New Eremophilane Sesquiterpenes from the Roots of *Ligularia fischeri*

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New eremophilane sesquiterpenes, (3*β*,6*β*,8*α*,10*β*)-3-acetyl-6,8,10-trihydroxyeremophil-7(11)-eno-12,8-lactone (**1**), (3*β*,6*β*,8*β*,10*β*)-3-acetyl-8,10-dihydroxy-6-(2-methyl-1-oxobutoxy) eremophil-7(11)-eno-12,8-lactone (**2**), (3*β*,6*β*,10*β*)- and (3*β*,6*β*,10*α*)-3-acetyl-6,10-dihydroxyeremophila-7(11),8-dieno-12,8-lactone (**3** and **4**, resp.), and a dinoreremophilane derivative, (3a*R*,4*R*,5*S*,7a*S*)-2-acetyl-3a,4,5,6,7,7a-hexahydro-7a-hydroxy-1*H*-inden-5-yl acetate (**5**), were isolated from the roots of *Ligularia fischeri.* Their structures were elucidated by spectroscopic methods including 1D and 2D NMR spectra, and the structure of **1** was further confirmed by a single-crystal X-ray diffraction experiment. Among the isolated compounds, lactone **1** exhibited inhibitory activity towards PTP1B with an IC_{50} value of 1.34 μM *in vivo*. The other compounds were inactive.

Introduction. – Taxonomically, the *Ligularia* genus has been placed in the compositae with *ca.* 100 species distributed within China. *Ligularia* species have long been used as folk remedies with antibiotic, antiphlogistic, and antitumour activities [1]. The most widespread chemical constituents of this genus are sesquiterpenes. A number of sesquiterpenoids, including a few unusual ones from *Ligularia* plants, have been reported in recent years [2–6]. *Ligularia fischeri,* which is common in southwestern China, has been used as a traditional Chinese medicine since ancient times for the treatment of coughs and inflammations, jaundice, scarlet fever, rheumatoidal arthritis, and hepatic diseases [2–4]. During our search for new natural products, the four new eremophilanolactones **1**–**4** and one new dinoreremophilane derivative **5**[1]) were isolated from the 95% EtOH extracts of this species. Here, we report the isolation and structural elucidation of these compounds.

Results and Discussion. – Compound **1** was obtained as colorless needles and gave a $[M + Na]^+$ peak at *m*/*z* 363 in the ESI-MS. The IR spectrum displayed absorption bands for OH groups (3490 cm^{-1}) and an *α*,*β*-unsaturated *γ*-lactone moiety (1750 and 1710 cm^{-1}) [5–7]. The ^{13}C-NMR spectrum (*Table 1*)[1]) displayed 17 C-atoms including four Me, three CH_2, and three CH groups (two oxygenated), and seven quaternary C-atoms (two ester carbonyl, one oxygenated, one acetal, two olefinic, and one sp^3 hybridized), as assigned by a DEPT experiment. There were some characteristic signals in the downfield region of the ^{13}C- and ^{1}H-NMR spectra (*Table 2*): *δ*(C) 161.3 and 123.2

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

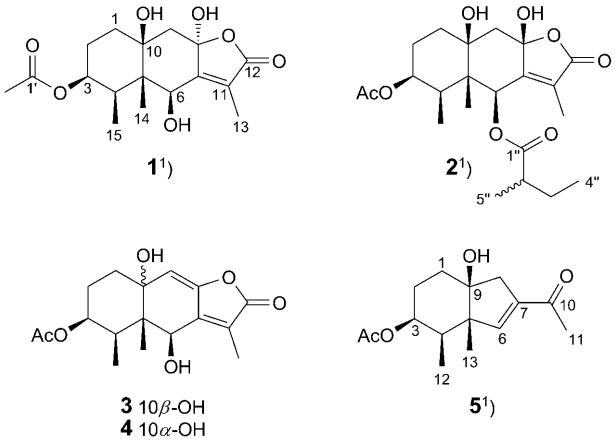

Table 1. *^{13}C-NMR Data* (150 MHz) *of Compounds* **1**–**5**[a])[1]). δ in ppm.

