Iván Brito*, Jorge Bórquez, Mario Simirgiotis and Alejandro Cárdenas

Crystal structure of 5-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3,7,8-trimethoxy-4*H*-chromen-4-one, C₁₉H₁₈O₈

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.22 × 0.20 × 0.10 mm
Wavelength:	Cu K α radiation (1.54178 Å)
μ :	0.94 mm ⁻¹
Diffractometer, scan mode:	Bruker D8-Venture, φ and ω -scans
$\theta_{\max}$, completeness:	59.6°, >98%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	27492, 2531, 0.317
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 1251
$N(\text{param})_{\text{refined}}$:	251
Programs:	Bruker programs [27], SHELX [28], OLEX2 [29]

ditions and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

The title compound is a highly biologically active polymethoxylated flavonoid, which is anti-inflammatory and antiproliferative [1, 2], can inhibit leukocyte chemotaxis and oxygen free radical formation [3, 4] and prevents cyclophosphamide and ifosfamide-induced hemorrhagic cystitis in rats [5]. The title compound was isolated using medium pressure column chromatography (MPCC) from *Parastrephia quadrangularis*, a medicinal plant used by the Aymara Amerindians [6, 7], a known producer of several flavonoids and benzoic acid derivatives with antioxidant activity [8–11]. Following our program to isolate interesting metabolites from the Atacama Desert Flora, Northern Chile [12–18], dried aerial parts of *P. quadrangularis* (1622 g) collected in april 2015 in “El Tatio”, Andean mountain range of the of Atacama Desert, II Region, Northern Chile, were defatted with hexane (3 liters, 3 times in the dark, 24 hours each time) and 54.82 g were obtained after evaporation of the solvent. Then the plant material was extracted with ethyl acetate (3 liters, 3 times in the dark, 24 hours each time). After evaporation of the solvent under *vacuo* at 40 °C, 485 g of a dark gummy extract was obtained. A portion of the extract (10.0 g) was filtered and submitted to a medium pressure column chromatography system composed of an 2.5 cm × 48 cm medium pressure column packed with silicagel using an isocratic solvent system of

<https://doi.org/10.1515/ncrs-2017-0141>

Received July 13, 2017; accepted October 23, 2017; available online November 16, 2017

Abstract

C₁₉H₁₈O₈, monoclinic, $P2_1/c$ (no. 14), $a = 12.689(2)$ Å, $b = 20.321(4)$ Å, $c = 7.0820(13)$ Å, $\beta = 105.368(13)^\circ$, $V = 1760.8(6)$ Å³, $Z = 4$, $R_{\text{gt}} = 0.0662$, $wR_{\text{ref}}(F^2) = 0.1788$, $T = 295$ K.

CCDC no.: 1581467

The title crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement con-

***Corresponding author: Iván Brito**, Departamento de Química, Facultad de Ciencias Básicas, Universidad de Antofagasta, Casilla 170, Antofagasta, Chile, e-mail: ivanbritob@yahoo.com

Jorge Bórquez: Departamento de Química, Facultad de Ciencias Básicas, Universidad de Antofagasta, Casilla 170, Antofagasta, Chile

Mario Simirgiotis: Instituto de Farmacia, Facultad de Ciencias, Universidad Austral de Chile, casilla 567, Valdivia 5090000, Chile

Alejandro Cárdenas: Departamento de Física, Facultad de Ciencias Básicas, Universidad de Antofagasta, Casilla 170, Antofagasta, Chile

