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Novel polycyclic meroterpenoids with protein tyrosine phosphatase 1B inhibitory activity isolated from desert-derived fungi *Talaromyces* sp. HMT-8

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Abstract

Seven previously undescribed polycyclic meroterpenoids talarines K–Q (**1–7**), along with five known ones (**8–12**), were isolated from desert-derived fungi *Talaromyces* sp. HMT-8. The structure of the novel compounds were elucidated using spectroscopic methods, including electronic circular dichroism (ECD), HRESIMS and nuclear magnetic resonance (NMR) spectroscopy. Among the isolated meroterpenoids, compounds **3**, **5**, and **7** exhibited rare chlorine substitution patterns. Halogenation, particularly chlorination, is uncommon in natural meroterpenoids and implies the involvement of halogenase enzymes during biosynthesis. Compounds **1–12** were evaluated for their inhibitory activity against protein tyrosine phosphatase 1B (PTP1B). Compounds **1–4** and **12** exhibited inhibitory activity against PTP1B with IC₅₀ values ranging from 1.74 to 17.60 μM. Among them, compounds **2** and **12** displayed significant inhibitory effects with an IC₅₀ value of 1.74 and 3.03 μM, respectively. Furthermore, Molecular docking analysis revealed that compounds **2** and **12** bind tightly to the catalytic site of PTP1B, forming key hydrogen bonding and hydrophobic interactions. Enzyme kinetics studies further demonstrated that both compounds act as competitive inhibitor.

Keywords *Talaromyces* sp., Polycyclic meroterpenoids, PTP1B, Enzyme kinetics, Molecular docking

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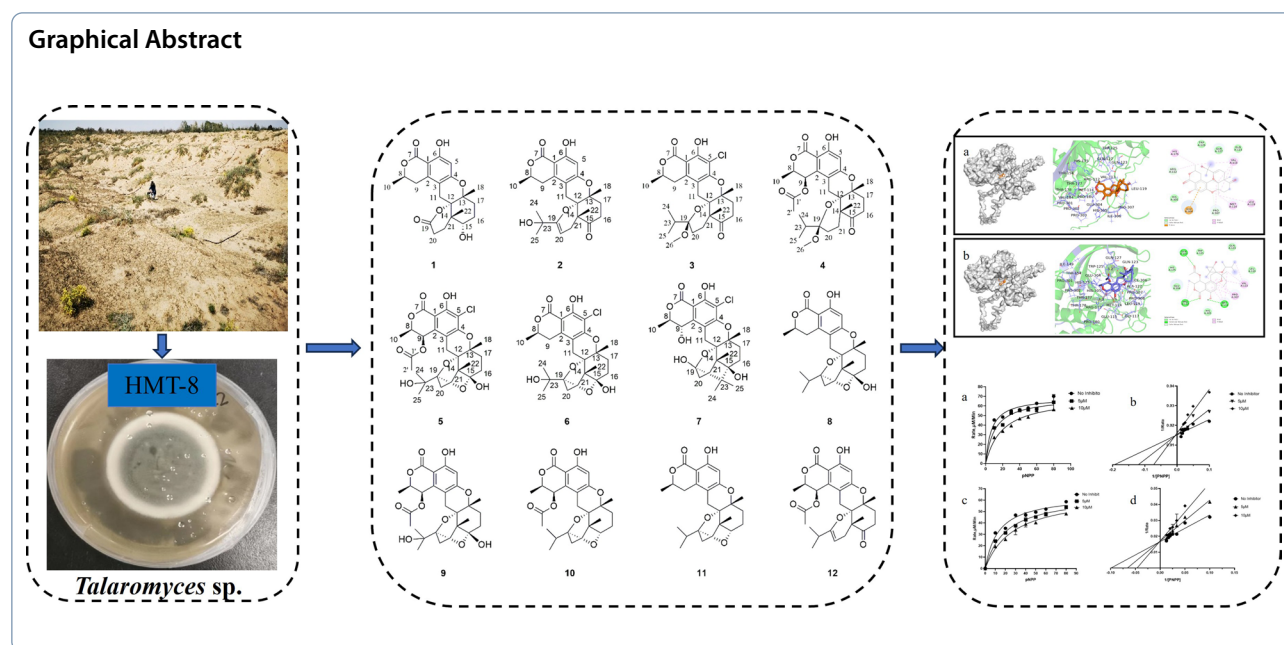
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Graphical Abstract



1 Introduction

The meroterpenoids are a highly diverse class of natural products. They are hybrid natural products, partially derived from the terpenoid biosynthetic pathway, exhibiting diverse core structures, among which some feature a C3-oxidized drimane skeleton [1, 6]. Recently, meroterpenoids have attracted attention due to their rich chemical diversity and biological activities. In the past decade, only 26 methoxysteroids, constructed from drimane-type sesquiterpenoid units and C10 polyketide moieties, have been reported [2–7]. Previous studies have indicated that *Talaromyces* sp. could produce secondary metabolites such as meroterpenoids, polyketides and furanosteroids with novel chemical structures. The meroterpenoids isolated from *Talaromyces* sp. contain polycyclic skeletons and exhibit significant in vitro enzyme inhibitory and antiviral activities [8, 9] (Figs. 1, 2, 3, 4, 5, 6).

Protein tyrosine phosphatase-1B (PTP1B) is a member of the protein tyrosine phosphatase (PTP) family and is localized in the endoplasmic reticulum of cells in tissues such as adipose and liver [10]. PTP1B plays an essential role across various physiological pathways, including cell proliferation, apoptosis, and differentiation [11]. The PTP1B functions by dephosphorylating insulin and leptin receptors, thereby inducing their inactivation [12, 13]. Inhibitors targeting this enzyme hold therapeutic promise for managing type 2 diabetes and obesity. Therefore, bioactive compounds with PTP1B inhibitory activity may exhibit enhanced therapeutic efficacy in the treatment of type 2 diabetes.

Finding bioactive compounds from natural products has become one of the important ways to develop innovative drugs. The extensive pharmacological activities and structural diversity of fungal natural products have attracted the attention of researchers [14]. We have been dedicated to discovering novel bioactive compounds from fungi. In this work, a desert-derived fungi *Talaromyces* sp. HMT-8 was isolated from soil collected in Alashan region in the west of Inner Mongolia Autonomous Region of China. The chemical investigation on HMT-8 led to the identification of seven novel polycyclic meroterpenoids talarines K–Q (1–7) and five known ones (8–12). All the isolated compounds were tested for their inhibitory activities against PTP1B. Many of these meroterpenoids exhibited inhibitory activities. This paper reports on the isolation, structural elucidation and PTP1B inhibitory activity of polycyclic meroterpenoids extracted from *Talaromyces* sp. HMT-8.

2 Results and discussion

2.1 Structure elucidation

Compound 1 displayed the molecular formula, $C_{22}H_{26}O_7$, by analysis of its HREIMS data ($[M+H]^+$ m/z 403.1748, calcd for $C_{22}H_{27}O_7$, 403.1757), indicating 10 degrees of unsaturation. The 1H NMR data (Table 2) of 1 showed resonances for one aromatic proton at δ_H 6.24 (1H, s, H-5), two oxygenated methine protons at δ_H 4.66 (1H, m, H-8) and 3.67 (1H, t, $J=3.0$ Hz, H-15), and three methyl groups at δ_H 1.51 (3H, d, $J=6.5$ Hz, H_3 -10), 1.40 (3H, s, H_3 -18), and 1.04 (3H, s, H_3 -22). The ^{13}C NMR data (Table 1) of 1 showed a total of 22 carbon signals,

