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PTP1B INHIBITORS FROM *ISODON TERNIFOLIUS* COLLECTED IN VIET NAM

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Abstract. From the whole plant of *Isodon ternifolius* collected in Viet Nam, four triterpenes including ursaldehyde (**1**), ursolic acid (**2**), *β*-sitosterol (**3**), and *β*-sitosteryl ferulate (**4**) were isolated. Their chemical structures were determined using NMR and MS spectroscopy methods in combination with literature comparison. Inhibitory activity against PTP1B enzyme activity of isolated compounds also evaluated using *in vitro* assay. Compounds **1** and **2** displayed potential activities with IC_{50} values of 16.92 ± 0.12 and 3.42 ± 0.45 μM, respectively. For the first time, compounds **1** and **4** were isolated from the *Isodon* genus and *I. ternifolius*, as well as evaluated for the PTP1B inhibitory activity.

Keywords: *Isodon ternifolius*, Lamiaceae, whole plant, ursane-type triterpene, PTP1B.

Classification numbers: 1.1.1, 1.2.1.

1. INTRODUCTION

Isodon ternifolius is a member of the *Isodon* genus, which belongs to the Lamiaceae family. This genus contained approximately 150 species worldwide which distributed mainly in tropical and subtropical countries [1]. There have been several records of the use of *Isodon* genus in traditional medicine to cure several diseases such as esophageal cancer, rheumatism, and chronic pharyngitis [2, 3]. *Isodon* species have been reported in previous studies to exhibit various pharmacological activities such as cytotoxic, anti-tumor, anti-inflammatory, antivirus, antibiosis, and anti-proliferative activities [1]. Previous data on chemical constituents of the *Isodon* genus indicated the presence of phenolics, diterpenoids and triterpenoids [1, 4-10]. *I. ternifolius* is rich in diterpenoids [4-7, 9, 10], lignans, and phenylethanoid [8]. This species was commonly

utilized in folk medicine to treat icterohepatitis, enteritis [11], inflammation [8 - 11], and cancer [5, 6]. Type 2 diabetes (T2D) used to be known as noninsulin-dependent diabetes mellitus, is the most common type among three types of diabetes which accounting for about 90 % of the total cases. Protein tyrosine phosphatase 1B (PTP1B) is described role as a negative regulator of leptin and insulin signaling. The overexpression of PTP1B was proved to inhibit the expression of insulin in insulin-resistant states; in addition, recent genetic evidence demonstrated the correlation between PTP1B gene variants and changes in insulin sensitivity. Thus, PTP1B is considered as a promising drug target for at-risk obese patients and T2D treatment [12 - 14].

Up to date, there has been no investigation on PTP1B inhibitory activity of *I. ternifolius* chemical constituents. Thus, this study presented the isolation, structural elucidation of four compounds from *I. ternifolius* and their activity against PTP1B enzyme.

2. MATERIALS AND METHODS

2.1. Plant material

The whole plant of *I. ternifolius* was collected in July, 2017 at Thai Nguyen province, Viet Nam (Longitude 105° 50' 53.41" E; Latitude 21° 35' 39.19" N) and authenticated by Assoc. Prof. Dr. Tran Huy Thai, Institute of Ecology and Biological Resources, VAST. A voucher specimen (IS20171001.HN) was deposited at the Institute of Natural Products Chemistry, VAST.

2.2. General experimental procedures

^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were measured on Bruker Avance 500 MHz spectrometer. Varian FT-MS spectrometer and MicroQ-TOF III (Bruker Daltonics, Ettlingen, Germany) were utilized to obtain ESI-MS spectral data. Column chromatography was conducted using silica gel (Si 60 F254, 40–63 mesh, Merck, St. Louis, MO, USA). Pre-coated thin layer chromatography (TLC) plates (Si 60 F254) were used for analytical purposes. Compounds were visualized using UV radiation (254, 365 nm) and by spraying plates with 10% H_2SO_4 followed by heating. All solvents were redistilled before use.

