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Eudesmanolide sesquiterpenes and protein tyrosine phosphatase 1B inhibitory *ent*-kaurene diterpenes from aerial parts of Indonesian *Wedelia prostata*

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ABSTRACT

Seven eudesmanolide sesquiterpenes (**1–7**) and two *ent*-kaurene diterpenes (**8** and **9**) including two new (9*R*)-eudesman-9,12-olides, named wedelolides I and J (**1** and **2**), were isolated from the aerial parts of Indonesian *Wedelia prostata*. The structures of **1** and **2** were assigned based on their spectroscopic data. Diterpenes **8** and **9** inhibited the activity of protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 8.3 and 28 μM, respectively. Among sesquiterpenes **1–7**, compound **4**, wedelolide D, exhibited 32% inhibitory activity against PTP1B at 20 μM.

1. Introduction

The genus *Wedelia* belongs to the family Asteraceae and consists of approximately 60 species, which are generally distributed in Japan (mainly in Okinawa), China, Southeast Asia (including Indonesia, India, Burma, and Viet Nam) (Li et al., 2007). A number of plants in this genus are used as a folk medicine, and, of these, *W. prostata* has been applied to the treatment of inflammatory diseases (Zhang et al., 2011; Li et al., 1959). Sesquiterpenes, diterpenes, triterpenes, flavonoids, and caffeic acid derivatives have been identified as chemical components of *W. prostata* (Li et al., 2007).

In studies on new types of protein tyrosine phosphatase 1B (PTP1B) inhibitors from terrestrial and marine organisms, we have identified various PTP1B inhibitors with unique structural features (Yamazaki et al., 2013; Yamazaki et al., 2015a; Yamazaki et al., 2015b; Abdjul et al., 2016; Lee et al., 2016), and found that the EtOH extract of the aerial parts of *W. prostata*, collected at Manado, Indonesia in 2016, exhibited PTP1B inhibitory activity. PTP1B inhibitors are promising lead compounds for the treatment of type-2 diabetes and obesity because PTP1B plays an important role as a negative regulator of cell signals from insulin and leptin receptors (Zhang and Zhang, 2007; Barr, 2010; Zhang et al., 2015; Jung et al., 2012; Popov, 2011). The bioassay-guided separation of the extract led to the isolation of seven sesquiterpene lactones (**1–7**) and two *ent*-kaurene diterpenes (**8** and **9**) including two new eudesmanolides, named wedelolides I and J (**1** and **2**) (Fig. 1). The wedelolide family possesses a rare type of sesquiterpene δ-lactone with the (9*R*)-eudesman-9,12-olide framework. Only nine derivatives have been reported from *W. trilobata* and *W. prostata* collected in Viet Nam and China (That et al., 2007; Li et al., 2013; Duc at al., 2016; Wu et al., 2016).

We herein describe the isolation, structure elucidation, and biological activity of compounds **1–9**.

2. Results and discussion

The EtOH extract from the aerial parts of *W. prostata* inhibited PTP1B activity (about 50% inhibition at 50 μg/mL) and was separated into seven fractions using an ODS column. The bioactive fractions were then purified by repeated HPLC (ODS) to yield compounds **1** (0.9 mg), **2** (1.2 mg), **3** (1.1 mg), **4** (3.3 mg), **5** (2.6 mg), **6** (3.3 mg), **7** (2.3 mg), **8** (4.5 mg), and **9** (25 mg).

Compounds **4–9** were identified as wedelolide D (Li et al., 2013), 1β-acetoxy-4α,9α-dihydroxy-6β-(isobutyryloxy)prostatolide (, 1993), 1β-acetoxy-4α,9α-dihydroxy-6β-(methacryloxy)prostatolide (Ragasa and Padolina, 1993), 1β-acetoxy-4α-hydroxy-6β-isobutyryloxy-9α-isovaleryloxyprostatolide (Wu et al., 2010), *ent*-3β-cinnamoyloxykaur-16-