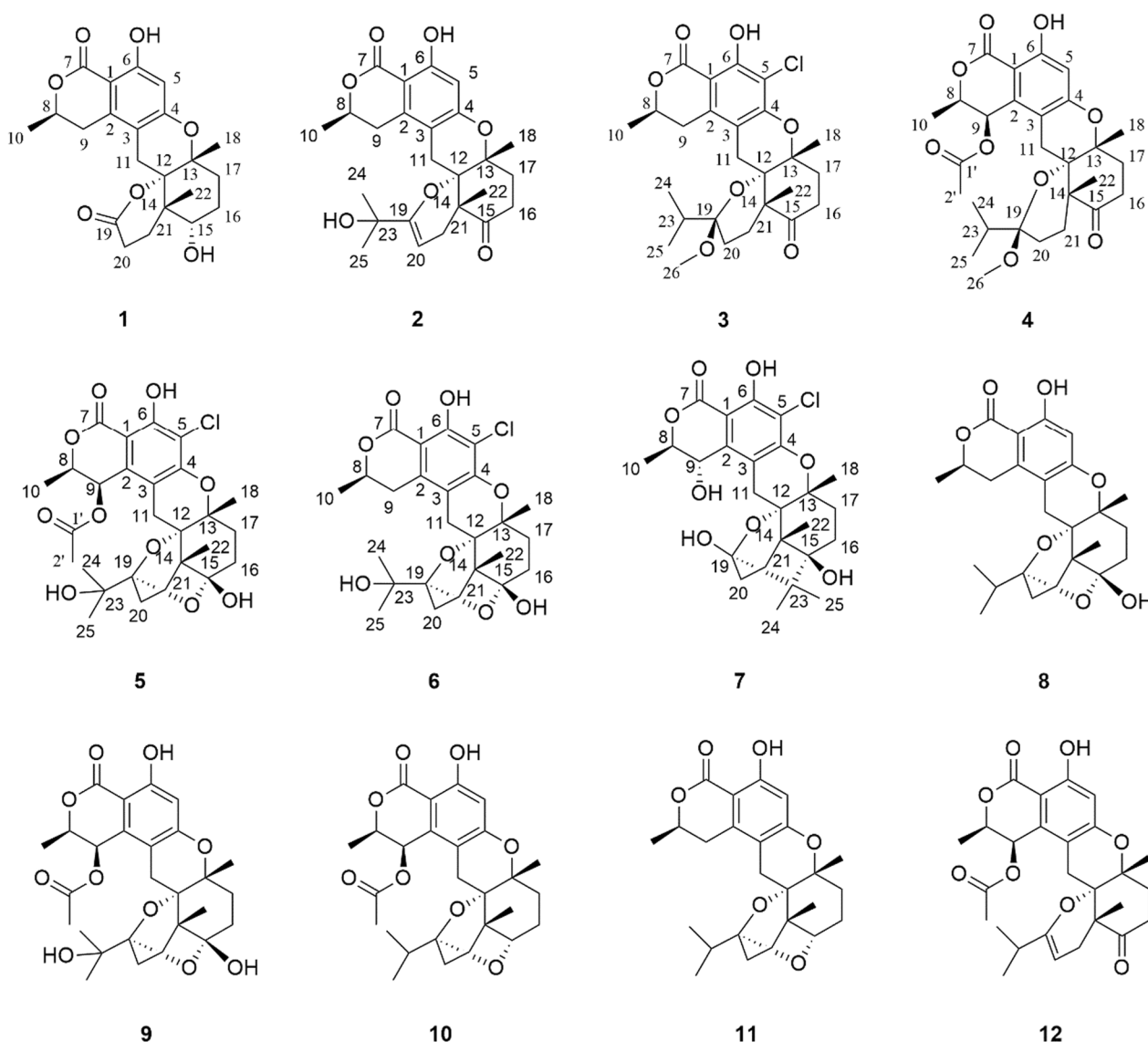


Fig. 1 Chemical structures of 1–12 isolated from HMT-8

including two ester carbonyls at δ_C 176.7 (C-19) and 171.9 (C-7), six aromatic carbons assignable to a benzene ring, six methylenes, two methines (including one oxygenated), three non-protonated carbons (including two oxygenated), and three methyls. The planar structure of **1** was further elucidated by 2D-NMR spectroscopic analysis. The ^1H – ^1H COSY correlations (Fig. 2) of H_3 -10/ H -8/ H -9 together with the HMBC correlations (Fig. 2) from H-9 to C-2, C-3, and C-11, and from H-5 to C-1, C-3, C-4, and C-6 confirmed the presence of the isochromanone moiety. The HMBC correlations from H_2 -11 to C-4, C-12, and C-13, from H_3 -18 to C-13 and C-17, from H_3 -22 to C-12, C-14, C-15, and C-21, and from H_2 -20 to C-19, along with the ^1H – ^1H COSY

correlations of H_2 -17/ H_2 -16/ H -15 and H_2 -10/ H_2 -21 established the remaining nor-sesquiterpene moiety. Therefore, the planar structure of **1** was determined, as depicted in Fig. 1.

The relative configuration of **1** was determined by NOESY experiment. The NOESY cross peaks (Fig. 3) of H_3 -22/ H -16 β (δ_{H} 1.97), H_3 -18/ H -16 β , H_3 -18/ H -11 β (δ_{H} 2.68), H_3 -22/ H -11 β , and H_3 -22/ H -15 indicated that H-15, H_3 -18, and H_3 -22 were β -orientations; simultaneously, C-12 was assigned as S^* -configuration. The absolute configuration at C-8 was proposed as *R* based on the biosynthetic origin [5, 15]. The calculated electronic circular dichroism (ECD) curve (Fig. 4) for compound **1** corresponded well with the experimental

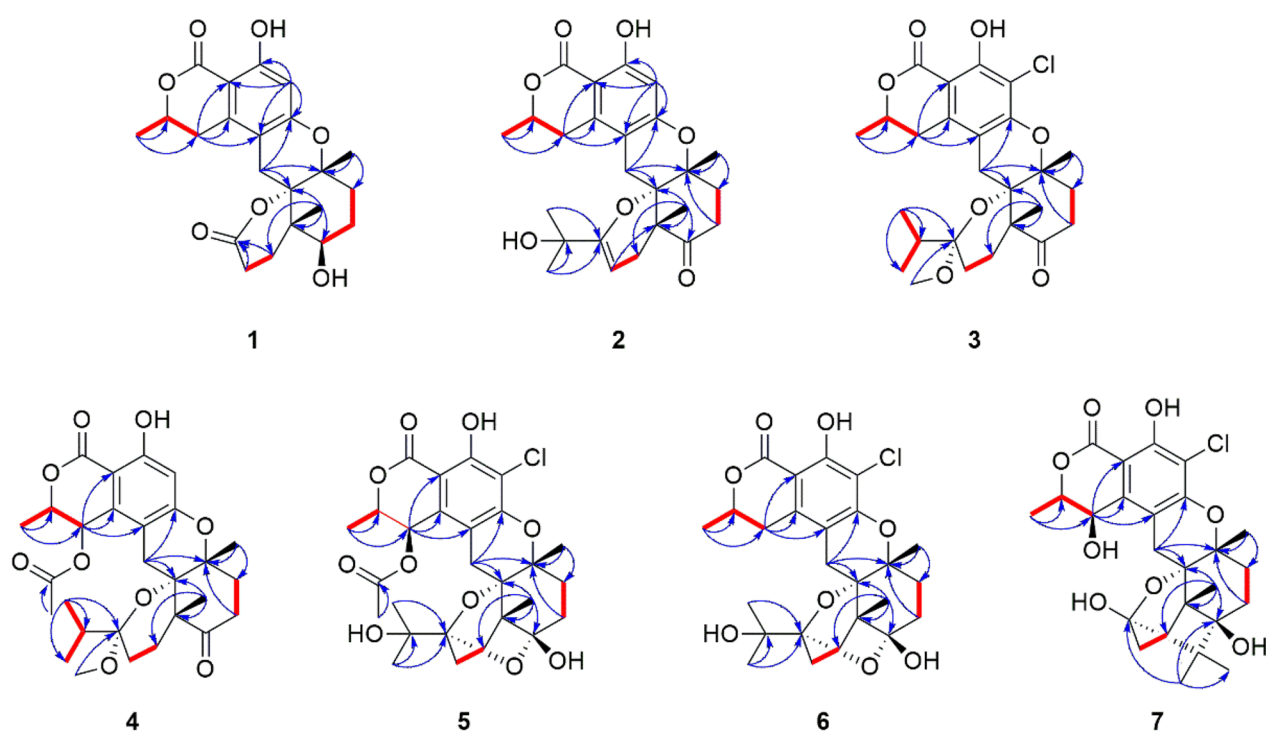


Fig. 2 Key HMBC (blue arrow) and ^1H - ^1H COSY (bold red line) correlations of 1–7

