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Furanoterpenes, new types of protein tyrosine phosphatase 1B inhibitors, from two Indonesian marine sponges, *Ircinia* and *Spongia* spp.

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ABSTRACT

Protein tyrosine phosphatase (PTP) 1B negatively regulates the insulin and leptin signaling pathways, and, thus, the clinical application of PTP1B inhibitors to the prevention and treatment of type 2 diabetes and obesity is expected. During our studies on PTP1B inhibitors, two furanosesterterpenes and a C21 furanoterpene were obtained as new types of PTP1B inhibitors from two Indonesian marine sponges. (7*E*, 12*E*, 20*Z*, 18*S*)-Variabilin (**1**) and (12*E*, 20*Z*, 18*S*)-8-hydroxyvariabilin (**2**) from *Ircinia* sp. and furospongin-1 (**3**) from *Spongia* sp. inhibited PTP1B activity with IC_{50} values of 1.5, 7.1, and 9.9 μM, respectively. The inhibitory activity of compound **1** against T-cell PTP (TCPTP) was approximately 2-fold that against PTP1B, whereas the *vaccinia* H-1-related phosphatase (VHR) inhibitory effects were 4-fold weaker than that of its PTP1B inhibitory activity. Compounds **1**–**3** at 50 μM did not show cytotoxicity against two human cancer cell lines, hepatoma Huh-7 and bladder carcinoma EJ-1. Compound **1** did not enhance the phosphorylation level of Akt, a key downstream effector of the cascade, in H[illegible]7 cells.

Protein tyrosine phosphatases (PTPs) have recently been attracting attention as promising targets for drug discovery and chemical biological studies because intracellular phosphorylation by PTPs is an important regulatory system for various biological functions.[1] Nevertheless, the development of their modulators has not yet been successful. Therefore, the search for novel types of PTP inhibitors is ongoing.

PTPs comprise a large family of 107 members that are characterized by their active site sequences.[1b] Among members of the PTP family, PTP1B has been studied in detail because of its function as a negative regulator of insulin and leptin signal transduction.[2] Consequently, PTP1B inhibitors are considered to have potential as drug candidates for the treatment of type 2 diabetes mellitus and obesity.[3]

Since marine organisms are sources of various types of bioactive substances with unique chemical structures,[4] we have been searching for PTP1B inhibitors among marine invertebrates[5] and previously reported the PTP1B inhibitory activities of dehydroeuryspongin A,[5a,5b] hyattellactones,[5c] 26-*O*-ethylstrongylophorine-14,[5d] isopetrosynol,[5e] and avapyran[5f] from marine sponges. Our continuous efforts revealed that the EtOH extracts of two Indonesia marine sponges inhibited PTP1B activity. Bioassay-guided separation of these extracts led to the isolation of two furanosesterterpenoids (**1** and **2**) from *Ircinia* sp. and a C21 furanoterpenoid (**3**) from *Spongia* sp. (Fig. 1).[6] Of these, compound **1** was found to be the most potent inhibitor of PTP1B and T-cell PTP (TCPTP) activities with moderate selectivity over *vaccinia* H-1-related phosphatase (VHR) in an enzyme assay. We herein describe the isolation and biological properties of furanoterpenoids **1**–**3**.

The PTP1B inhibitory activities of the EtOH extracts from marine organisms collected at Manado, Indonesia in 2013, were tested using a previously reported *in vitro* enzyme assay method.[7] Among the active extracts (>70% inhibition at 50 μg/mL), two marine sponges, *Ircinia* and *Spongia* spp., were examined in this study.

