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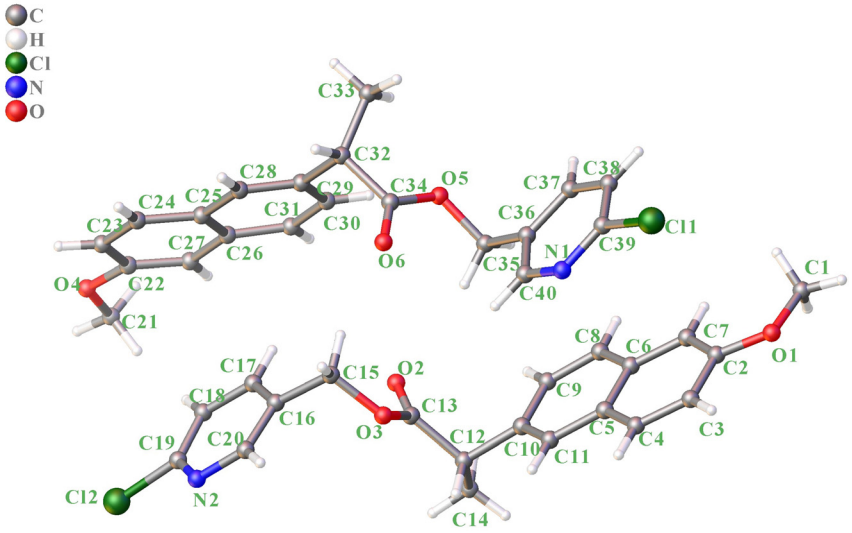
Crystal structure of (6-chloropyridin-3-yl)methyl 2-(6-methoxynaphthalen-2-yl)propanoate, $C_{20}H_{18}ClNO_3$



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Abstract

$C_{20}H_{18}ClNO_3$, monoclinic, $P2_1$ (no. 4), a = 11.6954(2) Å, b = 5.7274(10) Å, c = 26.5974(5) Å, β = 102.177(10)°, V = 1741.52(5) Å^3, Z = 4, $R_{gt}(F)$ = 0.0282, $wR_{ref}(F^2)$ = 0.0728, T = 170(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 × 0.1 mm
Wavelength:	Cu$K\alpha$ radiation (1.54178 Å)
μ:	2.10 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
θ_{max}, completeness:	68.2°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	13,354, 5868, 0.037
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 5516
$N(param)_{refined}$:	455
Programs:	Bruker [1], Olex2 [2], SHELX [3]

1 Source of materials

Naproxen acylchloride was synthesized according to the literature [4]. 2–Chloro-5-hydroxymethylpyridine (0.01 mol, 1.43 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 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.