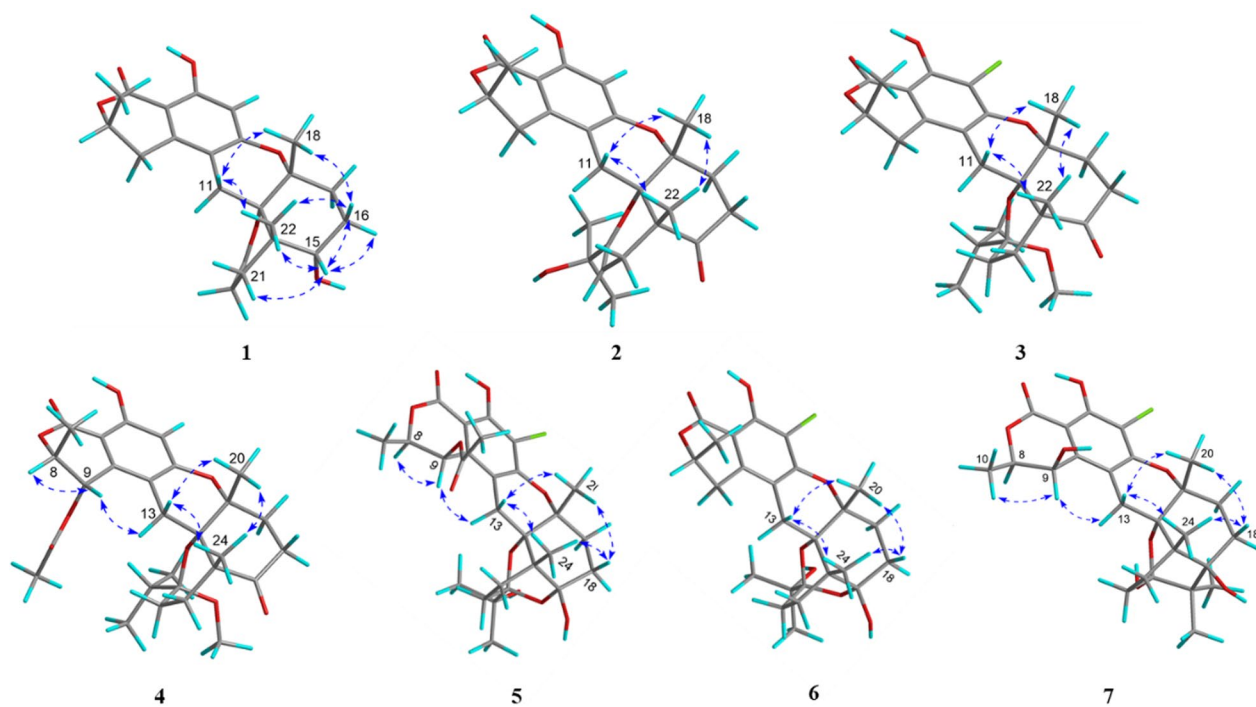


Fig. 3 Key NOESY (double blue arrows) correlations of 1–7

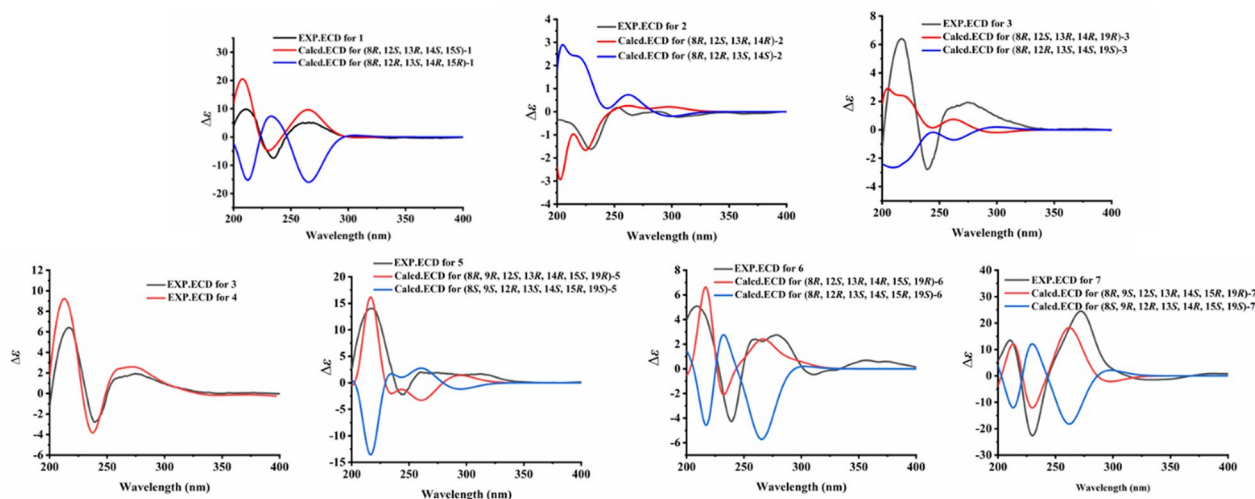


Fig. 4 Comparison of experimental and calculated ECD spectra of 1–7

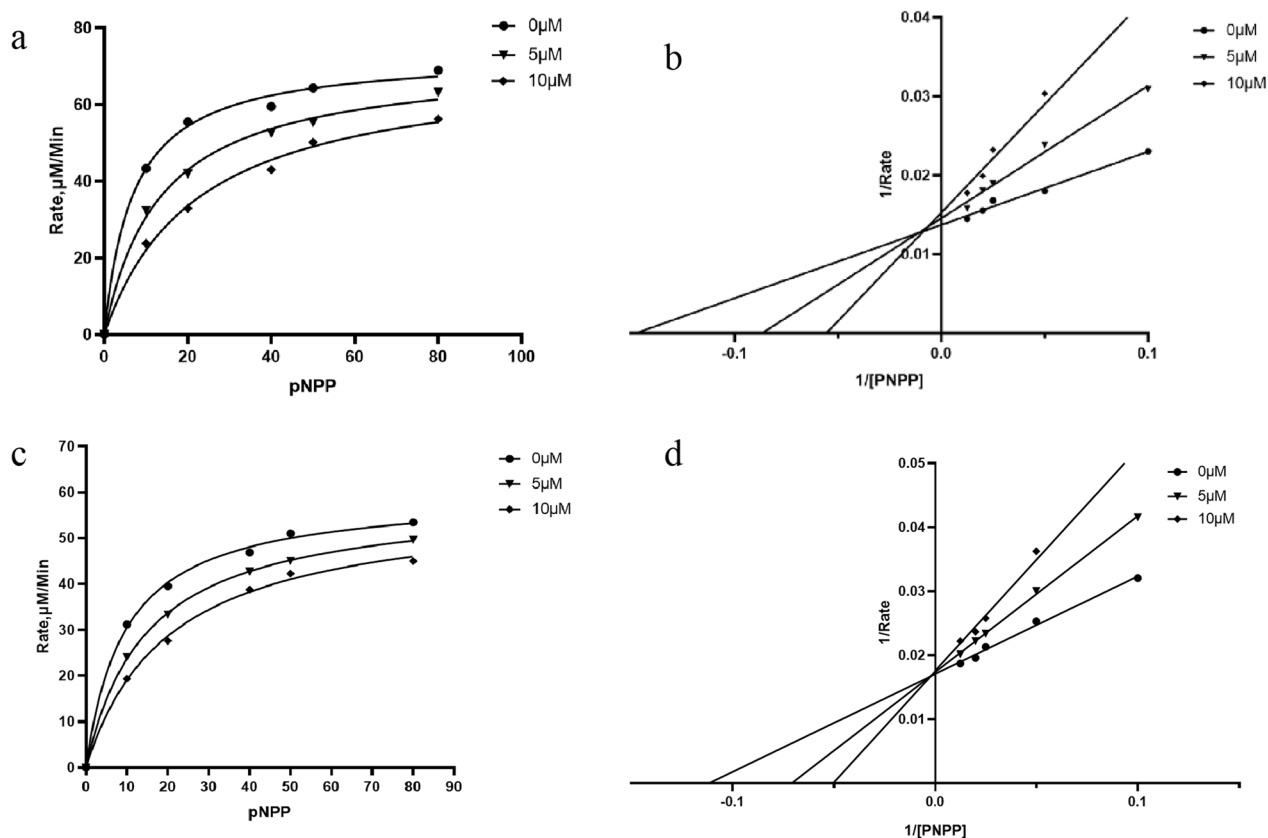


Fig. 5 Kinetic analysis of the inhibition of PTP1B by 2 (a, b) and 12 (c, d)

ECD curve, indicating its absolute configuration as 8*R*,12*S*,13*R*,14*S*,15*S*. Therefore, compound **1** was named talarine K.

