Callyspongiamides A and B, sterol O-acyltransferase inhibitors, from the Indonesian marine sponge Callyspongia sp.

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ABSTRACT

Callyspongiamides A (**1**) and B (**2**), two new sterol *O*-acyltransferase (SOAT) inhibitors, were isolated from the Indonesian marine sponge *Callyspongia* sp. together with a known congener, dysamide A (**3**). The structures of **1** and **2** were elucidated to be polychlorine-containing modified dipeptides based on their spectroscopic data. Compounds **1**–**3** inhibited both of the SOAT isozymes, SOAT1 and SOAT2, in cell-based and enzyme-based assays.

Marine sponges have proven to be a rich source of promising substances with unusual chemical structures and interesting biological properties.[1] Among marine animals, the genus *Callyspongia* belongs to the family Callyspongidae and is composed of more than 60 species, which are widely distributed in tropical oceans. Chemical studies on sponges have provided various types of structurally unique metabolites, such as polyketides,[2] polyacetylenes,[3] alkaloids,[4] diketopiperazines,[5] and cyclic peptides,[6] most of which were reported as cytotoxic components.

During our screening program on bioactive compounds from marine invertebrates, we found that the EtOH extract of the Indonesian marine sponge *Callyspongia* sp. exhibited sterol *O*-acyltransferase (SOAT, also known as acyl-CoA: cholesterol acyltransferase, EC 2.4.1.26) inhibitory activity in a cell-based assay. SOAT, an endoplasmic reticulum membrane protein, catalyzes the intracellular esterification of free cholesterol with long-chain fatty acids from acyl-CoA to form the cholesteryl ester (CE), and, thus, this enzyme has potential as a target for the treatment of hypercholesterolemia and related diseases.[7] Two SOAT isozymes, SOAT1 and SOAT2, have been characterized with distinct functions by molecular biology studies: SOAT1 is ubiquitously expressed in most tissues and cells, while SOAT2 is predominantly expressed in the liver (hepatocytes) and intestines.[8] Therefore, selective activity against SOAT1 and SOAT2 isozymes is one of the important properties for the development of SOAT inhibitors.[9] Activity-guided separation of the extract led to the isolation of two new polychlorine-containing modified dipeptides (Fig. 1), named callyspongiamides A (**1**) and B (**2**), together with a known polychlorinated diketopiperazine, dysamide A (**3**).[10] We herein describe the isolation, structural elucidation, and biological activities of polychlorinated compounds **1**–**3**.

The EtOH extract of the marine sponge was purified with preparative HPLC (ODS column) to give compounds **1** (6.8 mg), **2** (1.9 mg), and **3** (13 mg).[11]

The FABMS of **3** showed a cluster of isotope peaks characterized as a hexachlorinated compound, and its typical ^{13}C NMR signal at δ_C 105.4 indicated the presence of a trichloromethyl group.[10,12] A literature search yielded the structure of symmetric polychlorinated diketopiperazines as a candidate, and compound **3** was identified as dysamide A by comparing the spectroscopic data of **3** with that in the literature (Fig. 1).[10]

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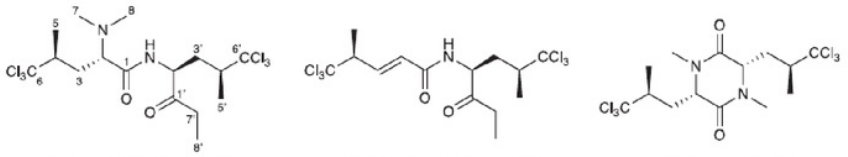

Figure 1. Structures of compounds **1**–**3** obtained from the Indonesian marine sponge *Callyspongia* sp.

Compounds **1** and **2** also had similar spectroscopic features in their EIMS and ^{13}C NMR spectra to those of **3**,[11] suggesting that the molecular structures of **1** and **2** possess trichloromethyl groups.