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
O1	0.6930(2)	0.39194(13)	0.6743(4)	0.0469(9)
O2	0.4768(2)	0.39502(15)	0.6405(5)	0.0586(10)
O3	0.3695(2)	0.28331(15)	0.6637(5)	0.0666(11)
O4	0.6911(2)	0.15607(13)	0.7049(5)	0.0654(10)
H4	0.7569	0.1618	0.7230	0.098*
O5	0.8656(2)	0.22207(14)	0.6981(5)	0.0586(10)
O6	0.9641(2)	0.34225(13)	0.6641(4)	0.0538(9)
O7	1.0806(2)	0.56956(13)	0.7812(5)	0.0570(10)
O8	0.9222(2)	0.66056(13)	0.6624(5)	0.0620(10)
H8	0.9888	0.6646	0.7001	0.093*
C1'	0.8346(3)	0.46317(19)	0.6687(7)	0.0406(12)
C2'	0.9446(3)	0.4822(2)	0.7249(7)	0.0453(13)
H2'	0.9983	0.4502	0.7637	0.054*
C3'	0.9753(3)	0.5473(2)	0.7243(6)	0.0423(12)
C4'	0.8951(4)	0.5955(2)	0.6645(7)	0.0458(12)
C5'	0.7876(3)	0.5781(2)	0.6054(7)	0.0486(13)
H5'	0.7347	0.6103	0.5619	0.058*
C6'	0.7563(3)	0.5127(2)	0.6097(7)	0.0479(13)
H6'	0.6825	0.5018	0.5729	0.057*
C2	0.8006(3)	0.3949(2)	0.6779(6)	0.0389(12)
C3	0.8600(3)	0.3391(2)	0.6846(6)	0.0424(12)
C4	0.8125(3)	0.2743(2)	0.6939(6)	0.0446(12)
C5	0.6404(4)	0.2148(2)	0.6947(7)	0.0473(13)
C6	0.5310(4)	0.2166(2)	0.6854(7)	0.0538(14)
H6	0.4926	0.1776	0.6859	0.065*
C7	0.4774(3)	0.2771(2)	0.6750(7)	0.0489(13)
C8	0.5325(3)	0.3358(2)	0.6675(7)	0.0464(12)
C9	0.6415(3)	0.3330(2)	0.6786(6)	0.0399(12)
C10	0.6998(3)	0.2739(2)	0.6918(6)	0.0419(12)
C16	0.4761(5)	0.4283(3)	0.8144(10)	0.109(2)
H16A	0.4480	0.4720	0.7836	0.163*
H16B	0.5492	0.4307	0.8977	0.163*
H16C	0.4306	0.4049	0.8805	0.163*
C17	0.3041(4)	0.2245(2)	0.6496(8)	0.0830(19)
H17C	0.3098	0.1992	0.5383	0.125*
H17A	0.2291	0.2365	0.6347	0.125*
H17B	0.3298	0.1988	0.7664	0.125*
C18	1.0481(4)	0.3224(2)	0.8311(8)	0.0777(19)
H18A	1.1181	0.3326	0.8109	0.117*
H18B	1.0430	0.2759	0.8505	0.117*
H18C	1.0396	0.3454	0.9446	0.117*
C19	1.1645(3)	0.5215(2)	0.8348(7)	0.0569(14)
H19A	1.1604	0.4923	0.7265	0.085*
H19B	1.1554	0.4968	0.9450	0.085*
H19C	1.2345	0.5429	0.8691	0.085*

n-hexane-ethyl acetate (8.0:2.0 v:v) pumped with a medium pressure pump with a flow rate of 10 mL-minute. The collected fractions (120) were combined according to TLC analysis (Kieselgel F254 plates, developed with hexane: EtOAc 7:3 v/v, and spots visualized by spraying with vanillin: sulfuric acid 2% in ethanol and heating) and twenty combined fractions were obtained. Fraction 15, enriched in flavonoids

