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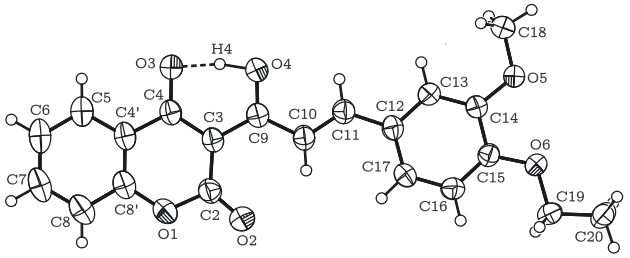
The crystal structure of (*E*)-3-((*E*)-3-(4-ethoxy-3-methoxyphenyl)-1-hydroxyallylidene) chroman-2,4-dione, $C_{21}H_{18}O_6$



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Abstract

$C_{21}H_{18}O_6$, triclinic, $P\bar{1}$ (no. 2), a = 7.2187(4) Å, b = 9.3833(7) Å, c = 13.6874(13) Å, α = 85.933(7)°, β = 81.991(7)°, γ = 69.983(7)°, V = 862.35(12) Å^3, Z = 2, $R_{gt}(F)$ = 0.0418, $wR_{ref}(F^2)$ = 0.1233, T = 295(2) K.

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Table 1: Data collection and handling.

Crystal:	Orange prism
Size:	0.47 × 0.15 × 0.05 mm
Wavelength:	Cu *K*α radiation (1.54184 Å)
μ:	0.86 mm^{-1}
Diffractometer, scan mode:	Gemini S (Oxford Diffraction), ω
θ_{max}, completeness:	71.9°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	11,582, 3,313, 0.037
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 2,711
$N(\text{param})_{refined}$:	250
Programs:	CrysAlis^{PRO},[1] SHELX,[2,3] PLATON[4]

The crystal structure of (*E*)-3-((*E*)-3-(4-ethoxy-3-methoxyphenyl)-1-hydroxyallylidene) chroman-2,4-dione is presented in the Figure. Table 1 provides the crystallographic data, while Table 2 lists the atoms along with their atomic coordinates and displacement parameters.

1 Source of material

The synthesis was performed in two reaction steps. First, 3-acetyl-4-hydroxycoumarin was obtained through the acetylation of 4-hydroxycoumarin, following a previously published method.[5] The final product was synthesized by condensing 3-acetyl-4-hydroxycoumarin and 4-ethoxy-3-methoxybenzaldehyde. The reaction was conducted in chloroform with a catalytic amount of piperidine. The resulting product was purified using silica gel column chromatography with a hexane/ethyl acetate solvent system (1.5:1, v/v) and dissolved in acetone. Crystals were formed by slow evaporation of the solvent.

2 Experimental details

All hydrogen atoms bonded to carbon were refined in idealized positions using the riding model, with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms) while the hydrogen atom associated with O4 was refined freely.

