Synthesis and Structure of 3,3'-[(4-Benzyloxyphenyl)methylene]bis-(4-hydroxy-2H-chromen-2-one)

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The structure of 3,3'-[(4-benzyloxyphenyl)methylene]bis-(4-hydroxy-2H-chromen-2-one) was determined by X-ray crystallography. The compound crystallized in a monoclinic system and was characterized thus: $P2_1/n$, $a = 12.2990(15)\text{\AA}$, $b = 10.8108(8)\text{\AA}$, $c = 21.277(2)\text{\AA}$, $Z = 4$, $V = 2787.7(5)\text{\AA}^3$. The crystal structure was solved by direct methods and refined by full-matrix least-squares on F^2 to final values of $R1 = 0.0860$ and $R2 = 0.1436$.

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Some biscoumarin derivatives are biologically active compounds with anticoagulant, cytostatic, cytotoxic, antioxidant and anti-HIV activity.¹⁻⁶ 3,3'-[(4-Benzyloxyphenyl)methylene]bis-(4-hydroxy-2H-chromen-2-one) was synthesized by Manolov *et al.*² by the reaction of 4-hydroxycoumarin and 4-(benzyloxy)benzaldehyde at a molar ratio of 2:1 in glacial acetic acid at reflux for 5 h. The new compound was characterized by elemental analysis, IR, ¹H and ¹³C NMR spectroscopy. Suitable crystals of 3,3'-[(4-benzyloxyphenyl)methylene]bis-(4-hydroxy-2H-chromen-2-one) for X-ray diffraction analysis were isolated and its structure was determined. The result of an X-ray diffraction study of 3,3'-[(4-benzyloxyphenyl)methylene]bis-(4-hydroxy-2H-chromen-2-one) is shown in Figs. 1 and 2. The compound crystallized in the monoclinic space group $P2_1/n$ with one molecule of acetone (see Table 1).

3,3'-[(4-Benzyloxyphenyl)methylene]bis-(4-hydroxy-2H-chromen-2-one) was synthesized by 4-hydroxycoumarin (3.24 g, 20 mmol) and 4-benzyloxybenzaldehyde (2.12 g, 10 mmol); 30 mL of glacial acetic acid was mixed under stirring and heated at reflux for 5 h until the appearance of an insoluble product. After cooling, the product was filtered and recrystallized by acetonitrile. Yield: 2.60 g (50%), m.p. 224 – 226°C. Crystals, suitable for X-ray data collection were grown by slow evaporation from acetone. Analysis calculated for $C_{32}H_{22}O_7$: C

74.13, H 4.25%. Found: C 74.10, H 4.43%. IR (nujol) cm^{-1} : 1669.0, 1607.0, 1377.0, 1182.0, 772.0. ¹H NMR (250 MHz; DMSO- d_6): 5.0 – 5.1 (1H, s), 5.2 – 5.6 (2H, s), 6.2 – 6.3 (2H, s), 6.8 – 8.0 (17H, m). MS: 518(38), 464(5), 427(40), 356(20), 265(6), 167(3), 162(39), 120(20), 91(100), 77(12), 41(19).

X-ray crystallographic study (general procedure on the diffraction method by a single crystal): Measurements⁷ were made at 173(2)K on a STOE IPDS II diffractometer with graphite-monochromated Mo- K_α ($\lambda = 0.71069\text{\AA}$). The crystal unit-cell and the orientation parameters were obtained from an

Table 1 Crystal and experimental data

Chemical formula: $C_{35}H_{28}O_8$	
Formula weight = 576.57	
$T = 173(2)\text{K}$	
Wavelength	0.71073 $\text{\AA}$
Crystal system: monoclinic	Space group: $P2_1/n$
$a = 12.2990(15)\text{\AA}$	$\alpha = 90^\circ$
$b = 10.8108(8)\text{\AA}$	$\beta = 99.808(9)^\circ$
$c = 21.277(2)\text{\AA}$	$\gamma = 90^\circ$
$V = 2787.7(5)\text{\AA}^3$	$Z = 4$
$D_x = 1.374\text{ g/cm}^3$	D_m (floatation) = 1.37 g/cm^3
Radiation: Mo K_α ($\lambda = 0.71073\text{\AA}$)	
$\mu(\text{Mo } K_\alpha) = 0.093\text{ mm}^{-1}$	$F(0\ 0\ 0) = 1208$
Crystal size = $0.40 \times 0.10 \times 0.10\text{ mm}^3$	
Theta range for data collection 6.85 to 26.37 deg.	
No. of reflections collected = 36901	
No. of independent reflections = 5600	
Θ range for data collection: 6.85 to 26.37°	
Data/restraints/parameters 5600/0/466	
Goodness-of-fit on $F^2 = 1.134$	
R indices [$I > 2\sigma(I)$]: $R_1 = 0.0860$, $wR_2 = 0.1436$	
R indices (all data): $R_1 = 0.1325$, $wR_2 = 0.1595$	
$(\Delta/\sigma)_{\text{max}} = 0.001$	
$(\Delta\rho)_{\text{max}} = -0.231\text{ e.\AA}^{-3}$	$(\Delta\rho)_{\text{min}} = -0.14\text{ e.\AA}^{-3}$
Measurement: STOE IPDS II diffractometer	
Program system: SHELX97	
Structure determination: SHELXS-97	
CCDC deposition number: 788621

Fig. 1 Chemical structure drawing.