2.3. Extraction and isolation

The dried powder of the whole plant of *I. ternifolius* (4.0 kg) was extracted with MeOH (3 × 8 L) accompanied by refluxing at 60 °C, to give 380 g of crude extract. The crude extract was suspended in water (800 mL) and successively partitioned with *n*-hexane (4 × 1.5 L), EtOAc (4 × 1.5 L), and BuOH (4 × 1.5 L). The *n*-hexane extract was chosen for further activity-guided fractionation study.

The *n*-hexane extract (48.84 g) was subjected to chromatography on a silica gel column (CC) using *n*-hexane-acetone as eluent (20:1 to 0:1) to yield ten fractions (CMH.1–CMH.10) based on their TLC profiles. The combined fractions (CMH.6 and CMH.7, 4.44 g) were further subjected to silica gel CC, eluting with *n*-hexane-EtOAc (8:1 to 0:1) to give nine small fractions (CMH.6-1 to CMH.6-9). Fraction CMH.6-2 was chromatographed on RP-C18 CC, using a stepwise gradient of acetone:water (1:1 to 1:0) to obtain twenty-five sub-fractions (CMH.6-2-1 to CMH.6-2-25). Further purification of sub-fraction CMH.6-2-12 (450 mg) by an RP-C18 column, eluting with acetone:water (3:1) yielded compounds **1** (152.0 mg) and **2** (19 mg). Fraction CMH.6-2-25 (650 mg) was further subjected to silica gel CC, using a gradient of *n*-hexane:acetone (10:1 to 5:1) yielded compounds **3** (443 mg) and **4** (153 mg).

Ursaldehyde (**1**): White powder; ESI-MS *m/z* 441.4 $[M + H]^+$ ($C_{30}H_{48}O_2$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 0.72 (1H, dd, *J* = 13.0, 1.5 Hz, H-5), 0.77 (3H, s, H-24), 0.78 (3H, s, H-25), 0.89 (3H, d, *J* = 7.0 Hz, H-29), 0.92 (3H, s, H-26), 0.97 (3H, d, *J* = 7.0 Hz, H-30), 0.98 (3H, s, H-23), 1.08 (3H, s, H-27), 3.21 (1H, dd, *J* = 11.0, 5.0 Hz, H-3), 5.31 (1H, t, *J* = 4.0 Hz, H-12), 9.32 (1H, d, *J* = 1.0 Hz, H-28); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): 207.4 (C-28), 137.8 (C-13), 126.2 (C-12), 79.0 (C-3), 55.2 (C-5), 52.6 (C-18), 50.1 (C-17), 47.6 (C-9), 42.2 (C-14), 39.8 (C-19), 39.0 (C-20), 38.8 (C-8), 38.7 (C-4), 38.7 (C-1), 37.0 (C-10), 33.1 (C-7), 31.7 (C-22), 30.2 (C-21), 29.7 (C-23), 28.1 (C-2), 27.2 (C-15), 26.9 (C-16), 23.3 (C-11), 23.2 (C-27), 21.0 (C-30), 18.3 (C-6), 17.2 (C-26), 16.6 (C-24), 15.6 (C-29), 15.5 (C-25).

Ursolic acid (**2**): White powder; ESI-MS *m/z* 457 $[M + H]^+$ ($C_{30}H_{48}O_3$); ^{1}H-NMR (500 MHz, $CDCl_3$+Methanol-d_4) δ_H (ppm): 0.72 (1H, br d, *J* = 11.5 Hz, H-5), 0.76 (3H, s, H-24), 0.87 (3H, d, *J* = 6.0 Hz, H-29), 0.93 (3H, s, H-25), 0.94 (3H, d, *J* = 6.0 Hz, H-30), 0.96 (3H, s, H-26), 0.96 (3H, s, H-23), 1.09 (3H, s, H-27), 3.15 (1H, dd, *J* = 11.5, 7.5 Hz, H-3), 5.31 (1H, br s, H-12); ^{13}C-NMR (125 MHz, $CDCl_3$+Methanol-d_4) δ_C (ppm): 181.0 (C-28), 139.3 (C-13), 126.6 (C-12), 79.5 (C-3), 56.5 (C-5), 54.1 (C-18), 49.1 (C-17), 48.7 (C-9), 43.1 (C-14), 40.5 (C-19), 40.2 (C-20), 40.1 (C-8), 39.8 (C-4), 39.7 (C-1), 37.9 (C-10), 34.1 (C-7), 31.7 (C-22), 29.0 (C-21), 28.8 (C-23), 27.7 (C-2), 25.2 (C-15), 25.2 (C-16), 24.2 (C-11), 24.2 (C-27), 21.7 (C-30), 19.3 (C-6), 17.7 (C-26), 17.7 (C-24), 16.4 (C-29), 16.1 (C-25).

