A tetramic acid derivative with protein tyrosine phosphatase 1B inhibitory activity and a new nortriterpene glycoside from the Indonesian marine sponge Petrosia sp.

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A tetramic acid derivative with protein tyrosine phosphatase 1B inhibitory activity and a new nortriterpene glycoside from the Indonesian marine sponge *Petrosia* sp.

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ABSTRACT

During the search for protein tyrosine phosphatase 1B (PTP1B) inhibitors from marine organisms, the known tetramic acid derivative, melophlin C (**1**), was isolated as an active component together with the new triterpenoid saponin, sarasinoside S (**2**), and the homologues: sarasinosides A_1 (**3**), I_1 (**4**), and J (**5**), from the Indonesian marine sponge *Petrosia* sp. The structure of **2** was elucidated on the basis of its spectroscopic data. Compound **1** inhibited PTP1B activity with an IC_{50} value of 14.6 μM, while compounds **2**–**5** were not active at 15.2–16.0 μM. This is the first study to report the inhibitory effects of a tetramic acid derivative on PTP1B activity.

Marine invertebrates, such as marine sponges and ascidians, are a rich source of a number of useful substances with unique structural and biological features.[1] To date, several marine-derived agents have been approved for clinical applications.[2]

In the course of our screening program for new types of protein tyrosine phosphatase 1B (PTP1B) inhibitors from marine organisms collected in Indonesia, we found that the EtOH extract of the marine sponge *Petrosia* sp. markedly inhibited PTP1B activity in an enzyme assay. PTP1B is known as an important negative regulator in the insulin and leptin signaling pathways.[3] Therefore, PTP1B inhibitors have potential as drug candidates for the treatment and prevention of type-2 diabetes and obesity.[4] Bioassay-guided separation of the extract led to the identification of the known tetramic acid derivative, melophlin C (**1**),[5] as an active component and the isolation of four nortriterpene glycosides **2**–**5** including the new compound **2** (Fig. 1). Compounds **2**–**5** belong to the sarasinoside family of 30-norlanostane-type triterpene oligoglycosides. Twenty-eight analogues have been reported in this family from marine sponges of the genera *Asteropus*, *Melophlus*, and *Lipastrotethya*,[6] and, thus, compound **2** was named sarasinoside S. We herein describe the isolation, structural elucidation, and biological activities of compounds **1**–**5**.

The EtOH extract of the marine sponge *Petrosia* sp.,[7] collected in the coral reefs of North Sulawesi, Indonesia in 2013, exhibited marked inhibitory activity (ca. 86% at 50 μg/mL) against PTP1B in the screening bioassay. The extract was separated into seven fractions using an ODS column, and compounds **1** (2.3 mg), **2** (10 mg), **3** (50 mg), **4** (15 mg), and **5** (10 mg) were isolated by preparative HPLC.[7]

The structure of compound **1** was confirmed to be melophlin C on the basis of its spectroscopic data and comparisons with values in the literature.[5] Melophlins are tetramic acid derivatives with a long alkyl chain and were initially obtained from the marine sponge *Melophlus sarasinorum*.[5,8] Melophlin C was previously reported as an inseparable mixture of four diastereomers at the C-5 and C-10 positions (Fig. 1)[5] and compound **1** was also obtained as the mixture of diastereomers.[7]

Compounds **3**–**5** were identified by comparing spectroscopic data for **3**–**5** with the reported values for sarasinosides A_1,[6a–c] I_1,[6d] and J,[6e] which possess norlanostane-triterpenoidal pentaglycoside skeletons (Fig. 1). Among marine organisms,

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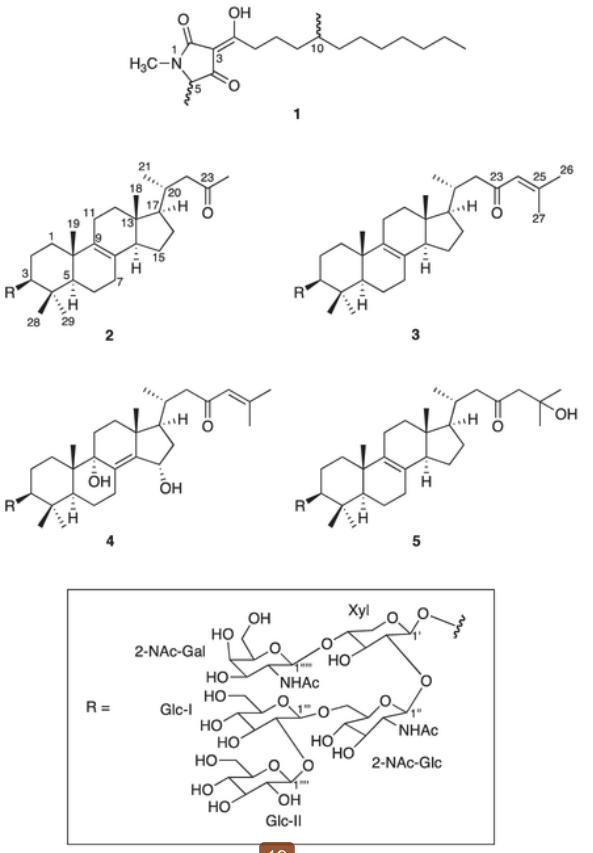

