# Cladosporamide A, a new protein tyrosine phosphatase 1B inhibitor, produced by an Indonesian marine sponge-derived Cladosporium sp.

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NOTE

# Cladosporamide A, a new protein tyrosine phosphatase 1B inhibitor, produced by an Indonesian marine sponge-derived *Cladosporium* sp.

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## Abstract

Cladosporamide A (**1**), a new protein tyrosine phosphatase (PTP) 1B inhibitor, was isolated together with a known prenylated flavanone derivative (**2**) from the culture broth of an Indonesian marine sponge-derived *Cladosporium* sp. TPU1507 by solvent extraction, ODS column chromatography, and preparative HPLC (ODS). The structure of **1** was elucidated based on 1D and 2D NMR data. Compound **1** modestly inhibited PTP1B and T-cell PTP (TCPTP) activities with $IC_{50}$ values of 48 and 54 μM, respectively. The inhibitory activity of **2** against PTP1B ($IC_{50}$ = 11 μM) was approximately 2-fold stronger than that against TCPTP ($IC_{50}$ = 27 μM).

**Keywords** Cladosporamide A · Marine sponge-derived fungus · *Cladosporium* sp. · Protein tyrosine phosphatase 1B · Inhibitor

## Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease primarily caused by insulin resistance and decreased insulin secretion, leading to hyperglycemia and the disruption of β-cell function [1]. Biguanides, sulfonylureas, thiazolidinediones, and α-glucosidase inhibitors are currently used as clinical agents to improve hyperglycemia [2]. Although new types of medicines, incretin analogs, dipeptidyl peptidase 4 (DPP4) inhibitors, and sodium–glucose co-transporter 2 (SGLT2) inhibitors have recently been approved [2], novel therapeutic applications are still required because these medicines have serious side effects. One of the potential molecular targets for the treatment of T2DM is protein tyrosine phosphatase (PTP) 1B, which is a key negative regulator in the insulin signaling pathway [3]. Moreover, this enzyme has been shown to control the leptin signaling cascade [4], and, thus, PTP1B inhibitors are expected to become candidate agents for the treatment of T2DM and obesity [5].

During our studies on new PTP1B inhibitors from Indonesian marine-derived microorganisms, we reported new merosesquiterpene and biphenyl ether derivatives [6, 7] and found that a culture broth of the Indonesian marine sponge-derived *Cladosporium* sp. TPU1507 exhibited PTP1B inhibitory activity. Bioassay-guided separation of the broth extract led to the isolation of a new tricyclic metabolite, cladosporamide A (**1**), along with a known prenylflavanone [8], (2*S*)-7,4′-dihydroxy-5-methoxy-8-(γ,γ-dimethylallyl)-flavanone (**2**; Fig. 1). Compound **1** inhibited PTP1B and T-cell PTP (TCPTP) activities with similar potencies, whereas the inhibitory activity of against PTP1B was stronger than that against TCPTP. In the present study, the fermentation, isolation, structural elucidation, and biological activities of compounds **1** and **2** are described.

## Results and discussion

The fungal strain TPU1507 was obtained from an unidentified marine sponge collected at Manado, Indonesia, in 2015, and its 212-bp ITS1 rDNA sequence was identical to 107 known species of the genus *Cladosporium* including *C.*

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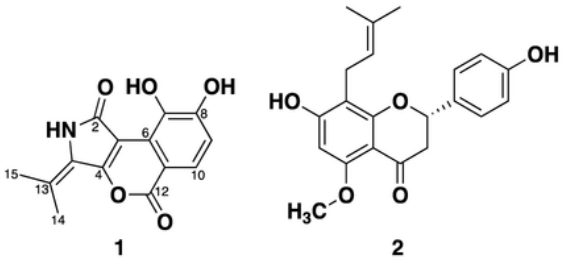


**Fig. 1** Structures of **1** and **2** produced by Indonesian marine sponge-derived *Cladosporium* sp. TPU1507

*sphaerospermum*, *C. halotolerans*, *C. cladosporioides*, and *C. minusculum* (100% match each).

The EtOAc extract from the seawater culture broth of strain TPU1507 inhibited PTP1B activity by approximately 66% at 100 μg/mL and was separated into 10 fractions by octadecyl-silica (ODS) column chromatography. The active fraction (approximately 68% at 50 μg/mL) was purified by preparative high-performance liquid chromatography (HPLC, ODS) to obtain compounds **1** (0.9 mg) and **2** (1.2 mg). The productivity of **1** was markedly reduced in freshwater medium.