***β*-sitosterol** (**3**): Colorless crystals; ESI-MS *m/z:* 415 $[M + H]^+$ ($C_{29}H_{50}O$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 5.35 (1H, t, *J* = 3.0 Hz, H-6), 3.53 (1H, m, H-3), 1.00 (3H, s, H-19), 0.92 (3H, d, *J* = 6.5 Hz, H-29), 0.85 (3H, d, *J* = 7.5 Hz, H-27), 0.83 (3H, d, *J* = 6.5 Hz, H-26), 0.81 (3H, t, *J* = 6.5 Hz, H-24), 0.68 (3H, s, H-28); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): 37.2 (C-1), 31.6 (C-2), 71.8 (C-3), 42.3 (C-4), 140.7 (C-5), 121.7 (C-6), 29.7 (C-7), 31.9 (C-8), 50.1 (C-9), 37.2 (C-10), 21.1 (C-11), 39.8 (C-12), 42.3 (C-13), 56.0 (C-14), 24.3 (C-15), 28.2 (C-16), 56.7 (C-17), 11.9 (C-18), 19.3 (C-19), 36.5 (C-20), 18.7 (C-21), 33.9 (C-22), 26.1 (C-23), 45.8 (C-24), 29.2 (C-25), 19.8 (C-26), 19.0 (C-27), 24.3 (C-28), 11.8 (C-29).

***β*-sitosteryl ferulate** (**4**): White solid; ESI-MS *m/z:* 591 $[M + H]^+$ ($C_{39}H_{58}O_4$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.60 (1H, d, *J* = 16.0 Hz, H-3′), 7.07 (1H, br d, *J* = 8.5 Hz, H-9′), 7.03 (1H, br s, H-5′), 6.91 (1H, d, *J* = 8.5 Hz, H-8′), 6.29 (1H, d, *J* = 16.0 Hz, H-2′), 5.34 (1H, t, *J* = 2.5 Hz, H-6), 3.92 (3H, s, 6′-OCH_3), 3.51 (1H, m, H-3), 1.00 (3H, s, H-19), 0.92 (3H, d, *J* = 6.5 Hz, H-29), 0.88 (3H, t, *J* = 7.0 Hz, H-24), 0.83 (3H, d, *J* = 7.0 Hz, H-26), 0.82 (3H, d, *J* = 7.0 Hz, H-27), 0.68 (3H, s, H-28); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): 37.3 (C-1), 31.7 (C-2), 71.8 (C-3), 42.3 (C-4), 140.8 (C-5), 121.7 (C-6), 29.7 (C-7), 31.9 (C-8), 50.1 (C-9), 37.3 (C-10), 21.1 (C-11), 39.8 (C-12), 42.3 (C-13), 55.9 (C-14), 24.3 (C-15), 28.2 (C-16), 56.8 (C-17), 12.0 (C-18), 19.4 (C-19), 36.5 (C-20), 18.8 (C-21), 34.0 (C-22), 26.1 (C-23), 45.9 (C-24), 29.2 (C-25), 19.8 (C-26), 19.0 (C-27), 24.3 (C-28), 11.8 (C-29), 167.3 (C-1′), 115.7 (C-2′), 144.6 (C-3′), 127.1 (C-4′), 109.3 (C-5′), 147.3 (C-6′), 146.8 (C-7′), 114.7 (C-8′), 123.0 (C-9′), 56.1 (6′-OCH_3).