	1[b])	**2**[c])	**3**[b])	**4**[c])	**5**[c])
C(1)	34.1	30.0	30.7	35.5	28.1
C(2)	21.9	27.2	27.3	21.0	27.0
C(3)	71.7	72.5	73.2	71.7	72.6
C(4)	34.9	36.5	36.6	34.8	41.6
C(5)	50.9	47.2	44.3	51.1	55.2
C(6)	69.1	71.0	67.5	68.3	152.3
C(7)	161.3	151.3	148.4	150.4	141.5
C(8)	102.2	103.1	147.8	146.1	41.6
C(9)	48.2	43.4	112.4	115.1	81.2
C(10)	71.8	74.1	74.3	73.2	197.2
C(11)	123.2	129.0	123.8	122.7	26.2
C(12)	172.2	170.3	170.9	171.4	13.0
C(13)	8.9	8.7	9.3	8.6	13.3
C(14)	13.3	12.6	13.2	14.4	
C(15)	10.2	12.6	12.4	10.3	
C(1′)	170.2	170.1	170.2	170.3	170.5
C(2′)	21.7	21.2	21.4	21.6	21.0
C(1″)		175.6			
C(2″)		41.4			
C(3″)		26.4			
C(4″)		11.5			
C(5″)		16.2			

[a]) Assignments are based on HSQC and HMBC experiments and comparison with literature data. [b]) In (D_6)DMSO. [c]) In $CDCl_3$.

of a C=C bond, δ(C) 172.2 of a C=O group of an α,β-unsaturated γ-lactone, δ(C) 71.7 and 69.1 and δ(H) 4.98 (*dt*, $J = 12.7, 4.3$ Hz, 1 H) and 4.68 (br. *d*, $J = 4.2$ Hz, 1 H) of two CH–O groups, δ(C) 71.8 of an O-bonded quaternary C-atom, and δ(C) 102.2 of a

Table 2. *^{1}H-NMR Data* (600 MHz) *of Compounds* **1**–**5**[a])[1]). δ in ppm, J in Hz.

	1[b])	**2**[c])	**3**[b])	**4**[b])	**5**[c])
CH_2(1)	1.96–2.01 (*m*), 1.49 (*dt*, *J* = 8.1, 4.0)	2.01–2.03 (*m*), 1.40–1.45 (*m*)	1.40–1.43 (*m*), 1.90–1.92 (*m*)	1.76 (br. *d*, *J* = 7), 1.54–1.56 (*m*)	1.73–1.78 (*m*)
CH_2(2)	1.87–1.88 (*m*), 1.42(*dt*, *J* = 11.7, 3.2)	1.80–1.82 (*m*), 1.62 (*ddt*, *J* = 4.1, 15, 15)	1.40–1.43 (*m*), 1.62–1.63 (*m*)	1.45–1.49 (*m*), 1.83 (br. *d*, *J* = 12)	1.63–1.65 (*m*), 1.93–1.98 (*m*)
H–C(3)	4.98 (*t*, *J* = 12.7, 4.3)	4.92 (*d*, *J* = 1.9)	4.69 (br. *s*)	5.06–5.08 (*m*)	4.89 (*ddd*, *J* = 3.0, 3.0, 3.0)
H–C(4)	1.75 (br. *s*)	1.38–1.40 (*m*)	1.40–1.43 (*m*)	2.35 (*t*, *J* = 6)	1.53 (*dq*, *J* = 3.0, 7.0)
H–C(6)	4.68 (br. *d*, *J* = 4.2)	5.67 (br. *s*)	4.55 (*d*, *J* = 5)	4.91 (*d*, *J* = 6)	6.62 (*d*, *J* = 1.8)
CH_2(8)					2.85 (*dd*, *J* = 16.8, 1.8), 2.55 (*d*, *J* = 16.8)
CH_2(9) or H–C(9)	2.31–2.39 (*m*)	2.29 (br. *s*)	5.65 (*s*)	5.41 (*s*)	
Me(11)					2.31 (*s*)
Me(12)					1.01 (*d*, *J* = 7.0)
Me(13)	1.88 (*d*, *J* = 1.2)	1.97 (*s*)	1.89 (*s*)	1.94 (*s*)	1.21 (*s*)
Me(14)	0.99 (*s*)	1.33 (*s*)	1.29 (*s*)	0.82 (*s*)	
Me(15)	1.08 (*d*, *J* = 7.3)	0.98 (*d*, *J* = 7.0)	0.77 (*d*, *J* = 6)	1.07 (*d*, *J* = 6)	
Me(2′)	2.01 (*s*)	2.08 (*s*)	1.99 (*s*)	2.01 (*s*)	2.10 (*s*)
H–C(2″)		2.40 (*dd*, *J* = 7.0, 13.9)			
CH_2(3″)		1.47–1.49 (*m*), 1.68–1.70 (*m*)			
Me(4″)		0.91 (*t*, *J* = 7.0)			
Me(5″)		1.18 (*d*, *J* = 7.0)			

[a]) Assignments are based on HSQC and HMBC experiments and comparison with literature data. [b]) In (D_6)DMSO. [c]) In $CDCl_3$.