Compound **2** was identified by comparing spectroscopic data for **2** with the reported values for (2*S*)-7,4′-dihydroxy-5-methoxy-8-(γ,γ-dimethylallyl)-flavanone [8] (Fig. 1), which was originally reported as a constituent in the roots of *Sophora flavescens* [8] and recently found in a culture broth of the actinomycete *Streptomyces* sp. neau-D50 [9]. However, compound **2** was not detected in the culture broth of strain TPU1507 fermented in seawater medium without Ebios. Ebios consists of a beer yeast cultured with hops (*Humulus lupulus*), which contains several prenylated chalcones including xanthohumol [10]. Therefore, compound **2** may have been transformed from these chalcones by the strain.

Compound **1** was obtained as a paleyellow oil, and its infrared (IR) bands at 3425, 1742, and 1661 $cm^{-1}$ indicated the presence of hydroxy, ester carbonyl, and amide carbonyl groups, respectively. The molecular formula was elucidated as $C_{14}H_{11}NO_5$ from high-resolution electron ionisation mass spectrometry (HREIMS, *m/z* 273.0629 $[M]^+$, Δ –0.8 mmu) and nuclear magnetic resonance (NMR) data for **1** (Table 1). The $^1H$ NMR spectrum of **1** (in DMSO-$d_6$) displayed 11 proton signals, three of which were revealed to be one secondary amine (δ 10.8) and two phenol (δ 12.5 and 10.2) protons. The $^{13}C$ NMR spectrum of **1** (in DMSO-$d_6$) showed 14 carbon signals, which were classified into two methyl, two $sp^2$ methine, five $sp^2$ quaternary, three $sp^2$ oxygenated quaternary, and two carbonyl carbons by analyzing the DEPT and HMQC spectra of **1** (Table 1). The HMBC correlations observed from 1-NH (δ 10.8) to C-3 (106.3), C-4 (154.2), and C-13 (125.3), from $H_3$-14 (2.05) to C-5 (130.4), C-13, and C-15 (19.7), and from $H_3$-15 (2.27) to C-5, C-13, and C-14 (21.5) established partial structure I (Fig. 2). An aromatic partial structure II was confirmed by the HMBC correlations from 7-OH (δ 12.5) to C-6 (118.9), C-7 (140.5) and C-8 (152.4), from 8-OH (10.2) to C-7, C-8, and C-9 (117.3), from H-9 (7.03) to C-7, and C-11 (109.8), from H-10 (7.63) to C-6, C-8, and C-12 (160.0), and $^1H$-$^1H$ COSY data (Fig. 2). The molecular formula and chemical shifts at C-4 and C-12 suggested that the partial structures I and II were bridged via an oxygen atom between C-4 and C-12 positions. Moreover, the connection of two partial structures between C-3 and C-6 positions was supported by a weak HMBC correlation from H-10 to C-3 ($^4J$; Fig. 2). Based on the remaining degree of unsaturation and a carbonyl carbon (δ 167.1) corresponding to an amide bond, a tricyclic skeleton with the 5/6/6 ring system was established as shown in Fig. 1.

**Table 1** $^{13}C$ (100 MHz) and $^1H$ (400 MHz) NMR data for **1** (DMSO-$d_6$)

| C# | $\delta_C$ | $\delta_H$, mult. (*J* in Hz) |
|---|---|---|
| 1-NH | | 10.8, s |
| 2 | 167.1 | |
| 3 | 106.3 | |
| 4 | 154.2 | |
| 5 | 130.4 | |
| 6 | 118.9 | |
| 7 | 140.5 | |
| 7-OH | | 12.5, s |
| 8 | 152.4 | |
| 8-OH | | 10.2, s |
| 9 | 117.3 | 7.03, d (8.2) |
| 10 | 123.5 | 7.63, d (8.2) |
| 11 | 109.8 | |
| 12 | 160.0 | |
| 13 | 125.3 | |
| 14 | 21.5 | 2.05, s |
| 15 | 19.7 | 2.27, s |

The PTP1B inhibitory activities of **1** and **2** were evaluated in an enzyme in vitro assay [11]. Compound

