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Oleanane triterpenes with protein tyrosine phosphatase 1B inhibitory activity from aerial parts of *Lantana camara* collected in Indonesia and Japan

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ABSTRACT

During the search for new protein tyrosine phosphatase (PTP) 1B inhibitors, EtOH extracts from the aerial parts of *Lantana camara* L. (lantana) collected at Manado (Indonesia) and two subtropical islands in Japan (Ishigaki and Iriomote Islands, Okinawa) exhibited potent inhibitory activities against PTP1B in an enzyme assay. Four previously undescribed oleanane triterpenes were isolated together with known triterpenes and flavones from the Indonesian lantana. The EtOH extracts of lantana collected in Ishigaki and Iriomote Islands exhibited different phytochemical profiles from each other and the Indonesian lantana. Triterpenes with a 24-OH group were isolated from the Indonesian lantana only. Five known triterpene compounds were detected in the Ishigaki lantana, and two oleanane triterpenes with an ether linkage between 3β and 25 were the main components together with five known triterpenes as minor components in the Iriomote lantana. The structures of previously undescribed compounds were assigned on the basis of their spectroscopic data. Among the compounds obtained in this study, oleanolic acid exhibited the most potent activity against PTP1B, and is used as a positive control in studies on PTP1B.

1. Introduction

In the course of our research on protein tyrosine phosphate (PTP) 1B inhibitors from natural resources in tropical and subtropical areas, we reported new PTP1B inhibitors with various structural features (Abdjul et al., 2016; Yamazaki et al., 2016; Maarisit et al., 2017; Sumilat et al., 2017) and demonstrated that EtOH extracts from the aerial parts of *Lantana camara* L. (lantana) in Indonesia (Manado) and two subtropical islands in Japan (Ishigaki and Iriomote Islands, Okinawa) inhibited PTP1B activity.

L. camara belongs to the family Verbenaceae and is commonly known as lantana (Ghisalberti, 2000). The plant is a hairy shrub native to tropical and subtropical America and is now growing throughout tropical, subtropical, and temperate regions. It is also cultivated as an ornamental plant. Several parts of the plant have been used as folk medicine to cure various diseases. Its leaves are used to treat scrapes and cuts in Indonesia, and a tea prepared from its leaves in Okinawa, Japan traditionally improved rheumatism (Ghisalberti, 2000). A number of phytochemical studies have been performed on *L. camara* and identified various triterpenoids as well as iridoid glycosides, furanonaphthoquinones, and flavonoids (Ghisalberti, 2000).

PTP1B is an enzyme that negatively regulates cell signaling transmitted from insulin and leptin receptors (Maheswari et al., 2017; Zhang and Zhang, 2007), and its small molecular inhibitors are considered to be promising drugs for the treatment of type 2 diabetes and obesity (Wang et al., 2015).

The bioassay-guided separation of extracts gave 22 oleanane triterpenes (**1**–**22**) and three flavonoids (**23**–**25**), including four previously undescribed compounds (**1**–**4**) (Fig. 1). The structures of

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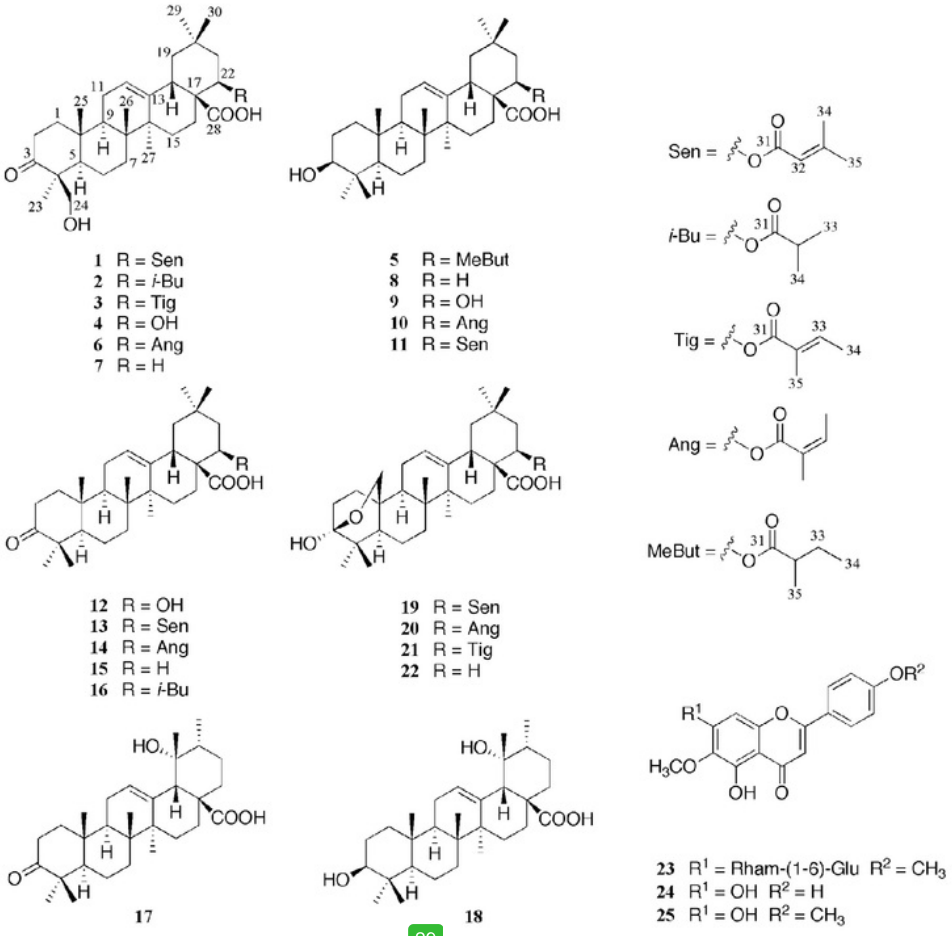

