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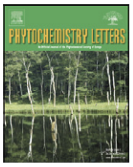

Antibacterial and cytotoxic xanthones from *Cratoxylum cochinchinense*

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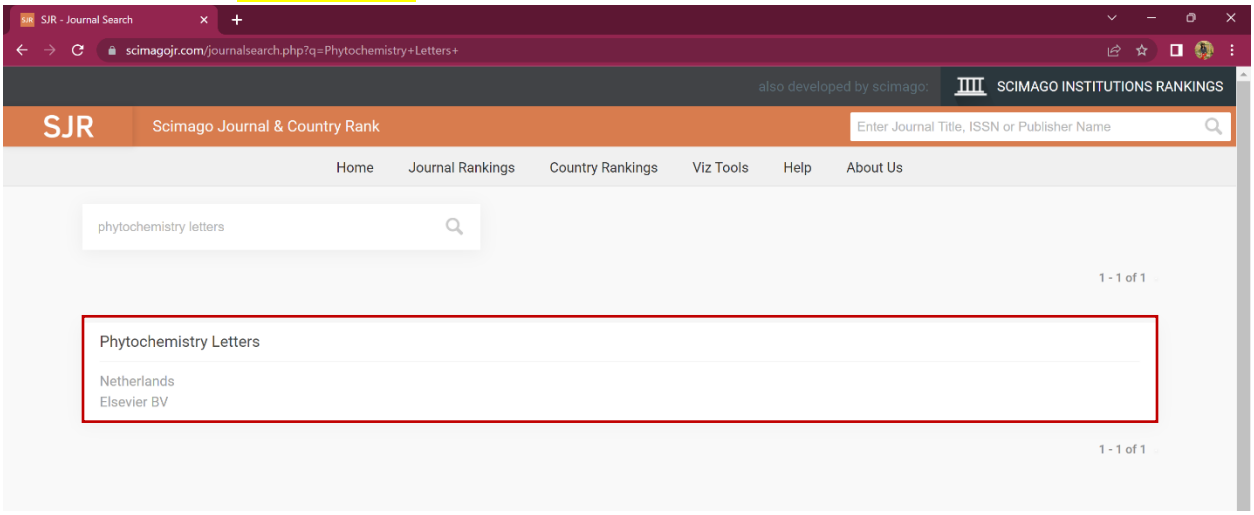

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Two furanoxanthones from the bark of *Cratoxylum cochinchinense*

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ABSTRACT

Two undescribed furanoxanthones, cratocochinones A (**1**) and B (**2**), along with eight known xanthones (**3–10**), were isolated from the bark of *Cratoxylum cochinchinense*. Their structures were elucidated using spectroscopic methods, mainly 1D and ^{2}D NMR. The isolated compounds were investigated for α-glucosidase inhibitory activity. Seven compounds, **3-6** and **8-10**, displayed stronger inhibitory effects than the positive control, acarbose. Especially, cochinxanthone A (**6**) showed remarkable inhibition with an IC_{50} value of 59.6 μM, which was approximately 16-fold more potent than acarbose.

1. Introduction

Cratoxylum cochinchinense (Lour.) Blume is one of six species in the *Cratoxylum* genus (Hypericaceae), which are widely distributed in many parts of Southeast Asia (Bennett and Lee, 1989; worldfloraonline.org, 2022). In Vietnam, it has been extensively used in folk medicine for the treatment of fevers, coughs, diarrhoea, itches, ulcers, scabies, burns, bruises and abdominal discomfort (Pham, 2006; Vo, 1997). In Thailand, the water extract of the roots and stems is used as a diuretic drug (Phuwapraisirisan et al., 2006). As a traditional Chinese medicine, it has been used to treat yellow jaundice, diarrhea, edema, the common cold and hoarseness (Yu et al., 2009). The species biosynthesizes a variety of polyisoprenylated xanthones as the major components (Duan et al., 2012; Juanda et al., 2019), which exhibit various biological activities including cytotoxic (Mahabusarakam et al., 2008), antioxidant (Phuwapraisirisan et al., 2006), antimalarial (Laphookhieo et al., 2009), antibacterial and antifungal (Boonnak et al., 2009) properties as well as enzyme inhibitory activities such as α-glucosidase, protein-tyrosine phosphatase 1B (Li et al., 2018a,b) and acetylcholinesterase (Raksat et al., 2015) inhibition.

