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Two new protein tyrosine phosphatase 1B inhibitors, hyattellactones A and B, from the Indonesian marine sponge *Hyattella* sp.

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ABSTRACT

Two unique sesterterpenes, hyattellactones A (**1**) and B (**2**), together with two known sesterterpenes, phyllofolactones F (**3**) and G (**4**), were isolated from the Indonesian marine sponge *Hyattella* sp. The structures of the two new compounds, **1** and **2** were assigned based on their spectroscopic data. Hyattellactone A (**1**) was a scalarane sesterterpene with an α,β-unsaturated-γ-lactone ring and C-ethyl group, while B (**2**) was an epimer of **1** at the C-24 position. Compounds **1** and **3** inhibited PTP1B activity with IC_{50} values of 7.45 and 7.47 μM, respectively. On the other hand, compounds **2** and **4** (24*S*-isomers of **1** and **3**, respectively) showed much reduced activity than the 24*R*-isomers.

Protein tyrosine phosphatase 1B (PTP1B) is an effective and attractive therapeutic target for the treatment of type-2 diabetes and plays a key role as a negative regulator in insulin and leptin signaling. Therefore, the development of PTP1B inhibitors has been expected to provide new medicines for type-2 diabetes mellitus and obesity.[1] To date, approximately 300 PTP1B inhibitors have been reported from various natural resources.[2] However, the activities and selectivities of these natural products against PTP1B were not satisfactory. Accordingly, the search for more potent and selective PTP1B inhibitors from natural resources is one of the most important subjects in natural product chemistry.

In the course of our research on PTP1B inhibitors from marine organisms, we have reported polybromodiphenyl ethers and dehydroeuryspongin from marine sponges.[3] Further investigations on extracts from marine invertebrates revealed that an extract from the Indonesian marine sponge *Hyattella* sp. exhibited prominent inhibitory activity against PTP1B. The bioassay-guided separation of this extract led to the isolation of two new sesterterpenes, hyattellactones A (**1**) and B (**2**), together with two known sesterterpenes, phyllofolactones F (**3**)[4] and G (**4**)[4] (Fig. 1). Compounds **1**–**4** were unique pentacyclic scalarane sesterterpenes that possessed an α,β-unsaturated-γ-lactone ring and C-ethyl group. Although a number of compounds in this class have been reported from several marine sponges,[5] compounds **1** and **2** are the first examples to possess an ethyl group at C-10. We herein described the isolation, structure elucidation including stereochemistry, and biological activities of compounds **1**–**4**.

The marine sponge (487 g, wet weight)[6] was extracted with ethanol, and the extract (11.3 g) was partitioned between hexane and 90% CH_3OH. The hexane extract (0.51 g) was separated by a Silica gel column (50 g) to give five fractions. The bioactive fraction was purified by repeated HPLC using an ODS column to yield compounds **1** (4.3 mg), **2** (1.8 mg), **3** (1.1 mg), and **4** (1.7 mg) as colorless oils.[7]

Compounds **3** and **4** were identified as the known sesterterpenes, phyllofolactones F and G, by comparing the spectral data obtained with reported values.[4c] Compounds **3** and **4** were the epimers at C-24 and were previously reported in several marine sponges of the genus *Phyllospongia*.[4]

The physicochemical properties of **1** and **2** were very similar to those of **3** and **4**, which suggested that these compounds shared the same skeleton.[8–11] The molecular formula of hyattellactone A (**1**)[10] was assigned as $C_{27}H_{42}O_3$ from HREIMS (*m*/*z* 414.3151 $[M]^+$, Δ +1.7 mmu) and NMR data for **1** (Table 1). The ^1H and ^{13}C NMR signals of **1** (in pyridine-d_5) were classified into six methyls, nine methylenes, three sp^3 methines, two sp^3 oxygenated methines, four sp^3 quaternary carbons, two sp^2 quaternary carbons, and

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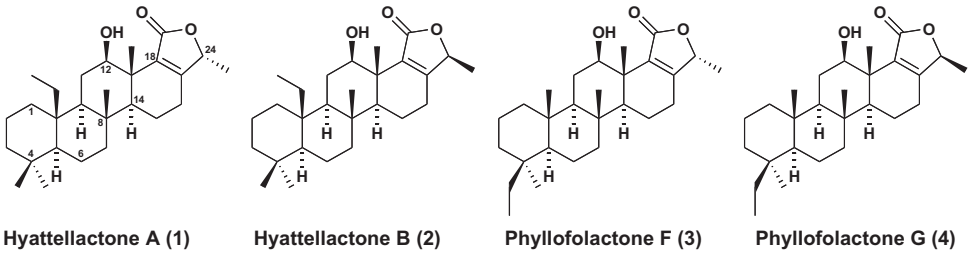

Figure 1. Structures of compounds **1**–**4** isolated from the marine sponge *Hyattella* sp. collected in North Sulawesi, Indonesia.