Fig. 1. Structures of **1**–**25** isolated from aerial parts of *Lantana camara*.

the previously undescribed compounds (**1**–**4**) were elucidated based on their spectroscopic data, particularly 2D NMR spectral analyses (Fig. 2). Compound **5** has been reported as a semisynthetic derivative, and, therefore, this is the first study to show this compound as a natural product.

The EtOH extracts from three collection sites showed different phytochemical profiles with HPLC (Fig. 3).

In the present study, we describe the isolation, structural elucidation, phytochemical profiles, and biological activities of constituents from the aerial parts of lantana collected in Indonesia and Japan.

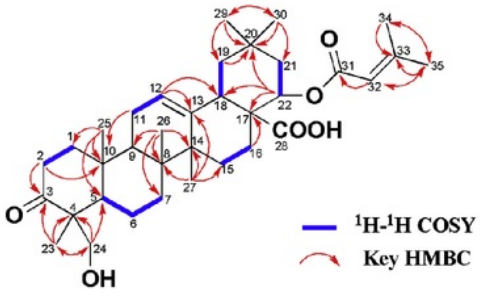

Fig. 2. ^{1}H–^{1}H COSY and key HMBC correlations for **1**.

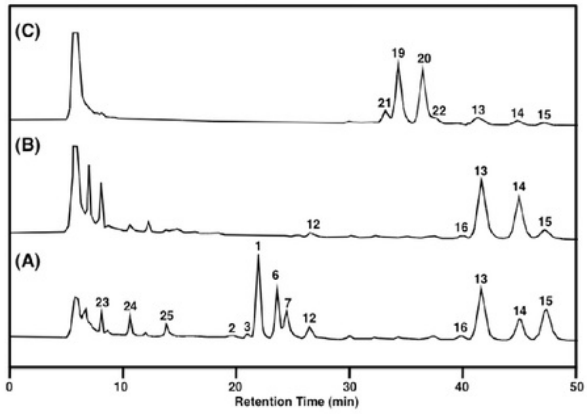

Fig. 3. HPLC profiles of EtOH extracts from aerial parts of *Lantana camara* collected at Manado (A), Ishigaki Island (B), and Iriomote Island (C).

2. Results and discussion

2.1. Isolation of compounds 1–20 and 23–25 from the Indonesian lantana

The EtOH extract of *L. camara* collected at Manado, Indonesia, inhibited PTP1B activity (*ca.* 57% at 50 μg/mL) and was separated using an ODS column followed by repeated HPLC (ODS) to yield compounds **1** (15 mg), **2** (5.4 mg), **3** (1.7 mg), **4** (35 mg), **5** (1.0 mg), **6** (13 mg), **7** (11 mg), **8** (10 mg), **9** (1.5 mg), **10** (0.9 mg), **11** (1.9 mg), **12** (11 mg), **13** (20 mg), **14** (14 mg), **15** (45 mg), **16** (10 mg), **17** (1.0 mg), **18** (2.0 mg), **19** (1.6 mg), **20** (1.0 mg), **23** (3.2 mg), **24** (2.2 mg), and **25** (1.7 mg).

