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Crystal structure of benzo[*d*][1,3]dioxol-5-yl-2-(6-methoxynaphthalen-2-yl)propanoate, $C_{21}H_{18}O_5$

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Abstract

$C_{21}H_{18}O_5$, monoclinic, $P2_1$ (no. 4), $a = 9.1511(4)$ Å, $b = 5.6679(3)$ Å, $c = 16.7731(9)$ Å, $\beta = 93.435(2)^\circ$, $V = 868.42(8)$ Å³, $Z = 2$, $R_{gt}(F) = 0.0410$, $wR_{ref}(F^2) = 0.1204$, $T = 296(2)$ K.

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The molecular structure is shown in Figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

Naproxen acylchloride was synthesized according to the literature method [5]. Naproxen (0.01 mol, 2.30 g) was dissolved in dichloromethane (10 mL), and then oxalyl chloride (0.012 mol, 1.1 mL) and two drops of *N,N*-dimethylformamide were dropwise added at 0 °C. The solution was stirred for 2 h at room temperature. After the solvent and excess oxalyl chloride was removed by vacuum distillation, a yellow solid was obtained.

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Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.16 × 0.15 × 0.12 mm
Wavelength:	Cu Kα radiation (1.54178 Å)
μ :	0.79 mm ⁻¹
Diffractometer, scan mode:	BRUKER D8 VENTURE, φ and ω
θ_{max} , completeness:	68.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int} :	14,578, 3182, 0.041
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 2705
$N(param)_{refined}$:	237
Programs:	Bruker [1], Olex2 [2], SHELX [3, 4]

3,4-(Methylenedioxy)phenol (sesamol, 0.01 mol, 1.38 g) and 4-(dimethylamino)-pyridin (DMAP, 0.0015 mol, 0.18 g) were dissolved in dry tetrahydrofuran (20 mL) and triethylamine (0.015 mol, 2 mL). The solution of naproxen acylchloride in dry tetrahydrofuran was dropwise added at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtrated and the filtrate was concentrated under vacuum to remove the solvent. The residue was dissolved in dichloromethane, successively washed with 5% NaOH solution and water to pH = 7, and finally dried with anhydrous Na_2SO_4 . The solution was filtrated, and concentrated under vacuum to obtain the crude product. The crude product was purified by recrystallization in ethyl acetate. The single crystals were obtained from tetrahydrofuran.

Experimental details

A suitable crystal was selected and tested on a Bruker D8 VENTURE diffractometer. Using OLEX2 [2], the structure was solved with the SHELXT [3] structure solution program using Intrinsic Phasing and refined with the SHELXL [4] refinement package.

Comment

Naproxen is a well-known nonsteroidal anti-inflammatory drug. It is usually used for treating rheumatic, rheumatoid arthritis and osteoarthritis. However, it often brings

