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SHORT REPORT

Mannodaidzein, a rare daidzein mannoside isolated from a rare actinomycete *Saccharothrix* sp. JS2

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Abstract: A rare isoflavone mannoside, mannodaidzein (**1**), along with three known isoflavones (**2**–**4**), was isolated from the culture broth of an actinomycete *Saccharothrix* sp. JS2. Their chemical structures were determined by 1D/2D NMR and HR(ESI)MS data analyses. Among them, only compound **2** exhibited weak anti-proliferative activity against HT1080 cells at 100 μM. The structure-activity relationship analysis revealed that modification of the C-4′ hydroxyl group adversely affected cytotoxicity. Mannodaidzein (**1**) represents the first mannoside of flavone.

Keywords: Isoflavone, mannoside, actinomycete, cytotoxicity

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1 Microbial Source

The strain *Saccharothrix* sp. JS2 was isolated from a soil sample collected in Okinawa, Japan, in 2020 and cultured on ISP Medium 2 agar plate (media composition: 1 L medium contains yeast extract 4 g, malt extract 10 g, dextrose 4 g, and agar 20 g). Based on 16S rRNA sequence analysis, it was finally identified as *Saccharothrix* sp.

2 Previous Studies

Microorganisms play a vital role in drug discovery (Demain & Sanchez, 2009; Kakeya, 2016). Around 50% of clinically approved drugs originate from natural product-related molecules, including natural products, natural product derivatives, and natural product mimics (Newman & Cragg, 2012). However, the discovery of new bioactive natural products has become increasingly challenging due to the limitations of natural resources. Therefore, rare microorganism resources that have not been investigated extensively may offer more opportunities for the discovery of novel bioactive natural products (Wei et al., 2024).

Isoflavones, flavones, and their glycosides constitute a large family of bioactive natural products and have been reported to exhibit various bioactivities, including antioxidant, anticancer, anti-aging, and anti-osteoporosis activities (Wang et al., 2020; Chen et al., 2023). Beans, especially soybeans, are well known to produce flavonoids and isoflavones. Besides plants, actinomycetes were also reported as producers of flavonoids (Wang et al., 2020). Sugars in naturally occurring flavone glycosides include glucose, galactose, glucuronide, rhamnose, xylose, and arabinose. The distinct types of sugars led to various bioactivities in these glycosides. Unnatural flavone glycosides were also synthesized to explore their potential biological applications (Khodzhaieva et al., 2021; Nguyen et al., 2020; Huang et al., 2025). Although flavone glycosides have been widely reported, their mannosides are rare. The results of the literature search with chemical structure and combined keywords (flavone + mannoside) in the database of SciFinder^n indicate that no flavone mannoside has been reported to date.

In our continuous investigation of bioactive natural products from actinomycetes (Lu et al., 2025; Mao et al., 2025), a new rare isoflavone mannoside, designated as mannodaidzein (**1**), together with daidzein (**2**) (Maatooq & Rosazza, 2005), formononetine (**3**) (Granados-Covarrubias & Maldonado, 2009), and tectorigenin (**4**) (Shriner et al., 1939), were isolated from a rare actinomycete *Saccharothrix* sp. JS2. This paper reports on the isolation, structure elucidation, and cytotoxicity of the four isoflavone derivatives.

3 Present Study

Through the analysis of the UV absorption and LC-MS profiles, we discovered a class of isoflavone derivatives **1**–**4** that

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Table 1. ^{1}H and ^{13}C NMR data for compound **1** in methanol-d_4

Position	δ_C, type	δ_H (mult, *J* in Hz)
1	–	–
2	155.0, CH	8.17 (s)
3	125.6, C	–
4	177.9[a], C	–
5	128.5, CH	8.06 (d, 8.9)
6	116.6[b], CH	6.94 (dd, 8.9, 2.3)
7	164.5[a], C	–
8	103.3, CH	6.85 (d, 2.1)
9	159.9, C	–
10	118.0, C	–
1′	127.4, C	–
2′	131.5, CH	7.48 (d, 8.7)
3′	117.6, CH	7.19 (d, 8.7)
4′	157.9[a], C	–
5′	117.6, CH	7.19 (d, 8.7)
6′	131.5, CH	7.48 (d, 8.7)
1″	100.2, CH	5.53 (d, 1.9)
2″	72.0, CH	4.03 (dd, 3.4, 1.9)
3″	72.4, CH	3.92 (dd, 9.5, 3.4)
4″	68.4, CH	3.75 (m)
5″	75.4, CH	3.61 (m)
6″	62.7, CH_2	3.73, 3.77 (m)

Note: [a]Assignment made by HMBC; [b]Assignment made by HMQC.

exhibit similar UV absorption and related MS signals. The *n*-BuOH residue was obtained from 6 L of culture broth and separated by repeated column chromatography on silica gel. Through tracing their characteristic UV absorption around 300 nm and LC-MS data of each fraction, four metabolites, including **1** (2.4 mg), **2** (1.4 mg), **3** (7.0 mg), and **4** (5.4 mg), were finally purified by semipreparative HPLC.