Compound **2** possessed a molecular formula $C_{25}H_{30}O_7$, as determined by the HRESIMS data ($[M+H]^+$ m/z

443.2061, calcd for $C_{25}H_{31}O_7$, 443.2070). The 1H NMR spectrum of **2** displayed characteristic signals including one oxygen-bearing methine proton at δ_H 4.57 (1*H*, *m*, H-8), and five distinct methyl signals (four singlets and one doublets). The ^{13}C NMR spectra of **2** showed

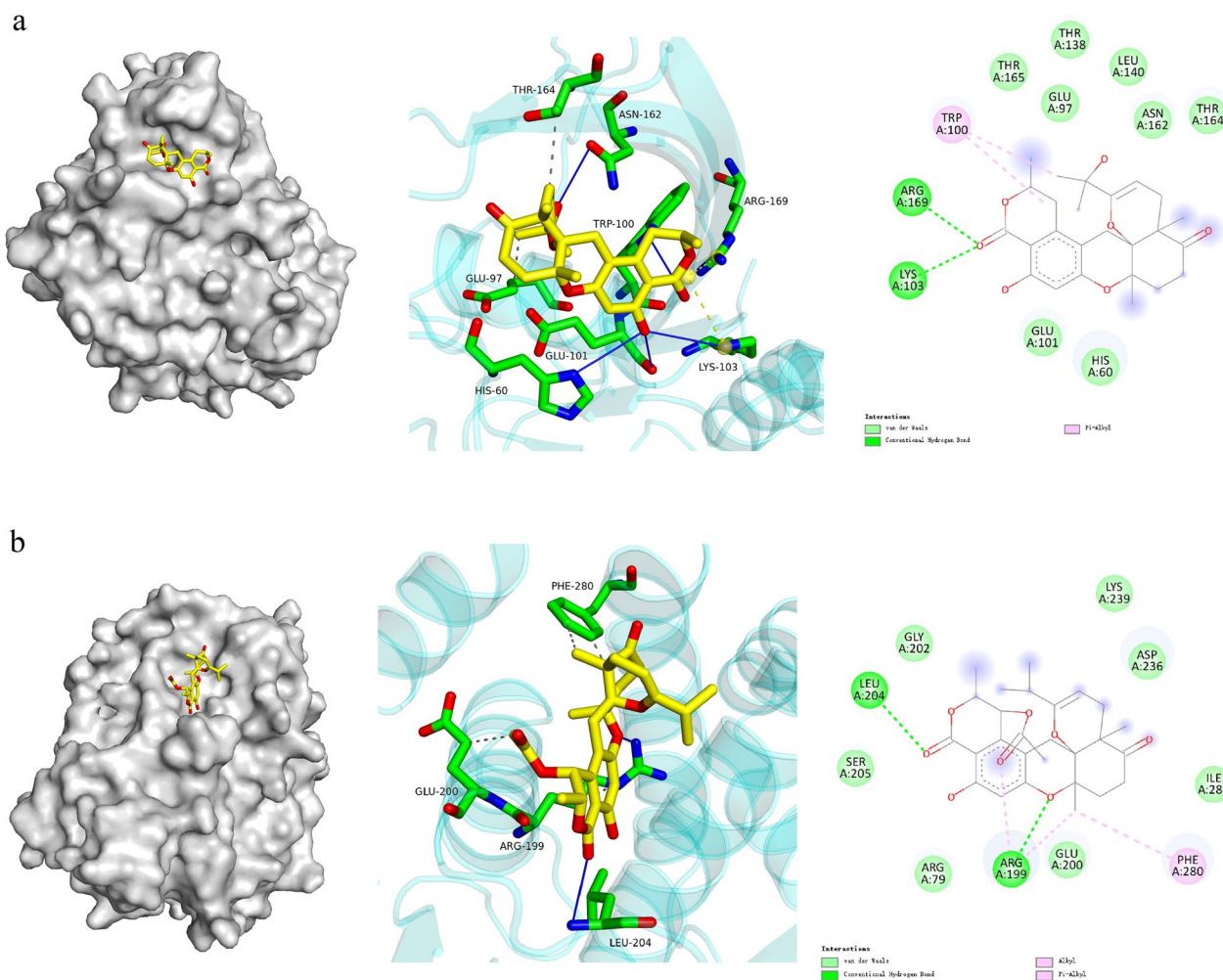


Fig. 6 Molecular docking pictures of compounds 2 (a) and 12 (b)

25 carbon resonances, including two carbonyl carbons (one ester carbonyl at δ_C 171.7 and one keto carbonyl δ_C 211.1), eight olefinic carbons containing a benzene ring, four nonprotonated carbons at δ_C 81.0 (C-12), 79.1 (C-13), 71.5 (C-23), and 50.4 (C-14), five methylenes at δ_C 34.7 (C-16), 34.5 (C-17), 31.9 (C-9), 28.7 (C-21), and 22.6 (C-11), one oxygenated methine at δ_C 76.5 (C-8), and five methyls at δ_C 27.9 (C-25), 27.8 (C-24), 24.3 (C-22), 23.5 (C-18), and 20.9 (C-10). The NMR data (Tables 1 and 2) of 2 closely resembled those of talaromyolide I [6], with the main difference being the presence of an oxygenated non-protonated carbon (C-23) and the absence of an oxygenated methine group (C-9), as supported by the HMBC correlations (Fig. 2) from H₃-25 to C-23 and the ¹H–¹H COSY correlations (Fig. 2) of H₃-10/H-8/H₂-9. The cross-peaks of H₃-18/H₃-22/H-11 β (δ_H 2.84) established the relative configuration of 2. The absolute configuration of compound 2 was determined by comparing its experimental ECD spectrum with the calculated spectra

(Fig. 4), confirming the assignment as 8*R*, 12*S*, 13*R*, 14*R*. Accordingly, it was named talarine L.

Compound 3 was purified as a colorless oil, and its HRESIMS analysis ($[M-H]^-$ m/z 491.1837, calcd for C₂₆H₃₂ClO₇, 491.1843) indicated a molecular formula C₂₆H₃₃ClO₇. The ¹H NMR spectral data (Table 2) of 3 showed one oxygenated methine proton at δ_H 4.72 (1H, m, H-8), five methyl signals (two singlets and three doublets), as well as a methoxyl signal at δ_H 2.57 (3H, s, H₃-26). The ¹³C NMR spectrum (Table 1) revealed the presence of 26 carbon signals, including two carbonyl carbons (one ester carbonyl and one keto carbonyl), six aromatic carbons, one ketal carbon at δ_C 104.4 (C-19), one oxygenated methine at δ_C 76.7 (C-8), six methylenes, three nonprotonated carbons containing two oxygenated at δ_C 81.5 (C-13) and 79.1 (C-12), and six methyls including an oxygenated at δ_C 48.7 (C-26). Detailed analyses of the above NMR data suggested that the structure of 3 was similar to that of 2, with the main difference being

Table 1 The ^{13}C NMR (150 MHz, CD_3OD) spectroscopic data for compounds **1–7**

NO	1	2	3	4	5	6	7
1	102.9, C	102.8, C	103.3, C	103.2, C	103.2, C	103.0, C	102.3, C
2	142.1, C	141.7, C	139.0, C	138.1, C	135.9, C	139.3, C	139.9, C
3	111.4, C	109.7, C	112.6, C	113.5, C	113.2, C	111.8, C	112.8, C
4	161.3, C	161.0, C	156.6, C	161.5, C	157.2, C	156.9, C	157.2, C
5	103.8, CH	103.4, CH	108.5, C	106.1, CH	111.2, C	108.5, C	110.0, C
6	163.3, C	163.5, C	158.7, C	163.3, C	158.8, C	158.7, C	158.6, C
7	171.9, C	171.7, C	171.6, C	170.6, C	170.6, C	171.7, C	171.4, C
8	76.6, CH	76.5, CH	76.7, CH	65.6, CH	77.8, CH	76.8, CH	79.4, CH
9	32.0, CH_2	31.9, CH	31.8, CH_2	77.5, CH	65.4, CH	31.6, CH	63.9, CH
10	21.0, CH_3	20.9, CH_3	21.0, CH_3	16.6, CH_3	16.5, CH_3	20.9, CH_3	16.5, CH_3
11	28.2, CH_2	22.6, CH_2	26.3, CH_2	26.2, CH_2	28.1, CH_2	28.4, CH_2	28.2, CH_2
12	77.1, C	81.0, C	79.1, C	78.9, C	78.5, C	78.8, C	79.4, C
13	81.0, C	79.1, C	81.5, C	80.7, C	81.9, C	81.5, C	82.3, C
14	43.3, C	50.4, C	51.1, C	51.0, C	38.3, C	38.3, C	41.5, C
15	72.9, CH	211.1, C	214.3, C	214.2, C	99.8, C	99.9, C	76.5, C
16	27.2, CH_2	34.7, CH_2	36.0, CH_2	36.1, CH_2	32.1, CH_2	32.1, CH_2	30.4, CH_2
17	28.6, CH_2	34.5, CH_2	32.7, CH_2	32.8, CH_2	32.8, CH_2	32.9, CH_2	35.1, CH_2
18	24.7, CH_3	23.5, CH_3	23.4, CH_3	23.3, CH_3	24.0, CH_3	23.9, CH_3	24.5, CH_3
19	176.7, C	156.6, C	104.4, C	104.4, C	100.5, C	100.5, C	100.9, C
20	29.3, CH_2	93.4, CH	24.8, CH_2	24.7, CH_2	25.3, CH_2	25.4, CH_2	30.8, CH_2
21	29.2, CH_2	28.7, CH_2	26.6, CH_2	26.7, CH_2	23.7, CH_2	23.7, CH_2	26.6, CH_2
22	19.8, CH_3	24.3, CH_3	25.6, CH_3	25.6, CH_3	19.2, CH_3	19.2, CH_3	19.6, CH_3
23		71.5, C	33.5, CH	33.5, CH	74.5, C	74.6, C	48.3, C
24		27.8, CH_3	18.0, CH_3	16.5, CH_3	24.8, CH_3	24.8, CH_3	25.0, CH_3
25		27.9, CH_3	16.5, CH_3	17.9, CH_3	24.6, CH_3	24.5, CH_3	18.7, CH_3
26			48.7, CH_3	49.0, CH_3			
1'				171.7, C	171.8, C		
2'				20.4, CH_3	20.4, CH_3		