Compounds **1** (28 mg) and **2** (12 mg) were isolated from *Ircinia* sp. by solvent extraction, an ODS column, and repeated HPLC (ODS), while compound **3** (24 mg) was obtained by an ODS column followed by HPLC (ODS) from *Spongia* sp.[8] The structures of compounds **1**–**3** were identified as (7*E*, 12*E*, 20*Z*, 18*S*)-variabilin,[6a–6d] (12*E*, 20*Z*, 18*S*)-8-hydroxyvariabilin,[6d] and furospongin-1,[6e]

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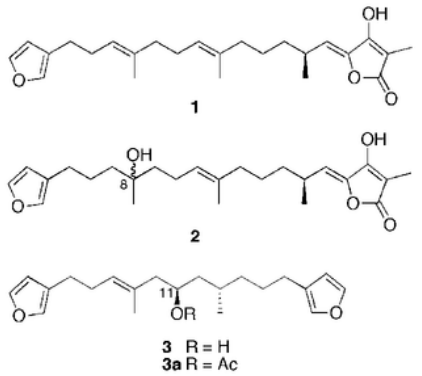

Fig. 1. Structures of compounds **1**–**3** from two marine sponges collected in Indonesia.

respectively, using comparisons of their spectroscopic data with previously reported values (Fig. 1).

The PTP1B inhibitory activities of compounds **1**–**3** were evaluated using an enzyme assay method that was similar to the screening bioassay.[7] Compounds **1**–**3** exhibited dose-dependent activities with IC_{50} values of 1.5, 7.1, and 9.9 μM (Fig. 2 and Table 1). Oleanolic acid, a positive control,[9] gave an IC_{50} value of 1.1 μM in the same bioassay (Table 1). Compound **1** was approximately fivefold more active than **2**, and thus, the OH group at C-8 in **2** was unfavorable for the inhibition of PTP1B activity.

Compound **1** was previously reported to be a modulator of the glycine receptor,[10] while the significant bioactivities of **2** and **3** have not yet been reported. Although we previously described the bicyclic furanosesquiterpene, dehydroeuryspongin A,[5a,5b] this is the first study on the PTP1B inhibitory activities of linear-type furanoterpenes.

Cellular signaling via insulin and leptin receptors is negatively controlled not only by PTP1B, but also by other protein tyrosine phosphatases such as T-cell PTP (TCPTP), which shares 72% sequence identity with PTP1B.[11] Therefore, the effects of compounds **1**–**3** on TCPTP activity were examined using an enzyme-based *in vitro* assay. The TCPTP inhibitory activities of **1** and **2** were approximately twofold more potent than their PTP1B inhibitory activities (IC_{50} of 0.8 μM versus 1.5 μM for **1** and 3.7 μM versus 7.1 μM for **2**) (Fig. 2 and Table 1). On the other hand, compound **3** equally inhibited TCPTP and PTP1B activities (IC_{50} of 9.6 μM versus 9.9 μM) (Fig. 2c and Table 1).

Previous studies using PTP1B knockout mice demonstrated improvements in insulin resistance and glucose homeostasis,[12] while TCPTP knockout mice died at 3–5 weeks old because of serious inflammatory phenotypes.[13] However, recent studies indicated the absence of any abnormalities in mice with the deletion of single copies of PTP1B and TCPTP.[14] Thus, the simultaneous inhibition of PTP1B and TCPTP may also be a promising therapeutic approach for type 2 diabetes and obesity.

PTPs have been divided into four groups (classes I–IV) on the basis of their sequences, catalytic residues, and functions. Among them, class I as a major group has been further classified into non-transmembrane PTPs including PTP1B and TCPTP, receptor-like PTPs, and dual-specificity phosphatases.[1] Therefore, the selectivities of **1**–**3** over the other types of PTPs were examined against CD45 tyrosine phosphatase (receptor-like PTP) and VHR (dual-specificity phosphatase).

Compound **1** exhibited similar inhibitory activities against CD45 and PTP1B, and the inhibitory activity of **1** against VHR was 4-fold less than that against PTP1B (Table 1). On the other hand, no marked differences were observed in the inhibitory activities of compound **2** against PTP1B, CD45, and VHR (Fig. 2b and Table 1). Compound **3** was inactive against CD45 up to 30 μM (Fig. 2c and Table 1). Moreover, an 11-*O*-acetyl derivative of **3** (**3a**) exhibited markedly reduced activity against TCPTP as well