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

Atom	x	y	z	U _{iso} */U _{eq}
O1	0.8702 (2)	0.4082 (4)	−0.13037 (14)	0.0781 (6)
C1	0.9623 (4)	0.2064 (6)	−0.1357 (2)	0.0857 (10)
H1A	1.004512	0.204937	−0.186693	0.128*
H1B	0.905430	0.065835	−0.129813	0.128*
H1C	1.038908	0.212750	−0.094039	0.128*
O2	0.7303 (4)	0.6910 (9)	0.35086 (17)	0.174 (2)
C2	0.8013 (3)	0.4413 (5)	−0.06060 (17)	0.0618 (7)
O4	0.8150 (3)	0.7959 (5)	0.66137 (15)	0.0911 (7)
C4	0.6420 (3)	0.6997 (5)	0.00671 (19)	0.0641 (7)
H4	0.585627	0.836180	0.006978	0.077*
O3	0.6102 (2)	0.4312 (4)	0.41733 (14)	0.0752 (6)
C3	0.7125 (3)	0.6448 (6)	−0.05937 (19)	0.0678 (7)
H3	0.702475	0.741461	−0.104177	0.081*
O5	0.9948 (2)	0.5118 (5)	0.67856 (13)	0.0858 (7)
C5	0.6520 (2)	0.5546 (5)	0.07557 (16)	0.0565 (6)
C6	0.7398 (3)	0.3488 (4)	0.07346 (17)	0.0571 (6)
C7	0.8140 (3)	0.2954 (5)	0.00438 (18)	0.0629 (7)
H7	0.871719	0.160564	0.003016	0.075*
C9	0.6749 (3)	0.2599 (5)	0.20812 (18)	0.0664 (7)
H9	0.681949	0.160417	0.252267	0.080*
C8	0.7475 (3)	0.2032 (5)	0.14261 (18)	0.0662 (7)
H8	0.803582	0.066310	0.142933	0.079*
C10	0.5885 (3)	0.4673 (5)	0.21099 (18)	0.0619 (7)
C11	0.5785 (3)	0.6087 (5)	0.14506 (18)	0.0593 (7)
H11	0.521681	0.744661	0.145859	0.071*
C12	0.5137 (3)	0.5211 (6)	0.2873 (2)	0.0702 (8)
H12	0.457599	0.381253	0.301181	0.084*
C13	0.6302 (3)	0.5624 (7)	0.35340 (19)	0.0775 (9)
C14	0.4106 (4)	0.7289 (8)	0.2831 (3)	0.0950 (11)
H14A	0.463138	0.868419	0.269444	0.142*
H14B	0.369852	0.750589	0.333989	0.142*
H14C	0.333130	0.700126	0.243096	0.142*
C15	0.7131 (3)	0.4501 (6)	0.48289 (18)	0.0654 (7)
C16	0.7019 (3)	0.6350 (6)	0.53592 (19)	0.0689 (7)
H16	0.629882	0.750197	0.528961	0.083*
C17	0.8034 (3)	0.6380 (5)	0.59936 (18)	0.0648 (7)
C18	0.9095 (3)	0.4664 (6)	0.61018 (18)	0.0648 (7)
C19	0.9197 (3)	0.2837(6)	0.55801(19)	0.0710(8)
H19	0.991755	0.168751	0.565455	0.085*
C20	0.8176 (3)	0.2765 (6)	0.4931 (2)	0.0696 (7)
H20	0.820141	0.153706	0.456370	0.084*
C21	0.9468 (4)	0.7325 (8)	0.7062 (2)	0.0866 (10)
H21A	1.021409	0.851297	0.699421	0.104*
H21B	0.929056	0.722591	0.762536	0.104*

gastrointestinal side effects such as ulcers, gastric perforation and bleeding in long-term administration because of its carboxylic acid group. In order to overcome the side effects, many researchers have transformed naproxen into a pro-drug. Studies also found that many prodrugs can improve the liposolubility, especially suitable for transdermal delivery mode. Because sesamol has anti-inflammatory and antioxidant effects [6, 7], we synthesized a naproxen-sesamol eater

as a prodrug based on the combination principles. We expect to reduce the side effects of naproxen and improve its bioavailability.

The title molecule consists of two moieties: the naphthalene moiety and the 1,2-methylenedioxybenzene group (see the figure). The naphthalene ring and 1,2-methylenedioxybenzene ring are not coplanar with a dihedral angle of 53.5°. One carbon–oxygen double bond exists in the compound, the C–O double bond distance (C13–O2) is 1.173(4) Å. The bond lengths of C1–O1 and C13–O3 are 1.427(4) and 1.327(4) Å, respectively. The other C–O bond lengths range from 1.372(4) to 1.429(4) Å. The C–C bond lengths from 1.352(5) to 1.518(4) Å. The torsion angles of C14–C12–C13–O2 and O3–C15–C16–C17 are −75.5(6)° and 178.3(2)°, respectively. All the bond lengths and angles are in the expected ranges [8].

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