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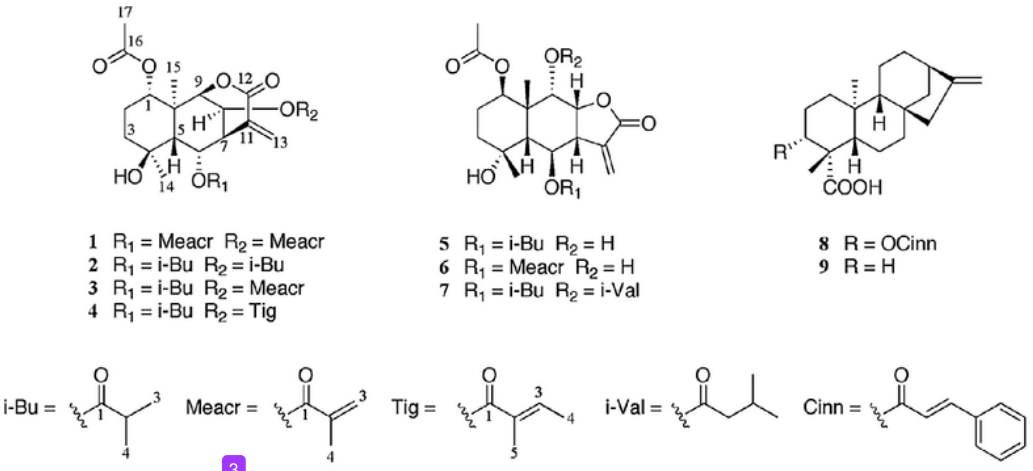

Fig. 1. Structures of **1**–**9** isolated from the aerial parts of Indonesian *Wedelia prostata*.

en-19-oic acid (Ragasa and Palina, 1993), and *ent*-kaur-16-en-19-oic acid (Bohlmann et al., 1982), respectively, by comparing their spectroscopic data with previously reported values (Fig. 1).

The molecular formula of compound **1** was assigned as $C_{25}H_{32}O_9$ from HREIMS (*m/z* 476.2055 $[M]^+$, Δ +0.9 mmu) and NMR data (Table 1). The ^1H and ^{13}C NMR spectra of **1** (in $CDCl_3$) indicated 31 protons and 25 carbon signals, which were classified into five methyls, two sp^3 methylenes, two sp^3 methines, four sp^3 oxygenated methines, one sp^3 quaternary carbon, one sp^3 oxygenated unprotonated carbon, three sp^2 methylenes, three sp^2 quaternary carbons and four carbonyl carbons from an analysis of the HMQC spectrum of **1** (Table 1). The ^1H and ^{13}C NMR data for **1** were very similar to those for **4**. Therefore, the skeletal structure of **1** was presumed to be the same as that of **4**, which was confirmed by COSY and HMBC correlations of **1** (Fig. 2a). The main difference observed in the NMR data between **1** and **4** were the presence of two methacryloxy groups at C-6 and C-8 in **1** [C-6 ester (δ_H 6.16, 5.71, and 2.00; δ_C 166.6, 135.5, 127.3, and 18.4) and a C-8 ester (δ_H 6.05, 5.59, and 1.87; δ_C 166.0, 135.2, 127.4, and 18.0)] instead of isobutyryloxy group at C-6 and a tigloyloxy group at C-8 in **4**. Thus, the planar structure of **1** was elucidated as 1-acetoxy-4-hydroxy-6,8-dimethacryloxy-eudesman-9,12-olide and named wedelolide I (Fig. 2a).

The relative configuration of **1** was assigned by its NOESY data (Fig. 2b). The correlations between H-1 (δ 4.95)/H-3 (1.71), H-1/H-5 (1.55), H-3/H-5, H-5/H-6 (5.59), H-8 (5.47)/H_3-15 (1.42), H-9 (4.47)/H_3-15, and H_3-14 (1.31)/H_3-15 in the NOESY spectrum of **1** indicated the same ring system as that of **4**. This configuration was also supported by comparing the coupling constants in the ^1H NMR spectrum of **1** with those of **4** and related compounds (That et al., 2007; Li et al., 2013; Duc et al., 2016; Wu et al., 2016).

