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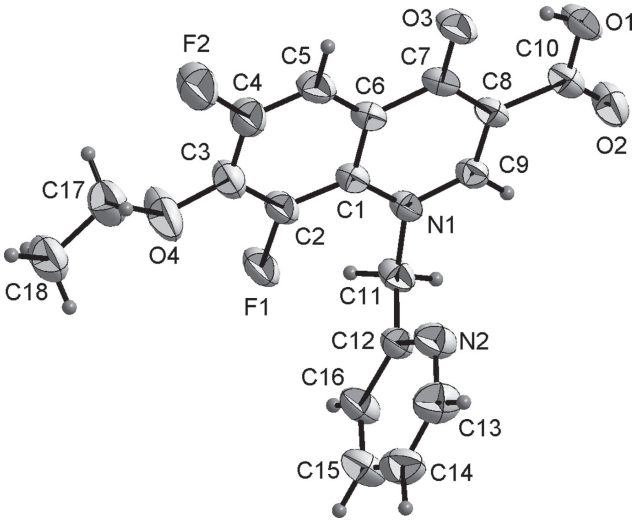
Crystal structure of 7-ethoxy-6,8-difluoro-4-oxo-1-pyridin-2-ylmethyl-1,4-dihydro-quinoline-3-carboxylic acid, $C_{18}H_{14}F_2N_2O_4$



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Abstract

$C_{18}H_{14}F_2N_2O_4$, triclinic, $P\bar{1}$ (no. 2), $a = 6.377(3)$ Å, $b = 9.466(5)$ Å, $c = 13.367(7)$ Å, $\alpha = 83.409(6)°$, $\beta = 83.283(6)°$, $\gamma = 83.728(6)°$, $V = 792.3(7)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0587$, $wR_{ref}(F^2) = 0.1814$, $T = 296(2)$ K.

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The molecular structure is shown in the figure. 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:	Colorless block
Size:	0.19 × 0.15 × 0.13 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.12 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
θ_{max}, completeness:	25.5°, 96%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	5426, 2843, 0.041
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 1825
$N(param)_{refined}$:	237
Programs:	Bruker [1], SHELX [2, 3], Diamond [4]

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Source of material

To a stirred solution of 6,7,8-trifluoro-4-oxo-1-pyridin-2-ylmethyl-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (36.2 g, 0.1 moL) in ethanol (200 mL) was added sodium hydroxide (4.0 g, 0.1 moL), and then the reaction mixture was refluxed for about 0.5 h. After the reaction had been completed (monitored by TLC), the ethanol was distillated under reduced pressure to give a crude product. The crude product was poured into water (40 mL) and extracted with EtOAc (50 mL × 3). The EtOAc solvent was evaporated to provide 7-ethoxy-6,8-difluoro-4-oxo-1-pyridin-2-ylmethyl-1,4-dihydro-quinoline-3-carboxylic acid being suitable for X-ray analysis in 85.5% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta = 1.33$-1.36 (t, $J = 8.0$ Hz, 3 H, CH_3), 4.23-4.29 (q, $J = 8.0$, 16.0 Hz, 2 H, OCH_2), 5.70 (s, 2H, NCH_2), 7.24-8.80 (m, 6 H, ArH), 14.50 (br, 1 H, COOH) ppm.

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

Atom	x	y	z	U_{iso}*/U_{eq}
C1	0.0338(4)	0.6786(3)	0.3201(2)	0.0374(6)
C2	0.1475(5)	0.7476(3)	0.3806(2)	0.0467(7)
C3	0.0867(5)	0.7612(4)	0.4815(2)	0.0567(9)
C4	−0.0974(5)	0.7005(4)	0.5253(2)	0.0565(9)
C5	−0.2151(5)	0.6337(3)	0.4698(2)	0.0500(8)
H5	−0.3386	0.5963	0.5003	0.060*
C6	−0.1519(4)	0.6211(3)	0.3681(2)	0.0387(7)
C7	−0.2776(5)	0.5457(3)	0.3109(2)	0.0419(7)
C8	−0.2015(4)	0.5319(3)	0.2085(2)	0.0381(6)
C9	−0.0209(4)	0.5922(3)	0.1665(2)	0.0385(7)
H9	0.0235	0.5834	0.0985	0.046*
C10	−0.3117(5)	0.4531(3)	0.1427(2)	0.0460(7)
C11	0.2754(4)	0.7323(3)	0.1591(2)	0.0431(7)
H11A	0.3068	0.6932	0.0945	0.052*
H11B	0.3999	0.7101	0.1954	0.052*
C12	0.2304(5)	0.8931(3)	0.1405(2)	0.0412(7)
C13	−0.0044(6)	1.0889(4)	0.1141(3)	0.0687(10)
H13	−0.1436	1.1284	0.1100	0.082*
C14	0.1522(7)	1.1788(4)	0.0984(3)	0.0645(10)
H14	0.1202	1.2768	0.0840	0.077*
C15	0.3554(6)	1.1222(4)	0.1044(3)	0.0660(10)
H15	0.4653	1.1810	0.0941	0.079*
C16	0.3980(5)	0.9772(4)	0.1258(3)	0.0569(9)
H16	0.5364	0.9364	0.1304	0.068*
C17	0.1701(7)	0.8753(4)	0.6228(3)	0.0792(12)
H17A	0.1606	0.7938	0.6737	0.095*
H17B	0.0350	0.9334	0.6269	0.095*
C18	0.3431(7)	0.9613(5)	0.6412(3)	0.0824(13)
H18A	0.4733	0.9004	0.6445	0.124*
H18B	0.3060	1.0024	0.7041	0.124*
H18C	0.3608	1.0361	0.5869	0.124*
F1	0.3271(3)	0.8062(2)	0.34132(13)	0.0661(6)
F2	−0.1595(4)	0.7071(3)	0.62488(14)	0.0873(8)
N1	0.0956(3)	0.6631(2)	0.21797(17)	0.0384(6)
N2	0.0306(4)	0.9465(3)	0.1350(2)	0.0574(7)
O1	−0.4862(4)	0.3988(2)	0.18767(18)	0.0618(7)
H1	−0.5087	0.4202	0.2460	0.093*
O2	−0.2505(4)	0.4374(3)	0.05602(18)	0.0623(7)
O3	−0.4459(4)	0.4949(2)	0.35270(16)	0.0609(7)
O4	0.2165(5)	0.8296(4)	0.5283(2)	0.0989(11)