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
Cl1	−0.34374 (6)	0.83578 (17)	0.63690 (3)	0.0624 (2)
N1	−0.11828 (18)	0.7835 (4)	0.66820 (8)	0.0394 (5)
O1	−0.32959 (13)	0.4564 (3)	0.50785 (7)	0.0420 (4)
C1	−0.3851 (2)	0.2463 (6)	0.51799 (13)	0.0517 (7)
H1A	−0.465894	0.244773	0.498222	0.078*
H1B	−0.384932	0.236562	0.554784	0.078*
H1C	−0.342660	0.112470	0.507949	0.078*
N2	0.71555 (17)	0.9956 (4)	0.78060 (9)	0.0410 (5)
O2	0.39573 (16)	0.3806 (3)	0.72291 (7)	0.0456 (4)
Cl2	0.91803 (5)	0.83284 (15)	0.82375 (3)	0.05241 (19)
C2	−0.21311 (18)	0.4805 (4)	0.53044 (9)	0.0301 (5)
C3	−0.16247 (19)	0.6886 (4)	0.51665 (8)	0.0310 (5)
H3	−0.209143	0.796354	0.494017	0.037*
O3	0.37154 (13)	0.7588 (3)	0.70261 (6)	0.0340 (4)
C4	−0.04707 (19)	0.7360 (4)	0.53558 (8)	0.0286 (4)
H4	−0.014540	0.878008	0.526573	0.034*
O4	0.85661 (14)	0.1987 (4)	0.97896 (7)	0.0469 (5)
C5	0.02454 (18)	0.5760 (4)	0.56844 (8)	0.0248 (4)
O5	0.10346 (14)	0.3451 (3)	0.80015 (6)	0.0374 (4)
C6	−0.02654 (17)	0.3667 (4)	0.58235 (7)	0.0240 (4)
O6	0.17294 (13)	0.7098 (3)	0.80022 (7)	0.0397 (4)
C7	−0.14748 (17)	0.3234 (4)	0.56311 (8)	0.0270 (4)
H7	−0.182648	0.185844	0.572895	0.032*
C8	0.04639 (18)	0.2048 (4)	0.61431 (8)	0.0267 (4)
H8	0.013339	0.066208	0.624789	0.032*
C9	0.16415 (18)	0.2450 (4)	0.63036 (8)	0.0277 (4)
H9	0.211780	0.132694	0.651271	0.033*
C10	0.21539 (18)	0.4518 (4)	0.61613 (8)	0.0272 (4)
C11	0.14636 (18)	0.6138 (4)	0.58629 (8)	0.0262 (4)
H11	0.180543	0.754160	0.577344	0.031*
C12	0.34708 (18)	0.4919 (5)	0.63329 (9)	0.0329 (5)
H12	0.368390	0.635619	0.615998	0.039*
C13	0.37546 (17)	0.5314 (4)	0.69088 (10)	0.0318 (5)
C14	0.4187 (2)	0.2867 (6)	0.61947 (11)	0.0472 (7)
H14A	0.395804	0.255605	0.582482	0.071*
H14B	0.403894	0.147711	0.638625	0.071*
H14C	0.502086	0.325650	0.628476	0.071*
C15	0.40019 (17)	0.8140 (5)	0.75732 (9)	0.0355 (5)
H15A	0.361931	0.699974	0.776392	0.043*
H15B	0.370228	0.971437	0.762948	0.043*
C16	0.53065 (17)	0.8071 (4)	0.77737 (8)	0.0296 (5)
C17	0.5870 (2)	0.6273 (5)	0.80751 (10)	0.0375 (5)
H17	0.543120	0.501827	0.817271	0.045*
C18	0.7074 (2)	0.6312 (5)	0.82334 (10)	0.0420 (6)
H18	0.748377	0.510043	0.844019	0.050*
C19	0.76555 (18)	0.8184 (5)	0.80783 (9)	0.0342 (5)
C20	0.5986 (2)	0.9865 (5)	0.76568 (10)	0.0377 (5)
H20	0.560261	1.112441	0.745719	0.045*
C21	0.8930 (2)	0.0040 (6)	0.95309 (12)	0.0499 (7)
H21A	0.881827	0.038808	0.916297	0.075*
H21B	0.846451	−0.133141	0.957938	0.075*
H21C	0.975930	−0.027710	0.967204	0.075*
C22	0.74210 (19)	0.2670 (5)	0.96335 (9)	0.0354 (5)
C23	0.7144 (2)	0.4753 (5)	0.98626 (10)	0.0397 (6)
H23	0.773387	0.553905	1.010379	0.048*
C24	0.6043 (2)	0.5657 (5)	0.97431 (9)	0.0368 (5)
H24	0.587671	0.708192	0.989602	0.044*
C25	0.51390 (19)	0.4487 (4)	0.93910 (8)	0.0294 (5)
C26	0.54148 (18)	0.2353 (4)	0.91741 (8)	0.0275 (4)
C27	0.65768 (19)	0.1482 (5)	0.92931 (9)	0.0323 (5)
H27	0.676879	0.008334	0.913762	0.039*
C28	0.39804 (19)	0.5350 (4)	0.92646 (9)	0.0302 (5)
H28	0.380336	0.679784	0.940518	0.036*
C29	0.31056 (19)	0.4142 (4)	0.89431 (8)	0.0300 (5)
C30	0.33770 (19)	0.1978 (4)	0.87369 (9)	0.0325 (5)
H30	0.277637	0.110988	0.852012	0.039*
C31	0.44962 (19)	0.1129 (4)	0.88473 (9)	0.0320 (5)
H31	0.466068	−0.031478	0.870152	0.038*
C32	0.18605 (19)	0.5100 (5)	0.88097 (9)	0.0333 (5)
H32	0.186871	0.669029	0.896559	0.040*
C33	0.1001 (2)	0.3597 (6)	0.90273 (9)	0.0434 (6)
H33A	0.020410	0.418451	0.890259	0.065*
H33B	0.119712	0.366603	0.940382	0.065*
H33C	0.104864	0.197731	0.891495	0.065*
C34	0.15229 (17)	0.5372 (5)	0.82292 (9)	0.0318 (5)
C35	0.0841 (2)	0.3373 (6)	0.74429 (9)	0.0418 (6)
H35A	0.079749	0.172320	0.732917	0.050*
H35B	0.151457	0.410526	0.733234	0.050*
C36	−0.0260 (2)	0.4607 (4)	0.71890 (9)	0.0336 (5)
C37	−0.1350 (2)	0.3667 (5)	0.71940 (9)	0.0422 (6)
H37	−0.140943	0.223390	0.736646	0.051*
C38	−0.2345 (2)	0.4818 (6)	0.69480 (11)	0.0462 (6)
H38	−0.310173	0.422251	0.695055	0.055*
C39	−0.2198 (2)	0.6875 (5)	0.66972 (9)	0.0387 (6)
C40	−0.0232 (2)	0.6686 (5)	0.69292 (9)	0.0358 (5)
H40	0.051183	0.734564	0.692552	0.043*