Compound **2** had the molecular formula of $C_{25}H_{36}O_9$, which was deduced from HREIMS (*m/z* 480.2363 $[M]^+$, Δ +0.4 mmu) and NMR data (Table 1). The ^1H and ^{13}C NMR spectra of **2** resembled those of **1** and **4**. Comparisons of NMR data for **2** with those for **4** revealed that a tigloyloxy group at C-8 in **4** was replaced by an isobutyryloxy group in **2** (Fig. 3a). Thus, the planar structure of **2** was elucidated to be 1-acetoxy-4-hydroxy-6,8-diisobutyryloxy-eudesman-9,12-olide and named wedelolide J (Fig. 3a). The relative configuration of **2** was confirmed by its similar NOESY data to **1** (Fig. 3b).

The molecular formula of compound **3** ($C_{25}H_{34}O_9$) was elucidated from HREIMS (*m/z* 478.2214 $[M]^+$, Δ +1.1 mmu) and NMR data (Table 1). The ^1H and ^{13}C NMR spectra of **3** revealed that it was also a wedelolide. The relative structure of **3** was assigned from the 1D and 2D NMR spectra of **3** (Fig. 4). Compound **3** was obtained as a new natural product in this study, however compound **3** was recently reported from the Chinese *W. prostata* as prostrolide A (Wu et al., 2016) during the preparation of this manuscript

The absolute configurations of wedelolides have been established by an X-ray crystallographic analysis and modified Mosher's method (That et al., 2007; Li et al., 2013). Compounds **1**–**3** were obtained together with a known derivative, wedelolide D (**4**), from the same plant, indicating that compounds **1**–**4** are biosynthesized by the same pathway. Therefore, the absolute configurations of **1**–**3** may be the same as that of **4**, which is supported by the same Cotton effects in ECD spectra of **1**–**4**.

The inhibitory effects of compounds **1**–**9** on PTP1B activity were examined, and the IC_{50} values of **1**–**9** and a positive control [oleanolic acid (Zhang et al., 2008)] are listed in Table 2. *ent*-Kaurene diterpene **8** inhibited PTP1B activity with an IC_{50} value of 8.3 μM, whereas compound **9**, a decinnamoyloxy derivative of **8**, exhibited markedly reduced activity (IC_{50} = 28 μM). Therefore, the cinnamoyl group in **8** is favorable for PTP1B inhibitory activity. Among the eudesmanolide sesquiterpenes examined (**1**–**7**), only wedelolide D (**4**) exhibited 32% inhibition against PTP1B at 20 μM. The other sesquiterpenes did not inhibit PTP1B activity at 25 μM.

In the present study, two new (9*R*)-eudesman-9,12-olide sesquiterpenes, wedelolides I (**1**) and J (**2**), were isolated together with seven known terpenoid components (**3**–**9**) from the aerial parts of Indonesian *W. prostata*. Inhibitory activity against PTP1B by the EtOH extract was reproduced by two *ent*-kaurene diterpenes (**8** and **9**) as the main active components. Although the PTP1B inhibitory activity of *ent*-kaur-16-en-19-oic acid (**9**) has already been reported (Na et al., 2006), we herein revealed that the cinnamoyl group enhanced the activity of this type of diterpene.

3. Experimental

3.1. General experimental procedures

EIMS was measured on a JMS-MS 700 mass spectrometer (JEOL, Tokyo, Japan). ^1H and ^{13}C NMR spectra were recorded on a JNM-AL-400 NMR spectrometer (JEOL) at 400 MHz for ^1H and 100 MHz for ^{13}C in $CDCl_3$ (δ_H 7.24, δ_C 77.0). Specific rotations were obtained with the digital polarimeter P-2300 (JASCO, Tokyo, Japan). UV spectra were measured on the UV–vis spectrophotometer U-3310 (Hitachi Ltd., Tokyo, Japan). ECD spectra were measured with a JASCO J-720 spectropolarimeter. IR spectra were recorded on the Fourier transform infrared spectrometer FT-710 (Horiba Ltd., Kyoto, Japan). Preparative HPLC was performed using an L-6200 HPLC system (Hitachi Ltd., Tokyo, Japan).