The molecular formula of **1**, $C_{16}H_{26}Cl_6N_2O_2$, was deduced from HRFABMS (*m*/*z* 491.017 [M + H]$^+$, calcd for $C_{16}H_{27}^{35}Cl_5^{37}ClN_2O_2$) and NMR data (Table 1). The ^1H NMR spectrum of **1** (in $CDCl_3$) displayed 26 proton signals, one of which was suggested to be an amine proton (δ_H 7.44). Two out of the 16 carbon signals observed in the ^{13}C NMR spectrum of **1** (in $CDCl_3$) were assigned as trichloromethyl carbons (δ_C 105.4 and 106.4), and the other signals were classified into three methyl, two *N*-methyl, three sp^3 methylene, four sp^3 methine, and two carbonyl carbons in analyses of DEPT and HMQC data (Table 1). COSY correlations revealed the presence of three partial structures I–III (Fig. 2). HMBC correlations from H-2 (δ_H 3.22) to C-1 (δ_C 172.7), from H-3 (1.76 and 2.36) and H-5 (1.38) to C-6 (106.4), and from H_3-7/ H_3-8 (2.37) to C-2 (66.9) established the substructure A containing the partial structure I. Partial structures II and III were connected to substructure B by cross peaks from H-2′ (4.70) to C-1′ (208.6), from H-3′ (1.82 and 2.11) and H_3-5′ (1.46) to C-6′ (105.4), and from H_3-8′ (1.09) to C-1′ in the HMBC experiment (Fig. 2). Considering the chemical shift at C-1 (δ_C 172.7) and remaining degree of unsaturation, two substructures A and B need to be bound via an amide linkage (Fig. 2). Thus, the structure of **1** was assigned as shown in Fig. 1 and named callyspongiamide A.

Compound **2** showed similar physico-chemical properties to **1**,[11] and the molecular formula of **2** was deduced as $C_{14}H_{19}Cl_6NO_2$ from HRFABMS (*m*/*z* 445.9 [M + H]$^+$, calcd for $C_{14}H_{20}^{35}Cl_5^{37}ClNO_2$) and NMR data (Table 1). The ^1H and ^{13}C NMR spectra of **2** also resembled those of **1**, except for the presence of two olefinic signals (δ_H 6.03/δ_C 126.5 and 6.94/142.2) in **2** instead of sp^3 methine (3.22/66.9) and methylene (1.76 and 2.36/30.3) signals in **1** as well

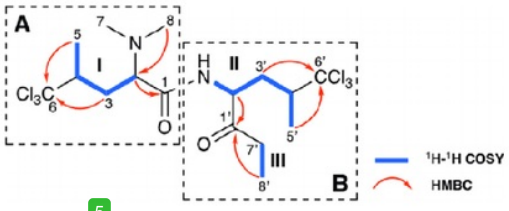

Figure 2. COSY and key HMBC correlations of **1**.

as the absence of two *N*-methyl signals in **2**. These differences were confirmed by analyses of COSY and HMBC spectra for **2** (Fig. 3), and skeletal structure of **2** was elucidated to be callyspongiamide B, as shown in Fig. 1.

The absolute configuration of dysamide A (**3**) has been deduced by X-ray crystallography.[10] Since compounds **1** and **2** were isolated together with **3** from the same marine sponge in this study, it is reasonable to propose that compounds **1** and **2** are also biosynthesized from two chlorinated L-leucines as precursors.[10,12]

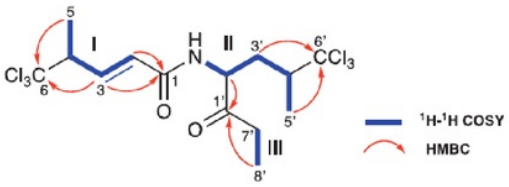

Figure 3. COSY and key HMBC correlations of **2**.

Table 1
^1H (400 MHz) and ^{13}C (100 MHz) NMR data for callyspongiamides A (**1**) and B (**2**) in $CDCl_3$.