Fig. 1. Structures of compounds **1–5** obtained from the Indonesian marine sponge *Petrosia* sp.

triterpene and steroid saponins have been obtained from echinoderms, such as starfish (Asteroidea) and sea cucumber (Holothuroidea).[9] Although a number of substances with diverse structures have been reported from marine sponges,[1] examples of sponge-derived saponins are rare. The sarasinoside family, including **3–5**, has been shown to exhibit anti-microbial, cytotoxic, and piscicidae activities.[6]

The molecular formula of sarasinoside S (**2**)[7] was deduced as $C_{59}H_{96}N_2O_{26}$ from HRFABMS (*m/z* 1247.6161 [M − H]$^-$, Δ −0.7 mmu) and NMR data (Tables 1 and 2). The ^{1}H and ^{13}C NMR spectra of **2** (in CD_3OD) were very similar to those of sarasinoside A_1 (**3**), suggesting that compound **2** was a nortriterpene saponin, similar to **3**. Analyses of the 2D NMR spectra of **2** and comparisons of spectroscopic data for **2** with those for **3** led to the elucidation of the sugar moieties of **2**, which consisted of the same pentaglycoside as **3**: xylose (Xly), 2-*N*-acetylglucosamine (2-NAc-Glc), two glucoses (Glc-I and Glc-II), and 2-*N*-acetylgalactosamine (2-NAc-Gal). The connectivity of the sugar residues was assessed by HMBC correlations, as shown in Fig. 2.

The difference in the molecular formulas of **2** and **3** was C_3H_4 (40 Da) and was detected in the ^{13}C NMR spectra of **2** and **3**. Four carbon signals (δ 125.2, 156.7, 20.8, and 27.6) due to C-24–C-27 in **3**[7] were not observed in the spectrum of **2**; a methyl signal was instead detected at δ_C 30.5 (δ_H 2.10) in the ^{1}H and ^{13}C NMR spectra of **2** (Table 1). The structure of the side chain in **2** was confirmed by the HMBC spectrum of **2** (Fig. 2). A HMBC correlation from the methyl signal (δ 2.10) to C-23 (δ 212.3) revealed the aglycone of **2** as 3-hydroxy-25,26,27,30-tetranorlanosta-8(9)-en-23-one. The position of the sugar moiety was assigned at C-3 from the HMBC correlation from H-1′ (δ 4.28) to C-3 (δ 91.9). Thus, the planar structure of **2** was elucidated as shown in Fig. 2.

Table 1
^{1}H and ^{13}C NMR data for the aglycone moiety of **1** in CD_3OD.

Position	δ_C	δ_H, mult. (*J* in Hz)	HMBC (^{1}H to ^{13}C)	COSY
1	37.1	1.20, m	10	2
		1.70, m		
2	28.2	1.72, m	3	1, 3
		1.82, m		
3	91.9	3.03, m	2	2
4	40.7			
5	52.1	1.12, m	6	6
6	19.4	1.51, m		5, 7
		1.71, m		
7	29.5	1.75, m	8, 9	6
		1.98, m		
8	128.8			
9	137.4			
10	37.9			
11	22.9	1.97, m	12, 13	12
		2.07, m		
12	38.1	1.40, m		11
		1.86, m		
13	43.3			
14	54.5	2.06, m		15
15	24.7	1.35, m	14	14, 16
		1.66, m		
16	29.8	1.33, m		15, 17
		1.89, m		
17	53.2	1.17, m	21, 22	16
18	11.7	0.66, s	12, 13, 14, 17	
19	20.4	1.00, s	1, 5, 10	
20	34.2	2.13, m	22, 23	22
21	20.1	0.91, d (7.2)	17, 20	
22	51.6	2.52, dd (13.6, 3.2)	20, 21, 23	20
		2.09, m		
23	212.3			
24	30.5	2.10, s	23	
28	17.2	0.92, s	3, 4, 5, 29	
29	28.4	1.08, s	3, 4, 5, 28	