Table 1
^{1}H and ^{13}C NMR Data for Compounds **1–3** in $CDCl_3$.

C#	1		2		3	
	δ_C, type	δ_H mult. (*J* in Hz)	δ_C, type	δ_H mult. (*J* in Hz)	δ_C, type	δ_H mult. (*J* in Hz)
1	73.0, CH	4.95, dd (11.0, 4.8)	73.0, CH	4.93, dd (11.1, 4.4)	73.0, CH	4.94, dd (11.0, 4.6)
2	24.1, CH_2	1.57, m 2.10, m	24.1, CH_2	1.57, m 2.09, m	24.1, CH_2	1.57, m 2.09, m
3	41.1, CH_2	1.57, m 1.71, m	41.1, CH_2	1.57, m 1.70, m	41.1, CH_2	1.57, m 1.71, dd (9.2, 3.4)
4	70.9, C		70.9, C		70.9, C	
5	43.8, CH	1.55, d (2.4)	43.6, CH	1.50, d (2.9)	43.6, CH	1.52, d (2.8)
6	74.3, CH	5.59, m	73.8, CH	5.49, dd (3.8, 2.9)	73.8, CH	5.51, dd (3.8, 2.8)
7	43.9, CH	3.31, brd (2.9)	43.8, CH	3.20, brd (2.8)	43.9, CH	3.24, brd (2.8)
8	64.8, CH	5.47, dd (3.9, 1.9)	64.3, CH	5.36, dd (3.6, 1.9)	64.8, CH	5.45, dd (3.4, 1.9)
9	81.2, CH	4.47, brs	81.2, CH	4.38, brs	81.2, CH	4.44, brs
10	43.4, C		43.4, C		43.4, C	
11	131.7, C		131.8, C		131.7, C	
12	162.4, C		162.6, C		162.6, C	
13	133.4, CH_2	5.85, s 6.66, s 6.68, s	133.3, CH_2	5.80, s 6.65, s 6.65, s	133.4, CH_2	5.82, s 6.66, s 6.66, s
14	25.1, CH_3	1.31, s	25.1, CH_3	1.30, s	25.1, CH_3	1.31, s
15	15.5, CH_3	1.42, s	15.5, CH_3	1.39, s	15.5, CH_3	1.41, s
1-OAc						
1	169.8, C	2.03, s (13.4, 13.4, 4.8)	169.8, C	2.03, s (13.4, 13.4, 4.8)	169.8, C	2.03, s (13.4, 13.4, 4.8)
2	21.2, CH_3	2.03, s	21.2, CH_3	2.03, s	21.2, CH_3	2.03, s
6-ester						
1	166.6, C		176.2, C		176.2, C	
2	135.5, C		34.5, CH	2.63, sept (6.8)	34.5, CH	2.63, sept (6.8)
3	127.3, CH_2	5.71, s 6.16, s	18.8, CH_3	1.26, d (6.8)	18.5, CH_3	1.26, d (6.8)
4	18.4, CH_3	2.00, s	19.1, CH_3	1.23, d (6.8)	19.1, CH_3	1.23, d (6.8)
8-ester						
1	166.0, C		176.2, C		166.2, C	
2	135.2, C		33.9, CH	2.51, sept (7.2)	135.3, C	
3	127.4, CH_2	5.59, m 6.05, s	18.5, CH_3	1.11, d (7.2)	127.4, CH_2	5.59, brs 6.05, s
4	18.0, CH_3	1.87, s	18.6, CH_3	1.09, d (7.2)	18.0, CH_3	1.87, s

3.2. Materials

PTP1B was purchased from Enzo Life Sciences (Farmingdale, NY, USA). *p*-Nitrophenyl phosphate (*p*NPP) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Oleanolic acid was purchased from Tokyo Chemical Industry (Tokyo, Japan). Plastic plates (96-well) were purchased from Corning Inc. (Corning, NY, USA). All other chemicals including organic solvents were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan).