The structures of known compounds were identified as icterogenin (**6**) (Hart et al., 1976; Mahato and Kundu, 1994), 4-*epi*-hederagonic acid (**7**) (Hart et al., 1976; Wen et al., 2010), oleanolic acid (**8**) (Seebacher et al., 2003), 22β-oleanolic acid (**9**) (Tailor et al., 2013), 3β-hydroxy-lantadene A (**10**) (Kumar et al., 2013), 3β-hydroxy-lantadene B (**11**) (Kumar et al., 2013), 22-hydroxy-oleanonic acid (**12**) (Sharma and Sharma, 2006), lantadene B (**13**) (Barton et al., 1954; Mahato and Kundu, 1994), lantadene A (**14**) (Barton et al., 1956; Singh et al., 1999), oleanonic acid (**15**) (Wen et al., 2008), lantadene D (**16**) (Sharma et al., 1990), pomonic acid (**17**) (Cheng and Cao, 1992), pomolic acid (**18**) (Cheng and Cao, 1992), lantanilic acid (**19**) (Barre et al., 1997), camaric acid (**20**) (Barre et al., 1997), pectolinarin (**23**) (Juang et al., 2005), hispidulin (**24**) (Juang et al., 2005), and pectolinarigenin (**25**) (Juang et al., 2005) by comparing their spectroscopic data with those of reported values.

2.2. Structural elucidation of 1–5

The molecular formula of compound **1** was assigned as $C_{35}H_{52}O_6$ from HRFABMS (*m/z* 569.3846 $[M + H]^+$, Δ +0.4 mmu) and NMR data (Table 1). The ^1H and ^{13}C NMR spectra of **1** (in $CDCl_3$) were very similar to those of lantadene B (**13**), except for the presence of an oxygenated methylene signal in **1** (δ_H 3.39 and 4.00, δ_C 65.7) instead of the methyl group at C-24 in **13** (δ_H 1.03, δ_C 21.5). The molecular weight (formula) of **1** was 16 Da (O) higher than that of **13**. Therefore, the structure of **1** was presumed to be a 24-hydroxy derivative of **13** and this was confirmed by COSY and HMBC data for **1** (Fig. 2). Hence, the planar structure of **1** was elucidated as 24-hydroxy-lantadene B (Fig. 1).

The relative configuration of **1** was elucidated as shown in Fig. 1 from the NOESY correlations between H-9 (δ 1.66)/H_3-27 (1.16), H-18 (3.03)/H_3-30 (0.99), H-21a (1.44)/H-22 (5.02), H-22/H_3-29 (0.86), H-24b (4.00)/H_3-25 (0.92), and H_3-25/H_3-26 (0.82) (Table 1).

The ^1H and ^{13}C NMR spectra of **2** resembled those of lantadene D (**16**). The molecular formula of **2** ($C_{34}H_{52}O_6$) deduced from HRFABMS (*m/z* 557.3843 $[M + H]^+$, Δ +0.1 mmu) possessed one oxygen more than that of **16**. Comparisons of NMR data for **2** (Table 2) with those for **16** revealed the planar structure of **2** as 24-hydroxy-lantadene D (Fig. 1). The relative configuration of **2** was confirmed by the NOESY data for **2**, similar to that for **1** (Table 2 and Fig. 1).

Compound **3** had the molecular formula of $C_{35}H_{52}O_6$, which was deduced from HRFABMS (*m/z* 569.3840 $[M + H]^+$, Δ −0.2 mmu) and NMR data (Table 3). The ^1H and ^{13}C NMR spectra of **3** ascribable to the triterpene skeleton were similar to those of **1** and **2**. The marked differences observed in NMR data among **1**–**3** were the presence of a tigloyloxy group at C-22 in **3** (δ_H 6.78, 1.74, and 1.75; δ_C 166.7, 128.6, 137.8, 14.5, and 12.0) instead of the senecloyloxy and isobutyryloxy groups at C-22 in **1** and **2**, respectively. Thus, the planar structure of **3** was elucidated as 24-hydroxy-lantadene X (Fig. 1). Lantadene X was previously reported to be biotransformed from lantadene A (**14**) using the Gram-negative bacterium, *Alcaligenes faecalis* (Singh et al., 1999). The relative configuration of **3** established by its NOESY spectrum was the same as those of **1** and **2** (Table 3 and Fig. 1).

Table 1
^{13}C (100 MHz) and ^1H (400 MHz) NMR spectroscopic data for **1** ($CDCl_3$).

