectrum of **1** gave two aromatic proton doublets at δ 7.62 and 7.10, a methoxy singlet at δ 3.88 and an *N*-CH_3 singlet at δ 2.93. HMBC correlations from H-7 to three aromatic carbons C-5, -9, and -11, from H-8 to C-6, -9, and -10, and from H_3-12 (OCH_3) to C-9 revealed the presence of a *p*-methoxyphenyl group. HMBC correlations were also detected from H_3-13 (*N*-CH_3) to C-1 and -3. The above spectral characteristics of **1** were very similar to those of **4**,[2,3,6] an alkaloid possessing two identical phenylimidazole moieties linked by a disulfide bridge. Therefore, **1** was revealed to have the same phenylimidazole unit as **4**. Since only 11 carbon signals were observed in the ^{13}C NMR spectrum of **1**, a symmetric element must be present in the structure of **1** to meet the molecular formula. Subtraction of the sum of two

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Table 1. ^{13}C (100 MHz) and ^{1}H (400 MHz) NMR data for compounds **1–3**

Position	**1** (CD_3OD)			**2** (DMSO-d_6)			**3** (DMSO-d_6)		
	δ_C	δ_H (J in Hz)	HMBC	δ_C	δ_H (J in Hz)	HMBC	δ_C	δ_H (J in Hz)	HMBC
1	113.1			127.5			114.9		
3	149.2			145.8			146.9		
4					12.47, br s			12.87, br s	
5	134.7			123.2			131.8		
6	120.3			120.2			119.7		
7 (11)	131.3	7.62, d (8.8)	5, 9, 11 (7)	131.3	7.47, d (8.4)	5, 9, 11 (7)	129.3	7.87, d (8.8)	5, 9, 11 (7)
8 (10)	115.6	7.10, d (8.8)	6, 9, 10 (8)	112.9	6.95, d (8.4)	6, 9, 10 (8)	113.9	7.03, d (8.8)	6, 9, 10 (8)
9	162.7			159.5			160.0		
12	56.0	3.88, s	9	55.2	3.78, s	9	55.3	3.79, s	9
13	30.3	2.93, s	1, 3	30.9	3.60, s	1, 3	29.7	3.49, s	1, 3
NH_2					7.52, s			7.71, s	

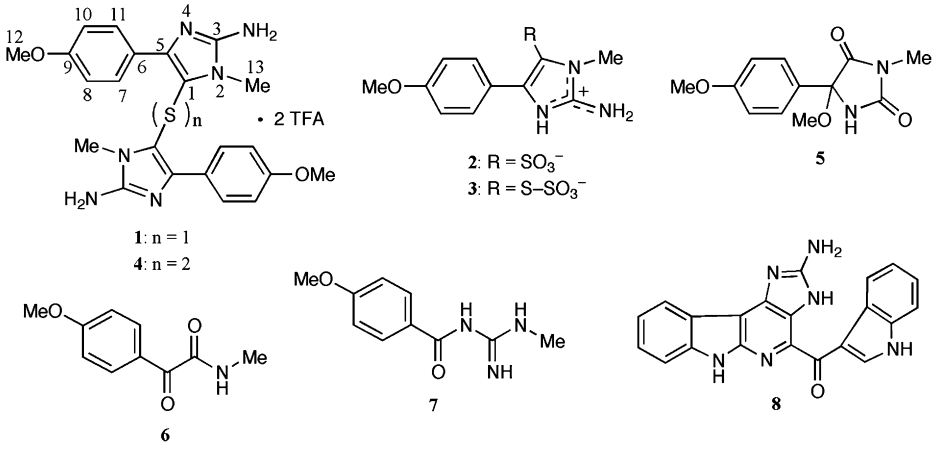
phenylimidazole units from the molecular formula of **1** left one sulfur atom; therefore, the structure of **1** was deduced as a dimeric monosulfide alkaloid.

The molecular formula of compound **2** was determined as $C_{11}H_{13}N_3O_4S$ from the HRFABMS and NMR spectra. ^{1}H and ^{13}C NMR data for **2** (Table 1) resembled those for **1** and **4** except for two ^{13}C signals at δ 127.5 and 123.2, which were assigned as C-1 and -5, respectively, according to the HMBC correlations from H_3-13 (N-CH_3) to δ 127.5 and from H-7 to δ 123.2. The ^{1}H NMR spectrum of **2** showed two exchangeable broad singlets at δ 12.47 (1H) and 7.52 (2H), which were ascribed to the equilibrium of the tautomeric forms of a guanidine moiety. Strong absorption at 1040 cm^{-1} in the IR spectrum of **2** suggested the presence of a sulfate group, which was confirmed by the negative FABMS fragment ion at m/z 80 (SO_3) and a difference of 80 Da between $[M+H]^+$ at m/z 284 and a fragment ion at m/z 204 in the positive FABMS (Fig. 1). The position of the sulfate group was assigned at C-1 from the comparison of ^{13}C NMR data for **2** with those for **1** and **4**.

Compound **3** had the molecular formula of $C_{11}H_{13}N_3O_4S_2$, which was deduced from the HRFABMS and NMR spectra. ^{1}H and ^{13}C NMR data (Table 1) for **3** suggested the presence of the same phenylimidazole moiety as that of **1** and **4**. Subtraction of the phenylimidazole unit, $C_{11}H_{13}N_3O$, from the molecular formula of **3** left S_2O_3. The negative FABMS of **3** showed ion peaks at m/z 80 (SO_3) and 112 (S–SO_3). In the positive FABMS of **3**, the fragment ion peaks at m/z 236 and 204, corresponding to the loss of 80 (SO_3) and 112 Da (S–SO_3) from the $[M+H]^+$ ion peak at m/z 316, respectively, were observed. These data suggested the presence of a thiosulfate group in the structure of **3**. The position of the thiosulfate group was assigned at C-1 by comparison of ^{13}C NMR data for **3** with those for **1**, **2**, and **4**.

A few natural sodium alkyl and alkenyl thiosulfates, such as *n*-propyl, *trans*-1-propenyl, *cis*-1-propenyl, and 2-propenyl thiosulfates, have been reported from onion and garlic as the causative agents of hemolytic anemia in dogs.[7] This is the first report of the isolation of a thiosulfate alkaloid from marine organisms.

The purified compounds (**1–8**) were examined for the effect on the rate of colony formation utilizing Chinese hamster V79 cells. This bioassay reflects the direct action of compounds on the cells. Compounds **1**, **3**, **4**, and **8** inhibited the colony formation of V79 cells with EC_{50} values of 6.8, 8.6, 3.8, and 10 μM, respectively. Compounds **2** and **7** showed modest activity against V79 cells (EC_{50}>10 μM).



3. Experimental

3.1. General

UV and IR spectra were recorded on a Hitachi U-3310 and a Perkin–Elmer Spectrum One FTIR spectrometer, respectively. NMR spectra were measured on a JEOL AL 400 NMR spectrometer. Mass spectra were obtained by a JEOL

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