3.3. Isolation of compounds 1–9

The aerial parts of *Wedelia biflorata* were collected at Manado, North Sulawesi, Indonesia in 2016. A voucher specimen was deposited at the Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University as TMH-1.

The plant (1.0 kg, wet weight) was cut into small pieces and exhaustively extracted three times with EtOH. The EtOH extract (47.0 g) was separated into seven fractions (Frs. 1–7) using an ODS column (100 g) with the stepwise elution of CH_3OH in H_2O (0, 30, 50, 70, 85, 100% CH_3OH, and 100% CH_3OH containing 0.05% TFA). Fr. 4 (274.8 mg, eluted with 70% CH_3OH) was subjected to HPLC separation [column, PEGASIL ODS (Senshu Sci. Co. Ltd., Tokyo, Japan), i.d. 10 mm × 250 mm; solvent, 62% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV 210 nm] to give four subfractions (Frs. 4.1–4.4). Compounds **1** (0.9 mg, t_R = 103 min), **2** (1.2 mg, t_R = 123 min), **3** (1.1 mg, t_R = 132 min), and **4** (3.3 mg, t_R = 140 min) were isolated from Fr. 4-4 (19.4 mg) by preparative HPLC [column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 58% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV 210 nm]. Fr. 4-1 (114.8 mg) was purified by HPLC [column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 50% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV 210 nm] to give compounds **5** (2.6 mg, t_R = 100 min) and **6** (3.3 mg, t_R = 110 min). Compound **7** (2.3 mg, t_R = 90 min) was isolated from Fr. 4-2 (107.5 mg) by preparative HPLC [column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 57% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV 210 nm]. Compounds **8** (4.5 mg, t_R = 45 min) and **9** (25 mg, t_R = 41 min) were obtained from Fr. 6 (2800 mg, eluted with 100% CH_3OH) by preparative HPLC [column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 86% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV 210 nm].

3.3.1. Wedelolide I (1)

Colorless solids; $[\alpha]_D^{25}$ −7.0 (*c* 0.05, CH_3OH); UV (CH_3OH) λ_{max} nm (log ε) 203 (4.3), 211 (4.3) nm; ECD (2.1 × 10^{-4} M, CH_3CN) λ_{max} (Δε) 216 (−7.2) nm; IR (KBr) ν_{max} 3432, 2947, 1723, 1636, 1455, 1385, 1295, 1244, 1157, 1038, 812 cm^{-1}; ^{1}H and ^{13}C NMR in $CDCl_3$, see Table 1; EIMS *m/z* 476 $[M]^+$; HREIMS *m/z* 476.2055 $[M]^+$, (calcd for $C_{25}H_{32}O_9$, 476.2046).

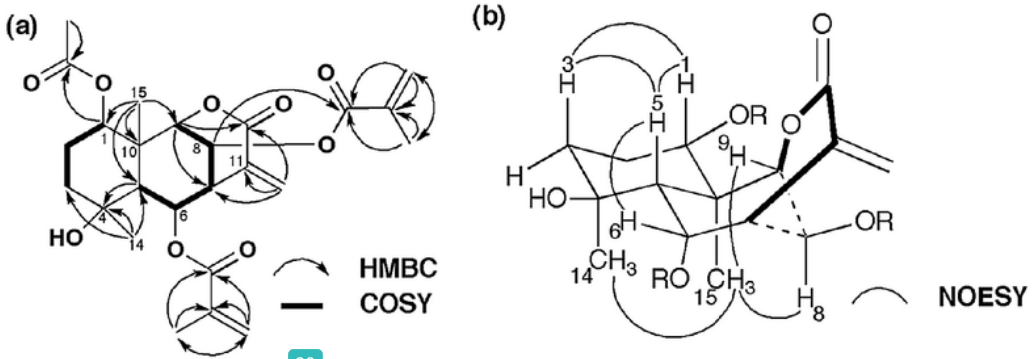

Fig. 2. (a) COSY and key HMBC correlations and (b) key NOESY data for **1**.