O–C–O quaternary C-atom; δ(C) 170.2 and 21.7 and δ(H) 2.01 (*s*, 3 H) indicated the presence of an acetyl group. Based on the above spectral data, compound **1** was considered to be an α,β-unsaturated γ-lactone sesquiterpene with an acetyl group and three OH groups. The ^{1}H- and ^{13}C-NMR spectra of **1** were close to those of eremophilenolactones isolated from *Cacalia roborowskii* [8], indicating the same skeleton for **1** and these compounds. The Me *s* at δ(H) 0.99 (Me(14)) appeared upfield from the Me *d* at δ(H) 1.08 (J = 7.3 Hz, Me(15)), which indicated that the *A*/*B* rings are *cis*-fused in **1**, and OH–C(8) is in α configuration, as suggested by comparison with published data [8][9]. The β configuration of OH–C(10) of **1** was confirmed by means of single-crystal X-ray diffraction studies (*Fig. 1*). Thus, compound **1** was determined to be (3β,6β,8α,10β)-3-acetyl-6,8,10-trihydroxyeremophil-7(11)-eno-12,8-lactone[1]).

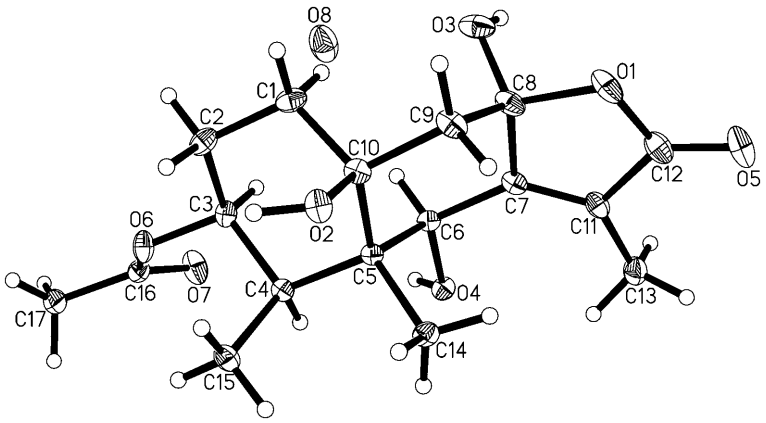

Fig. 1. X-*Ray crystal structure of compound* **1**

Compound **2** was obtained as colorless gum and exhibited a molecular-ion [M + Na]$^+$ peak at m/z 447 in the ESI-MS, corresponding to the molecular formula $C_{22}H_{32}O_8$. Its NMR (*Tables 1* and *2*) and IR spectra were very close to the ones of (3β,6β,8β,10β)-3-acetyl-8,10-dihydroxy-6-methoxyeremophilenolactone [7], except for the presence of a 2-methylbutanoyloxy group instead of the Me group at C(6), leading to the observed upfield shift of C(6) in **2**. This revealed that compound **2** possesses the same molecular C-skeleton as (3β,6β,8β,10β)-3-acetyl-8,10-dihydroxy-6-methoxyeremophilenolactone. The resonances at δ(H) 2.40 (*dd*, J = 13.9, 7.0 Hz, H–C(2″)), 1.47–1.49 and 1.68–1.70 (*m*, CH_2(3″)), 0.91 (*t*, J = 7.0 Hz, Me(4″)), and 1.18 (*d*, J = 7.0 Hz, Me(5″)) in the ^{1}H-NMR spectrum of **2** and at δ(C) 175.6 (C(1″)), 41.4 (C(2″)), 26.4 (C(3″)), 11.5 (C(4″)), and 16.2 (C(5″)) in the ^{13}C-NMR spectrum established the presence of a 2-methylbutanoyl group [7]. The other substructures assembled into a structure were also unambiguously assigned by HMBC data (*Fig. 2*). The relative configuration of **2** could be determined on the basis of key NOESY correlations (*Fig. 2*). Hence, compound **2** was determined as (3β,6β,8β,10β)-3-acetyl-8,10-dihydroxy-6-(2-methyl-1-oxo-butoxy)eremophil-7(10)-eno-12,8-lactone[1]).

