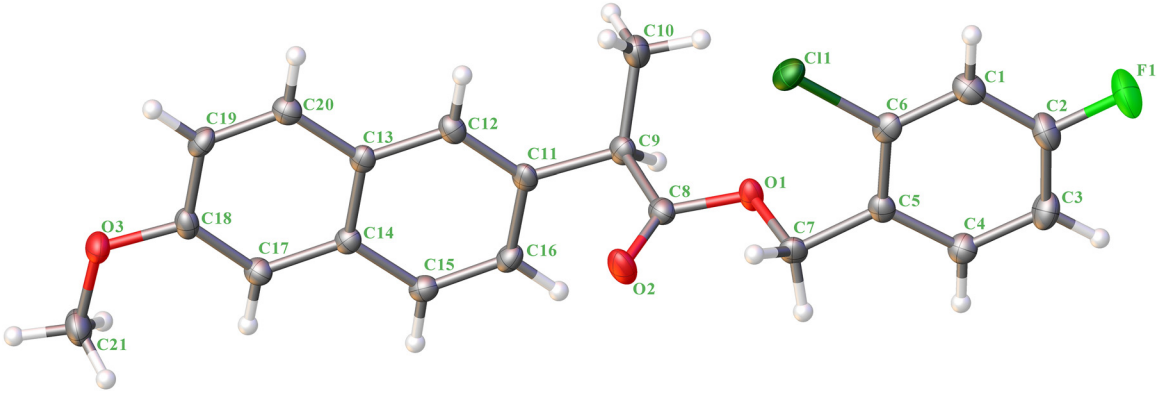
Guohua Chen*

Crystal structure of 2-chloro-4-fluorobenzyl (*R*)-2-(6-methoxynaphthalen-2-yl)propanoate, $C_{21}H_{18}ClFO_3$



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Abstract

$C_{21}H_{18}ClFO_3$, monoclinic, $P2_1/c$ (no. 14), a = 34.657(5) Å, b = 6.0214(8) Å, c = 8.2301(11) Å, β = 93.883(5)°, V = 1713.5(4) Å^3, Z = 4, $R_{gt}(F)$ = 0.0683, $wR_{ref}(F^2)$ = 0.1435, T = 205(2) K.

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Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.12 × 0.11 × 0.10 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.25 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
θ_{max}, completeness:	27.6°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	30,930, 3,940, 0.095
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 3,058
$N(param)_{refined}$:	237
Programs:	Bruker,[1] Olex2,[2] SHELX[3]

1 Source of materials

Naproxen acylchloride was synthesized according to the literature method.[4] 2-Chloro-4-fluorobenzyl alcohol (0.01 mol, 1.60 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 to remove the solid 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 dried with anhydrous Na_2SO_4 The solution was filtrated, and concentrated under vacuum to obtain crude product. The crude product was purified by recrystallization in ethanol. The crystals were obtained from tetrahydrofuran solution.

***Corresponding author: Guohua Chen**, Liao cheng Vocational and Technical College, Liao cheng, 252000, China,
E-mail: chenguohuachg@163.com. https://orcid.org/0009-0004-0683-2665