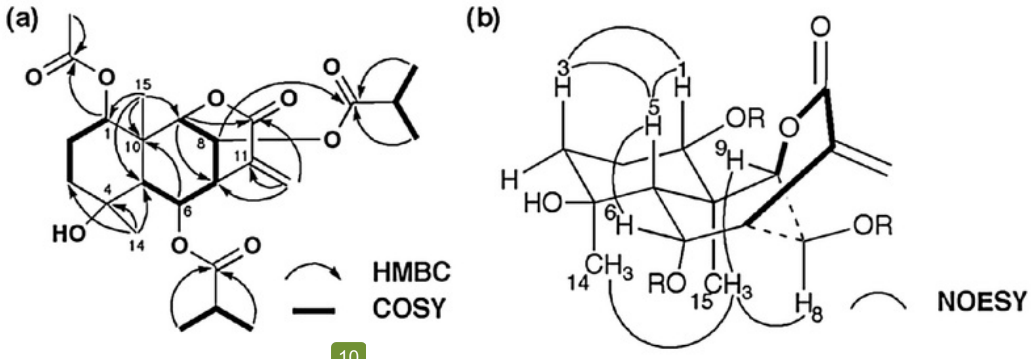

Fig. 3. (a) COSY and key HMBC correlations and (b) key NOESY data for 2.

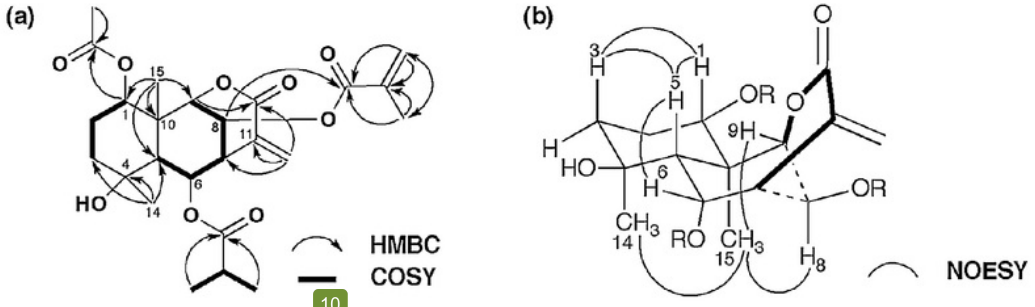

Fig. 4. (a) COSY and key HMBC correlations and (b) key NOESY data for 3.

Table 2
PTP1B Inhibitory Activities of Compounds **1–9**.

Compound	IC_{50} (μM)
1	> 21
2	> 21
3	> 21
4	32% inhibition at 20 μM
5	> 24
6	> 25
7	> 20
8	8.3
9	28
Oleanolic acid (positive control)[11]	1.1

3.3.2. *Wedelolide J* (2)

Colorless solids; $[\alpha]_D^{25}$ −12.1 (*c* 0.05, CH_3OH); UV (CH_3OH) λ_{max} nm (log ε) 201 (4.0), 211 (3.9) nm; ECD (2.1 × 10^{-4} M, CH_3CN) λ_{max} (Δε) 209 (–2.0) nm; IR (KBr) 3402, 2946, 1737, 1471, 1387, 1245, 1203, 1155, 1033, 805 cm^{-1}; ^1H and ^{13}C NMR in $CDCl_3$, see Table 1; EIMS *m/z* 480 $[M]^+$; HREIMS *m/z* 480.2363 $[M]^+$, (calcd for $C_{25}H_{36}O_9$, 480.2359).

3.3.3. *Prostrolide A* (3)

Colorless solids; $[\alpha]_D^{24}$ −46.8 (*c* 0.1, CH_3OH); lit. $[\alpha]^{25}_D$ −44.1 (*c* 1.05, CH_3OH) (Wu et al., 2016); UV (CH_3OH) λ_{max} nm (log ε) 203 (4.3), 212 (4.2) nm; ECD (2.1 × 10^{-4} M, CH_3CN) λ_{max} (Δε) 213 (–9.2) nm; IR (KBr) ν_{max} 3409, 2947, 1726, 1633, 1389, 1245, 1157, 1032, 924 cm^{-1}; ^1H and ^{13}C NMR in $CDCl_3$, Table 1; EIMS *m/z* 478 $[M]^+$; HREIMS *m/z* 478.2214 $[M]^+$ (calcd for $C_{25}H_{34}O_9$, 478.2203).