the presence of a methoxyl group (C-26), a methine group (C-23), and a methylene group (C-20), coupled with the absence of two olefinic carbons and the singlet H-5 proton signal, as supported by the HMBC correlations (Fig. 2) from H_3 -24 to C-19, C-23, and C-25, and the ^1H – ^1H COSY correlations (Fig. 2) of H_3 -24/ H -23/ H_3 -25, combined with the molecular formula. Finally, the relative configuration of **3** was determined by the cross peaks of H_3 -18/ H -11 β (δ_{H} 2.85)/ H_3 -22. To determine the configuration at C-19, DFT calculations of ^1H and ^{13}C NMR chemical shifts were performed for four possible diastereomers (see SI). Subsequent DP4+ analysis (Fig. S50) revealed that the C-19 stereocenter as *R*. The absolute configuration of **3** was determined from ECD spectrum in comparison to calculated spectra (Fig. 4), confirming the absolute configuration of (8*R*,12*S*,13*R*,14*R*,19*R*)-**3**. Therefore, compound **3** was named talarine M.

Compound **4** had a molecular formula $\text{C}_{28}\text{H}_{36}\text{O}_9$, as disclosed by the HRESIMS spectrum ($[\text{M}+\text{H}]^+$ m/z 517.2438, calcd for $\text{C}_{28}\text{H}_{37}\text{O}_9$, 517.2435). The ^1H NMR

spectral data (Table 2) of **4** showed two oxygen-bearing methine protons at δ_{H} 6.19 (1H, d, $J=2.0$ Hz, H-9) and 4.85–4.79 (1H, m, H-8), an aromatic proton signal at δ_{H} 6.46 (1H, s, H-5), five methyl signals (two singlets and three doublets), as well as a methoxyl signal at δ_{H} 2.59 (3H, s). The ^{13}C NMR spectrum (Table 1) showed a total of 28 carbon signals, including three carbonyl carbons (two ester carbonyls and one keto carbonyl), six aromatic carbons, one ketal carbon at δ_{C} 104.4 (C-19), two oxygen-bearing methines at δ_{C} 77.5 (C-9) and 65.6 (C-8), five methylenes at δ_{C} 36.1 (C-16), 32.8 (C-17), 26.7 (C-21), 26.2 (C-11), and 24.7 (C-20), three nonprotonated carbons containing two oxygenated at δ_{C} 80.7 (C-13) and 78.9 (C-12), and six methyls including an oxygenated at δ_{C} 49.0 (C-26). These ^1H and ^{13}C NMR data closely resembled those of **3**, suggesting that their structures were closely related. The key structural distinction was characterized by the presence of an acetyl group, an oxygenated methine group, and the H-5 singlet proton signal, concomitant with the absence of both a methylene group

Table 2 The ^1H NMR (600 MHz, CD_3OD , J in Hz) spectroscopic data for compounds **1–7**

NO	1	2	3	4	5	6	7
1	–	–	–	–	–	–	–
2	–	–	–	–	–	–	–
3	–	–	–	–	–	–	–
4	–	–	–	–	–	–	–
5	6.24, s	6.29, s	–	6.46, s	–	–	–
6	–	–	–	–	–	–	–
7	–	–	–	–	–	–	–
8	4.66, m	4.57, m	4.72, m	4.85–4.79, m	4.84, m	4.70, m	4.62, qd, (6.7, 1.8)
9	3.07, dd, (16.9, 3.4)	2.97, overlapped	3.11, dd, (17.2, 3.6)	6.19, d, (2.0)	6.25, d, (1.9)	3.14, dd, (16.9, 3.5)	4.70, d, (2.0)
	2.63, m	2.70, overlapped	2.75, dd, (17.0, 11.3)	–	–	2.67, dd, (17.0, 11.3)	–
10	1.51, d, (6.5)	1.50, d, (6.3)	1.55, d, (6.2)	1.47, d, (6.5)	1.45, d, (6.5)	1.52, d, (6.2)	1.57 (3H, d, $J=6.6$ Hz)
11	2.68, m	2.84, d, (17.1)	3.64, d, (16.7)	3.72, d, (17.1)	3.02, d, (16.8)	2.92, d, (16.5)	3.13, d, (16.9)
	–	2.79, d, (17.1)	2.85, d, (16.7)	2.76, d, (17.1)	2.90, d, (16.8)	2.81, d, (16.5)	3.06, d, (16.9)
12	–	–	–	–	–	–	–
13	–	–	–	–	–	–	–
14	–	–	–	–	–	–	–
15	3.67, t, (3.0)	–	–	–	–	–	–
16	1.97, m	2.97, overlapped	2.85, overlapped	2.83, td, (15.0, 6.6)	1.97, overlapped	1.97, overlapped	1.97, overlapped
	1.86, m	2.34, m	2.44, overlapped	2.44–2.38, m	1.77, overlapped	1.77, overlapped	1.81, overlapped
17	2.35, m	2.54, td, (13.6, 5.4)	2.72, overlapped	2.65, td, (13.8, 5.0)	2.57, td, (13.2, 5.1)	2.57, td, (13.0, 5.3)	2.60, m
	1.60, m	2.12, ddd, (12.7, 6.8, 2.1)	2.04, overlapped	1.99–1.93, m	1.77, overlapped	1.77, overlapped	1.82, overlapped
18	1.40, s	1.67, s	1.56, s	1.52, s	1.32, s	1.34, s	1.35, s
19	–	–	–	–	–	–	–
20	2.55, overlapped	4.91, overlapped	1.77, td, (13.7, 5.7)	1.75, td, (13.8, 5.4)	2.03, overlapped	2.02, overlapped	1.97, overlapped
	1.70, m	–	1.37, m	1.42–1.36, m	1.90, overlapped	1.92, overlapped	1.78, overlapped
21	2.55, overlapped	2.66, overlapped	2.00, overlapped	2.06–2.00, m	2.03, overlapped	2.02, overlapped	2.09, m
	2.41, m	1.95, dd, (17.7, 2.2)	1.93, overlapped	1.88, td, (13.7, 4.7)	1.90, overlapped	1.92, overlapped	1.77, overlapped
22	1.04, s	1.32, s	1.26, s	1.19, s	1.08, s	1.13, s	1.02, s
23	–	–	1.97, overlapped	1.98–1.92, m	–	–	–
24	–	1.04, s	0.78, d, (6.7)	0.70, d, (6.9)	1.17, s	1.18, s	1.06, s
25	–	0.67, s	0.70, d, (6.9)	0.76, d, (6.7)	1.12, s	1.13, s	1.19, s
26	–	–	2.57, s	2.59, s	–	–	–
1'	–	–	–	–	–	–	–
2'	–	–	–	2.13, s	2.12, s	–	–

and a non-protonated aromatic carbon in **4**. The HMBC correlations (Fig. 2) from $\text{H}_3\text{-2}'$ to $\text{C-1}'$, and from H-9 to $\text{C-1}'$, as well as the $^1\text{H}\text{--}^1\text{H}$ COSY correlations (Fig. 2) of $\text{H}_3\text{-10/H-8/H-9}$, confirmed that the C-9 methylene group in **3** was replaced by an acetyl group in **4**. Therefore, the planar structure of **4** was assigned, and its relative configuration was determined according to the NOESY correlations (Fig. 3) of $\text{H}_3\text{-18/H-11}\beta$ (δ_{H} 2.78)/ $\text{H}_3\text{-22}$, $\text{H-9/H-11}\alpha$ (δ_{H} 3.72), and H-9/H-8 . A strong NOE correlation is observed between H-9 and H-8 , along with a weak correlation between H-9 and H-10 , implying that H-9 and H-8 reside on the same face of the six-membered ring. The

configuration at C-19 was established by DP4+ probability analysis based on calculated ^1H and ^{13}C NMR chemical shifts of four possible diastereomers, which indicated that structure **4-2** (see SI) best matched the experimental data with 100% probability, supporting the assignment of the C-19 stereocenter as *R*. The similar ECD spectra of indicated that compounds **3** and **4** share absolute configurations, so confirming the absolute configuration of (*8R*, *12S*, *13R*, *14R*, *19R*)-**4**. Therefore, compound **4** was named talarine N.