No.	1		2	
	δ_C, type	δ_H mult. (*J* in Hz)	δ_C, type	δ_H mult. (*J* in Hz)
1	172.7, C		164.2, C	
2	66.9, CH	3.22, m	126.5, CH	6.03, d (15.5)
3	30.3, CH_2	1.76, m	142.2, CH	6.94, d (15.5, 8.0)
		2.36, m		
4	53.0, CH	2.73, m	57.3, CH	3.37, br q (7.1)
5	17.2, CH_3	1.38, d (6.3)	17.3, CH_3	1.47, d (6.3)
6	106.4, C		104.2, C	
7	41.9, CH_3	2.37, s		
8	41.9, CH_3	2.37, s		
1′	208.6, C		208.7, C	
2′	55.2, CH	4.70, ddd (11.7, 8.8, 2.7)	55.4, CH	4.85, m
2-NH		7.44, d (8.8)		6.18, d (7.8)
3′	35.8, CH_2	1.82, m	36.0, CH_2	1.85, ddd (13.8, 11.7, 3.0)
		2.11, dd (12.9, 11.7)		2.12, dd (12.7, 11.7)
4′	52.1, CH	2.54, m	51.7, CH	2.57, m
5′	16.4, CH_3	1.46, d (6.3)	16.5, CH_3	1.47, d (6.3)
6′	105.4, C		105.4, C	
7′	33.4, CH_2	2.64, m	33.5, CH_2	2.66, m
8′	7.6, CH_3	1.09, t (7.1)	7.6, CH_3	1.11, t (7.1)

Table 2
Effects of compounds **1–3** on SOAT isozymes in cell-based and enzyme-based assays.

Compound	IC_{50} for CE synthesis[a] (μM)					
	Cell-based assay[b]			Enzyme-based assay[b]		
	SOAT1	SOAT2	SI[c]	SOAT1	SOAT2	SI[c]
1	0.78 ± 0.19[d]	2.8 ± 0.72	−0.56	0.23 ± 0.092	0.86 ± 0.071	−0.57
2	1.2 ± 0.31	2.4 ± 0.96	−0.30	1.0 ± 0.092	3.2 ± 1.4	−0.51
3	5.2 ± 0.93	4.2 ± 0.76	+0.092	2.1 ± 0.46	5.3 ± 0.17	−0.40
BeauIII[d]	1.1 ± 0.23	>20	< −1.3	2.8 ± 0.56	3.1 ± 0.56	−0.044

[a] CE; cholesteryl ester.
[b] Data represented as mean ± SD (standard deviation) (n = 3).
[c] SI (selectivity index) = log (IC_{50} for SOAT1)/(IC_{50} for SOAT2).
[d] BeauIII; beauveriolide III (authentic SOAT inhibitor)[9]

Consequently, the absolute configurations of **1** and **2** were tentatively considered to be the same as that of **3**.

The effects of **1–3** on CE synthesis by the SOAT1 and SOAT2 isozymes were evaluated in cell-based and enzyme-based assays,[9,13,14] and the results obtained are summarized in Table 2. In the cell-based assay, compounds **1–3** inhibited both SOAT1 and SOAT2 with selectivity index (SI) of −0.56, −0.30, and +0.092 (dual inhibition; −1.00 < SI < +1.00) and showed almost no effect on phospholipid synthesis or cell morphology up to 21–23 μM in SOAT1- and SOAT2-expressing Chinese hamster ovary (CHO) cells. The respective IC_{50} values against SOAT1 and SOAT2 were 0.78 ± 0.19 and 2.8 ± 0.72 μM for callyspongiamide A (**1**) and 1.2 ± 0.31 and 2.4 ± 0.96 μM for callyspongiamide B (**2**), whereas dysamide A (**3**) showed slightly weaker inhibitory activity with IC_{50} values of 5.2 ± 0.93 and 4.2 ± 0.76 mM toward SOAT1 and SOAT2, respectively. As listed in Table 2, the IC_{50} and SI values of **1–3** in the enzyme-based assay were consistent with those in the cell-based assay. These results suggest that compounds **1–3** are dual inhibitors of SOAT1 and SOAT2, and the linear structure is more favorable for both SOAT inhibitory activities.

