New flavonoids and xanthone from the stem bark of Artocarpus rigidus blume and cytotoxicity

S Rattanaburi, K Sriklung, R Watanapokasin, W Mahabusarakam. Natural product research 35 (21), 4010-4017

มีการอ้างอิงในช่วง 8 มิ.ย. 69 จำนวน 1 บทความ

Journal of Pharmaceutical Innovation (2026) 21:563
https://doi.org/10.1007/s12247-026-10799-1

RESEARCH

# Dual Inhibition of PTP1B and DPP-IV by Metabolites from *Artocarpus elasticus* Leaves Enhances Insulin Signaling and Sensitivity

**Abdul Bari Shah[1,2,3] · Muhammad Tayyab Khan[3] · Safeer Ullah[3] · Aizhamal Baiseitova[2,3] · Muhammad Idrees[3] · Il-Keun Kong[3] · Ki Hun Park[3]**

Received: 12 January 2026 / Accepted: 2 June 2026


## Abstract

**Background** Protein tyrosine phosphatase 1B (PTP1B) and dipeptidyl peptidase-IV (DPP-IV) play key roles in the regulation of insulin sensitivity and insulin resistance, which are central to the pathogenesis of diabetes. *Artocarpus elasticus* has been traditionally used for diabetes treatment; however, specific bioactive compounds responsible for antidiabetic effects remain unclear.

**Objectives** Study aimed to isolate and characterize compounds from *A. elasticus* leaves and to evaluate their inhibitory activities against PTP1B and DPP-IV, enzyme inhibition mechanisms, binding affinities, molecular docking and effects on insulin signaling in adipocyte cells.

**Methods** Different techniques were used for isolation and characterization of compounds. Their inhibitory activities against PTP1B and DPP-IV, mode of inhibition and binding affinities were performed carefully. Compounds **1** and **5** were tested in 3T3-L1 adipocytes for insulin receptor substrate (IRS) phosphorylation and downstream signalling markers. Molecular docking of **1**, **5**, and **6** against PTP1B was also performed.

**Results** All compounds inhibited PTP1B ($IC_{50}$ = 0.25 to 3.00 µM), whereas **1**–**4** showed significant DPP-IV inhibition ($IC_{50}$ = 1.01–15.75 µM). Compound **1** showed potent dual inhibitory activity. Kinetic studies revealed mixed-type inhibition for **1**–**4** and competitive inhibition of PTP1B by **5** and **6.** Binding affinity results correlated well with enzyme inhibitory potency. Cellular assays showed that **1** and **5** enhanced insulin signaling by modulating phosphorylated IRS, PI3K, and p-AKT expression. In docking analysis, **1**, **5**, and **6** showed strong binding affinity with PTP1B.

**Conclusion** *A. elasticus* compounds **1** and **5**, inhibit PTP1B and increase insulin signalling, making them promising antidiabetic therapeutic leads.

**Keywords** *Artocarpus elasticus* · Dipeptidyl peptidase-IV (DPP-IV) · Enzyme kinetics · Molecular docking · Protein tyrosine phosphatase 1B (PTP1B) · 3T3-L1 cells

## Introduction

Diabetes mellitus (DM) represents a significant public health issue globally, marked by a significant increase in prevalence in recent years. The International Diabetes Federation indicated that almost 463 million people aged 20 to 79 were diagnosed with diabetes in 2019. This projection estimate that 578 million individuals would be affected in 2030 and 700 million in 2045 [1, 2]. The data reveal a significant increase in diabetes incidence, highlighting the urgent requirement for action to tackle this escalating global health concern. Type 2 diabetes mellitus (T2D) represents the predominant manifestation of diabetes, containing more than 90% of all cases [3]. T2D is distinguished

✉ Ki Hun Park
khpark@gnu.ac.kr

1 College of Pharmacy, Korea University, Sejong 30019, Republic of Korea

2 The Research Center for Medicinal Plants, Al-Farabi Kazakh National University, Al-Farabi Ave. 71, Almaty 050040, Kazakhstan