Position	δ_C	δ_H mult. (*J* in Hz)	HMBC	NOESY
1	38.5	1.55 m		
		1.91 m		
2	34.2	2.38 m	3, 10	
		2.57 m	10	
3	221.1	–		
4	50.4			
5	55.5	1.60 m		
6	19.1	1.29 m		
		1.52 m		
7	32.4	1.30 m	5	
		1.48 m		
8	39.2	–		
9	46.4	1.66 m		27
10	36.5	–		
11	23.7	1.94 m	10	
12	122.2	5.37 brs	11, 13, 18	
13	143.2	–		
14	42.1	–		
15	27.7	1.52 m		
16	24.0	1.88 m	15, 17	
17	50.5	–		
18	38.7	3.03 dd (13.9, 3.9)		30
19	46.0	1.29 m	20	
		1.68 m		
20	30.1	–		
21	37.7	1.44 m		22, 29
		1.74 m		
22	75.1	5.02 brs	17, 18, 20	21a
23	22.2	1.25 s	3, 4, 5, 24	
24	65.7	3.39 d (11.2)	3, 4, 5	
		4.00 d (11.2)	3, 23	25
25	16.1	0.92 s	1, 5, 9, 10	24b, 26
26	16.7	0.82 s	7, 8, 9, 14	25
27	25.7	1.16 s	8, 13, 14, 15	9
28	176.6	–		
29	33.8	0.86 s	19, 20, 21, 30	21a
30	26.3	0.99 s	19, 20, 21, 29	18
31	165.4	–		
32	116.1	5.55 s	31, 34, 35	
33	157.1	–		
34	20.2	2.12 s	32, 33, 35	
35	27.4	1.83 s	32, 33, 34	

Although the ^1H and ^{13}C NMR spectra of **4** (Table 4) were similar to those of 4-*epi*-hederagonic acid (**7**), an oxygenated methine signal in **4** (δ_H 3.91, δ_C 74.3) was detected instead of the methylene signal at C-22 in **7**. The HRFABMS of **4** (*m/z* 487.3415 $[M]^+$, Δ −0.8 mmu) gave the molecular formula of $C_{30}H_{46}O_5$, which possessed one oxygen more than that of **7**. Therefore, the planar structure of **4** was assigned as 22-hydroxy-4-*epi*-hederagonic acid (Fig. 1). The relative configuration of **4** was elucidated by an analysis of NOESY data for **4**, similar to those for **1**–**3** (Table 4 and Fig. 1).

The molecular formula of compound **5** was deduced as $C_{35}H_{56}O_5$ from HRFABMS (*m/z* 555.4031 $[M - H]^+$, Δ −1.9 mmu) and NMR data (Table 5). The ^1H and ^{13}C NMR spectra of **5** were similar to those of lantadene C (Johns et al., 1983), except for the presence of an oxygenated methine signal (δ_H 3.20, δ_C 79.0) in **5** instead of the carbonyl signal at the C-3 position in lantadene C. The planar structure of **5** was assigned as 3-hydroxy-lantadene C by an analysis of 1D and 2D NMR data for **5** (Table 5 and Fig. 1). The relative stereostructure of **5** was elucidated as 3β-hydroxy-lantadine C by NOESY data for **5** (Table 5 and Fig. 1). This structure was previously reported to be a semisynthetic derivative from lantadene C (Brown and Rimington, 1963). Therefore, this is the first study to report

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

Position	δ_C	δ_H mult. (*J* in Hz)	HMBC	NOESY
1	38.4	1.59 m		
		1.89 m		
2	34.1	2.37 m	1, 3	
		2.56 m		
3	221.8	–		
4	49.8	–		
5	55.2	1.59	4, 6, 10, 23	
6	19.1	1.29 m	4	
		1.52 m		
7	32.3	1.31 m		
		1.50 m		
8	39.1	–		
9	46.3	1.68 m		
10	36.4	–		27
11	23.6	1.92 m	10	
12	122.1	5.38 brs	9, 14, 18	
13	143.3	–		
14	42.0	–		
15	27.7	1.52 m		
16	24.0	1.86 m	15, 17	
17	50.3	–		
18	38.5	3.04 (13.0 3.9)		30
19	46.0	1.31 m		
		1.67 m		
20	30.1	–		
21	37.9	1.45 m		22, 29
		1.74 m		
22	75.6	5.00 brs	18, 20	21a
23	22.3	1.26 s	3, 4, 5, 24	
24	65.6	3.37 d (11.1)	3, 4, 5, 23	
		4.03 d (11.1)	3, 23	25
25	16.2	0.91 s	1, 5, 9, 10	24b, 26
26	16.6	0.82 s	7, 8, 9, 14	26
27	25.6	1.16 s	8, 13, 14, 15	9
28	176.3	–		
29	33.7	0.87 s	19, 20, 21, 30	21a
30	26.4	0.99 s	19, 20, 21, 29	18
31	175.6	–		
32	34.4	2.42 m	31, 33, 34	
33	18.5	1.09 d (6.8)	31, 32, 34	
34	19.1	1.08 d (6.8)	31, 32, 33	

Table 3
^{13}C (100 MHz) and ^{1}H (400 MHz) NMR spectroscopic data for **3** ($CDCl_3$).