2.4. PTP1B inhibition assay

PTP1B (human recombinant) was obtained from Biomol International LP, Plymouth Meeting, PA, USA. All isolated compounds were tested for inhibitory activities using the method as described [15]. Briefly, 0.05−0.1 μg of PTP1B and 4 mM *p*-NPP in a buffer containing 1 mM EDTA, 1 mM dithiothreitol, 0.1 M NaCl and 50 mM citrate (pH 6.0), with or

without test compounds, were added as 100 µL of a final volume to each of the 96 well plate. After incubation for 30 mins at 37 °C, the reaction mixture was quenched by adding 10 M NaOH. PTP1B enzyme activity was determined by measuring the amount of *p*-nitrophenol produced at 405 nm. The non-enzymatic hydrolysis of the substrate means the control sample without PTP1B enzyme.

3. RESULTS AND DISCUSSION

The methanol extract of the whole plant of *I. ternifolius* was partitioned into *n*-hexane, ethyl acetate, *n*-butanol, and water-soluble fractions. The inhibitory effect of these fractions were tested *in vitro* using PTP1B enzyme assay. Obtained results showed that the *n*-hexane fraction exhibited the most inhibitory effect against enzyme activity (Table 1). Therefore, this fraction was selected for further studies. Repeated column chromatography of the *n*-hexane fraction resulted in the isolation of four known compounds (**1**–**4**) (Figure 1).

Compound **1** was isolated as a white powder. The electrospray impact ionization mass spectrometry (ESI-MS) showed the pseudo-molecular ion $[M + H]^+$ at *m/z* 441.4 suggesting the molecular formula $C_{30}H_{48}O_2$. The ^{1}H-NMR spectrum of **1** revealed seven methyl groups [δ_H 0.98 (3H, s, H-23), 0.77 (3H, s, H-24), 0.78 (3H, s, H-25), 0.92 (3H, s, H-26), 1.08 (3H, s, H-27), 0.89 (3H, d, H-29) and 0.97 (3H, d, H-30)], an axial oxymethine proton at δ_H 3.21 (1H, dd, H-3), an olefinic proton [δ_H 5.31 (1H, t, H-12), and an aldehyde proton at δ_H 9.32 (1H, d, H-28). Furthermore, the presence of five methines and nine methylene groups were displayed in the ^{1}H-NMR spectrum (Figure 1).

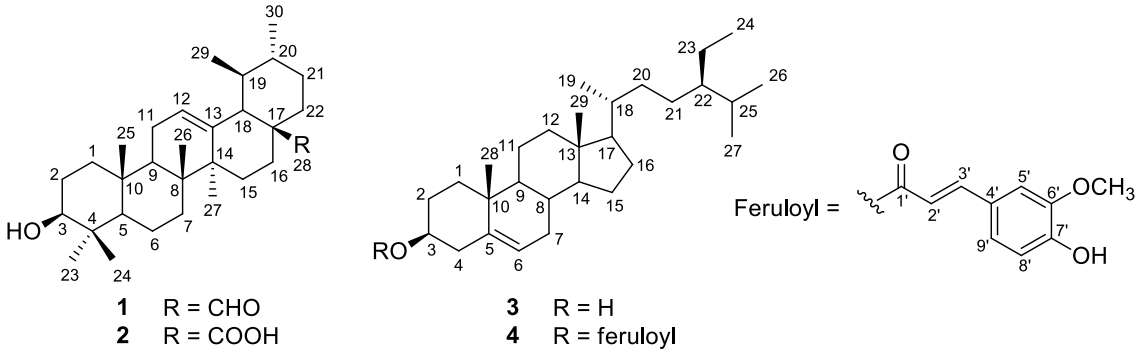

Figure 1. Chemical structure of compounds **1**–**4** isolated from *I. ternifolius*.

The ^{13}C NMR spectrum of **1** exhibited thirty carbon signals, including one aldehyde carbon at δ_C 207.4 (C-28), two olefinic carbons at δ_C 137.8 (C-13) and 126.2 (C-12), an oxymethine carbon at δ_C 79.0, and seven methyl carbons at δ_C 29.7 (C-23), 16.6 (C-24), 15.5 (C-25), 17.2 (C-26), 23.2 (C-27), 15.6 (C-29) and 21.0 (C-30). The other carbon signals were observed and assigned to five methines and nine methylene carbons (Figure 1). The obtained ^{1}H- and ^{13}C-NMR spectral data suggested compound **1** to be an ursane-type triterpene [14, 15]. In the HMBC spectrum, the correlations from H-23 and H-24 to C-3 and C-5, as well as from H-9 to C-2 and H-27 to C-13 confirmed the positions of the oxymethine and olefinic groups (Figure 2). In addition, the HMBC correlations from H-18 to C-28, as well as the HMBC correlation from aldehyde proton H-28 to C-16 and C-22 confirmed the position of the aldehyde group at C-28

(Figure 2). Based on the above evidences in comparison with the published data, compound **1** was identified as ursaldehyde [16].