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
O1	0.26373 (18)	0.70819 (13)	0.86845 (8)	0.0602 (3)
O2	0.2553 (2)	0.53547 (13)	0.77192 (9)	0.0678 (3)
O3	0.12419 (17)	1.04453 (12)	0.65729 (8)	0.0557 (3)
O4	0.14091 (17)	0.86308 (12)	0.53843 (8)	0.0548 (3)
H4	0.130 (4)	0.953 (3)	0.583 (2)	0.122 (10)*
O5	0.24167 (19)	0.31571 (11)	0.17054 (8)	0.0582 (3)
O6	0.321 (15)	0.05743 (10)	0.26467 (7)	0.0490 (3)
C2	0.2402 (2)	0.66694 (17)	0.77696 (11)	0.0500 (3)
C3	0.19975 (19)	0.78362 (16)	0.69980 (10)	0.0436 (3)
C4	0.16871 (19)	0.93618 (16)	0.72158 (10)	0.0447 (3)
C4′	0.1915 (2)	0.97158 (18)	0.81951 (11)	0.0485 (3)
C5	0.1675 (2)	1.1184 (2)	0.84629 (13)	0.0584 (4)
H5	0.132310	1.198722	0.800924	0.070*
C6	0.1960 (3)	1.1437 (2)	0.93970 (14)	0.0675 (5)
H6	0.179293	1.241616	0.957415	0.081*
C7	0.2492 (3)	1.0251 (2)	1.00784 (13)	0.0681 (5)
H7	0.268985	1.043694	1.070749	0.082*
C8	0.2730 (3)	0.8802 (2)	0.98301 (13)	0.0647 (4)
H8	0.308835	0.800238	1.028627	0.078*
C8′	0.2428 (2)	0.85469 (19)	0.88864 (11)	0.0524 (4)
C9	0.18834 (19)	0.75110 (16)	0.60012 (11)	0.0444 (3)
C10	0.2306 (2)	0.60057 (17)	0.56356 (11)	0.0469 (3)
H10	0.271504	0.516090	0.605324	0.056*
C11	0.2108 (2)	0.58292 (17)	0.46991 (11)	0.0472 (3)
H11	0.169091	0.671376	0.431655	0.057*
C12	0.24665 (19)	0.44193 (16)	0.42081 (11)	0.0443 (3)
C13	0.2254 (2)	0.44822 (16)	0.32027 (11)	0.0464 (3)
H13	0.190514	0.541941	0.287236	0.056*
C14	0.2546 (2)	0.31961 (16)	0.26875 (10)	0.0434 (3)
C15	0.30254 (19)	0.17798 (15)	0.31929 (10)	0.0421 (3)
C16	0.3243 (2)	0.17098 (16)	0.41879 (11)	0.0474 (3)
H16	0.357210	0.077651	0.452321	0.057*
C17	0.2978 (2)	0.30107 (17)	0.46894 (11)	0.0482 (3)
H17	0.314339	0.293961	0.535489	0.058*
C18	0.2124 (4)	0.4547 (2)	0.11566 (14)	0.0791 (6)
H18A	0.228927	0.435567	0.046462	0.119*
H18B	0.307867	0.499006	0.128861	0.119*
H18C	0.080710	0.523295	0.134654	0.119*
C19	0.3832 (2)	−0.09025 (16)	0.31191 (12)	0.0505 (3)
H19A	0.292204	−0.092990	0.370696	0.061*
H19B	0.515258	−0.114294	0.330931	0.061*
C20	0.3828 (3)	−0.20250 (17)	0.23895 (13)	0.0587 (4)
H20A	0.250577	−0.179521	0.222362	0.088*
H20B	0.427211	−0.303074	0.267506	0.088*
H20C	0.470343	−0.196606	0.180379	0.088*

3 Comment

Naturally and synthetically derived hybrid molecules integrate two or more pharmacophoric units into one molecular scaffold. These structures are promising candidates for developing therapeutic agents due to their ability to exhibit diverse modes of action.[6] Coumarins and chalcones are two important classes of natural products recognized for their wide range of pharmacological activities.[7–13] These compounds are excellent building blocks for synthesizing the coumarin–chalcone hybrid scaffolds, which may serve as potent bioactive agents.[14] 4-Hydroxycoumarin occurs as the structural core of many natural products. At the same time, its chemical properties make it particularly interesting for chemical transformations.[15] The acetylation of 4-hydroxycoumarin produces 3-acetyl-4-hydroxycoumarin, an excellent precursor for synthesizing targeted coumarin–chalcone hybrids via Claisen–Schmidt condensation with aromatic aldehydes. Here, we report the crystal structure of one such compound.

The structure exhibits prototropic tautomerism, where a hydrogen atom migrates from the hydroxyl group O3 to the adjacent keto group O4. Similar behavior has been previously reported in 3-(1-(2-(4-hydroxy-3,5-dimethoxybenzylidene)hydrazinyl)ethylidene)chroman-2,4-dione dihydrate,[16] 3-(1-(2-((5-methylthiophen-2-yl) methylene)hydrazinyl)ethylidene)chroman-2,4-dione,[17] and (*Z*)-3-(1-(2-((*E*)-4-isopropylbenzylidene)hydrazinyl) ethylidene) chroman-2,4-dione,[18] where the hydrogen atom migrates from the hydroxyl group to a neighboring nitrogen atom.

The electron delocalization is evident in the O3–C4–C3–C9–O4 fragment, a feature characteristic of keto-enol tautomerism, where two oxygen atoms are bridged by resonance-assisted hydrogen bond. The formally double C4–O3 bond and formally single C9–O4 bond exhibit comparable lengths (1.2804(18) and 1.2817(18) Å, respectively), which are longer than typical C=O double bonds in cyclohexanones (1.211 Å), and shorter than C–OH single bonds in enols (1.333 Å).[19] Furthermore, the C3–C4 bond (1.418(2) Å) is shorter than typical Csp^2–Csp^2 single bonds (1.465 Å), while the C3–C9 bond (1.4383(19) Å) is longer than the expected Csp^2=Csp^2 double bond in enol tautomers (1.362 Å).[19] Geometrical parameters of the O4–H4···O3 hydrogen bond are as follows: *d*(D–H) = 1.05(3) Å, *d*(H···A) = 1.36(3) Å, *d*(D···A) = 2.3995(14) Å, *α*(D–H···A) = 167(3)°.