In conclusion, two new polychlorine-containing modified dipeptides, callyspongiamides A (**1**) and B (**2**), were obtained along with a known chlorinated diketopiperazine, dysamide A (**3**), from the EtOH extract of the marine sponge *Callyspongia* sp. collected in Indonesia. To date, some linear chlorinated peptides have been reported from several marine sponges.[15] Regarding their significant biological activities, sintokamides have been shown to exhibit inhibitory activities on the N terminus transactivation of the androgen receptor in prostate cancer cells.[15a] In the present study, linear polychloro-modified peptides **1** and **2** were shown for the first time to exhibit SOAT1 and SOAT2 inhibitory activities.

Acknowledgments

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11. The marine sponge was collected by scuba diving in the coral reef at Manado, North Sulawesi, Indonesia, in 2013 and identified as Callyspongia. A voucher specimen was deposited at the Faculty of Mathematic and Natural Sciences, Sam Ratulangi University as 13–12-10 = 2-132.
The sponge (84.8 g, wet weight) was cut into small pieces, and extracted with EtOH (1.5 L). The EtOH extract was evaporated, and the residue (248 mg) was subjected to preparative HPLC [column, PEGASIL ODS SP100 (Senshu Sci. Co., Ltd.), i.d. 10 mm × 250 mm; solvent, 84% CH_3OH; flow rate, 2.0 mL/min; detection, UV 210 nm] to give **1** (6.8 mg, t_R = 30 min), **3** (13 mg, t_R = 22 min), and a subfraction (150 mg). Compound **2** (1.9 mg, t_R = 44 min) was further purified from the subfraction by repeated HPLC [column, PEGASIL ODS SP100, i.d. 10 mm × 250 mm; solvent, 76% CH_3OH; flow rate, 2.0 mL/min; detection, UV 210 nm].
Callyspongiamide A (1): Colorless oils; $[\alpha]_D^{20}$ −36.8 (c 0.10, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 201 (3.8) nm; IR (KBr) ν_{max} 3420, 2941, 1721, 1642, 1460, 1385, 1033, 961 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 1; FABMS *m/z* 489/491/493/495 $[M + H]^+$; HRFABMS *m/z* 491.0174 ($[M + H]^+$, calcd for $C_{16}H_{27}^{35}Cl_2^{37}ClN_2O_2$, 491.0174).
Callyspongiamide B (2): Colorless oils; $[\alpha]_D^{20}$ −23.2 (c 0.10, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 197 (4.1), 213 (4.0) nm; IR (KBr) ν_{max} 3431, 2929, 1722, 1672, 1637, 1539, 1385, 1130 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 1; FABMS *m/z* 444/446/448/450 $[M + H]^+$; HRFABMS *m/z* 445.9583 ($[M + H]^+$, calcd for $C_{14}H_{20}^{35}Cl_5^{37}ClNO_2$, 445.9596).
Dysamide A (3): Colorless oils; $[\alpha]_D^{20}$ −31.1 (c 0.10, CH_3OH); lit. $[\alpha]_D$ −36.6 (c 0.265, CH_3OH)[7]; UV (CH_3OH) λ_{max} (log ε) 202 (4.3) nm; ^1H NMR ($CDCl_3$) δ 3.97 (2H, t, *J* = 7.1 Hz), 3.03 (6H, s), 2.98 (2H, m), 2.50 (2H, ddd, *J* = 14.6, 6.3, 2.4 Hz), 1.80 (2H, ddd, *J* = 14.6, 7.3, 7.3 Hz), 1.39 (6H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 105.4, 61.7, 52.1, 39.0, 33.6, 17.9; FABMS *m/z* 459/461/463/465 $[M + H]^+$.
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13. Two cell lines, CHO cells expressing the SOAT1 and SOAT2 isozymes of the African green monkey (SOAT1- and SOAT2-CHO cells, respectively),[16] were kind gifts from Dr. L. L. Rudel (Wake Forest University). Briefly, both cell lines were maintained at 37 °C in 5% CO_2 in Ham's F-12 medium supplemented with MEM vitamins, geneticin (300 μg/mL), and 10% heat-inactivated fetal bovine serum (hereafter referred to as medium A). The assay for the synthesis of neutral lipids ([^{14}C]CE, [^{14}C]triglyceride (TG), and [^{14}C]PL) from [^{14}C]oleic acid in SOAT1- or SOAT2-CHO cells was performed using our established method.[9] Briefly, SOAT1- or SOAT2- CHO cells (1.25×10^5 cells in 250 μL of medium A) were cultured in a 48-well plastic microplate in the culture medium described above and allowed to recover at 37 °C overnight in 5% CO_2. Assays were conducted with cells that were at least 80% confluent. Following the overnight recovery, a test sample (2.5 μL; 0, 0.01, 0.1, and 1 mg/mL in CH_3OH) and [1-^{14}C] oleic acid (5 μL of 10% EtOH–PBS solution, 1 nmol, 1.85 KBq) were added to each culture. After a 6-h incubation at 37 °C in 5% CO_2, the medium was removed, and the cells in each well were washed twice with PBS. Cells were lysed by adding 0.25 mL of 10 mM Tris-HCl (pH 7.5) containing 0.1% (w/v) sodium dodecyl sulfate, and cellular lipids were extracted by the method of Bligh and Dyer.[17] After concentrating the organic solvent, total lipids were separated on a thin-layer chromatography plate (silica gel F254, 0.5 mm thick, Merck) and analyzed with an FLA7000 analyzer (Fuji Film). In this cell-based assay, [^{14}C]CE was produced by the reaction of SOAT1 or SOAT2. SOAT inhibitory activity (%) is defined as ([1-^{14}C]CE-drug/[^{14}C]CE-control) × 100. The