Compound **1** was obtained as a yellow powder. The molecular formula was determined to be $C_{21}H_{20}O_9$ by analysis of the HR-TOF-MS ion peak at *m/z* 417.1170 $[M+H]^+$ (calcd. 417.1186). Analysis of its ^{1}H and ^{13}C NMR data revealed that the structure of **1** was very similar to **2**, except for the presence of a set of signals characteristic of one sugar unit in the molecule (Table 1). The 1,3,4-trisubstituted benzene was deduced from the proton signals H-5 (δ_H 8.06, d, 8.9 Hz), H-6 (δ_H 6.94, dd, 8.9, 2.3 Hz), and H-8 (δ_H 6.85, d, 2.1 Hz). The ketone group was placed at C-4, as inferred from the HMBC cross peak between H-2 and H-5, and C-4. The presence of 1,4-disubstituted benzene was deduced from the proton signals H-2′/6′ (δ_H 7.48, d, 8.7 Hz) and H-3′/5′ (δ_H 7.19, d, 8.7 Hz), which was assigned to C-3, due to the strong cross signals of H-2′/6′ to C-3 (δ_C 125.6) in the HMBC spectrum of **1** (Figure 1A).

The sugar moiety showed five methine groups, CH-1″ to CH-5″ and a methylene group, CH_2-6″, resonating in the range δ_H 3.61 to 5.53 and δ_C 62.7 to 100.2, respectively. The COSY and HMBC correlations from CH-1″ to CH_2-6″ established a pyranose moiety (Figure 1A). The NMR data of the sugar moiety of **1** are identical to those of a reported synthetic mannoside (Klein et al., 2010), suggesting that the sugar moiety of **1** is a mannose (Table S1). A comparison of the coupling constant (*J* value) between H-2″ and H-3″ (3.4 Hz in **1**) with that in delphinidin-3-*O*-glucoside (9.3 Hz), a structurally related flavonoid glucoside, further supports the hypothesis that the sugar moiety of compound **1** is mannose rather than glucose (Figure 1B) (Wu et al., 2024). Based on the chemical shift of H-1″ (δ_H 5.53) and coupling constant between H-1″ and H-2″ (1.9 Hz) (Figure 1C), the anomeric configuration of the mannose was considered as α. The analysis of the

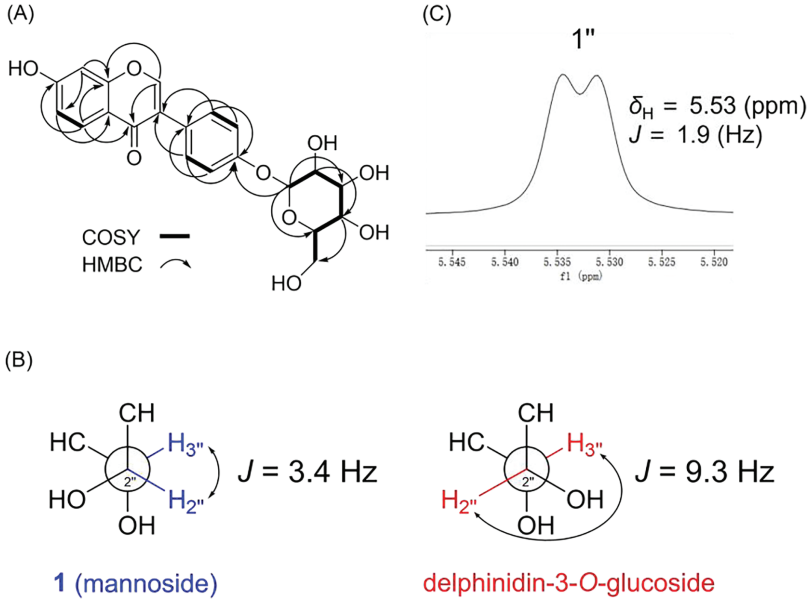

Figure 1. NMR data of compound **1**. (A) ^{1}H–^{1}H COSY and Key HMBC correlations. (B) A comparison of the *J* values between H-2″ and H-3″ in the sugar parts of compound **1** and delphinidin-3-*O*-glucoside. (C) δ_H and *J* value for the proton at C-1″ in **1**