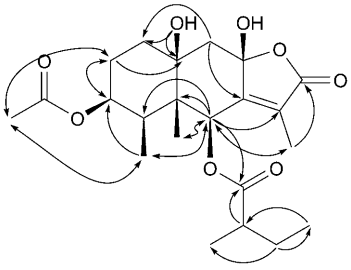

Fig. 2. *Key HMBC* (H → C) *and NOESY correlations* (↔) *of compound* **2**

Compounds **3** and **4** were obtained as a *ca.* 1:1 mixture (by ^{1}H- and ^{13}C-NMR), as a white amorphous powder. They exhibited a $[2M+Na]^+$ peak at *m/z* 667 and a $[M-H]^-$ peak at *m/z* 321 in the ESI-MS. Compounds **3** and **4** shared similar ^{1}H- and ^{13}C-NMR spectral patterns with those of **1**, though additional signals and noticeable chemical-shift differences suggested the presence of a slightly different functionality. The relative molecular mass of **3**/**4** was 18 mass units less than that of **1**, indicating the loss of a molecule of H_2O from **1**. The presence of two olefinic H-atom resonances in the ^{1}H-NMR spectrum of **3**/**4** in addition to a downfield shift of the C(8) signal (δ(C) 147.8 and 146.1) suggested a change in ring *B*. In the HMBC experiment, the following long-range correlations were observed: H–C(9) (δ(H) 5.65)/C(8) (δ(C) 147.8), C(7) (δ(C) 148.4), and C(5) (δ(C) 44.3) for **3**, and H–C(9) (δ(H) 5.41)/C(8) (δ(C) 146.1), C(7) (δ(C) 150.4), and C(5) (δ(C) 51.1) for **4**. Thus, the C=C bond was between C(8) and C(9). The ^{1}H- and ^{13}C-NMR spectra of **3** and **4** (*Tables 2* and *1*) were close to those of tsoongianolide A and B [8][10]. The major differences in the ^{1}H-NMR spectra of **3** and **4** were the signals of Me(14) (δ(H) 1.29 for **3** and 0.82 for **4**) and H–C(4) (δ(H)1.40–1.43 for **3** and 2.35 for **4**), indicating that the OH–C(10) group was α-configured in **4** but β-configured in **3**. The NOESY cross-peaks observed between Me(2′) and H–C(4), H–C(2), and Me(15) implied that the acetyloxy group is located at C(3). According to the above data, compounds **3** and **4** were identified to be (3β,6β,10β)- and (3β,6β,10α)-3-acetyl-6,10-dihydroxyeremophila-7(11),8-dieno-12,8-lactone[1]) (**3** and **4**, resp.)

Compound **5** was isolated as a colorless gum and showed a molecular-ion peak at *m/z* 289 ($[M+Na]^+$) in the ESI-MS. The IR spectrum displayed absorption bands for an OH group (3420 cm^{-1}), an ester C=O group (1737 cm^{-1}), and an α,β-unsaturated ketone moiety (1650 cm^{-1}) [11][12]. The ^{1}H- (*Table 2*) and ^{13}C-NMR spectra (*Table 1*) showed signals of two tertiary Me groups (δ(H) 1.21 (*s*, Me(13)), δ(C) 13.3 (C(13)); δ(H) 2.31 (*s*, Me(11)), δ(C) 26.2 (C(11))), a secondary Me group (δ(H) 1.01 (*d*, J = 7.0 Hz, Me(12)), δ(C) 13.0 (C(12))), a CH_2 group (δ(H) 2.85 (*dd*, J = 16.8, 1.8 Hz, H_a–C(8)) and 2.55 (*d*, J = 16.8 Hz, H_b–C(8)), δ(C) 41.6 (C(8))), an acetyl group (δ(H) 2.10 (*s*, Me(2′)), δ(C) 21.0 and 170.5 (AcO)), an α,β-unsaturated ketone (δ(H) 6.62 (*d*, J = 1.8 Hz, H–C(6)), δ(C) 152.3 (C(6)), 141.5 (C(7)), and 197.2 (C(10))), and a CH–O group (δ(H) 4.89 (*ddd*, J = 3.0, 3.0, 3.0 Hz, H–C(3)), δ(C) 72.6 (C(3))). The coupling pattern and constants for H–C(3) implied that AcO–C(3) is in a β-configuration. These spectral data suggested that compound **5** is a dinorsesquiterpene [12][13]. The ^{1}H,^{1}H-COSY, HMBC, and HSQC data allowed to deduce, the constitu-

tional formula of **5**. The relative configuration was determined by the NOESY data, *i.e.*, by the NOEs H–C(4)/H_a–C(8), H–C(6)/Me(12) and H_a–C(8), H–C(6)/Me(13), and Me(12)/Me(13) (*Fig. 3*). On the basis of the above data, compound **5** was determined as *rel*-(3a*R*,4*R*,5*S*,7a*S*)-2-acetyl-3a,4,5,6,7,7a-hexahydro-7a-hydroxy-1*H*-inden-5-yl acetate.