Four compounds (**2–5**) were found to have the same sugar moiety with the β-anomeric configurations from their ^{1}H/^{13}C chemical shifts and coupling constants in the ^{1}H NMR spectra.[6c] Although the correlations detected in the NOESY spectrum of **2** were limited, ^{13}C NMR data for the asymmetric carbons in compounds **2** and **3** were similar to each other, and the specific rotations of **2** ($[\alpha]_D^{19}$ −1.9) and **3** ($[\alpha]_D^{19}$ −2.8) in CH_3OH were also very similar.[7] Since compounds **2–5** were obtained from the same marine sponge, these compounds were biosynthesized via the same pathway. Therefore, the absolute configuration of **2** was assumed to be the same as that of **3**, which was elucidated by X-ray crystallography and chemical degradation experiments.[6a,6c]

Nortriterpenes possessing a degraded side chain are very rare, and few compounds have been reported from terrestrial plants.[10] Compound **2** is the first example of a nortriterpene with a degraded side chain in the sarasinoside family.

Compounds **2–5** did not inhibit PTP1B activity at 15.2–16.0 μM.[11] The mixture of $\Delta^{8(9)}$- and $\Delta^{8(14)}$-aglycones, prepared by acid hydrolysis from **3**,[12] was not active against PTP1B. Although some sarasinoside derivatives have been reported to exhibit weak cytotoxicity against several cancer cell lines,[6] compounds **2–5** were not cytotoxic against two human solid cancer cell lines, Huh-7 (hepatocarcinoma) and A549 (lung carcinoma).[13] The PTP1B inhibitory activity of the EtOH extract of the sponge at 50 μg/mL was reproduced by melophlin C (**1**), which had an IC_{50} value of 14.6 μM. Oleanolic acid (a positive control)[14] showed an IC_{50} value of 1.3 μM in the same bioassay.

Nineteen melophlins have been identified to date,[5,8] some of which exhibit various biological activities,[15] such as anti-dormant

Table 2
^{1}H and ^{13}C NMR data for the sugar moiety of **1** in CD_3OD.

	Position	δ_C	δ_H, mult. (*J* in Hz)	HMBC (^{1}H to ^{13}C)
Xyl	1′	106.6	4.28, d (7.6)	3
	2′	78.2	4.07, t (11.6)	1″
	3′	77.6	3.50, m	2′
	4′	79.8	3.68, m	3′, 1‴″
	5′	63.6	3.11, m	3′
			3.88, m	
2-Nac-GLc	1″	101.9	4.82, d (7.6)	2′
	2″	57.9	3.68, m	1″, 3″
	3″	76.9	3.41, m	
	4″	72.4	3.14, m	3″
	5″	78.1	3.63, m	4″
	6″	70.0	3.91, m	1‴′
			3.75, m	
	Ac	23.0	1.98, s	
		171.1		
Glc-I	1‴′	102.6	5.08, d (7.6)	6″
	2‴′	83.6	3.35, m	1‴′, 1‴
	3‴′	77.8	3.68, m	2‴′, 4‴
	4‴′	69.8	3.30, t	5‴′
	5‴′	77.2	3.41, m	
	6‴′	63.1	3.70, m	
			3.83, m	
Glc-II	1‴	105.8	4.61, d (7.6)	
	2‴	75.9	3.40, m	3‴
	3‴	77.9	3.40, m	
	4‴	71.4	3.31, t	5‴
	5‴	78.7	3.27 m	1‴
	6‴	62.5	3.71, m	5‴
			3.91, m	
2-Nac-Gal	1‴″	102.6	4.48, d (8.8)	4′
	2‴″	56.0	3.85, m	1‴″, 3‴″
	3‴″	72.8	3.63, m	
	4‴″	71.4	3.78, m	5‴″
	5‴″	77.2	3.63, m	
	6‴″	62.6	3.72 m	
			3.88, m	
	Ac	23.0	1.97, s	

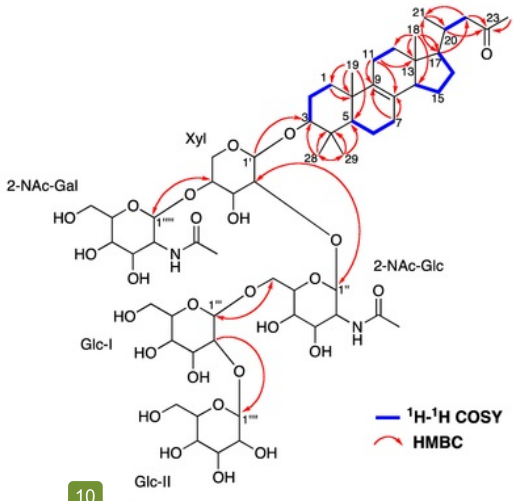

Fig. 2. ^{1}H-^{1}H COSY and key HMBC correlations of **2**.