IC_{50} value is defined as the drug concentration causing the 50% inhibition of biological activity and is calculated from triplicated experiments (n = 3).

14. An enzyme-based assay using microsomes prepared from SOAT1- and SOAT2-CHO cells was carried out by our established method.[9] Briefly, SOAT1 or SOAT2-CHO cells (2.0×10^8 cells) were homogenized in 5 mL cold buffered sucrose solution (pH 7.2, 100 mM sucrose, 50 mM KCl, 40 mM KH_2PO_4, and 30 mM EDTA, hereafter referred to as Buffer A) in the Potter-type homogenizer. The microsomal fraction was pelleted by centrifugation at 100,000×g at 4 °C for 1 h (TLA110, Beckman Coulter), resuspended in the same buffer at a concentration of 5.0 mg protein/mL, and stored at −80 °C until used. An assay mixture for SOAT1 and SOAT2 acitivities contained 500 mg BSA (fatty acid free), [1-^{14}C] oleoyl-CoA (20 mM, 3.7 kBq), a test sample (5.0 mL in methanol solution) and microsomes of SOAT1- or SOAT2-CHO cells in a total volume of 200 mL Buffer A. The SOAT reaction was started by adding [1-^{14}C]oleoyl-CoA. After a 5-min incubation at 37 °C, the reaction was stopped by adding chloroform : methanol (2 : 1, 1.2 mL). The product [^{14}C]CE was extracted by the method of Bligh and Dyer.[17] After the organic solvent was removed by evaporation, lipids were separated on a TLC plate and the radioactivity of [^{14}C]CE was measured with an FLA7000 analyzer (Fuji Film).
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