Position	δ_C	δ_H mult. (*J* in Hz)	HMBC	NOESY
1	37.7	1.57 m		
		1.87 m		
2	34.2	2.38 m		
		2.52 m		
3	221.1	–		
4	50.4			
5	55.5	1.60 m		
6	19.2	1.30 m		
		1.53 m		
7	32.3	1.30 m		
		1.49 m		
8	39.1	–		
9	46.4	1.66 m		27
10	36.5	–		
11	23.7	1.94 m		
12	122.3	5.41 brs		
13	142.9	–		
14	42.1	–		
15	27.7	1.53 m		
16	23.9	1.87 m		
17	50.5	–		
18	38.6	3.09 d (10.1)	17	30
19	46.0	1.32 m		
		1.66 m		
20	30.0	–		
21	37.7	1.45 m		22, 29
		1.78 m		
22	76.1	5.03 brs	18	21a
23	22.2	1.25 s	3, 4, 5, 24	
24	65.6	3.39 d (11.1)	3	
		4.00 d (11.1)	3, 5, 23	25
25	16.1	0.92 s	1, 5, 9, 10	24b, 26
26	16.6	0.82 s	7, 8, 9, 14	25
27	25.7	1.16 s	8, 13, 14, 15	9
28	176.0	–		
29	33.7	0.87 s	19, 20, 21, 30	21a
30	26.1	0.97 s	19, 20, 21, 29	18
31	166.7	–		
32	128.6	–		
33	137.8	6.78 q (6.8)		
34	14.5	1.74 d (6.8)	32, 33	
35	12.0	1.75 s	31, 32, 33	

compound **5** as a natural product. Since spectroscopic data and the configuration at C-3 were previously unknown, we described them herein.

The absolute configurations of oleanane triterpenes have been established by X-ray crystallographic analyses (Pattabhi et al., 1991; Nethaji et al., 1993). Since compounds **1**–**5** were obtained together with known derivatives from the same plant, these compounds appear to be biosynthesized via the same pathway. Therefore, the absolute configurations of **1**–**5** must be identical with those of the other components (**6**–**22**), which were supported by the same positive signs of specific rotations for **1**–**22**.

2.3. Phytochemical profiles of lantana from three collection sites

The EtOH extracts of *L. camara* collected at Ishigaki and Iriomote Islands (Okinawa, Japan) in 2016 inhibited PTP1B activity by 58 and 84%, respectively, at 50 μg/mL.

Fig. 3 shows the HPLC profiles of EtOH extracts from lantana collected at Manado (A), Ishigaki (B), and Iriomote (C). The peaks of 24-OH derivatives (**1**–**3**, **6**, and **7**) were detected in the Indonesian lantana only (Fig. 3A). The chromatogram of the Ishigaki lantana showed two major (**13** and **14**) and three minor peaks (**12**, **15**, and **16**). Two major peaks (**19** and **20**) were observed with five minor peaks (**13**–**15**, **21**, and **22**) in the chromatogram of the Iriomote lantana. Compounds **21** and **22** were isolated and identified as 22β-tigloyloxylantanolic acid and lantanolic acid, respectively, by a comparison of spectroscopic data for **21** and **22** with those for reported values (Barre et al., 1997). Therefore, the Iriomote lantana mainly produced oleanane triterpenes with an ether bridge between C-3β and C-25. The same species of plant collected at three islands exhibited different phytochemical components. The enzymes oxidizing the C-24 and C-25 methyl groups will be involved in biosynthesis in the Indonesian and Iriomote species, respectively. On the other hand, the Ishigaki species may not have these enzymes.

2.4. Biological activity

The inhibitory effects of compounds **1**–**25** on PTP1B activity were evaluated using an enzyme assay according to a previously described method (Yamazaki et al., 2013). Oleanolic acid (**8**) exhibited the most potent activity with an IC_{50} value of 2.0 μM (Table 6). This compound is used as a positive control in studies on PTP1B (Zhang et al., 2008), and commercial oleanolic acid hydrate showed an IC_{50} value of 1.3 μM in the same bioassay. The inhibitory activities of compounds **7**, **8**, **15**, and **22** revealed that oxidation at C-3, hydroxylation at C-24, and the ether linkage between C-3 and C-25 were unfavorable for this activity.