As a part of our continuous search for xanthones having α-glucosidase inhibition (Trinh et al., 2017; Nguyen et al., 2017), we investigated the bark of *C. cochinchinense*. In this work, we report the isolation and structure elucidation of ten xanthones including two undescribed ones, cratocochinones A (**1**) and B (**2**). All the isolated compounds were evaluated *in vitro* for their α-glucosidase inhibitory activity.

2. Results and discussion

The EtOAc extract of the bark of *C. cochinchinense* was subjected to extensive column chromatography to afford two undescribed xanthones, cratocochinones A (**1**) and B (**2**), and eight known ones, 1,3,7-trihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-4-(3-methylbut-2-enyl) xanthone (**3**) (Nguyen et al., 2011), cratoxanthone A (**4**) (Ito et al., 2017), cratoxanthone F (**5**) (Li, b et al., 2018), cochinxanthone A (**6**) (Laphookhieo et al., 2008), 12α-mangostanin (**7**) (Han et al., 2009), 6-hydroxycalabaxanthone (**8**) (Trisuwan et al., 2012), mangostenol (**9**) (Suksamrarn et al., 2002) and garcinone B (**10**) (Sen et al., 1982) (Fig. 1).

Compound **1** was obtained as yellowish needles, m.p. 235–240 °C, $[\alpha]_D^{25}$ + 42.0 (*c* 0.47, MeOH). The UV spectrum showed four maxima at 239, 268, 324 and 318 nm whilst the IR spectrum exhibited absorption bands at 3428 (O–H), 1654 (conjugated C=O), 1230 (C–O) cm^{-1}. HRESIMS revealed the molecular formula to be $C_{23}H_{24}O_6$ (*m/z* 395.1501 $[M\text{-}H]^-$, calcd. 395.1500), *i.e.*, the molecule had 12 degrees of unsaturation. The ^{1}H and ^{13}C NMR spectra (Table 1) displayed resonances for a chelated hydroxy group [δ_H 13.45 (s, 1-OH)] and the corresponding chelated xanthone carbonyl [δ_C 181.1 (C-9)], a free phenolic hydroxy group [δ_H 9.04 (s, 7-OH)], an alcoholic hydroxy group [δ_H 3.85 (br s, 18-OH)], a 1,2,4-trisubstituted benzene ring [δ_H 7.57 (1H, d, *J* =

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Table 2
α-Glucosidase inhibition of **3–6** and **8–10**.

Compound	IC_{50} values (μM)
3	136.1 ± 3.22
4	222.6 ± 6.98
5	114.9 ± 2.47
6	59.6 ± 3.67
8	334.8 ± 7.19
9	437.6 ± 5.55
10	292.6 ± 2.42
Acarbose[a]	950.4 ± 9.36

Values are expressed as mean ± standard deviation (n = 3)
[a] Positive control.

yield eight subfractions (E6.1–8). Repeated CC of fraction E6.4 (1.5 g) (Diol silica, 0–10% isopropanol−hexane and 0–30% EtOAc−$CHCl_3$) followed by purification using CC (RP-18, 60–100% acetone−H_2O) furnished cratoxanthone A (**4**, 4.6 mg) and cratoxanthone F (**5**, 7.8 mg). Purification of fraction E7 (16.3 g) using repeated CC (silica gel, 0–70% EtOAc−hexane) afforded 1,3,7-trihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)− 4-(3-methylbut-2-enyl)xanthone (**3**, 7.4 mg) and mangostenol (**9**, 5.9 mg). In a similar way, fraction E8 (8.4 g) produced 12α-mangostanin (**7**, 5.5 mg).

Cratocochinone A (**1**): yellowish needles, m.p. 235–240 °C (isopropanol-hexane), $[\alpha]_D^{25}$ + 42.0 (*c* 0.47, MeOH), UV (EtOH) λ_{max} (nm): 239, 268, 324 and 318. IR ν_{max} (cm^{-1}): 3428, 2919, 2854, 1654, 1465, 1388, 1230, 1126, 771. ^1H (500 MHz) and ^{13}C (125 MHz) NMR, acetone-d_6: see Table 1. HMBC: see Table 1, Fig. 2. HRESIMS: *m/z* $[M\text{-}H]^-$ calcd. for $C_{23}H_{23}O_6^-$ 395.1500, found 395.1501.