Intermolecular interaction energies were calculated using the CE-B3LYP model[20] via *CrystalExplorer*[21] revealing that two strongest interactions occur between the reference molecule and two neighbors stacked along crystallographic axis *a*. The dimer comprising the reference molecule and neighboring molecule, related by the symmetry operation $1-x, 1-y, 1-z$ exhibits an interaction energy of E_{int} = −88 kJ mol^{-1}, while the interaction with the neighboring molecule described by the symmetry operation $-x, 1-y, 1-z$ has E_{int} = −86 kJ mol^{-1}. Distances between mean molecular

planes are approximately 3.4 Å, with the molecules stacking in such a way that virtually all atoms are separated by slightly more than their van der Waals contact distances.

Three rings are involved in stacking interactions (Cg⋯Cg distance less than 4.5 Å): Ω(1) – O3–C4–C3–C9–O4–H4; Ω(2) – O1–C2–C3–C4–C4′–C8′, and Ω(3) – C12–C13–C14–C15–C16–C17. Dimer with strongest interaction involves Ω(1)⋯Ω(4) stacking with parameters d(Cg1⋯Cg4) = 3.864(5) Å, α = 1.9(4)°, and Ω(2)⋯Ω(4) stacking with d(Cg1⋯Cg4) = 3.8768(9) Å, α = 4.72(7)°, where α is dihedral angle between mean ring planes. In contrast, the second strongest dimer interaction involves Ω(1)⋯Ω(4) stacking with d(Cg1⋯Cg4) = 4.162(5) Å and α = 1.9(4)°.

These interactions form a columnar arrangement of molecules, which constitutes the basic structural motif (BSM) of the crystal structure.[22] The interaction energies within the BSM account for 57.4 % of the total interaction energies within the first coordination sphere of the reference molecule.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