3 Division of Applied Life Science (BK21 Four), IALS, Gyeongsang National University, Jinju 52828, Republic of Korea

Published online: 08 June 2026

Am Chem Soc. 2024;9:9053–62. https://doi.org/10.1021/acsomega.3c07471.
14. Baiseitova A, Shah AB, Khan AM, Idrees M, Kim JH, Lee YH, et al. Antioxidant potentials of furanodihydrobenzoxanthones from *Artocarpus elasticus* and their protection against oxLDL induced injury in SH-SY5Y cells. Biomed Pharmacother. 2023;165:115278. https://doi.org/10.1016/j.biopha.2023.115278.
15. Daus M, Chaithada P, Phongpaichit S, Watanapokasin R, Carroll AR, Mahabusarakam W. New prenylated dihydrochalcones from the leaves of *Artocarpus elasticus*. Phytochem Lett. 2017;19:226–30. https://doi.org/10.1016/j.phytol.2017.01.007.
16. Jenis J, Baiseitova A, Yoon SH, Park C, Kim JY, Li ZP, et al. Competitive α-glucosidase inhibitors, dihydrobenzoxanthones, from the barks of *Artocarpus elasticus*. J Enzyme Inhib Med Chem Taylor Francis. 2019;34:1623–32. https://doi.org/10.1080/14756366.2019.1660653.
17. Ramli F, Rahmani M, Ismail IS, Sukari MA, Abd Rahman M, Zajmi A, et al. A new bioactive secondary metabolite from *Artocarpus elasticus*. Nat Prod Commun. 2016;11:1103–6.
18. Shah AB, Yoon S, Kim JH, Zhumanova K, Ban YJ, Lee KW, et al. Effectiveness of cyclohexyl functionality in ugonins from *Helminthostachys zeylanica* to PTP1B and α-glucosidase inhibitions. Int J Biol Macromol. 2020;165:1822–31. https://doi.org/10.1016/j.ijbiomac.2020.10.061
19. Nongonierma AB, Cadamuro C, Le Gouic A, Mudgil P, Maqsood S, FitzGerald RJ. Dipeptidyl peptidase IV (DPP-IV) inhibitory properties of a camel whey protein enriched hydrolysate preparation. Food Chem. 2019;279:70–9. https://doi.org/10.1016/j.foodchem.2018.11.142.
20. Shah AB, Baiseitova A, Kim JH, Lee YH, Park KH. Inhibition of bacterial neuraminidase and biofilm formation by Ugonins Isolated From *Helminthostachys Zeylanica* (L.) Hook. Front Pharmacol. 2022;13:10.
21. Pan J, Zhang Q, Zhang C, Yang W, Liu H, Lv Z, et al. Inhibition of dipeptidyl peptidase-4 by flavonoids: Structure–activity relationship, kinetics and interaction mechanism. Front Nutr. 2022;9:892426. https://doi.org/10.3389/fnut.2022.892426.
22. Boston MA. Principles of fluorescence spectroscopy. Springer US; 2006. [cited 2025 Apr 15]. https://doi.org/10.1007/978-0-387-46312-4.
23. Etesami B, Ghaseminezhad S, Nowrouzi A, Rashidipour M, Yazdanparast R. Investigation of 3T3-L1 cell differentiation to adipocyte, affected by aqueous seed extract of phoenix dactylifera L. Rep Biochem Mol Biology. 2020;9:14. https://doi.org/10.29252/rbmb.9.1.14.
24. Hanwell MD, Curtis DE, Lonie DC, Vandermeersch T, Zurek E, Hutchison GR. Avogadro: an advanced semantic chemical editor, visualization, and analysis platform. J Cheminform. 2012;4:17. https://doi.org/10.1186/1758-2946-4-17.
25. Liu Y, Yang X, Gan J, Chen S, Xiao Z-X, Cao Y. CB-Dock2: improved protein–ligand blind docking by integrating cavity detection, docking and homologous template fitting. Nucleic Acids Res. 2022;50:W159–64. https://doi.org/10.1093/nar/gkac394.
26. Rattanaburi S, Sriklung K, Watanapokasin R, Mahabusarakam W. New flavonoids and xanthone from the stem bark of *Artocarpus rigidus* blume and cytotoxicity. Nat Prod Res. 2021;35:4010–7. https://doi.org/10.1080/14786419.2020.1753734.
27. Uvais M, Sultanbawa S, Surendrakumar S. Two pyranodihydrobenzoxanthones from *Artocarpus nobilis*. Phytochemistry. 1989;28:599–605. https://doi.org/10.1016/0031-9422(89)80059-7.
28. Ren Y, Kardono LBS, Riswan S, Chai H, Farnsworth NR, Soejarto DD, et al. Cytotoxic and NF-κB Inhibitory Constituents of *Artocarpus rigida*. J Nat Prod. 2010;73:949–55. https://doi.org/10.1021/np1002065.
29. Hakim EH, Asnizar null, Yurnawilis null, Aimi N, Kitajima M, Takayama H, Artoindonesianin P. a new prenylated flavone with cytotoxic activity from Artocarpus lanceifolius. Fitoterapia. 2002;73:668–73. https://doi.org/10.1016/s0367-326x(02)00226-5
30. Ee GCL, Teo SH, Kwong HC, Mohamed Tahir MI, Silong S. 12-Acetyl-6-hydroxy-3,3,9,9-tetramethylfuro[3,4-b]pyrano[3,2-h]xanthene-7,11(3H,9H)-dione. Acta Crystallogr Sect E Struct Rep Online. 2010;66:o3331–2. https://doi.org/10.1107/S1600536810048592.
31. Nabeno M, Akahoshi F, Kishida H, Miyaguchi I, Tanaka Y, Ishii S, et al. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. Biochem Biophys Res Commun. 2013;434:191–6. https://doi.org/10.1016/j.bbrc.2013.03.010.
32. Barr AJ. Protein tyrosine phosphatases as drug targets: strategies and challenges of inhibitor development. Future Med Chem. 2010;2:1563–76. https://doi.org/10.4155/fmc.10.241.
33. Adelusi TI, Oyedele A-QK, Boyenle ID, Ogunlana AT, Adeyemi RO, Ukachi CD, et al. Molecular modeling in drug discovery. Inf Med Unlocked. 2022;29:100880. https://doi.org/10.1016/j.imu.2022.100880.