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.56867 (9)	0.6643 (6)	0.2273 (4)	0.0235 (7)
H1	0.559856	0.800577	0.183236	0.028*
C2	0.54551 (9)	0.5333 (6)	0.3171 (4)	0.0255 (7)
C3	0.55694 (9)	0.3314 (6)	0.3815 (4)	0.0254 (7)
H3	0.540310	0.246131	0.442098	0.031*
C4	0.59387 (9)	0.2575 (6)	0.3540 (3)	0.0197 (6)
H4	0.602112	0.118872	0.395847	0.024*
C5	0.61908 (8)	0.3827 (5)	0.2661 (3)	0.0178 (6)
C6	0.60570 (9)	0.5863 (6)	0.2046 (3)	0.0194 (6)
C7	0.65894 (8)	0.2981 (5)	0.2404 (4)	0.0191 (6)
H7A	0.661194	0.141883	0.273022	0.023*
H7B	0.664127	0.309462	0.125058	0.023*
C8	0.72348 (9)	0.4139 (5)	0.2960 (4)	0.0184 (6)
C9	0.75061 (9)	0.5581 (5)	0.4041 (4)	0.0194 (6)
H9	0.748188	0.510047	0.518034	0.023*
C10	0.73774 (9)	0.8004 (6)	0.3920 (4)	0.0262 (8)
H10A	0.737979	0.849733	0.279860	0.039*
H10B	0.755298	0.891514	0.460339	0.039*
H10C	0.711775	0.814028	0.428080	0.039*
C11	0.79217 (9)	0.5148 (5)	0.3638 (3)	0.0179 (6)
C12	0.81306 (8)	0.6578 (6)	0.2744 (3)	0.0185 (6)
H12	0.801849	0.792884	0.238691	0.022*
C13	0.85128 (8)	0.6062 (5)	0.2347 (3)	0.0166 (6)
C14	0.86826 (8)	0.4021 (5)	0.2886 (3)	0.0164 (6)
C15	0.84630 (9)	0.2582 (6)	0.3820 (3)	0.0184 (6)
H15	0.857114	0.122752	0.419161	0.022*
C16	0.80965 (9)	0.3126 (5)	0.4194 (3)	0.0191 (6)
H16	0.795793	0.214793	0.482722	0.023*
C17	0.90624 (9)	0.3481 (5)	0.2466 (3)	0.0180 (6)
H17	0.917794	0.214372	0.283389	0.022*
C18	0.92607 (9)	0.4908 (6)	0.1526 (3)	0.0189 (6)
C19	0.90920 (9)	0.6949 (5)	0.0995 (3)	0.0196 (7)
H19	0.923017	0.792041	0.035427	0.024*
C20	0.87305 (8)	0.7509 (6)	0.1408 (3)	0.0191 (6)
H20	0.862383	0.887895	0.106347	0.023*
C21	0.98148 (9)	0.2552 (6)	0.1569 (4)	0.0288 (8)
H21A	0.966883	0.127575	0.115182	0.043*
H21B	0.983216	0.251878	0.274962	0.043*
H21C	1.007280	0.251069	0.118051	0.043*
Cl1	0.63552 (2)	0.74993 (15)	0.09212 (9)	0.02457 (19)
F1	0.50929 (6)	0.6088 (4)	0.3409 (3)	0.0400 (6)
O1	0.68645 (6)	0.4323 (4)	0.3386 (2)	0.0201 (5)
O2	0.73216 (6)	0.2976 (4)	0.1861 (3)	0.0278 (6)
O3	0.96238 (6)	0.4547 (4)	0.1014 (3)	0.0225 (5)

2 Experimental details

The U_{iso} values of hydrogen atoms were set to be $1.5U_{eq}$ of the carrier atom for methyl H atoms and $1.2U_{eq}$ for the remaining H atoms.

3 Comment

Naproxen, a powerful non-steroidal anti-inflammatory drug (NSAID), inhibits both COX-1 and COX-2 enzymes, essential elements of the cyclooxygenase pathway. Naproxen frequently induces gastrointestinal issues, including gastroduodenal ulcers. The carboxyl group in naproxen might be responsible for these adverse effects. Studies indicate that modifying this carboxyl group through esterification can lessen these gastrointestinal reactions.[5,6] Naproxen is presently employed in clinical settings to manage or mitigate pain and inflammation associated with conditions like rheumatoid arthritis[7] and gout.[8] Moreover, it has certain therapeutic effects on migraines[9] but may cause certain side effects. Additionally, research indicates that naproxen has a preventive effect on Lynch syndrome.[10] Consequently, creating derivatives of naproxen that have reduced side effects is crucial.

The title compound contains one naphthyl ring and one phenyl ring. The bond distances of C–O are 1.453(3) Å (C7–O1), 1.358(4) Å (C8–O1), 1.198(4) Å (C8–O2), 1.371(4) Å (C18–O3) and 1.431(4) Å (C21–O3). The bond distance of C8–O2 are shorter than others, indicating a double bond. The bond distance of C–Cl are 1.739(3) Å (C6–Cl1) and the bond distance of C–F are 1.362(4) Å (C2–F1). The dihedral angels of ring 1 (C1–C2–C3–C4–C5–C6) and ring 2 (C11–C12–C13–C14–C15–C16), ring 1 (C1–C2–C3–C4–C5–C6) and ring 3 (C13–C14–C17–C18–C19–C20), and ring 2 (C11–C12–C13–C14–C15–C16) and ring 3 (C13–C14–C17–C18–C19–C20) are 0.8(1)°, 2.1(1)° and 1.33(8)°. The other bond distances and angles are in their normal ranges according to the previously reported compounds.[11,12]

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