The leaf and fruit extracts of *L. camara* have recently been

Table 4
^{13}C (100 MHz) and ^{1}H (400 MHz) NMR spectroscopic data for **4** ($CDCl_3$).

Position	δ_C	δ_H mult. (*J* in Hz)	HMBC	NOESY
1	38.6	1.56 m		
		1.89 m		
2	34.3	2.40 m	10	
		2.52 m	3	
3	220.8	–		
4	50.8	–		
5	55.6	1.54	10	
6	19.2	1.30 m		
		1.52 m		
7	32.4	1.33 m	5	
		1.48 m		
8	39.2	–		
9	46.5	1.67 m		27
10	36.5	–		
11	23.8	1.93 m		
12	122.4	5.36 brs		
13	143.3	–		
14	42.2	–		
15	27.8	1.51 m		
16	24.3	1.86 m	17	
17	52.3	–		
18	38.2	3.00 (14.0, 3.9)	16	30
19	46.1	1.23 m		
		1.65 m		
20	30.2	–		
21	41.3	1.48 m		22, 29
		1.70 m		
22	74.3	3.91 brs	20	21a
23	22.2	1.25 s	3, 4, 5, 24	
24	65.8	3.44 d (11.1)	3, 4	
		3.96 d (11.1)	23	25
25	16.1	0.94 s	1, 5, 9, 10	24b, 26
26	16.7	0.81 s	7, 8, 9, 14	25
27	25.6	1.14 s	8, 13, 14, 15	9
28	178.5	–		
29	33.9	0.88 s	19, 20, 21, 30	21a
30	27.1	1.10 s	19, 20, 21, 29	18

Table 5
^{13}C (100 MHz) and ^{1}H (400 MHz) NMR spectroscopic data for **5** ($CDCl_3$).

Position	δ_C	δ_H mult. (*J* in Hz)	HMBC	NOESY
1	38.5	1.54 m	3	
		1.78 m		
2	27.2	1.50 m		
		1.59 m		
3	79.0	3.20 dd (11.3, 4.4)		23
4	39.2	–		
5	55.2	0.73 d (12.0)		9
6	18.3	1.28 m		
		1.54 m		
7	32.7	1.26 m	28	
		1.45 m		
8	38.5	–		
9	47.6	1.57 m		5, 27
10	37.0	–		
11	23.4	1.93 m		
12	122.8	5.38 brs		
13	142.9	–		
14	42.0	–		
15	27.7	1.48 m		
16	24.1	1.88 m		
17	50.4	–		
18	38.5	3.02 d (12.7)		30
19	45.9	1.28 m		
		1.71 m		
20	30.0	–		
21	38.0	1.45 m		22, 29
		1.74 m		
22	75.6	5.03 brs		21a
23	28.1	0.77 s	3, 4, 5, 24	3
24	15.6	0.97 s	3, 4, 5, 23	25
25	15.4	0.90 s	1, 5, 9, 10	24, 26
26	16.8	0.78 s	7, 8, 9, 14	25
27	25.9	1.15 s	8, 13, 14, 15	9
28	178.4	–		
29	33.7	0.88 s	19, 20, 21, 30	21a
30	26.6	1.01 s	19, 20, 21, 29	18
31	175.2	–		
32	41.6	2.25 brq (6.8)		
33	26.2	1.37 m		
34	11.8	0.85 t (7.6)	32, 33	
35	16.6	1.07 d (6.8)	31, 32, 33	

reported to improve blood glucose levels, HbA1c profiles, and body weights (Govindappa, 2015). Consequently, the relationship between anti-diabetic properties and PTP1B inhibition will be interest in future studies on clinical applications of the plant for the treatment of type 2 diabetes.

3. Conclusions

The aerial parts of *L. camara* L. (lantana) were collected in Indonesia (Manado) and Japan (Ishigaki and Iriomote Islands, Okinawa), and the phytochemical study gave four previously undescribed oleanane triterpenes (**1**–**4**) together with 21 known constituents (**5**–**25**). The Indonesian lantana contained the most diverse components. Since plants grown in tropical regions are generally exposed to severe environments, such as UV, microorganisms, and insects, a wide variety of chemical components will be produced to defend against these insults. Most of the isolated compounds exhibited PTP1B inhibitory activity, suggesting that *L. camara* has potential as a prospective drug for type 2 diabetes and obesity with a new therapeutic approach.