Table 1
^{1}H and ^{13}C NMR data for hyattellactones A (**1**) and B (**2**) in C_5D_5N

Position	**1**			**2**		
	δ_C	δ_H (J in Hz)		δ_C	δ_H (J in Hz)	
1	35.6	0.58 ddd	(12.8,12.8,3.6)	35.7	0.61 ddd	(12.9,12.9,3.4)
		2.09 d	(12.8)		2.11 m	
2	18.8	1.15 m		18.8	1.15 m	
		1.37 m			1.32 m	
3	42.3	1.11 m		42.2	1.11 m	
		1.39 m			1.32 m	
4	33.2			33.2		
5	58.3	0.77 m		58.5	0.78 m	
6	18.0	1.40 m		18.1	1.40 m	
		1.73 m			1.72 m	
7	42.3	0.72 m		42.6	0.72 m	
		1.71 m			1.71 d	(12.4)
8	37.6			37.6		
9	59.1	0.80 m		59.3	0.80 m	
10	40.5			40.5		
11	29.5	1.82 dd	(13.4, 2.4)	29.5	1.82 dd	(13.4, 2.4)
		2.16 m			2.20 m	
12	77.0	3.65 m		76.7	3.65 m	
13	42.6			42.5		
14	55.8	0.91 m		55.5	0.91 m	
15	16.7	1.51 m		16.9	1.50 m	
		1.78 m			1.75 m	
16	24.9	1.54 m		24.6	1.54 m	
		2.25 m			2.33 dd	(19.3, 5.6)
17	167.6			167.7		
18	135.6			135.6		
19	34.7	0.89 s		34.7	0.89 s	
20	22.2	0.83 s		22.3	0.84 s	
21	17.2	0.95 s		17.2	0.95 s	
22	21.2	1.62 q	(7.6)	21.3	1.62 q	(7.6)
23	16.8	1.25 s		17.0	1.23 s	
24	80.0	4.95 m		79.7	4.99 m	
25	175.7			175.7		
26	18.1	1.36 d	(6.8)	18.3	1.28 d	(6.8)
27	10.7	0.85 brd	(7.6)	10.7	0.86 brd	(7.6)
12-OH		6.49 brs			6.50 brs	

one carbonyl carbon, and then assigned by an analysis of 2D NMR spectra (Table 1). The presence of an OH group was elucidated from ^{1}H NMR data (δ 6.49) and IR absorption at 3386 cm^{-1}. The ^{1}H–^{1}H COSY spectrum of **1** revealed the partial structures I–VI, as shown by the blue bold lines in Figure 2. The connectivities of partial structures I–VI were elucidated from the HMBC spectrum of **1** (Fig. 1) and confirmed by a comparison of NMR data for **1** with those for phyllofolactones F (**3**) and G (**4**). The position of an ethyl group (partial structure III) was assigned at C-10 based on HMBC correlations from H_2-22 (δ 1.62) to C-1 (δ 35.6), C-9 (δ 59.1), and C-10 (δ 40.5) and from H_3-27 (δ 0.85) to C-10 (Fig. 2).

The relative stereochemistry of **1** was determined by an analysis of the NOESY spectrum in pyridine-d_5 (Fig. 3) and comparison of NMR data with those for **3** and **4**. The ring junctions at A/B, B/C, and C/D were revealed as the *trans*-configuration from NOE correlations between H_3-20 (δ 0.83)/H_2-22 (δ 1.62), H_3-21 (δ 0.95)/H_2-22, H_3-21/H_3-23 (δ 1.25), Hα-1 (δ 0.58)/H-5 (δ 0.77), H-5/H-9 (δ 0.80), and H-12 (δ 3.65)/H-14 (δ 0.91) (Fig. 3). An

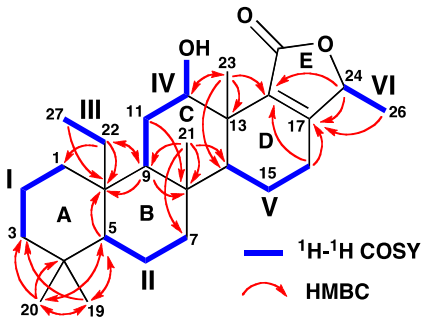

Figure 2. ^{1}H–^{1}H COSY and key HMBC data for hyattellactones A (**1**) and B (**2**).