Cratocochinone B (**2**): yellowish needles, m.p. 190–192 °C (isopropanol-hexane), UV (EtOH) λ_{max} (nm): 220 (sh), 229 (sh), 264, 274. IR ν_{max} (cm^{-1}): 3436, 2919, 2854, 1720, 1646, 1461, 1376, 1272, 1110, 767, 728. ^1H (500 MHz) and ^{13}C (125 MHz) NMR, $CDCl_3$: see Table 1. HMBC: see Table 1, Fig. 2. HRESIMS: *m/z* $[M\text{-}H]^-$ calcd. for $C_{20}H_{15}O_5^-$ 335.0925, found 335.0927. Table 2.

3.4. *In vitro α-glucosidase inhibition assay*

The α-glucosidase inhibitory activity was determined according to the method of Kim et al. (Kim et al., 2008) with modification. The experiment was performed with 1.6 mL phosphate buffer (0.01 mM, pH 7.0), 300 μL sample (at five different concentrations in DMSO) and 20 μL α-glucosidase (10 U/mL). All were incubated at 37 °C for 10 min, and then, 20 μL of pNPG (1.5 mM) was added to the reaction mixture, stood at 37 °C for 30 min. The reaction was stopped by adding 2 mL of Na_2CO_3 solution (0.1 M). Enzymatic activity was quantified by measuring absorbance at 405 nm using a UV-Vis spectrophotometer. The α-glucosidase inhibition was calculated as follows: *α-glucosidase inhibition activity (%)* $= 100 \times [1\text{-}(A_{sample} - A_{s\_blank})/A_{control}]$, where A_{sample} represents the absorbance of the reaction system containing the test sample, enzyme, and substrate, whilst A_{s_blank} represents the absorbance of the reaction system containing the test sample and substrate but no enzyme; $A_{control}$ represents the absorbance of the reaction system containing the enzyme and substrate but no test sample. Acarbose was used as the positive control. Compounds were first screened at 500 μg/mL concentration, at which % inhibition was measured, to identify the active compounds. Compounds with a percent inhibition greater than 50% were chosen for the IC_{50} determination. The IC_{50} values were determined by a nonlinear regression analysis using Excel 2016 (Office 365).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phytol.2022.07.002.