Compound **2** was obtained as a white powder. The molecular formula of **2** was clarified as $C_{30}H_{48}O_3$ based on the ion at *m/z* 457 $[M + H]^+$ in the ESI-MS spectrum. The ^{1}H- and ^{13}C-NMR spectra of **2** were similar to those of **1** except for the replacement of an aldehyde group [δ_H 9.32 (1H, d, H-28) and δ_C 207.4 (C-28)] in **1** by a carboxyl group [δ_C 181.0 (C-28)] in **2** (Figure 1). It was confirmed by HMBC correlations from H-16, H-18, and H-22 to C-28 (Figure 2). Compared with literature data, compound **2** was determined as ursolic acid [17].

Compound **3** was identified as β-Sitosterol by comparison of co-TLC and data from the literature [18].

Compound **4** was obtained as a white solid. Its molecular formula was determined as $C_{39}H_{58}O_4$ using ESI-MS measurement with $[M + H]^+$ peak at *m/z* 591. The ^{1}H-NMR spectrum of **4** indicated the presence of six methyls [δ_H 1.00 (3H, s, H-19), 0.92 (3H, d, H-29), 0.88 (3H, t, H-24), 0.83 (3H, d, H-26), 0.82 (3H, d, H-27) and 0.68 (3H, s, H-28)], an oxymethine proton at δ_H 351 (1H, m, H-3) and an olefinic proton [δ_H 5.34 (1H, t, H-6)]. Furthermore, the presence of seven methines, eleven methylenes and a feruloyl moiety [δ_H 7.60 (1H, d, J = 16.0 Hz, H-3′), 7.07 (1H, br d, J = 8.5 Hz, H-9′), 7.03 (1H, br s, H-5′), 6.91 (1H, d, J = 8.5 Hz, H-8′), 6.29 (1H, d, J = 16.0 Hz, H-2′) and 3.92 (3H, s, 6′-OCH_3)] were also presented in the ^{1}H NMR spectrum (Figure 1). The ^{13}C-NMR spectrum of **3** exhibited 39 carbon signals, consisting of six methyl carbons, an oxymethine carbon at δ_C 71.8 (C-3), two olefinic carbons [δ_C 140.8 (C-5) and 121.7 (C-6)] and eleven methylene carbon signals (Figure 1). Furthermore, the carbon signals of feruloyl moiety [δ_C 167.3 (C-1′), 115.7 (C-2′), 144.6 (C-3′), 127.1 (C-4′), 109.3 (C-5′), 147.3 (C-6′), 146.8 (C-7′), 114.7 (C-8′), 123.0 (C-9′), 56.1 (6′-OCH_3)] were also indicated in the ^{13}C-NMR spectrum (Figure 1). These above ^{1}H- and ^{13}C-NMR spectral data suggested compound **4** to be a sterol containing a feruloyl moiety in the side chain [19, 20]. In the HMBC spectral data, the correlations from the H-1 to C-3, H-3 and H-28 to C-5, H-4 and H-8 to C-6, as well as from H-6 to C-10 confirmed the positions of the oxymethine and olefinic groups (Figure 2). The correlations from H-19 to C-17 and C-20, as well as the correlation from H-24, H-26, and H-27 to C-22, were observed in the HMBC further confirming compound **4** was to be a sterol (Figure 2). In the feruloyl moiety, the HMBC correlations from H-2′ to C-4′, H-3′ to C-1′ and C-9′, H-5′ to C-3′, as well as from H-8′ and $OC\underline{H}_3$ to C-6′ were also observed (Figure 2). Especially, the HMBC correlations from H-3 to C-1′ confirmed the feruloyl moiety located at C-3 (Figure 2). Base on above information in comparison with literature data [17, 18], compound **4** was determined as β-sitosterol ferulate.