3.4. *PTP1B inhibitory assay*

Inhibitory activity against protein tyrosine phosphatase 1B (PTP1B) was assessed by measuring the rate of hydrolysis of the substrate, *p*-nitrophenyl phosphate (*p*NPP, Sigma-Aldrich), according to a previously described method with a slight modification (Cui et al., 2006; Yamazaki et al., 2013). Briefly, PTP1B (100 of 0.5 μg/mL stock solution, Enzo Life Sciences) in 50 mM citrate buffer (pH 6.0) containing 0.1 M NaCl, 1 mM dithiothreitol (DTT), and 1 mM *N,N,N′,N′*-ethylenediamine tetraacetate (EDTA) was added to each well of a 96-well plastic plate (Corning Inc). Each sample (2.0 μL CH_3OH) was added to each well to make a final concentration and incubated at 37 °C for 10 min. The reaction was initiated by the addition of *p*NPP (100 μL of 4.0 mM stock solution) to the citrate buffer, incubated at 37 °C for 30 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})] × 100. 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, whereas ABS_{sample} was that with a test sample. Assays were performed in two independent experiments for all samples. Oleanolic acid (Tokyo Chemical Industry), a known phosphatase inhibitor (Zhang et al., 2008), was used as a positive control.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the

online version, at http://dx.doi.org/10.1016/j.phytol.2017.04.018.

References

Abdjul, D.B., Yamazaki, H., Takahashi, O., Kirikoshi, R., Ukai, K., Namikoshi, M., 2016. Sesquiterpene hydroquinones with protein tyrosine phosphatase 1B inhibitory activities from a *Dysidea* sp. marine sponge collected in Okinawa. J. Nat. Prod. 79 733–449.

Barr, A.J., 2010. Protein tyrosine phosphatases as drug targets: strategies and challenges of inhibitor development. Future Med. Chem. 2, 1563–1576.

Bohlmann, F., Ziesche, J., King, R.M., Robinson, H., 1982. 1,11-Diarylundecan-1-one and 4-aryltetralone neolignans from *Virola sebifera*. Phytochemistry 20, 751–755.

Duc, T.P., Thien, T.V.N., Jossang, A., Kim, P.P.N., Grellier, P., Jaureguiberry, G., That, Q.T., 2016. New wedelolides, (9R)-eudesman-9, 12-olide δ-lactones, from *Wedelia trilobata*. Phytochem. Lett. 17, 304–309.

Jiang, C.S., Liang, L.F., Guo, Y.W., 2012. Natural products possessing protein tyrosine phosphatase 1B (PTP1B) inhibitory activity found in the last decades. Acta Pharmacol. Sin. 33, 1217–1245.

Lee, J.S., Maarisit, W., Abdjul, D.B., Yamazaki, H., Takahashi, O., Kirikoshi, R., Kanno, S., Namikoshi, M., 2016. Structures and biological activities of triterpenes and sesquiterpenes obtained from *Russula lepida*. Phytochemistry 127, 63–68.

Li, C.L., Liu, F.X., Wu, H.Z., Zheng, Y.K., 1959. Clinical application of *Wedelia prostrate*. Fujian J. Tradit. Chin. Med. 10, 448–449.

Li, X., Dong, M., Liu, Y., Shi, Q.W., Kiyota, H., 2007. Structures and biological properties of the chemical constituents from the genus *Wedelia*. Chem. Biodivers. 4, 823–836.

Li, Y., Hao, X., Li, S., He, H., Yan, X., Chen, Y., Dong, J., Zhang, Z., Li, S., 2013. Eudesmanolides from *Wedelia trilobata* (L.) Hitchc. as potential inducers of plant systemic acquired resistance. J. Agric. Food. Chem. 61, 3884–3890.