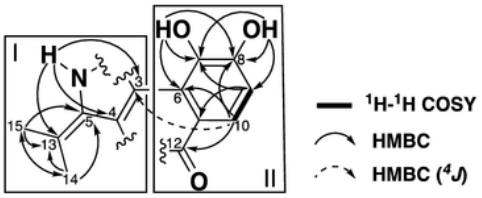


**Fig. 2** $^1H$-$^1H$ COSY and HMBC correlations of **1**

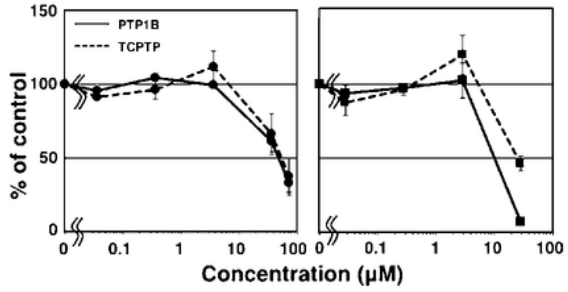


**Fig. 3** Effects of compounds **1** (●) and **2** (■) on PTP1B (—) and TCPTP (---)

**Table 2** $IC_{50}$ values of compounds **1** and **2** against PTP1B and TCPTP activities

| Compound | Protein tyrosine phosphatases ($IC_{50}$, μM) | |
|---|---|---|
| | PTP1B | TCPTP |
| **1** | 48 | 54 |
| **2** | 11 | 27 |
| Oleanolic acid[a] | 0.9 | 0.8 |

[a]Positive control [12]

**1** modestly inhibited PTP1B activity with an $IC_{50}$ value of 48 μM, while compound **2** exhibited moderate inhibitory activity against PTP1B with an $IC_{50}$ value of 11 μM (Fig. 3 and Table 2). Oleanolic acid [12] was tested in the same experiment as a positive control ($IC_{50}$ = 0.9 μM; Table 2). The PTP1B inhibitory activity of **2** has not yet been reported, although a number of prenylflavonoids have been identified as PTP1B inhibitors [13].

In the insulin and leptin signaling pathways, various PTPs, such as TCPTP, leukemia antigen-related (LAR) PTP, and SH2-domain-containing phosphatase 2 (SHP2), control cellular functions in addition to PTP1B [3]. Of these, TCPTP shares the highest structure similarity with PTP1B [14], and, thus, the inhibitory effects of **1** and **2** on TCPTP were assessed using an enzyme-based assay [15]. Compound **1** showed approximately equivalent $IC_{50}$ values against TCPTP and PTP1B, whereas the inhibitory effect of **2** on TCPTP was more than 2-fold weaker than that on PTP1B (Fig. 3 and Table 2). Although previous research demonstrated that serious inflammatory phenotypes were observed in TCPTP knockout (*tcptp* $^{-/-}$) mice [16, 17], a recent study on knockout mice with a one-copy deletion of PTP1B and TCPTP reported no significant abnormalities [18]. Accordingly, selective and dual inhibitors against PTP1B and/or TCPTP will be a new treatment strategy for T2DM and obesity.

## Materials and methods

### General experimental procedures

UV spectra were measured on a U-3310 UV–Visible spectrophotometer (Hitachi High Technologies Co., Ltd., Tokyo, Japan) and IR spectra on a PerkinElmer Spectrum One Fourier transform infrared spectrometer (PerkinElmer, Waltham, MA, USA). NMR spectra (400 and 600 MHz for $^{1}$H/100 and 150 MHz for $^{13}$C) were recorded on a JEOL JNM-AL-400 and JNM-ECZ600R NMR spectrometer (JEOL, Tokyo, Japan) in DMSO-$d_6$ ($\delta_H$ 2.49, $\delta_C$ 39.5). EIMS and HREIMS were performed using a JMS-MS 700 mass spectrometer (JEOL). Preparative HPLC was performed using a Hitachi L-6200 system (Hitachi High Technologies Co., Ltd.).

### Materials

Human recombinant PTP1B was purchased from Enzo Life Sciences (Farmingdale, NY, USA). Human recombinant TCPTP was purchased from R&D Systems (Minneapolis, MN, USA). *p*-Nitrophenyl phosphate (*p*NPP) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Oleanolic acid was purchased from Tokyo Chemical Industry (Tokyo, Japan). Potato dextrose agar (PDA) was purchased from BD (Franklin Lakes, NJ, USA). Ebios was purchased from Asahi Food & Healthcare Co., Ltd. (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).