References

Bennett, G.J., Lee, H.H., 1989. Xanthones from guttiferae. Phytochemistry 28, 967–998.
Boonnak, N., Karalai, C., Chantrapromma, S., Ponglimanont, C., Fun, H.K., Kanjana-Opas, A., Chantrapromma, K., Kato, S., 2009. Anti-*Pseudomonas aeruginosa* xanthones from the resin and green fruits of *Cratoxylum cochinchinense*. Tetrahedron 65, 3003–3013.
Duan, Y., Dai, Y., Chen, L., Liu, M., Li, Y., Yao, X., 2012. Xanthones from the stems of *Cratoxylum cochinchinense*. Magn. Reson. Chem. 50, 642–645.
Han, A.R., Kim, J.A., Lantvit, D.D., Kardono, L.B.S., Riswan, S., Chai, H., Kinghorn, A.D., 2009. Cytotoxic xanthone constituents of the stem bark of *Garcinia mangostana* (Mangosteen). J. Nat. Prod. 72, 2028–2031.
Ito, C., Matsui, T., Niimi, A., Tan, H., Itoigawa, M., 2017. Four new xanthones from *Cratoxylum cochinchinense* and their *in vitro* antiproliferative effects. Planta Med. 83, 812–818.
Juanda, D., Fidrianny, I., Ruslan, K., Insanu, M., 2019. Overview of phytochemical compounds and pharmacology activities of *Cratoxylum* genus. Rasayan J. Chem. 12, 2065–2073.
Kim, K.Y., Nam, K.A., Kurihara, H., Kim, S.M., 2008. Potent α-glucosidase inhibitors purified from the red alga *Grateloupia elliptica*. Phytochemistry 69, 2820–2825.
Laphookhieo, S., Maneerat, W., Buatip, T., Syers, J.K., 2008. New xanthones from *Cratoxylum cochinchinense*. Can. J. Chem. 86, 757–760.
Laphookhieo, S., Maneerat, W., Koysomboon, S., 2009. Antimalarial and cytotoxic phenolic compoundsfrom *Cratoxylum maingayi* and *Cratoxylum cochinchinense*. Molecules 14, 1389–1395.
Li, Z.P., Song, Y.H., Uddin, Z., Wang, Y., Park, K.H., 2018a. Caged xanthones displaying protein tyrosine phosphatase 1B (PTP1B) inhibition from *Cratoxylum cochinchinense*. Bioorg. Chem. 78, 39–45.
Li, Z.P., Song, Y.H., Uddin, Z., Wang, Y., Park, K.H., 2018b. Inhibition of protein tyrosine phosphatase 1B (PTP1B) and α-glucosidase by xanthones from *Cratoxylum cochinchinense*, and their kinetic characterization. Bioorg. Med. Chem. 26, 737–746.
Mahabusarakam, W., Rattanaburi, S., Phongpaichit, S., Kanjana-Opas, A., 2008. Antibacterial and cytotoxic xanthones from *Cratoxylum cochinchinense*. Phytochem. Lett. 1, 211–214.
Nguyen, C.N., Trinh, B.T.D., Tran, T.B., Nguyen, L.T.T., Jäger, A.K., Nguyen, L.H.D., 2017. Anti-diabetic xanthones from the bark of *Garcinia xanthochymus*. Bioorg. Med. Chem. Lett. 27, 3301–3304.
Nguyen, H.D., Trinh, B.T.D., Nguyen, N.K., Dang, S.V., Pham, H.D., Nguyen, L.H.D., 2011. Xanthones from the twigs of *Cratoxylum cochinchinense*. Phytochem. Lett. 4, 48–51.
Pham, H.H., 2006. Vietnamese Medicinal Plants. Youth Publishing House, Ho Chi Minh City.
Phuwapraisirisan, P., Udomchotphruet, S., Surapinit, S., Tip-Pyang, S., 2006. Antioxidant xanthones from *Cratoxylum cochinchinense*. Nat. Prod. Res. 20, 1332–1337.
Raksat, A., Sripisut, T., Maneerat, W., 2015. Bioactive xanthones from *Cratoxylum cochinchinense*. Nat. Prod. Commun. 10, 1969–1972.
Schmidt, J.S., Lauridsen, M.B., Dragsted, L.O., Nielsen, J., Staerk, D., 2012. Development of a bioassay-coupled HPLC-SPE-ttNMR platform for identification of α-glucosidase inhibitors in apple peel (*Malus* × *domestica* Borkh.). Food Chem. 135, 1692–1699.
Sen, A.K., Sarkar, K.K., Mazumder, P.C., Banerji, N., Uusvuori, R., Hase, T.A., 1982. The structures of garcinones A, B and C: three new xanthones from *Garcinia mangostana*. Phytochemistry 21, 1747–1750.
Suksamrarn, S., Suwannapoch, N., Ratananukul, P., Aroonlerk, N., Suksamrarn, A., 2002. Xanthones from the green fruit hulls of *Garcinia mangostana*. J. Nat. Prod. 65, 761–763.
Trinh, B.T.D., Quach, T.T., Bui, D.N., Staerk, D., Nguyen, L.H.D., Jäger, A.K., 2017. Xanthones from the twigs of *Garcinia oblongifolia* and their anti-diabetic activity. Fitoterapia 118, 126–131.
Trisuwan, K., Ritthiwigrom, T., 2012. Benzophenone and xanthone derivatives from the inflorescences of *Garcinia cowa*. Arch. Pharm. Res. 10, 1733–1738.
Vo, V.C., 1997. Dictionary of Vietnamese Medicinal Plants, Medical Publishing House, Ha Noi.
Yu, H.Y., Jin, S.L., Zhang, X., Liu, Y., Ou, Y.F., Wang, N.L., Yao, X.S., 2009. Two new benzophenone glucosides from *Cratoxylon cochinchinensis*. Chin. Chem. Lett. 20, 459–461.
WFO (2022): *Cratoxylum* Blume, ⟨http://www.worldfloraonline.org/taxon/wfo-4000009617⟩. Accessed on: 28 Apr 2022.