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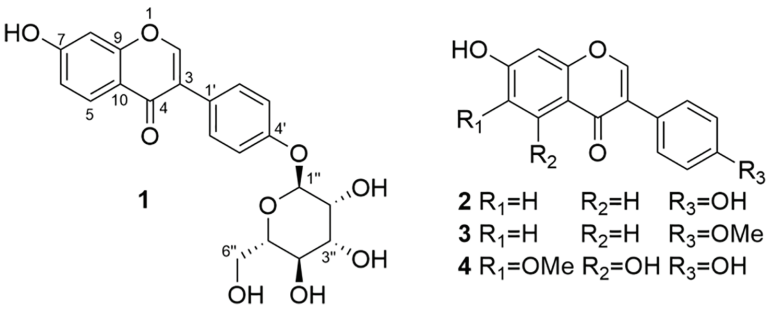

Figure 2. Chemical structures of mannodaidzein (**1**), daidzein (**2**), formononetine (**3**), and tectorigenin (**4**)

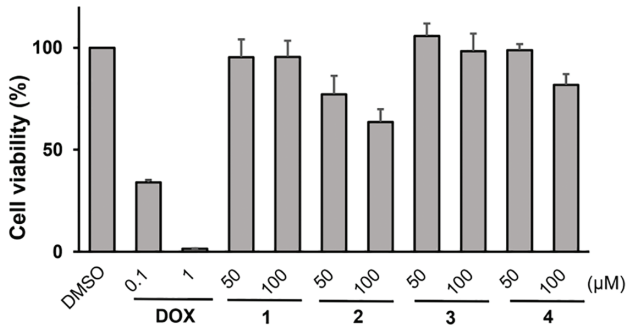

Figure 3. Cytotoxicity of compounds **1**–**4**. Negative control: DMSO; Positive control: doxorubicin (DOX)

HMBC correlations from the methine proton of H-1″ to C-4′ indicated a linkage between C-1″ and C-4′. Taken together, the structure of **1** was elucidated as drawn in Figure 2.

It is intriguing that daidzein glycoside was not detected in the culture broth, despite the presence of glucose in the ISP2 medium. A possible explanation is that the rare actinomycete *Saccharothrix* sp. JS2 may utilize the glucose to produce mannose.

The four compounds (**1**–**4**) were finally tested for their cytotoxicity against HT1080 cells, with doxorubicin serving as a positive control and DMSO as a negative control. Among the four isoflavones, only **2** exhibited weak cytotoxicity against HT1080 cells at 100 μM (Figure 3). The result was consistent with the previous report, which indicated that daidzein (**2**) exhibited weak anti-proliferative activity against cancer cells at high doses (Han et al., 2015). Both compound **1**, a glycosylated derivative of **2**, and compound **3**, a methylated derivative of **2**, showed no cytotoxicity even at 100 μM, indicating that the -OH group at the C-4′ position played an important role in its cytotoxicity, and modifications of the -OH group gave a negative effect on its cytotoxicity.

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Author Contributions

Shan Lu and Xinhang Su: Original draft preparation, performing the experiments. Linging Ren and Chengqian Pan: data analysis. Shan Lu, Chengqian Pan, and Di Mao: review and editing, funding acquisition, and supervision. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and the Supplementary Information file.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Supporting Information

Supplementary data associated with this article can be found online at: http://www.acgpubs.org/journal/records-of-natural-products.

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References

Chen, S., Wang, X., Cheng, Y., Gao, H. & Chen, X. (2023). A review of classification, biosynthesis, biological activities and potential applications of flavonoids. *Molecules*, *28*(13), 4982. DOI: 10.3390/molecules28134982.

Demain, A. L. & Sanchez, S. (2009). Microbial drug discovery: 80 years of progress. *The Journal of Antibiotics*, *62*(1), 5–16. DOI: 10.1038/ja.2008.16.

Granados-Covarrubias, E. H. & Maldonado, L. A. (2009). A Wacker-Cook synthesis of isoflavones: formononetine. *Tetrahedron Letters*, *50*(14), 1542–1545. DOI: 10.1016/j.tetlet.2009.01.041.

Han, B. J., Li, W., Jiang, G. B., Lai, S., Zhang, C., Zeng, C. & Liu, Y. (2015). Effects of daidzein in regards to cytotoxicity in vitro, apoptosis, reactive oxygen species level, cell cycle arrest and the expression of caspase and Bcl-2 family proteins. *Oncology Reports*, *34*(3), 1115–1120. DOI: 10.3892/or.2015.4133.