Compound **5** was isolated as a colorless oil, whose molecular formula was established as $\text{C}_{27}\text{H}_{33}\text{ClO}_{10}$ by

the HRESIMS data ($[M+H]^+$ m/z 553.1841, calcd for $C_{27}H_{34}O_{10}Cl$, 553.1829), bearing one more chlorine substituent than talaromyolide H [7]. The 1H NMR data (Table 2) of **5** showed two oxygen-bearing methine protons at δ_H 6.25 (1H, d, $J=1.9$ Hz, H-9) and 4.84 (1H, m, H-8), one acetyl signal at δ_H 2.12 (3H, s, H-2'), and five methyl signals (four singlets and one doublet). The ^{13}C NMR data of **5** (Table 1) exhibited 27 carbon resonances, including two ester carbonyl carbons at δ_C 171.8 (C-1') and 170.6 (C-7), six aromatic carbons assignable to a benzene ring, two ketal carbons at δ_C 100.5 (C-19) and 99.8 (C-15), two oxygen-bearing methines at δ_C 77.8 (C-8) and 65.4 (C-9), five methylenes at δ_C 32.8 (C-17), 32.1 (C-16), 28.1 (C-11), 25.3 (C-20), and 23.7 (C-21), four nonprotonated carbons including three oxygenated at δ_C 81.9 (C-13), 78.5 (C-12), and 74.5 (C-23), and six methyls at δ_C 24.8 (C-24), 24.6 (C-25), 24.0 (C-18), 20.4 (C-2'), 19.2 (C-22), and 16.5 (C-10). These data suggested that **5** was a polycyclic meroterpenoid possessing a secodrimane unit and an isocoumarin core structure, similar to that of talaromyolide H. The main difference between them lied in the disappearance of the singlet proton signal. HMBC correlations from H-9 to C-1, C-2, and C-3, and from H₂-11 to C-4, C-12, and C-13, along with the 1H - 1H COSY correlations of H₃-10/H-8/H-9 were observed. The above data, with the aid of a molecular formula that showed the presence of a Cl atom, assigned **5** as 5-chlorotalaromyolide H. The relative configuration of **5** was determined to be the same as that of talaromyolide H based on the key NOESY correlations (Fig. 3) of H₃-18/H-11 β (δ_H 2.90), H₃-22/H-11 β , H₃-18/H-16 β (δ_H 1.97), H₃-22/H-16 β , and H-9/H-11 α (δ_H 3.02). A strong NOE between H-9 and H-8, together with a weaker interaction with H-10, indicates that H-9 and H-8 are located on the same face of the six-membered ring. The absolute configuration of compound **5** was determined as 8R, 9R, 12S, 13R, 14R, 15S, 19R through comparative analysis of the experimental ECD spectrum (Fig. 4) with the calculated ECD spectrum. Therefore, compound **5** was named talarine O.

Compound **6**, a colorless oil, exhibited the molecular formula $C_{25}H_{31}ClO_8$ according to the HRESIMS data ($[M+H]^+$ m/z 495.1775, calcd for $C_{25}H_{32}O_8Cl$, 495.1786). The 1H NMR data (Table 2) displayed resonances for one oxygen-bearing methine protons at δ_H 4.70 (1H, m, H-8), and five methyl protons (four singlets and one doublet). The ^{13}C NMR data (Table 1) showed a total of 25 carbon signals, including an ester carbonyl carbon at δ_C 171.7 (C-7), six aromatic carbons at δ_C 158.7 (C-6), 156.9 (C-4), 139.3 (C-2), 111.8 (C-3), 108.5 (C-5), and 103.0 (C-1), two ketal carbons at δ_C 100.5 (C-19) and 99.9 (C-15), one oxygen-bearing methine at δ_C 76.8 (C-8), six methylenes at δ_C 32.9 (C-17), 32.1 (C-16), 31.6 (C-9), 28.4 (C-11), 25.4

(C-20), and 23.7 (C-21), four nonprotonated carbons including three oxygenated at δ_C 81.5 (C-13), 78.8 (C-12), and 74.6 (C-23), and five methyls at δ_C 24.8 (C-24), 24.5 (C-25), 23.9 (C-18), 20.9 (C-10), and 19.2 (C-22). These data were nearly identical with those of **5**, except for the absence of an acetyl group at C-9, as proved by the 1H - 1H COSY correlations (Fig. 2) of H₃-10/H-8/H₂-9 along with the HMBC correlations from H₃-10 to C-8 and C-9. Additionally, the NOESY correlations (Fig. 3) of H₃-18/H-11 β (δ_H 2.92), H₃-22/H-11 β , H₃-18/H-16 β (δ_H 1.97), and H₃-22/H-16 β indicated that **6** and **5** had similar relative configurations. The absolute configuration of **6** was determined by the experimental ECD spectrum in comparison to calculated spectra (Fig. 4), confirming the absolute configuration of (8R,12S,13R,14R,15S,19R)-**6**. Therefore, compound **6** was named talarine P.

Compound **7** was isolated as a colorless oil, whose molecular formula was established as $C_{25}H_{31}ClO_8$ by HRESIMS ($[M+H]^+$ m/z 495.1779, calcd for $C_{25}H_{32}O_8Cl$, 495.1786). The 1H NMR spectral data (Table 2) of **7** showed two oxygen-bearing methine protons at δ_H 4.70 (1H, d, $J=2.0$ Hz, H-9) and 4.62 (1H, qd, $J=6.7, 1.8$ Hz, H-8), as well as five methyl signals including four singlets at δ_H 1.35 (3H, s, H₃-18), 1.19 (3H, s, H₃-25), 1.06 (3H, s, H₃-24), 1.02 (3H, s, H₃-22), and one doublet at δ_H 1.57 (3H, d, $J=6.6$ Hz, H₃-10). The ^{13}C NMR data (Table 1) showed 25 carbons, containing one ester carbonyl carbon at δ_C 171.4 (C-7), six aromatic carbons, one ketal carbon at δ_C 100.9 (C-19), two oxygen-bearing methines at δ_C 79.4 (C-8) and 63.9 (C-9), five methylenes at δ_C 35.1 (C-17), 30.8 (C-20), 30.4 (C-16), 28.2 (C-11), and 26.6 (C-21), five nonprotonated carbons containing three oxygen-bearing at δ_C 82.3 (C-13), 79.4 (C-12), and 76.5 (C-15), and five methyls at δ_C 25.0 (C-24), 24.5 (C-18), 19.6 (C-22), 18.7 (C-25), and 16.5 (C-10). The comparative NMR analysis (Tables 1 and 2) between **7** and **6** demonstrated their structural congruence, with the notable exceptions of an oxygenated methine and nonprotonated carbon appearing in **7**, while the ketal carbon and methylene group present in **6** were absent. 1H - 1H COSY correlations (Fig. 2) of H₃-10/H-8/H-9 and HMBC correlations from H-9 to C-1, C-2, and C-3, indicated that C-9 methylene in **6** was replaced by the oxygenated methine in **7**. Furthermore, the HMBC correlations from H₃-24 to C-15, C-19, C-23, C-25, and H₃-25 to C-15, C-23 suggested the linkage of C-15 and C-23. Finally, the relative configuration of **7** was further identified through the NOESY correlations (Fig. 3) of H₃-10/H-9, H₃-18/H-11 β (δ_H 3.13), H-11 β /H₃-22, H₃-18/H-16 β (δ_H 1.81), H₃-22/H-16 β , and H-9/H-11 α (δ_H 3.06). The absolute configuration of **7** was determined by the experimental ECD spectrum in comparison to calculated spectra (Fig. 4), confirming the absolute configuration of

(8*R*,9*S*,12*S*,13*R*,14*S*,15*R*,19*R*)-7. Therefore, compound 7 was named talarine Q.