### Isolation and identification of strain TPU1507

Fungal strain TPU1507 was isolated from an unidentified marine sponge collected at Manado, Indonesia, in September 2015. A piece of the marine sponge was minced using a pestle and mortar with 1 mL of sterilized seawater, and approximately 100 μL of the solution was spread on a PDA plate containing 0.005% rose bengal and 0.01% kanamycin. The plate was incubated at 25 °C for 1 week, and strain TPU1507 was inoculated onto another PDA plate. Strain TPU1507 was identified as the genus *Cladosporium* from the ITS1 rDNA sequence (212 nucleotides; 100% similarity).

### Fermentation

Strain TPU1507 maintained on a PDA plate was inoculated into a 100-mL Erlenmeyer flask containing 50 ml of seed medium (2.0% glucose, 0.50% polypeptone, 0.050%

$MgSO_4 \cdot 7H_2O$, 0.20% yeast extract, 0.10% $KH_2PO_4$, and 0.10% agar in natural seawater; adjusted to pH 6.0 before sterilization). The flask was shaken reciprocally on a rotary shaker (150 rpm) at 25 °C for 3 days in order to obtain the seed culture, which was then transferred to production medium (3.0% sucrose, 3.0% soluble starch, 1.0% malt extract, 0.30% Ebios, 0.50% $KH_2PO_4$, and 0.050% $MgSO_4 \cdot 7H_2O$ in seawater; adjusted to pH 6.0 before sterilization). The production culture was performed at 25 °C for 7 days under agitation on a rotary shaker (150 rpm).

## Isolation of compounds 1 and 2

The culture broth (2.4 L) was treated with acetone (2.4 L) and filtered. The filtrate was concentrated in vacuo to remove acetone and extracted three times with EtOAc (2.4 L). The EtOAc extract was evaporated to dryness (ca. 66% PTP1B inhibition at 100 μg/mL), and the brown residue (2.8 g) was suspended in 30% $CH_3OH$ in $H_2O$ and applied to an ODS column (100 g). The ODS column was eluted stepwise with 30, 50, 70, 85, and 100% $CH_3OH$ in $H_2O$ (each 200 mL × 2) to divide into 10 fractions (Fr. 1–Fr. 10). Fr. 6 (the second 200 mL of the 70% $CH_3OH$ eluate) inhibited PTP1B activity (ca. 68% inhibition at 50 μg/mL) and was concentrated to obtain a black oil (36.6 mg), which was purified by preparative HPLC [column; PEGASIL ODS (Senshu Scientific Co., Ltd., Tokyo, Japan), 10 × 250 mm; mobile phase, 60% $CH_3CN$ containing 0.05% trifluoroacetic acid; detection, UV at 210 nm; flow rate, 2.0 ml/min] to yield compounds **1** (0.9 mg, $t_R$ = 32.5 min) and **2** (1.2 mg, $t_R$ = 41.8 min).

*Cladosporamide A* (**1**): a paleyellow oil; IR (KBr) $\nu_{max}$ 3425, 2953, 1742, 1661, 1460, 1206, 1037 $cm^{-1}$; UV ($CH_3OH$) $\lambda_{max}$ nm (log ε) 229 (4.0), 250 (3.9), 285 (4.0), 351 (3.4); EIMS *m/z* 273 $[M]^+$; HRESIMS *m/z* 273.0629 ($[M]^+$; calcd, for $C_{14}H_{11}NO_5$, 273.0637); $^1H$ and $^{13}C$ NMR (DMSO-$d_6$), see Table 1.

## Inhibitory activities against PTP1B and TCPTP

The effects of compounds **1** and **2** on PTP1B and TCPTP were evaluated by measuring the rate of hydrolysis of the substrate, *p*NPP, according to the method previously described with slight modifications [11, 15, 19].

PTP1B (14 μL of a 0.5 μg/mL stock solution) or TCPTP (100 μL of a 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 EDTA was added to each well of a 96-well plastic plate. A sample (2.0 μL in $CH_3OH$) was added to each well to make the final concentration and then incubated at 37 °C for 10 min. The reaction was initiated by the addition of *p*NPP in citrate buffer (100 μL of a 4.0 mM stock solution), incubated at 37 °C for 30 min, and then terminated using 10 μL of a stop solution (10 M NaOH). Optical density in each well was measured at 405 nm using an MTP-500 microplate reader (Corona Electric Co., Ltd., Ibaraki, Japan). PTP1B/TCPTP inhibitory activity (%) was defined as $\left[1-\left(ABS_{sample}-ABS_{blank}\right)/\left(ABS_{control}-ABS_{blank}\right)\right] \times 100$. $ABS_{blank}$ 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 three duplicate experiments for all test samples. Oleanolic acid, a known phosphatase inhibitor [12], was used as a positive control.

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