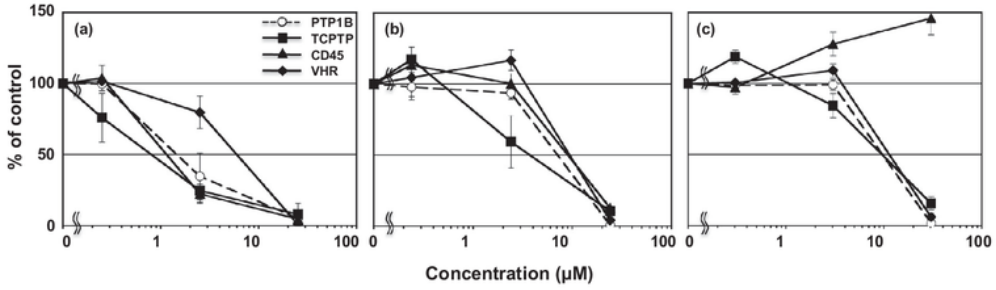

Fig. 2. Protein tyrosine phosphatase inhibitory activities of compounds **1** (a), **2** (b), and **3** (c).

Table 1
Biological activities of compounds **1**–**3** against four protein tyrosine phosphatases and in two human cancer cell lines.

Compound	Protein tyrosine phosphatase (IC_{50}, μM)				Cytotoxicity (IC_{50}, μM)	
	PTP1B	TCPTP	CD45	VHR	Huh-7	EJ-1
1	1.5	0.8	1.2	6.0	>50	>50
2	7.1	3.7	9.0	9.4	>50	>50
3	9.9	9.6	>30	11	>50	>50
3a	9.2	21.5	>27	8.5	nt[c]	nt
Oleanolic acid[a]	1.1	1.6	1.0	5.4		
Doxorubicin[b]					0.36	0.023

[a] Positive control for the protein tyrosine phosphatase assay.
[b] Positive control for cytotoxicity.
[c] Not tested.

as CD45 (Table 1). These results suggest that the length of and modifications to the carbon chain affect selectivity.

In order to evaluate the cellular properties of **1**–**3**, their cytotoxic effects in Huh-7 (hepatoma) and EJ-1 (bladder carcinoma) cell lines were measured using the WST-1 assay.[15] Compounds **1**–**3** did not inhibit the proliferation of these cancer cells at 50 μM for 72 h.

Since PTP1B mainly regulates the insulin signaling pathway in the liver, the phosphorylation level of Akt, a key downstream effector of the cascade, in Huh-7 cells was detected by Western blotting.[16] Huh-7 cells were incubated with **1** (50 μM) for 2 h, and the effects of **1** on insulin-stimulated p-Akt levels were evaluated. Although sodium orthovanadate (SOV), a pan-PTP inhibitor, enhanced p-Akt levels at 5 μM, compound **1** did not (Fig. S1).

In conclusion, two furanosesterterpenes, (7*E*, 12*E*, 20*Z*, 18*S*)-variabilin (**1**) and (12*E*, 20*Z*, 18*S*)-8-hydroxy-variabilin (**2**), and the C21 furanoterpene, furo spongin-1 (**3**), were revealed as new types of PTP1B inhibitors isolated from two Indonesian marine sponges. The IC_{50} values of **1** were the most potent in the PTP1B and TCPTP enzyme assays (Fig. 2a and Table 1). However, compound **1** did not enhance p-Akt levels in Huh-7 cells. This discrepancy between the results obtained in the enzyme- and cell-based experiments of **1** may be attributed to low cell permeability and poor selectivity toward other PTPs. Compounds **3** and **3a**, possessing different lengths of carbon chains from those of **1** and **2**, exhibited better PTP1B selectivity over CD45 and TCPTP activities. Further studies on the structure-activity relationship of marine furanoterpenes will be interesting because several types of these congeners have been reported from marine sponges.[4] Compound **1** will be more attractive than **2** and **3** because it exhibited potent inhibitory activities against PTP1B and TCPTP with moderate selectivity over VHR and no cytotoxic properties against the two human cancer cell lines, Huh-7 and EJ-1. Therefore, further studies on compound **1** as a lead compound for the treatment of type 2 diabetes and obesity are warranted.

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A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2017.01.071.

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