Na, M., Oh, W.K., Kim, Y.H., Cai, X.F., Kim, S., Kim, B.Y., Ahn, J.S., 2006. Inhibition of protein tyrosine phosphatase 1B by diterpenoids isolated from *Acanthopanax koreanum*. Bioorg. Med. Chem. Lett. 16, 3061–3064.

Popov, D., 2011. Novel protein tyrosine phosphatase 1B inhibitors: interaction requirements for improved intracellular efficacy in type 2 diabetes mellitus and obesity control. Biochem. Biophys. Res. Commun. 410, 377–381.

Ragasa, C.Y., Padolina, W.G., 1993. New eudesmanolide sesquiterpenes from a Philippines collection of *Wedelia prostata*. J. Nat. Prod. 56, 386–393.

That, Q.T., Jossang, J., Jossang, A., Kim, P.P.N., Jaureguiberry, G., 2007. Wedelolides A and B: novel sesquiterpene delta-lactones, (9R)-eudesman-9,12-olides, from *Wedelia trilobata*. J. Org. Chem. 72, 7102–7105.

Wu, M.L., Zhang, D.Z., Xu, Q.J., Xie, R.R., Li, Q.Q., 2010. Chemical constituents of *Wedelia trilobata*. Zhongcaoyao 41, 681–685.

Wu, Z.N., Zhang, Y.B., Chen, N.H., Yang, L., Jiang, L., Jiang, S.Q., Li, G.Q., Li, Y.L., Wang, G.C., 2016. Three new eudesmanolides from the herbs of *Wedelia prostrata*. Chem. Lett. 45, 1150–1152.

Yamazaki, H., Sumilat, D.A., Kanno, S., Ukai, K., Rotinsulu, H., Wewengkang, D.S., Ishikawa, M., Mangindaan, R.E.P., Namikoshi, M., 2013. A polybromodiphenyl ether from an Indonesian marine sponge *Lamellodysidea herbacea* and its chemical derivatives inhibit protein tyrosine phosphatase 1B, an important target for diabetes treatment. J. Nat. Med. 6, 730–735.

Yamazaki, H., Takahashi, O., Kanno, S., Nakazawa, T., Takahashi, S., Ukai, K., Sumilat, D.A., Ishikawa, M., Namikoshi, M., 2015a. Absolute structures and bioactivities of eurysponginsand eurydiene obtained from the marine sponge *Euryspongia* sp. collected at Iriomote Island. Bioorg. Med. Chem. 23, 797–802.

Yamazaki, H., Nakayama, W., Takahashi, O., Kirikoshi, R., Izumikawa, Y., Iwasaki, K., Toraiwa, K., Ukai, K., Rotinsulu, H., Wewengkang, D.S., Sumilat, D.A., Mangindaan, R.E.P., Namikoshi, M., 2015b. Verruculides A and B: two new protein tyrosine phosphatase 1B inhibitors from an Indonesian ascidian-derived *Penicillium verruculosum*. Bioorg. Med. Chem. Lett. 25, 3087–3090.

Zhang, S., Zhang, Z.Y., 2007. PTP1B as a drug target: recent developments in PTP1B inhibitor discovery. Drug Discov. Today 12, 373–381.

Zhang, Y.N., Zhang, W., Hong, D., Shi, L., Shen, Q., Li, J.Y., Li, J., Hu, L.H., 2008. Oleanolic acid and its derivatives: new inhibitor of protein tyrosine phosphatase 1B with cellular activities. Bioorg. Med. Chem. 16, 8697–8705.

Zhang, X.G., Yan, W.Q., Lin, Y.T., Liu, X.J., Lin, X.Y., Zhang, Y.H., 2011. Studies on the diterpenoids of *Wedelia prostrate*. J. Chin. Med. Mater. 34, 383–386.

Zhang, Z.Y., Dodd, G.T., Tiganis, T., 2015. Protein tyrosine phosphatases in hypothalamic insulin and leptin signaling. Trends Pharmacol. Sci. 36, 661–674.

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