mycobacterium activity,[15a] Ras-pathway modulation,[15b] and influences on IL-8 production[15c] in addition to general cytotoxic and antimicrobial activities.[5,8] Therefore, this is the first study on the inhibitory activity of a tetramic acid derivative on PTP1B. The isolation of other melophlin derivatives detected in the active fraction is now being conducted in order to investigate the structure-activity relationship of melophlins.

Acknowledgments

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7. The marine sponge *Petrosia* sp. was collected by scuba diving at Manado, North Sulawesi, Indonesia, in December 2013, and was identified by Dr K. Ogawa (Z. Nakai Laboratory). A voucher specimen is deposited at the Faculty of Mathematic and Natural Sciences, Sam Ratulangi University, as 13-12-10 = 1-145.The sponge (504.2 g, wet weight) was cut into small pieces and soaked in EtOH (1.5 L) on a boat immediately after collection. The EtOH extract (4.0 g) was separated into seven fractions (Frs. 1–7) by an ODS column (100 g) with the stepwise elution of CH_3OH in H_2O. Compounds **2** (10 mg), **3** (50 mg), **4** (15 mg), and **5** (10 mg) were isolated from Fr. 5 (500 mg, eluted with 80% CH_3OH) by preparative HPLC [column; PEGASIL ODS SP100 (Senshu Scientific Co., Ltd., Tokyo, Japan), 10 × 250 mm; mobile phase, 75% CH_3OH containing 0.05% TFA; detection, UV at 210 nm; flow rate, 2.0 mL/min]. Fr. 6 (700 mg, 100% CH_3OH eluate) was separated into ten fractions (Frs. 6-1–6-10) by preparative HPLC [column; PEGASIL ODS SP100, 10 × 250 mm; mobile phase, 70% CH_3OH containing 0.05% TFA; detection, UV at 210 nm; flow rate, 2.0 mL/min], and fr. 6-10 (30.5 mg) were further purified by repeated HPLC [column; PEGASIL ODS SP100, 10 × 250 mm; mobile phase, 92% CH_3OH containing 0.05% TFA; detection, UV at 210 nm; flow rate, 2.0 mL/min] to give compound **1** (2.3 mg).*Melophlin C* (**1**): a yellow oil; $[\alpha]_D^{20}$ −5.3 (*c* 0.10, CH_3OH); lit. $[\alpha]_D^{20}$ −5.8 (*c* 0.35, CH_3OH)[5];UV λ_{max} (CH_3OH) nm (log ε): 202 (4.1), 243 (4.0), 284 (4.3); EIMS *m/z* 323 $[M]^+$; ^{1}H NMR ($CDCl_3$) δ 3.66 (1H, q, *J* = 7.0), 2.95 (3H, s), 2.80 (2H, t, *J* = 6.8), 1.62 (2H, m), 1.33 (3H, d, *J* = 7.0), 1.20–1.38 (14H, m), 1.09 (2H, m), 0.86 (3H, t, *J* = 6.8), 0.81 (3H, d, *J* = 6.4).*Sarasinoside S* (**2**): a yellow amorphous solid; $[\alpha]_D^{19}$ −1.9 (*c* 0.10, CH_3OH); IR (KBr) cm^{-1}: 3303, 2979, 1679, 1382; UV λ_{max} (CH_3OH) nm (log ε): 201 (3.3), 250 (2.9); FABMS *m/z*: 1247 $[M-H]^-$; HRFABMS *m/z*: 1247.6166 $[M-H]^-$ (Calcd for $C_{59}H_{96}N_2O_{26}$: 1247.6173); ^{1}H and ^{13}C NMR (CD_3OD), see Tables 1 and 2.*Sarasinoside A$_1$* (**3**): a white amorphous solid; $[\alpha]_D^{19}$ −2.8 (*c* 0.10, CH_3OH); lit. $[\alpha]_D$ −7.4 (*c* 0.3, CH_3OH)[6b]; UV λ_{max} (CH_3OH) nm (log ε): 201 (3.1), 244 (2.8); FABMS *m/z*: 1287 $[M-H]^-$; ^{13}C NMR data for the aglycone moiety (CD_3OD) δ 203.7 (C-23), 156.7 (C-25), 137.3 (C-9), 128.6 (C-8), 125.2 (C-24), 91.7 (C-3), 56.2 (C-17), 53.1 (C-14), 51.6 (C-22), 52.0 (C-5), 43.3 (C-13), 40.6 (C-4), 38.1 (C-12), 37.8 (C-10), 37.0 (C-1), 34.9 (C-20), 30.0 (C-16), 29.4 (C-7), 28.4 (C-29), 28.2 (C-2), 27.6 (C-27), 24.7 (C-15), 23.0 (C-11), 20.8 (C-26), 20.4 (C-19), 20.1 (C-21), 19.4 (C-6), 17.1 (C-28), 11.7 (C-18); ^{13}C NMR data for the sugar moiety (CD_3OD) Xyl δ 106.5 (C-1′), 79.7 (C-4′), 78.2 (C-2′), 77.5 (C-3′), 64.2 (C-5′); 2-NAc-Glc δ 174.0 (NHCO), 101.7 (C-1″), 77.9 (C-5″), 77.1 (C-3″), 72.3 (C-4″), 70.0 (C-6″), 57.9 (C-2″), 23.0 (Ac); Glc-I δ 102.5 (C-1‴), 83.5 (C-2‴), 78.1 (C-3‴), 77.0 (C-5‴), 71.4(C-4‴), 62.6 (C-6‴); Glc-II δ 105.8 (C-1‴′), 78.1 (C-5‴′), 77.8 (C-3‴′), 75.8 (C-2‴′), 71.4 (C-4‴′), 62.7 (C-6‴′); 2-NAc-Gal δ 173.9 (NHCO), 105.5 (C-1‴″), 77.3 (C-5‴″), 72.3 (C-3‴″), 69.8 (C-4‴″), 63.0 (C-6‴″), 54.4 (C-2‴″), 23.1 (Ac).