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Fig. 2 Tertiary structure with an ORTEP-style drawing and atom-labeling scheme.

auto indexing procedure, as implemented in X-AREA.⁸⁻¹⁰ Intensities recorded up to a maximum 2θ value of 52.75° using the ω scan technique were integrated with X-AREA. The structure was solved by direct methods using SHELXS, and refined by full-matrix least-squares techniques on F^2 using SHELX-L 97.¹¹ All non-hydrogen atoms were anisotropically and fully refined at the calculated positions. Most hydrogen atoms were located in difference electron-density maps. The hydrogen atoms for O112 and O130 and the solvent molecules were calculated. The methyl groups were refined as rigid pyramidal groups (AFIX 33) and the O-H with AFIX 147. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. (CCDC).

Two 4-hydroxycoumarin moieties were linked through a methylene bridge on which one hydrogen atom was replaced with a benzyloxyphenyl residue. The bond distances and angles are given in Table 2. Most of the bond distances are of the expected length. The C1–C11 distance of 1.529(4) Å is longer than an unstrained C(sp³)–C(Ar) bond. We established that all of the bonds are shorter than those in the unsubstituted aromatic nucleus in an analogous biscoumarin derivative. Two 4-hydroxycoumarin residues are arranged at a position that permits the formation of two intramolecular hydrogen bonds between a hydroxyl group of one coumarin fragment and a lactone carbonyl group of the other coumarin fragment.

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Table 2 Selected bond length and angles

O 1 – C 14	1.373(4)	C 14 – O 1 – C 2	116.5(3)
O 1 – C 2	1.428(4)	O 1 – C 2 – C 21	108.5(3)
C 1 – C 11	1.529(4)	C 11 – C 1 – C 111	112.9(2)
C 1 – C 111	1.529(5)	C 121 – C 1 – C 111	112.0(2)
O 101 – C 101	1.201(7)	O 101 – C 101 – C 103	122.5(6)
O 120 – C 120	1.215(4)	O 120 – C 120 – C 111	125.7(3)
O 122 – C 122	1.322(4)	C 112 – C 111 – C 1	122.9(3)
O 129 – C 130	1.352(4)	C 120 – O 119 – C 118	121.5(3)
O 129 – C 128	1.381(4)	C 130 – O 129 – C 128	121.3(3)
O 130 – C 130	1.215(4)	O 130 – C 130 – C 121	124.7(3)
C 121 – C 122	1.357(5)	C 122 – C 121 – C 1	127.1(3)
C 111 – C 112	1.355(5)	C 112 – C 111 – C 1	122.8(3)

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References

1. O. Zaneva, I. Manolov, and N. Danchev, *Farmatsiya (Sofia)*, **2005**, 85.
2. I. Manolov, C. Maichle-Moessmer, and N. Danchev, *Eur. J. Med. Chem.*, **2006**, 882.
3. S. Raleva, A. Savov, L. Froloshka, D. Dundarova, I. Manolov, and R. Argirova, *Biotechnol. Biotechnol. Eq.*, **2005**, 11.
4. He Zhao, N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, G. W. A. Milne, Y. Pomier, and T. R., Jr. Burke, *J. Med. Chem.*, **1997**, 242.
5. J. Deng, K. W. Lee, T. Sanchez, M. Cui, N. Neamati, and J. M. Briggs, *J. Med. Chem.*, **2005**, 1496.
6. S. Vilar, L. Santana, and E. Uriarte, *J. Med. Chem.*, **2006**, 1118.
7. B. V. Nonius, "Collect" data collection software, **1999**.
8. H. Yuan and A. Parrill, *Bioorg. Med. Chem.*, **2002**, 4169.
9. H. Yuan and A. Parrill, *J. Molec. Graphics Modelling*, **2005**, 317.
10. I. Manisha and A. J. Hopfinger *J. Chem. Inform. Modeling*, **2007**, 1945.
11. G. M. Sheldrick, SHELX97. Program for the Refinement of Crystal Structures from Diffraction Data, University of Göttingen, Germany, **1997**.