(120 mg) was re-chromatographed using Sephadex LH 20 (200 g, solvent methanol) and 60 fractions (S1–S60) were obtained. From fractions S25–33, the known compound: 5,7,4'-trihydroxy-3,8,3'-trimethoxyflavone (25 mg) was isolated and from fractions S45–57 the title compound (15 mg) was isolated. The NMR data for both compounds are consistent with literature [19–23]. Recrystallization from ethyl acetate at room temperature yielded pure yellow crystals of the title compound (8 mg). Yellow crystals, m.p. 215–217 °C. The molecular weight was determined by **HESI-MS/MS** with a mass spectrometer (Q-exactive Focus, Bremen, Germany) [M–H][–]: 373.09290, calcd. for C₁₉H₁₇O₈[–]: 373.09289. **¹H NMR** (Bruker Avance 300 MHz, CDCl₃) δ ppm: 7.80 (1H, s, H-2'), 7.79 (1H, d, J = 9.0 Hz, H-6'), 7.07 (1H, d, J = 9.0 Hz, H-5'), 6.42 (1H, s, H-6), 6.09 (1H, s, 4'-OH), 12.5 (1H, s, 5-OH), 3.99 (3H, s, OCH₃), 3.95 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 3.88 (3H, s, OCH₃). **¹³C NMR** (¹³C NMR Bruker Avance 75 MHz, DMSO-d₆) δ ppm: 158.4 (C-2), 138.6 (C-3), 179.01 (C-4), 157.3 (C-5), 95.4 (C-6), 155.8 (C-7), 128.7 (C-8), 148.5 (C-9), 105.3 (C-10), 122.9 (C-1'), 110.8 (C-2'), 148.4 (C-3'), 146.4 (C-4'), 114.8 (C-5'), 122.6 (C-6'), 61.6 (O-CH₃), 60.2 (O-CH₃), 56.4 (O-CH₃), 56.0 (O-CH₃). These data, together with ESI-MS/MS and correlations observed in the HSQC and HMBC spectra, are consistent with the structure of the title compound (*cf.* the figure) confirmed by comparison of spectroscopic data with those reported in the literature for this structure [19, 20] and other similar methoxylated flavones [21–23].

Experimental details

H atoms were refined with fixed individual displacement parameters, using a riding model with C–H distances of 0.93 Å (for aromatic rings), 0.96 Å (for CH₃ group) and O–H of 0.86 Å with U(H) values of 1.2U_{eq}(C,O) (for CH in aromatic moiety and OH group), and 1.5U_{eq}(C) (for CH₃). Problems during data collection and the successive reduction yielded many reflections with a negative intensity, which produced a non-optimal *R*_{int} factor. Nevertheless the topology of this structure is in any case correct.

Discussion

The title compound (1) is a positional isomer of 5-hydroxy-2-(3'-hydroxy-4-methoxyphenyl)-3,6,7'-trimethoxychromen-4-one (casticin) (2) [24] and 5,12-Dihydroxy-2,6,7,13-tetramethoxyflavone (3) [25]. In the compounds (2) and (3) the fused chromene ring system and the benzene ring bonded to it are close to coplanar, with a dihedral angle between their respective mean planes of: 8.30(12)° and 2.7(1)° for (2) and (3) respectively, however for the compound (1) the dihedral angle value is 17.17(18)°, which is the main difference with the isomers (2) and (3). The two hydroxy H atoms of the title compound are involved in intramolecular and

intermolecular O—H···O hydrogen bonding in the solid state. Intramolecular O4—H4···O5 and intermolecular O8—H8···O5 ($2 - x$, $1/2 + y$, $1/2 - z$) hydrogen bonds and π - π interactions help to stabilize the crystal structure. In the crystal packing the molecules are associated by one strong intermolecular hydrogen bond forming zig-zag chain with graph-set motif C(10) [26] along [010] direction. All distances and angles are normal and comparable with the compounds (2) and (3).

Acknowledgements: IB thanks to Fondecup (EQM13-0021). JB and MS thanks to FONDECYT (Chile) (Grant 1140178) and DID-PEF 2017 Universidad Austral de Chile for financial support.