In addition to the seven novel compounds described above, five known compounds were also isolated (Fig. 1), including talaromyolide C (8) [6], talaromyolide H (9) [7], talarine C (10) [16], talarine A (11) [16] and talaromyolide J (12) [7]. All of these compounds were identified by comparing their ^1H and ^{13}C NMR data with those reported in the literatures.

2.2 PTP1B inhibitory activity evaluation

This study systematically investigated the antidiabetic potential of compounds (1–12) by evaluating their inhibitory activity against PTP1B (Table 3). The results revealed that compounds 2, 3, 5 and 12 exhibited significant inhibitory effects with IC_{50} values of 1.74, 8.54, 6.57, and 3.03 μM , respectively. Compared to the positive control sodium vanadate (Na_3VO_4 , $\text{IC}_{50}=0.83\text{ }\mu\text{M}$), compound 2 ($\text{IC}_{50}=1.74\text{ }\mu\text{M}$) displayed superior inhibitory efficacy. Notably, compounds 1–4 and 12 ($\text{IC}_{50}=1.74$ – $17.60\text{ }\mu\text{M}$) feature a pentacyclic system, while other compounds form peroxide rings at the C-15 and C-19. The former group demonstrated higher inhibitory activity compared to the latter. This observation suggests that the presence of peroxide rings at the C-15 and C-19 diminishes the inhibitory effects on PTP1B (Table 3).

2.3 Kinetic analysis and molecular docking

To further elucidate the inhibitory mechanisms of 2 and 12, which exhibit significant inhibitory activity against PTP1B (Table 3), kinetic analysis and molecular docking simulations were performed.

In the absence of the inhibitor, PTP1B catalyzed *p*-NPP with a K_m of 6.82 μM (Fig. 5a). However, addition of compound 2 to the reaction shifted the K_m to the right without affecting the V_{max} . Accordingly, the K_m was 13.31 μM and 22.13 μM at 5 μM and 10 μM compound 2, respectively. The Lineweaver–Burk or double-reciprocal plot further showed that 2 inhibits PTP1B competitively (Fig. 5b). These findings demonstrate that 2 was indeed

a competitive PTP1B inhibitor. In the case of 12, PTP1B catalyzed *p*-NPP with a K_m of 9.56 μM in control group (Fig. 5c). The trend lines (Fig. 5b and d) of 2 and 12 exhibit similarity and intersected on the Y-axis. A gradual increase in K_m values accompanied by an unchanged V_{max} indicated that compounds 2 and 12 were competitive inhibitors of PTP1B.

The binding interactions of 2 and 12 with PTP1B are depicted in Fig. 6. The molecular docking analysis of 2 (Fig. 6a) against PTP1B revealed a thermodynamically favorable binding profile ($\Delta G=-8.0\text{ kcal/mol}$), indicative of strong target engagement. Key stabilizing interactions included that 2 formed Van der Waals interactions with THR165/GLU97/THR138/LEU140/ASN162/THR164 / GLU101/HIS60. This indicated a π -alkyl interactions with TRP100, and established hydrogen bonds with ARG169/LYS103. In the case of 12 (Fig. 6b), the hydroxyl group and two carbonyl groups established hydrogen bonds with residues LEU204/ARG199, respectively. Additionally, A hydrophobic cluster comprising ARG199 (alkyl) and PHE280 (π -alkyl), and formed Van der Waals interactions with GLY202/LYS239/ASP236/ILE281/GLU200/ARG79.

3 Conclusions

In this study, twelve polycyclic meroterpenoids, including seven previously undescribed compounds (talarines K–Q), were isolated from the desert-derived fungus *Talaromyces* sp. HMT-8. Comprehensive structural elucidation was conducted using NMR, HRESIMS, and ECD techniques. Bioactivity assays demonstrated that several of these compounds exhibit notable inhibitory effects against PTP1B, an important therapeutic target for type 2 diabetes and obesity. Notably, compounds 2 and 12 showed potent PTP1B inhibition with IC_{50} values of 1.74 and 3.03 μM , respectively, and were identified as competitive inhibitors through kinetic and molecular docking studies. These findings not only expand the chemical diversity of fungal meroterpenoids, but also highlight their potential as promising lead compounds for the development of novel antidiabetic agents.

4 Materials and methods

4.1 General experimental procedures

ECD spectra were measured on Bio-Logic MOS-450 spectropolarimeter. IR spectra were recorded on a Thermo Nicolet iS 10 spectrometer. The NMR spectra were recorded on a Bruker AM-600 spectrometer with TMS as an internal standard. HRESIMS spectra were obtained on a Thermo U3000 spectrometer fitted with an ESI source. Semipreparative HPLC was carried out using an ODS column (YMC-pack ODS-A, $10\times 250\text{ mm}$, 5 μm , 2.5 mL/min). All solvents used were of analytical and

Table 3 Inhibitory activities for compounds against PTP1B

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
1	16.48 ± 0.60	8	12.69 ± 1.30
2	1.74 ± 3.81	9	35.12 ± 3.30
3	17.60 ± 0.98	10	11.13 ± 1.31
4	8.54 ± 1.52	11	18.42 ± 2.16
5	6.57 ± 1.47	12	3.03 ± 2.25
6	14.26 ± 0.86	Na_3VO_4	0.83 ± 2.57
7	15.60 ± 1.60		

chromatographic grade. Silica gel (200–300 mesh; Qingdao Haiyang Chemical Co., Ltd., Qingdao, Shandong, China), C18 reversed-phase silica gel (YMC ODS-A gel, YMC Co., Ltd., Kyoto, Japan).

4.2 Fungal material

The HMT-8 was isolated from the desert soil in Alashan region in the west of Inner Mongolia Autonomous Region of China. The strain was identified as *Talaromyces* sp. based on microscopic examination and by internal transcribed spacer (ITS1–4) sequencing. The ITS sequence has been deposited in GenBank (<http://www.ncbi.nlm.nih.gov>) with accession number No. PV436706. The purified strain was cultivated in a PDA medium plate (containing 200 g potatoes, boil 20 min, take filtrate; 20 g glucose; 20 g agar in 1 L water) at 28 °C for 7 days. Then, it was cut into small pieces and cultured in PDB medium plate (containing 200 g potatoes, boil 20 min, take filtrate; 20 g glucose; in 1 L water) for 5 days.

4.3 Fermentation, Extraction and Isolation

The fermentation was carried out in 400 flasks (500 mL), each containing 100 g of rice and 80 mL H₂O, autoclaving at 15 psi for 30 min. After cooling to room temperature, each flask was inoculated with 20 mL of the spore inoculum and incubated at room temperature for 30 days.

The fermented material was extracted with EtOAc for three times, then the EtOAc solutions were combined and evaporated under reduced pressure to get 210 g of crude extract. The extract was fractionated by a silica gel VLC column using different solvents of increasing polarity, from EtOAc-petroleum ether (PE) to yield eleven fractions (Fr.1–11). Fr.4 was eluted with EtOAc-PE to obtain ten subfractions (Fr.4.1–4.10). Fr.4.3 was purified by a semipreparative reversed-phase (RP) HPLC column using MeCN/H₂O=43:57 (3 mL/min) to afford **7** (3.6 mg), **8** (4.9 mg) and **9** (6.2 mg). Fr.4.6 also purified by semi-preparative RP-HPLC using MeCN/H₂O=70:30 (3 mL/min) to yield **10** (5.7 mg) and **11** (4.8 mg). Fr.6 was separated using a silica gel VLC column (EtOAc-PE) to yield nine subfractions (Fr.6.1–6.9). Fr.6.2 was chromatographed by C18 reversed-phase (RP-18) silica gel using MeOH/H₂O to collect subfractions (Fr.6.2.1–6.2.12). Fr.6.2.8 was separated by semi-preparative RP-HPLC using MeCN/H₂O=64:36 (3 mL/min) to afford **1** (5.4 mg), **2** (6.2 mg), **3** (5.7 mg), **4** (3.8 mg) and **5** (4.0 mg). Fr.6.2.11 was purified by semi-preparative RP-HPLC column using MeCN/H₂O=60:40 (4 mL/min) to afford **6** (4.6 mg). Fr.10 was purified by RP-18 using MeOH/H₂O to collect six subfractions (Fr.10.1–10.6). Fr.10.3 and Fr.10.4 were also purified by semi-preparative RP-HPLC column using MeCN/H₂O=20:80 (3 mL/min) to afford **12** (5.2 mg).