Experimental details

All H atoms were included in calculated positions and refined as riding atoms, with O—H = 0.82 Å with U_{iso} (H) = 1.2 U_{eq} (O), C—H = 0.93–0.98 Å with U_{iso}(H) = 1.2–1.5 U_{eq}(C) [3].

Comment

Over the last six decades, quinolones have been a focus of synthetic attention from academia and industry because of their unique structures and potent broad-spectrum antibacterial activities [5–8] owing the characteristics of a wide antibacterial spectrum, strong antibacterial activity, convenient administration and no cross resistance with commonly used antibiotics, quinolones have been popularized rapidly in clinic, and become the key drug in production and application in the world [9]. However, quinolones having been used or even abused for a long time, some bacteria have become resistant to quinolones through mutation. Thus it is of interest to find new quinolones which are effective against drug-resistant bacteria [10]. Recently, an expedient and high-yielding method for the synthesis of fluoroquinolones is explored in our group, and crystals of several key intermediates are achieved. We have reported the synthesis and crystals structures of two key intermediates 7-ethoxyl-6,8-difluoro-4-oxo-1-phenyl-1,4-dihydro-quinoline-3-carboxylic acid and 1-(4-chloro-phenyl)-7-ethoxyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid [11, 12].

In the molecule of the title compound bond lengths and angles within the title molecule are very similar to those given in the literature for dimethyl 4-oxo-1-phenyl-1,4-dihydroquinoline-2,3-dicarboxylate [13, 14]. The title molecule consists of two moieties: quinoline and a pyridinyl ring. The pyridinyl group is connected to the nitrogen atom (N1) of quinoline through methylene. The atoms of quinoline and pyridine ring are not coplanar, and the dihedral angle of quinoline ring, pyridinyl moiety and the carboxlate group C10—O1—O2 plane are 84.5(1)°, 2.0(2)° and 82.6(2)°, respectively. The torsion angles of C4—C3—O4—C17 and C3—O4—C17—C18 are −13.0(6)° and −173.1(4)°, respectively.

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References

1. Bruker. APEX2, SAINT and SADABS. Bruker AXS Inc., Madison, WI, USA (2009).
2. Sheldrick, G. M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
3. Sheldrick, G. M.: Crystal structure refinement with SHELXL. Acta Crystallogr. **C71** (2015) 3–8.

4. Brandenburg, K.: DIAMOND. Visual Crystal Structure Information System. Ver. 4.0. Crystal Impact, Bonn, Germany (2015).
5. Ma, Y.; Jin, S. H.: Development of fluoroquinolones. Foreign Med. Sci. **28** (2001) 240–242.
6. Xia, K. H.; Zhou, L.; Hao, L. F.: Progress in the research of the quinolone antibiotic. World Notes Antibiot. **25** (2004) 138–141.
7. Schellhorn, C.: Classification of quinolones by vadriole. Infect. **26** (1998) 64–64.
8. Graves, P. R.; Kwiek, J. J.; Fadden, P.; Ray, R.; Hardeman, K.; Coley, A. M.; Foley, M.; Haystead, T. A. J.: Discovery of novel targets of quinoline drugs in the human purine binding proteme. Mol. Pharmacol. **62** (2002) 1364–1364.
9. Chen, H. J.: Research progress of Quinolone compounds. Chin. J. Liaoning Chem. Ind. **48** (2019) 792–799.
10. Wang, A. P.; Feng, L. S.; Liu, M. L.; Guo, H. Y.: The latest research progress of fluoroquinolone. World Notes Antibiot. **40** (2019) 171–179.
11. Huang, J. X.; Huang, C. X.; Huang, G. P.; Xiong, Y. Z.; Huang, J. P.: Crystal structure of 7-ethoxyl-6,8-difluoro-4-oxo-1-phenyl-1,4-dihydro-quinoline-3-carboxylic acid, $C_{18}H_{13}F_2N_1O_4$. Z. Kristallogr. NCS **235** (2020) DOI:https://doi.org/10.1515/ncrs-2019-0885.
12. Zou, L.-H.; Nie, X.-L.; Zhao, L.; Huang, G.-P.; Huang, J.-P.: Crystal structure of 1-(4-chloro-phenyl)-7-ethoxyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid, $C_{18}H_{12}ClF_2NO_4$. Z. Kristallogr. NCS **235** (2020) 967–969.
13. Weiss, R.; Bess, M.; Huber, S. M.; Heinemann, F. W.: Nucleophilic β-oniovinylation: concept, mechanism, scope and applications. J. Am. Chem. Soc. **130** (2008) 4610–4617.
14. Kuramoto, Y.; Ohshita, Y.; Yoshida, J.; Yazaki, A.; Shiro, M.; Koike, T.: A novel antibacterial 8-chloroquinolone with a distorted orientation of the N1-(5-amino-2,4-difluorophenyl) group. J. Med. Chem. **46** (2003) 1905–1917.