References

- Pessoa, C.; Silveira, E. R.; Lemos, T. L. G.; Wetmore, L. A.; Moraes, M. O.; Leyva, A.: Antiproliferative effects of compounds derived from plants of Northeast Brazil. *Phytother. Res.* **14** (2000) 187–119.
- Souza, M. F.; Rao, V. S. N.; Silveira, E. R.: Antianaphylactic and antiinflammatory effects of ternatin, a flavonoid isolated from *egletes-viscosa* less. *Braz. J. Med. Biol. Res.* **25** (1992) 1029–1032.
- Souza, M. F.; Cunha, G. M. A.; Fontenele, J. B.; Viana, G. S. B.; Rao, V. S. N.; Silveira, E. R.: Antithrombotic activity of ternatin, a tetramethoxy flavone from *Egletes viscosa* less. *Phytother. Res.* **8** (1994) 478–481.
- Rao, V. S. N.; Figueiredo, E. G.; Melo, C. L.; Viana, G. S. B.; Menezes, D. B.; Matos, M. S. F.; Silveira, E. R.: Protective effect of ternatin, a flavonoid isolated from *Egletes viscosa* less., in experimental liver injury. *Pharmacology* **48** (1994) 392–397.
- Vieira, M. M.; Macedo, F. Y. B.; Belarmino, J. N.; Costa, A.; Cunha, A. N.; Silveira, E. R.; Brito, G. A. C.; Ribeiro, R. A.: Ternatin, a flavonoid, prevents cyclophosphamide and ifosfamide-induced hemorrhagic cystitis in rats. *Phytother. Res.* **18** (2004) 135–141.
- Cortes, A.; Rau, J. R.; Miranda, E.; Jimenez, J. E.: Hábitos alimenticios de *Lagidium viscacia* y *Abrocoma cinerea*: roedores sintópicos en ambientes altoandinos del norte de Chile. *Rev. Chil. Hist. Nat.* **75** (2002) 583–593.
- Moreira-Munoz, A.; Munoz-Schick, M.; Marticorena, A.; Morales, V.: Catálogo de Asteraceae (Compositae) de la Región de Arica y Parinacota, Chile. *Gayana Bot.* **73** (2016) 226–267.
- Loyola, L. A.; Naranjo, J.; Morales, G.: 5,7-Dihydroxy-3,8,3',4'-tetramethoxyflavone from *Parastrephia quadrangularis*. *Phytochemistry* **24** (1985) 1871–1872.
- Bohlmann, F.; Fritz, U.; King, R. M.: Tremeton-derivate aus *parastrephia lepidophylla*. *Phytochemistry* **18** (1979) 1403–1405.
- D'Almeida, R. E.; Alberto, M. R.; Quispe, C.; Schmeda-Hirschmann, G.; Isla, M. I.: Antimicrobial phenylpropanoids from the argentinean highland plant *Parastrephia lucida* (Meyen). *J. Ethnopharmacol.* **142** (2012) 407–414.
- Echiburú-Chau, C.; Pastén, L.; Parra, C.; Bórquez, J.; Mocan, A.; Simirgiotis, M. J.: High resolution UHPLC-MS characterization and isolation of main compounds from the antioxidant medicinal plant *Parastrephia lucida* (Meyen). *Saudi Pharm. J.* **25** (2017) 1032–1039.
- Bórquez, J.; Ardiles, A.; Loyola, L. A.; Peña-Rodríguez, L. M.; Molina-Salinas, G. M.; Vallejos, J.; Collado, I. G.; Simirgiotis, M. J.: Further mulinane and azorellane diterpenoids isolated from *mulinum crassifolium* and *azorella compacta*. *Molecules* **19** (2014) 3898–3908.
- Bórquez, J.; Bartolucci, N. L.; Echiburú-Chau, C.; Winterhalter, P.; Vallejos, J.; Jerz, G.; Simirgiotis, M. J.: Isolation of cytotoxic diterpenoids from the Chilean medicinal plant *Azorella compacta* Phil from the Atacama Desert by high-speed counter-current chromatography. *J. Sci. Food Agric.* **96** (2016) 2832–2838.