1. Rigaku Oxford Diffraction. CrysAlis^{PRO} *Software System*; Rigaku Corporation: Wroclaw: Poland, 2022.
2. Sheldrick, G. M. *SHELXT* – Integrated Space-Group and Crystal Structure Determination. *Acta Crystallogr.* **2015**, *A71*, 3–8.
3. Sheldrick, G. M. Crystal Structure Refinement with *SHELXL*. *Acta Crystallogr.* **2015**, *C71*, 3–8.
4. Spek, A. L. Structure Validation in Chemical Crystallography. *Acta Crystallogr.* **2009**, *D65*, 148–155.
5. Ristić, M.; Radulović, N.; Dekić, B.; Dekić, V.; Ristić, N.; Stojanović-Radić, Z. Synthesis and Spectral Characterization of Asymmetric Azines Containing a Coumarin Moiety: the Discovery of New Antimicrobial and Antioxidant Agents. *Chem. Biodivers.* **2019**, *16*, e1800486.
6. Viegas–Junior, C.; Danuello, A.; da Silva Bolzani, V.; Barreiro, E. J.; Fraga, C. A. Molecular Hybridization: A Useful Tool in the Design of New Drug Prototypes. *Curr. Med. Chem.* **2007**, *14*, 1829–1852.
7. Ritter, M.; Mastelari Martins, R.; Dias, D.; Pereira, C. M. P. Recent Advances on the Synthesis of Chalcones with Antimicrobial Activities: A Brief Review. *Lett. Org. Chem.* **2014**, *11*, 498–508.
8. Mahapatra, D. K.; Bharti, S. K.; Asati, V. Chalcone Derivatives: Anti-inflammatory Potential and Molecular Targets Perspectives. *Curr. Top. Med. Chem.* **2017**, *17*, 3146–3169.
9. Mittal, A.; Vashistha, V. K.; Das, D. K. Recent Advances in the Antioxidant Activity and Mechanisms of Chalcone Derivatives: A Computational Review. *Free Radic. Res.* **2022**, *56*, 378–397.
10. Radulović, N.; Stojanović-Radić, Z.; Stojanović, P.; Stojanović, N.; Dekić, V.; Dekić, B. A Small Library of 4-(alkylamino)-3-Nitrocoumarin Derivatives with Potent Antimicrobial Activity against Gastrointestinal Pathogens. *J. Serb. Chem. Soc.* **2015**, *80*, 315–327.
11. Pérez-Cruz, K.; Moncada-Basualto, M.; Morales-Valenzuela, J.; Barriga-González, G.; Navarrete-Encina, P.; Núñez-Vergara, L.; Squella, J.; Olea-Azar, C.; Barriga, G. Synthesis and Antioxidant Study of New Polyphenolic Hybrid-Coumarins. *Arab. J. Chem.* **2018**, *11*, 525–537.
12. Tătărîngă, G.; Tüzün, B.; Zbancioc, A. Experimental and Theoretical Investigation of Antioxidant Activity of Some Derivatives with Coumarin Scaffold. *Farmacia* **2023**, *71*, 359–366.
13. Liu, Y. P.; Yan, G.; Xie, Y. T.; Lin, T. C.; Zhang, W.; Li, J.; Wu, Y. J.; Zhou, J. Y.; Fu, Y. H. Bioactive Prenylated Coumarins as Potential Anti-inflammatory and Anti-HIV Agents from *Clausena Lenis*. *Bioorg. Chem.* **2020**, *97*, 103699.
14. Wei, H.; Ruan, J.; Zhang, X. Coumarin–Chalcone Hybrids: Promising Agents with Diverse Pharmacological Properties. *RSC Adv.* **2016**, *6*, 10846–10860.
15. Abdou, M. M.; El-Saeed, R. A.; Bondock, S. Recent Advances in 4-Hydroxycoumarin Chemistry. Part 1: Synthesis and Reactions. *Arab. J. Chem.* **2019**, *12*, 88–121.
16. Radnović, N. D.; Dekić, B. R.; Ristić, M. N.; Sejmanović, D. M.; Aksić, M. S.; Krüger, B.; Rodić, M. V. The Crystal Structure of 3-(1-(2-(4-hydroxy-3,5-dimethoxybenzylidene)hydrazinyl)ethylidene)chroman-2, 4-dione Dihydrate, $C_{20}H_{22}N_2O_8$. *Z. Kristallogr. N. Cryst. Struct.* **2023**, *238*, 171–173.
17. Radulović, N. S.; Sejmanović, D. M.; Ristić, M. N.; Dekić, V. S.; Krüger, B.; Kahlenberg, V.; Rodić, M. V. The Crystal Structure of 3-(1-(2-((5-methylthiophen-2-yl)methylene)hydrazinyl)ethylidene)chroman-2,4-dione, $C_{17}H_{14}N_2O_3S$. *Z. Kristallogr. N. Cryst. Struct.* **2022**, *237*, 775–777.
18. Dekić, V. S.; Dekić, B. R.; Sejmanović, D. M.; Janićević, S.; Krüger, B.; Kahlenberg, V.; Rodić, M. V. The Crystal Structure of (*Z*)-3-(1-(2-((*E*)-4-isopropylbenzylidene)hydrazinyl)ethylidene)chroman-2,4-dione, $C_{21}H_{20}N_2O_3$. *Z. Kristallogr. N. Cryst. Struct.* **2023**, *238*, 521–524.
19. Allen, F. H.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. Typical Interatomic Distances: Organic Compounds. In *International Tables for Crystallography*; Fuess, H.; Hahn, T.; Wondratschek, H.; Müller, U.; Shmueli, U.; Prince, E., Eds.; Wiley: Hoboken, Vol. C, 2006; pp. 790–811.
20. Mackenzie, C. F.; Spackman, P. R.; Jayatilaka, D.; Spackman, M. A. CrystalExplorer Model Energies and Energy Frameworks: Extension to Metal Coordination Compounds, Organic Salts, Solvates and Open-Shell Systems. *IUCrJ* **2017**, *4*, 575–587.
21. Spackman, P. R.; Turner, M. J.; McKinnon, J. J.; Wolff, S. K.; Grimwood, D. J.; Jayatilaka, D.; Spackman, M. A. CrystalExplorer: A Program for Hirshfeld Surface Analysis, Visualization and Quantitative Analysis of Molecular Crystals. *J. Appl. Cryst.* **2021**, *54*, 1006–1011.
22. Shishkin, O. V.; Dyakonenko, V. V.; Maleev, A. V. Supramolecular Architecture of Crystals of Fused Hydrocarbons Based on Topology of Intermolecular Interactions. *CrystEngComm* **2012**, *14*, 1795–1804.