2 Experimental details

The U_{iso} values 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 is often used for treating rheumatic, rheumatoid arthritis and osteoarthritis as a nonsteroidal anti-inflammatory drug. There is a carboxylic acid group in the structure which can bring ulcers, gastric perforation and bleeding gastrointestinal side effects for long-term using [5, 6]. Studies have shown that esterification of naproxen as a prodrug can reduce gastrointestinal side effects of naproxen and improve its bioavailability [7]. This study esterifies the carboxyl group in the naproxen molecule with the 2-chloro-5-hydroxymethylpyridine hydroxyl group to

form a prodrug, with the aim of changing the physicochemical properties of naproxen and providing a prodrug with a tendency to reduce gastric irritation.

The compound contains two twist (6-chloropyridin-3-yl)methyl 2-(6-methoxynaphthalen-2-yl)propanoate molecules in the asymmetric unit (see the figure). The title compound contained one pyridine ring and one naphthyl moiety. The C=O double bond lengths in the independent molecule are 1.201(3) Å (C13=O2) and 1.209(3) Å (C34=O6), respectively, exhibiting the double bond character. The dihedral angles of ring 1 (C2–C3–C4–C5–C6–C7) and ring 2 (C5–C6–C8–C9–C10–C11), ring 1 (C2–C3–C4–C5–C6–C7) and ring 3 (C16–C17–C18–C19–N2–C20), ring 2 (C5–C6–C8–C9–C10–C11) and ring 3 (C16– C17–C18–C19–N2–C20), ring 4 (C22–C23–C24–C25–C26–C27) and ring 5 (C26–C25–C28–C29–C30–C31), ring 4 (C22–C23–C24–C25–C26–C27) and ring 6 (C36–C37–C38–C39–N1–C40), ring 5 (C26–C25–C28–C29–C30–C31) and ring 6 (C36–C37–C38–C39–N1–C40) are 3.1°, 8.0°, 5.3°, 2.6°, 62.9°, 60.7°, respectively. The other bond distances and angles are in their normal ranges according to the previously reported compounds [8–10].

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Competing interests: The authors declare no conflicts of interest regarding this article.

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