Talarine K (**1**), yellow amorphous powder; $[\alpha]_D^{25}$ –102 (c 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 223 (3.21) nm, 274 (4.01) nm, 309 (3.22) nm; ECD (MeOH) $\lambda_{\max}$ ($\Delta\epsilon$): 211 (+9.80), 235 (–7.50), 265 (5.13) nm; IR (KBr) $\nu_{\max}$ (cm^{–1}): 2933, 1701, 1478, 1326, 1165; ¹H and ¹³C NMR data, see Tables 1 and 2; HR-ESI-MS m/z : 403.1748 [M+H]⁺ (Calcd. for C₂₂H₂₇O₇, 403.1757).

Talarine L (**2**), yellow amorphous powder; $[\alpha]_D^{25}$ –93 (c 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 222 (3.01) nm, 278 (4.76) nm, 314 (3.15) nm; ECD (MeOH) $\lambda_{\max}$ ($\Delta\epsilon$): 229 (–1.62), 253 (+0.16), 267 (–0.14) nm; IR (KBr) $\nu_{\max}$ (cm^{–1}): 2951, 1743, 1633, 1365, 1201; ¹H and ¹³C NMR data, see Tables 1 and 2; HR-ESI-MS m/z : 443.2061 [M+H]⁺ (Calcd. for C₂₅H₃₁O₇, 443.2070).

Talarine M (**3**), yellow amorphous powder; $[\alpha]_D^{25}$ –112 (c 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 219 (3.33) nm, 277 (4.15) nm, 313 (3.66) nm; ECD (MeOH) $\lambda_{\max}$ ($\Delta\epsilon$): 217 (+2.40), 239 (–2.80), 275 (+1.94) nm; IR (KBr) $\nu_{\max}$ (cm^{–1}): 2941, 1745, 1620, 1255, 1113; ¹H and ¹³C NMR data, see Tables 1 and 2; HR-ESI-MS m/z : 491.1837 [M–H]⁺ (Calcd. for C₂₆H₃₂ClO₇, 491.1843).

Talarine N (**4**), yellow amorphous powder; $[\alpha]_D^{25}$ –87 (c 0.05, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 220 (3.16) nm, 277 (4.11) nm, 315 (3.01) nm; ECD (MeOH) $\lambda_{\max}$ ($\Delta\epsilon$): 212 (+9.20), 238 (–3.81), 272 (+2.59) nm; IR (KBr) $\nu_{\max}$ (cm^{–1}): 2930, 1712, 1689, 1257, 1099; ¹H and ¹³C NMR data, see Tables 1 and 2; HR-ESI-MS m/z : 517.2438 [M+H]⁺ (Calcd. for C₂₈H₃₇O₉, 517.2435).

Talarine O (**5**), white powder; $[\alpha]_D^{25}$ –121 (c 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 223 (3.78) nm, 274 (4.66) nm, 319 (3.24) nm; ECD (MeOH) $\lambda_{\max}$ ($\Delta\epsilon$): 227 (+14.07), 245 (–2.18) nm, 260 (+1.97); IR (KBr) $\nu_{\max}$ (cm^{–1}): 2914, 1764, 1636, 1358, 1150; ¹H and ¹³C NMR data, see Tables 1 and 2; HR-ESI-MS m/z : 553.1841 [M+H]⁺ (Calcd. for C₂₇H₃₄O₁₀Cl, 553.1829).

Talarine P (**6**), white powder; $[\alpha]_D^{25}$ –79 (c 0.05, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 222 (4.01) nm, 269 (4.31) nm, 311 (3.11) nm; ECD (MeOH) $\lambda_{\max}$ ($\Delta\epsilon$): 209 (+5.07), 239 (–4.29), 278 (+2.74) nm; IR (KBr) $\nu_{\max}$ (cm^{–1}): 2942, 1733, 1616, 1369, 1104; ¹H and ¹³C NMR data, see Tables 1 and 2; HR-ESI-MS m/z : 495.1775 [M+H]⁺ (Calcd. for C₂₅H₃₂O₈Cl, 495.1786).

Talarine Q (**7**), white powder; $[\alpha]_D^{25}$ –67 (c 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 211 (+13.42) nm, 230 (–22.63) nm, 272 (24.49) nm; ECD (MeOH) $\lambda_{\max}$ ($\Delta\epsilon$): 221 (7.04), 239 (–2.33) nm; IR (KBr) $\nu_{\max}$ (cm^{–1}): 2913, 1688, 1436, 1356, 1138, 1007; ¹H and ¹³C NMR data, see Tables 1 and 2; HR-ESI-MS m/z : 495.1779 [M+H]⁺ (Calcd. for C₂₅H₃₂O₈Cl, 495.1786).

4.4 Quantum chemistry calculations

The theoretical calculations of compounds were performed using Gaussian 09 [17]. The possible

conformations were initially obtained from the program Spartan'14 and then optimized at B3LYP/6-31G* level in the gas phase. Room-temperature equilibrium populations were calculated according to the Boltzmann distribution law. The ECD calculations were performed using Time Dependent Density Functional Theory (TDDFT) [18] at wB97xd/ 6-311G** level in methanol with PCM model. The ECD spectra of compounds were obtained by weighing the Boltzmann distribution rate of each geometric conformation, and the sigma/gamma value for processing the calculated ECD was 0.3 eV [19]. All calculated curves were shifted +15 nm to better simulate experimental spectra. The NMR calculations were performed using GIAO method at MPW1PW91/6-311G**//B3LYP/6-31G* level in METHANOL with PCM model [20]. The shielding constants (including ^{13}C and ^1H) obtained were directly performed statistical analyses with experimental chemical shifts by using DP4+ probability [21].

4.5 PTP1B inhibitory assay

The *p*-nitrophenyl phosphate (*p*-NPP) was used as a substrate to evaluate enzyme inhibition assays, following a previously established protocol. The final assay volume was 100 μL . The 75 μL reaction buffer containing 50 mM HEPES, 100 mM NaCl, 1 mM EDTA, and 1 mM dithiothreitol, 10 μL protein, and 5 μL sample were added to a 96-well plate and incubated at room temperature for 15 min. Subsequently, 10 μL of reaction buffer containing *p*-NPP was added to the reaction system. Sodium orthovanadate (Na_3VO_4) and dimethyl sulfoxide (DMSO) were used as the positive and negative controls, respectively. Enzymatic activity was determined by measuring absorbance at 405 nm. The half-maximal inhibitory concentration (IC_{50}) values were obtained from three independent experiments. The percentage of inhibition was calculated using the following equation:

$$\frac{[(\text{OD}_{\text{control}} - \text{OD}_{\text{blank}}) - (\text{OD}_{\text{compound}} - \text{OD}_{\text{blank}})]}{(\text{OD}_{\text{control}} - \text{OD}_{\text{blank}})} \times 100\%$$

4.6 Inhibition kinetic analysis

To determine the type of inhibition exerted by the most effective compound against PTP1B, enzyme kinetics analyses were performed using varying concentrations of the substrate (2, 1, 0.5, 0.25, 0.125, 0.0625, 0.03125 mM *p*-NPP for PTP1B) in the presence of different concentrations of the inhibitor. The experimental procedure followed that described in the enzyme inhibition assay. The data were represented using Lineweaver–Burk

double-reciprocal plots. The inhibition constants (K_i and K_{is}) were determined from the secondary plots of the slopes and intercepts derived from the Lineweaver–Burk plots.

4.7 Molecular docking

Molecular docking studies were carried out using the AutoDock software suite. The 3D conformations of compounds were generated and energy-minimized using the MM2 force field in Chem3D Ultra 11.0. The crystal structure of PTP1B (PDB ID: 2NT7) was retrieved from the RCSB Protein Data Bank. Prior to docking, all water molecules and co-crystallized ligands were removed. The hydrogen atoms were added to the protein structures using AutoDock tools (v1.5.6). Docking using AutoDock Vina 1.1.2. Default docking parameters were employed throughout the process. Visualization and analysis of docking poses were conducted using PyMOL 2.3.0 (<https://pymol.org>).

4.8 Statistical analysis

All experiments were repeated three times ($n=3$). The results are expressed as mean $\pm$ SD. Statistical analysis was performed using GraphPad Prism 8.0. The two-tailed Student's *t*-test was used to assess significance.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s13659-025-00530-x>.

Additional file 1.

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Author contributions

Xin-Yi Zhai conducted the experiments; Jin-Jie Liu, Cui-Duan Wang and Yi-Fan Dou participated in the experiments; Jian-Hua Lv performed the ECD calculations; Li-An Wang collected the samples; Jin-Xiu Zhang drafted the manuscript; Zhuang Li designed the experiments and revised the manuscript. All authors reviewed and approved the final manuscript.

Data availability

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

These authors have no competing interests to declare.

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