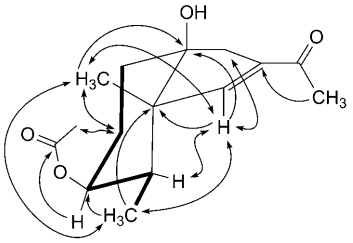

Fig. 3. *Key* $^1H,^1H$ *COSY* (—), *HMBC* (H → C), *and NOESY correlations* (↔) *of compound* **5**

The isolated compounds **1**–**5** were evaluated for their inhibitory activity against protein tyrosine phosphatase (PTP1B) *in vivo*. Compound **1** exhibited moderate inhibitory activity with $IC_{50} = 1.34$ μM. Compounds **2** and **5** and the mixture of **3**/**4** were inactive.

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Experimental Part

General. Column chromatography (CC): commercial silica gel (200–300 mesh; *Qingdao Haiyang Chemical Group Co.*). Optical rotation: *Perkin-Elmer 341* polarimeter. IR Spectra: *Perkin-Elmer* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker Avance-600* spectrometer; at 600 MHz for ^1H and 150 MHz for ^{13}C; δ in ppm rel. to Me_4Si, *J* in Hz. ESI-MS: *Finnigan LCQDECA* spectrometers; in *m*/*z*.

Plant Material. The roots of *Ligularia fischeri* were purchased from the Hehuachi Chinese Traditional Medicine Market (Chengdu, P. R. China). The plant material was identified by Prof. *X. F. Gao* at the Chengdu Institute of Biology, Chinese Academy of Sciences. A voucher specimen (CDLR 061008) was deposited with the Research Center for Natural Products, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, P. R. China.

Extraction and Isolation. The air-dried roots of *L. fischeri* (10.0 kg) were powdered and extracted at r.t. with 95% EtOH three times successively (each time 25 l for 7 days). The extracts were concentrated under vacuum until most of the solvents were removed to obtain a residue (360 g), which was subjected to CC (silica gel (200–300 mesh, 2000 g), 10.0 × 18.0 cm column, acetone/petroleum ether 0 → 100%): *Fractions 1–12* (by TLC). *Fr. 7* (6 g) was further fractionated by repeated CC (silica gel, petroleum ether/acetone 30:1 → 1:1 or petroleum ether/AcOEt 15:1 → 1:1): **2** (30 mg). *Fr. 8* (9 g) was further fractionated by CC (silica gel (180 g), petroleum ether/acetone 15:1 → 1:1): *Fr. 8a–8f*). *Fr. 8d* (1.5 g) was further fractionated by CC (silica gel (18 g), petroleum ether/AcOEt 10:1 → 1:1), and then purified by prep. TLC (petroleum ether/acetone 6:1; twice): pure **5** (9 mg). *Fr. 8e* (2.0 g) was further fractionated by repeated CC (silica gel, petroleum ether/acetone 10:1 → 1:1): **3**/**4** (20 mg). *Fr. 10* (7 g) was further fractionated by repeated CC (silica gel, petroleum ether/acetone 15:1 → 1:1 or petroleum ether/AcOEt 10:1 → 1:1): **1** (28 mg).

(3β,6β,8α,10β)-3-Acetyl-6,8,10-Trihydroxyeremophil-7(11)-eno-12,8-lactone (= *(4*S*,4a*S*,5*R*,6*S*,8a-*S*,9a*R*)-6-(Acetyloxy)-4a,5,6,7,8,8a,9,9a-octahydro-4,8a,9a-trihydroxy-3,4a,5-trimethylnaphtho[2,3-*

b]*furan-2(4*H)*-one*; **1**): Colorless needles (MeOH). $[\alpha]_D^{25} = +12.5$ ($c = 0.40$, MeOH). IR (KBr): 3490, 3321, 1750, 1710, 1388, 1262, 1197, 1027, 996, 958, 753. ^{1}H- and ^{13}C-NMR: *Tables 2* and *1*. ESI-MS (pos.): 363 ($[M+Na]^+$).