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11. PTP1B inhibitory activity was assessed by measuring the rate of hydrolysis of the substrate, *p*NPP, according to the reported method with a slight modification.[16,17] Briefly, PTP1B (100 μL of a 0.5 μg/mL stock solution) in 50 mM citrate buffer (pH 6.0) containing 0.1 M NaCl, 1 mM dithiothreitol (DTT), and 1 mM EDTA was added to each well of a 96-well plastic plate. Each sample (2.0 μL in CH_3OH) was added to each well to make the final concentration and incubated at 37 °C for 10 min. The reaction was initiated by the addition of *p*NPP (100 μL of a 4.0 mM stock solution) to citrate buffer, incubated at 37 °C for 30 min, and terminated with the addition of 10 μL of a stop solution (10 M NaOH). The optical density of each well was measured at 405 nm using an MTP-500 microplate reader (Corona Electric Co., Ltd.). PTP1B inhibitory activity (%) was defined as $[1 - (ABS_{sample} - ABS_{blank})/(ABS_{control} - ABS_{blank})] \times 100$, in which ABS_{blank} was the absorbance of wells containing only the buffer and *p*NPP, $ABS_{control}$ was the absorbance of *p*-nitrophenol liberated by the enzyme in the assay system without a test sample, and ABS_{sample} was that with a test sample. Oleanolic acid, a known phosphatase inhibitor,[14] was used as a positive control.
12. Compound **3** (10 mg) and 3 M HCl (1.5 mL) were stirred at 70 °C for 1 h. After cooling, the solution was extracted with EtOAc to obtain a mixture (1.7 mg) of $\Delta^{8(9)}$- and $\Delta^{8(14)}$-aglycones[6h]; FABMS, *m*/*z* 427 $[M+H]^+$.
13. Cytotoxicity was assessed using the water-soluble tetrazolium (WST-1; sodium 5-(2,4-disulfophenyl)-2-(4-iodophenyl)-3-(4-nitrophenyl)-2H tetrazolium inner salt) assay, which detects metabolically competent cells with an intact mitochondrial electron transport chain.[18] Briefly, 1×10^4 cells were seeded on each well of 96-well plastic plates and cultured overnight. Cells were treated with each test compound and incubated for 72 h, and medium containing WST-1 solution (0.5 mM WST-1 and 0.02 mM 1-methoxy-5-methylphenazinium methylsulfate; 1-PMS) was then added to each well. Cells were incubated at 37 °C for 60 min, and absorption at 438 nm (reference 620 nm) was measured using an SH-1200 Microplate Reader (Corona Electric). Control cells were treated with 0.1% EtOH. Cell viability was calculated using the formula: absorbance in the treated sample/absorbance in the control × 100 (%).
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