Huang, W., Xu, S., Lin, R., Xiong, X., Song, J., Liu, Y. & Li, J. (2025). Enzymatic synthesis of biflavonoid glycosides with enhanced antitumor activity using glycosyltransferase and sucrose synthase. *Journal of Agricultural and Food Chemistry*, *73*(8), 4807–4819. DOI: 10.1021/acs.jafc.4c11335.

Kakeya, H. (2016). Natural products-prompted chemical biology: phenotypic screening and a new platform for target identification. *Natural Product Reports*, *33*(5), 648–654. DOI: 10.1039/c5np00120j.

Khodzhaieva, R. S., Gladkov, E. S., Kyrychenko, A. & Roshal, A. D. (2021). Progress and achievements in glycosylation of flavonoids. *Frontiers in Chemistry*, *9*, 637994. DOI: 10.3389/fchem.2021.637994.

Klein, T., Abgottspon, D., Wittwer, M., Rabbani, S., Herold, J., Jiang, X., Kleeb, S., Luthi, C., Scharenberg, M., Bezençon, J., Gubler, E., Pang, L., Smiesko, M., Cutting, B., Schwardt, O. & Ernst, B. (2010). FimH antagonists for the oral treatment of urinary tract infections: from design and synthesis to in vitro and in vivo evaluation. *Journal of Medicinal Chemistry*, *53*(24), 8627–8641. DOI: 10.1021/jm101011y.

Lu, S., Li, Z., Jiang, P., Jiang, B., Huang, S., Su, X., Ma, K., Xu, Y., Ding, L. & Mao, D. (2025). Design, synthesis and biological evaluation of Streptazolin analogs as anti-inflammatory agents. *Bioorganic & Medicinal Chemistry Letters*, *120*, 130139. DOI: 10.1016/j.bmcl.2025.130139.

Maatooq, G. T. & Rosazza, J. P. N. (2005). Metabolism of daidzein by Nocardia species NRRL, 5646 and Mortierella isabellina ATCC 38063. *Phytochemistry*, *66*(9), 1007–1011. DOI: 10.1016/j.phytochem.2005.03.013.

Mao, D., Wei, B., Liu, C., Zhang, B., Zhang, Z., Zhang, Y., Li, Z., Ding, B., Ye, H., Wang, J., Sun, L., Gai, Y., Yu, P., Kakeya, H. & Lu, S. (2025). Discovery, total synthesis, and biological evaluation of tyrcinnamins as antibacterial agents and tyrosinase activators. *European Journal of Medicinal Chemistry*, *291*, 117665. DOI: 10.1016/j.ejmech.2025.117665.

Newman, D. J. & Cragg, G. M. (2012). Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of Natural Products*, *75*(3), 311–335. DOI: 10.1021/np200906s.

Nguyen, T. T. H., Jin, J., Septiana, I., Quereshi, D., Pal, K. & Kim, D. (2020). Enzymatic synthesis of flavonoid glucosides and their biochemical characterization. In: *Biopolymer-Based Formulations*. Elsevier, 47–66. DOI: 10.1016/B978-0-12-816897-4.00002-3.

Shriner, R. L., Matson, E. J. & Damschroder, R. E. (1939). Derivatives of Coumaran. IV. The structure of tectorigenin. *Journal of the American Chemical Society*, *61*(9), 2322–2327. DOI: 10.1021/ja01878a017.

Wang, J. F., Liu, S. S., Song, Z. Q., Xu, T. C., Liu, C. S., Hou, Y. G., Huang, R. & Wu, S. H. (2020). Naturally occurring flavonoids and isoflavonoids and their microbial transformation: a review. *Molecules*, *25*(21), 5112. DOI: 10.3390/molecules25215112.

Wei, B., Luo, X., Zhou, Z., Hu, G., Li, L., Lin, H. & Wang, H. (2024). Discovering the secondary metabolic potential of Saccharothrix. *Biotechnology Advances*, *70*(2), 108295. DOI: 10.1016/j.biotechadv.2023.108295.

Wu, G., Zhao, Z., Hu, J., Li, Y., Sun, J. & Bai, W. (2024). Optimized synthesis and antioxidant activity of anthocyanins delphinidin-3-O-glucoside and petunidin-3-*O*-glucoside. *Journal of Agricultural and Food Chemistry*, *72*(26), 15005–15012. DOI: 10.1021/acs.jafc.4c03237.