(3β,6β,8β,10β)-3-Acetyl-8,10-dihydroxy-6-(2-methyl-1-oxobutoxy)eremophil-7(11)-eno-12,8-lactone (= *(4*S*,4a*S*,5*R*,6*S*,8a*S*,9a*S*)-6-(Acetyloxy)-2,4,4a,5,6,7,8,8a,9,9a-decahydro-8a,9a-dihydroxy-3,4a,5-trimethylnaphtho[2,3-*b*]furan-4-yl 2-Methylbutanoate*; **2**): Colorless gum. $[\alpha]_D^{25} = -8.8$ ($c = 0.34$, MeOH). IR (KBr): 3788, 3571, 3406, 2927, 2373, 2358, 1760, 1637, 1458, 1235, 1158, 1035, 668. ^{1}H- and ^{13}C-NMR: *Tables 2* and *1*. ESI-MS (pos.): 447 ($[M+Na]^+$).

(3β,6β,10β)- and (3β,6β,10α)-3-Acetyl-6,10-dihydroxyeremophila-7(11),8-dieno-12,8-lactone (= *(4*S*,4a*S*,5*R*,6*S*,8a*S*)- and (4*S*,4a*S*,5*R*,6*S*,8a*R*)-6-(Acetyloxy)-4a,5,6,7,8,8a-hexahydro-4,8a-dihydroxy-3,4a,5-trimethyl(naphtho[2,3-*b*]furan-2(4*H*)-one*; **3** and **4**, resp.): Colorless powder. $[\alpha]_D^{25} = +88.2$ ($c =$ 0.34, MeOH). IR (KBr): 3360, 1748, 1714, 1391, 1055. ^{1}H- and ^{13}C-NMR: *Tables 2* and *1*. ESI-MS (pos.): 667 ($[2M+Na]^+$). ESI-MS (neg.): 321 ($[M-H]^-$).

rel-*(3a*R*,4*R*,5*S*,7a*S*)-2-Acetyl-3a,4,5,6,7,7a-hexahydro-7a-hydroxy-1*H*-inden-5-yl Acetate* (= rel-*1-[(3a*R*,4*R*,5*S*,7a*S*)-5-(Acetyloxy)-3a,4,5,6,7,7a-hexahydro-7a-hydroxy-3a,4-dimethyl-1*H*-inden-2-yl]ethanone*; **5**): Colorless gum. $[\alpha]_D^{25} = +38.5$ ($c = 0.26$, MeOH). IR (KBr): 3420, 1737, 1650, 1375, 1252. ^{1}H- and ^{13}C NMR: *Tables 2* and *1*. ESI-MS (pos.): 289 ($[M+Na]^+$).

X-Ray Crystallographic Data for **1**. $C_{17}H_{24}O_7 \cdot 0.14\ H_2O$, $M_r + 0.14\ H_2O$ 342.80, orthorhombic, $P2_12_12_1$, *a* 6.6237(3) Å, *b* 13.1393(7) Å, *c* 19.5176(8) Å, *V* 1698.63(14) Å^3; *Z* 4, $D_{calc.}$ 1.340 Mg m^{-3}, *F*(000) 733, λ(MoK_α) 0.71073 Å, *T* 293(2) K, 16707 reflections collected. Final g.o.f. 1.002, final *R* indices R_1 0.0389, wR_2 0.1095, 243 parameters, μ 0.104 mm^{-1}, *R* indices based on 2246 reflections with $I > 2\sigma(I)$, absorption corrections applied.

Biological Activity. The tests were performed against recombinant PTP/1B protein in *E. coli* with 4-nitrophenyl phosphate (PNPP) as the substrate. The reaction system amounted to 200 μl including PTP/1B (recombinant expression), 100 mM sodium acetate buffer (1 mM EDTA, 0.1% *Triton-X-100*, 15 mM DTT, pH 6.0) and sample. At the same time, two control groups were set up: one was a control soln. (without PTP/1B and sample, the other was the negative control without sample). After 10 min at 37°, the substrate PNPP was added and then, after 1/2 h, 1M NaOH was added to stop the reaction. The *OD* values were then measured at 405 nm. Inhibitory rate = [1 – (*OD* of sample – *OD* of normal)/(*OD* of model – *OD* of normal)] · 100. When the inhibitory rate was more than 70% in a first screening, the sample needed a second screening. IC_{50} Values can be calculated based on the inhibitory rate with the software 4 Parameter Logistic Model.

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