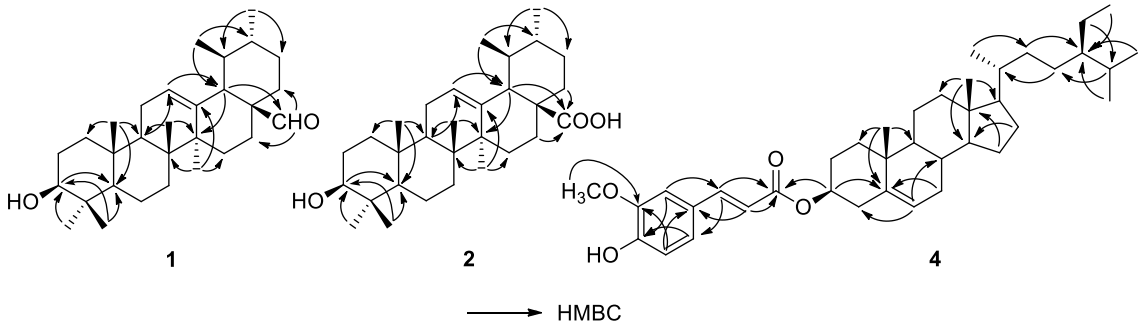

Figure 2. HMBC correlations (H→C) of compounds **1**, **2** and **4**.

PTP1B was confirmed to play an important role in obesity and diabetes diseases through inhibiting the expression of insulin in insulin-resistant states [13, 14]. Therefore, all the isolated compounds (**1**–**4**) were evaluated for inhibitory effect against PTP1B enzyme activity, the results are presented as IC_{50} values (Table 1). In this study, RK-682 was selected as positive control which displayed an IC_{50} value of 4.52 ± 0.25 μM. Among the tested samples, compounds **1** and **2** displayed potential inhibitory activities with IC_{50} values of 16.92 ± 0.12 and 3.42 ± 0.45 μM, respectively. Compounds **3** and **4** showed no activity (IC_{50} value > 50 μM). Ursolic acid (**2**) was previously identified from persimmon as the major constituent and showed potential PTP1B inhibitory activity (IC_{50} value was 3.1 ± 0.2 μM) [21]. In our assay, compound **2** also indicated as the major compound of *I. ternifolius* and showed the similar results of its activity with the value in the published article indicating the reliability of the data obtained. In addition, compound **1** has been identified from this plant for the first time together with its PTP1B inhibitory activity.

Table 1. Results of PTP1B inhibition effect of studied compounds.

Compounds	IC_{50}, μM[a]
1	16.92 ± 0.12
2	3.42 ± 0.45
3	> 50
4	> 50
n-Hexane fraction	63.37 ± 1.42[c]
RK-682[b]	4.52 ± 0.25

[a] Results are expressed as IC_{50} values (μM), determined by regression analysis and expressed as the means ± SD of three replicates; [b] Positive control; [c] % inhibition at a final concentration of 30 μg/mL.

4. CONCLUSIONS

The methanol extract of the whole plant of *I. ternifolius* was partitioned into *n*-hexane-, ethyl acetate-, *n*-butanol soluble fractions, and a water-soluble fractions. Four compounds, ursaldehyde (**1**), ursolic acid (**2**), *β*-sitosterol (**3**), and *β*-sitosteryl ferulate (**4**) were isolated for the first time from the whole plant of *Isodon ternifolius*. The chemical structures of these compounds were clarified using NMR spectroscopy, mass spectra and compare with data from literatures. For the first time, ursaldehyde (**1**) and sitosteryl ferulate (**4**) were isolated from the *Isodon* genus. In addition, ursaldehyde (**1**) and ursolic acid (**2**) showed potent inhibition against PTP1B with IC_{50} values of 16.92 ± 0.12 and 3.42 ± 0.45 μM, respectively. Obtained results suggested that *I. ternifolius* and its major constituents might exert the hypoglycemic effect via the insulin signaling pathway targeting inhibition of PTP1B enzyme activity.

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