4. Experimental

4.1. General experimental procedure

FABMS was performed using a JMS-MS 700 mass spectrometer (JEOL, Tokyo, Japan). ^{1}H and ^{13}C NMR spectra were recorded on a JNM-AL-400 NMR spectrometer (JEOL) at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$ (δ_H 7.24, δ_C 77.0). Optical rotations were

Table 6
Effects of **1**–**25** on protein tyrosine phosphatase 1B activity.

Compound	PTP1B (IC_{50}, μM)
1	7.3
2	>18
3	>18
4	>21
5	7.3
6	11
7	8.1
8	2.0
9	7.9
10	7.2
11	5.1
12	6.9
13	5.5
14	5.2
15	6.9
16	7.9
17	10.5
18	10.6
19	7.5
20	5.1
21	>18
22	13
23	>16
24	>33
25	36% inhibition at 32 μM
Oleanolic acid[a]	1.3

[a] Positive control.

measured with a JASCO P-2300 digital polarimeter (JASCO, Ltd., Tokyo, Japan). UV spectra were obtained on a Hitachi U-3310 UV–Visible spectrophotometer (Hitachi, Ltd., Tokyo, Japan) and IR spectra on a PerkinElmer Spectrum One Fourier transform infrared spectrometer (Waltham, MA, USA). Preparative HPLC was performed using the L-6200 system (Hitachi Ltd.).

4.2. 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 hydrate 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).

4.3. Isolation of compounds **1**–**25**

The aerial parts of *Lantana camara* L. (family Verbenaceae) were collected at Manado in North Sulawesi (Indonesia) at GPS coordinates (N1°15′7.2″, E124°51′21.6″) and Ishigaki and Iriomote Islands in Okinawa (Japan) at GPS coordinates (N24°22′55.2″, E124°10′33.6″ and N24°21′14.9″, E123°56′14.4′, respectively) in 2016. The plants were identified by Mr. Mamoru Yamada (Banna Park, Okinawa, Japan). Voucher specimens have been deposited at the Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University as 16-2-27 = LAN-S (Manado), 16-9-4 = P2-2 (Ishigaki Island), and 16-9-8 = P3-2 (Iriomote Island).

The Indonesian lantana (16-2-27 = LAN-S) (1.0 kg, wet weight) was extracted with EtOH (1.0 L × 3) at room temperature and evaporated to give a crude extract (21 g). A portion (10 g) of the extract was separated by an ODS column (100 g) with the stepwise elution of CH_3OH in H_2O into seven fractions (Frs. 1–7).

Fr. 6 (891 mg, eluted with 100% CH_3OH) was subjected to preparative HPLC [column, PEGASIL ODS (Senshu Sci. Co. Ltd., Tokyo, Japan), i.d. 10 mm × 250 mm; solvent, 88% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV at 210 nm] to give **1** (15 mg), **6** (13 mg), **7** (11 mg), **12** (11 mg), **13** (20 mg), **14** (14 mg), **15** (45 mg), **16** (10 mg), and **11** (1.9 mg), and four subfractions (Frs. 6-1–6-4). Compounds **4** (1.8 mg), **17** (10 mg), and **18** (2.0 mg) were obtained from Fr. 6-1 (29 mg) by preparative HPLC (column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 77% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV at 210 nm). Fr. 6-2 (38 mg) was purified by repeated HPLC (column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 81% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV at 210 nm) to yield **2** (5.4 mg), **3** (1.7 mg), and **9** (1.5 mg). Compounds **19** (1.6 mg) and **10** (0.9 mg) were isolated from Fr. 6-3 (9.5 mg) using preparative HPLC (column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 80% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV at 210 nm). Compounds **20** (1.0 mg), **5** (1.0 mg), and **8** (10 mg) were obtained from Fr. 6-4 (20 mg) 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 at 210 nm). Fr. 4 (110 mg, eluted with 70% CH_3OH) was subjected to HPLC separation (column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 63% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV at 210 nm) to afford **23** (3.2 mg), **24** (2.2 mg), and **25** (1.7 mg).

The aerial parts of *L. camara* (182 g, wet weight) collected at Iriomote Island (16-9-8 = P3-2) were extracted three times with EtOH (1.0 L) at room temperature, and the extract was evaporated (3.8 g). A portion (250 mg) of the extract was purified by HPLC (column, PEGASIL ODS, i.d. 10 mm × 250 mm; solvent, 88% CH_3OH in H_2O; flow rate, 2.0 mL/min; detection, UV at 210 nm) to give **19** (4.8 mg), **20** (7.7 mg), **21** (0.4 mg), and **22** (0.9 mg).