- Brito, I.; Bórquez, J.; Simirgiotis, M.; Neves-Vieira, M.; Jerz, G.; Winterhalter, P.; Bolte, M.; Cárdenas, A.: Crystal structure of nor-1,2-secolycoserone, C₂₄H₃₂O₄. *Z. Kristallogr. NCS* **229** (2014) 399–400.
- Brito, I.; Bórquez, J.; Simirgiotis, M.; Cardenas, A.; Lopez-Rodríguez, M.: 5-Dihydroxy-7-methoxyflavanone dihydrate 4'. *Acta Crystallogr.* **E68** (2012) o32–o33.
- Brito, I.; Bórquez, J.; Simirgiotis, M.; Cardenas, A.; Molina-Salinas, G. M.; Jerz, G.; Pena-Rodríguez, L. M.; Winterhalter, P.: Crystal structure of methyl 8-hydroxy-3-isopropyl-5a,8-dimethyl-2,3,4,5,5a,6,7,8,10a,10bdecahydrocyclohepta[e]indene-3a(1H)-carboxylate, C₂₁H₃₄O₃. *Z. Kristallogr. NCS* **231** (2016) 579–582.
- Brito, I.; Simirgiotis, M.; Jerz, G.; Werner, M. R.; Bórquez, J.; Winterhalter, P.; Cardenas, A.: Crystal structure of 3',4',5-trihydroxy-3,7-dimethoxyflavone, C₁₇H₁₄O₇. *Z. Kristallogr. NCS* **231** (2016) 113–115.
- Brito, I.; Simirgiotis, M.; Muñoz, R.; Benites, J.; Pasten, L.; Bórquez, J.; Cárdenas, A.: Crystal structure of 11-(p-coumaroyloxy)-tremetone, C₂₂H₂₀O₅. *Z. Kristallogr. NCS* **232** (2017) 13–14.
- Wollenweber, E.; Fischer, R.; Dörr, M.; Irvine, K.; Pereira, C.; Stevens Jan, F.: Chemodiversity of exudate flavonoids in *cassia* and *ozothamnus* (asteraceae, naphalieae). *Z. Naturforsch., C: Biosci.* **63** (2008) 731–739.
- Gedara Sahar, R.; Abdel-Halim Osama, B.; El-Sharkawy Saleh, H.; Salama Osama, M.; Shier Thomas, W.; Halim Ahmed, F.: New erythroxane-type diterpenoids from *fagonia boveana* (hadidi) hadidi & graf. *Z. Naturforsch. C* **58** (2003) 23–32.
- Yoo, H.; Kim, S. H.; Lee, J.; Kim, H. J.; Seo, S. H.; Chung, B. Y.; Jin, C.; Lee, Y. S.: Synthesis and antioxidant activity of 3-methoxyflavones. *Bull. Korean Chem. Soc.* **26** (2005) 2057–2060.
- Agrawal, P. K.: Carbon-13 NMR of Flavonoids. Elsevier, Michigan (1989).
- Modak, B.; Rojas, M.; Torres, R.: Chemical analysis of the resinous exudate isolated from *Heliotropium taltalense* and evaluation of the antioxidant activity of the phenolics components and the resin in homogeneous and heterogeneous systems. *Molecules* **14** (2009) 1980–1989.
- Asker, E.; Akin, S.; Hökelek, T.: 5,3'-Dihydroxy-3,6,7,4'-tetramethoxyflavone. *Acta Crystallogr.* **E62** (2006) o4159–o4161.
- Meng, Z.-L.; Qi, Y.-Y.; Liu, R.-M.; Sun, A.-L.; Wang, D.-Q.: 5,12-Dihydroxy-2,6,7,13-tetramethoxyflavone. *Acta Crystallogr.* **E62** (2006) o3831–o3832.

26. Bernstein, J.; Davis, R. E.; Shimon, L.; Chang, N.-L.: Patterns in hydrogen bonding: functionality and graph set analysis in crystals. *Angew. Chem. Int. Ed. Engl.* **34** (1995) 1555–1573.
27. Bruker: APEX3, SAINT Bruker AXS Inc., Madison, WI, USA (2016).
28. Sheldrick, G. M.: Crystal structure refinement with SHELXL. *Acta Crystallogr.* **C71** (2015) 3–8.
29. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H.: OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **42** (2009) 339–341.