4.3.1. 24-Hydroxy-lantadene B (**1**)

Yellow solids; $[\alpha]^{22}_D$ +50.5 (*c* 0.20, CH_3OH); IR (KBr) ν_{max} 3446, 2948, 2343, 1717, 1459, 1381, 1229, 1140, 1073, 1037, 852 cm^{-1}; UV (CH_3OH) λ_{max} nm (log ε) 210 (4.4); FABMS *m/z* 569 $[M + H]^+$; HRFABS *m/z* 569.3846 ($[M + H]^+$, calcd for $C_{35}H_{53}O_6$, 569.3842); ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 1.

4.3.2. 24-Hydroxy-lantadene D (**2**)

Colorless solids; $[\alpha]^{22}_D$ +57.4 (*c* 0.20, CH_3OH); IR (KBr) ν_{max} 3448, 2952, 2347, 1733, 1698, 1459, 1388, 1259, 1189, 1147, 1034, 814 cm^{-1}; UV (CH_3OH) λ_{max} nm (log ε) 202 (4.2); FABMS *m/z* 557 $[M + H]^+$; FABMS *m/z* 557.3843 ($[M + H]^+$, calcd for $C_{34}H_{53}O_6$, 557.3842); ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 2.

4.3.3. 24-Hydroxy-lantadene X (**3**)

Colorless solids; $[\alpha]^{22}_D$ +39.2 (*c* 0.20, CH_3OH); IR (KBr) ν_{max} 3422, 2948, 2361, 1716, 1459, 1385, 1267, 1135, 1036, 805 cm^{-1}; UV (CH_3OH) λ_{max} nm (log ε) 201 (4.3); FABMS *m/z* 569 $[M + H]^+$; FABMS *m/z* 569.3840 ($[M + H]^+$, calcd for $C_{35}H_{53}O_6$, 569.3842); ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 3.

4.3.4. 22-Hydroxy-4-epi-hederagonic acid (**4**)

Colorless solids; $[\alpha]^{22}_D$ +36.5 (*c* 0.20, CH_3OH); IR (KBr) ν_{max} 3447, 2947, 2362, 1705, 1459, 1387, 1260, 1188, 1036, 802 cm^{-1}; UV (CH_3OH) λ_{max} nm (log ε) 202 (4.0); FABMS *m/z* 487 $[M + H]^+$; HRFABMS *m/z* 487.3415 ($[M + H]^+$, calcd for $C_{30}H_{47}O_5$, 487.3423); ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 4.

4.3.5. 3β-Hydroxy-lantadene C (**5**)

Colorless solids; $[\alpha]^{22}_D$ +43.1 (*c* 0.05, CH_3OH); IR (KBr) ν_{max} 3447, 2946, 2362, 1690, 1459, 1386, 1261, 1208, 1188, 1140, 1030, 804 cm^{-1}; UV (CH_3OH) λ_{max} nm (log ε) 202 (3.0); FABMS *m/z* 555 $[M - H]^-$; HRFABMS *m/z* 555.4031 ($[M - H]^-$, calcd for $C_{35}H_{55}O_5$, 555.4050); ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 5.

4.4. PTP1B inhibitory assay

PTP1B inhibitory activity was assessed by measuring the rate of hydrolysis of a substrate, *p*NPP, according to the previously described method with a slight modification (Cui et al., 2006; Yamazaki et al., 2013). PTP1B (100 μL of 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 *N,N,N′,N′*-ethylenediamine tetraacetate (EDTA) was added to each well of a 96-well plastic plate. A sample (2.0 μL in MeOH) 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 in the citrate buffer (100 μL of 4.0 mM stock solution), incubated at 37 °C for 30 min, and terminated using 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., Ibaraki, Japan). PTP1B inhibitory activity (%) was defined as $[1 - (ABS_{sample} - ABS_{blank})/(ABS_{control} - ABS_{blank})] \times 100$. ABS_{blank} is the absorbance of wells containing only the buffer and *p*NPP. $ABS_{control}$ is the absorbance of *p*-nitrophenol liberated by the enzyme in the assay system without a test sample, whereas ABS_{sample} is that with a test sample. Assays were performed in two independent experiments for all test samples. Oleanolic acid, a known phosphatase inhibitor (Zhang et al., 2008), was used as a positive control. Data are expressed as the average of three independent experiments performed in duplicate.

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