Jian-Xiong Huang, Cui-Xin Huang, Guo-Ping Huang, Yuan-Zhen Xiong* and Jian-Ping Huang*

Crystal structure of 7-ethoxyl-6,8-difluoro-4-oxo-1-phenyl-1,4-dihydro-quinoline-3-carboxylic acid, $C_{18}H_{13}F_2N_1O_4$

<https://doi.org/10.1515/ncrs-2019-0885>

Received December 5, 2019; accepted January 16, 2020; available online February 12, 2020

Abstract

$C_{18}H_{13}F_2NO_4$, triclinic, $P\bar{1}$ (no. 2), $a = 7.9002(13)$ Å, $b = 9.9371(16)$ Å, $c = 10.6852(17)$ Å, $\alpha = 101.390(2)^\circ$, $\beta = 93.169(2)^\circ$, $\gamma = 104.901(2)^\circ$, $V = 789.7(2)$ Å³, $Z = 2$, $R_{gt}(F) = 0.0567$, $wR_{ref}(F^2) = 0.1223$, $T = 296(2)$ K.

CCDC no.: 1978259

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:	Colourless block
Size:	0.17 × 0.15 × 0.13 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.12 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} :	7108, 3570, 0.020
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2 \sigma(I_{obs})$, 2540
$N(param)_{refined}$:	241
Programs:	Bruker [1], SHELX [2, 3], Diamond [4]

Source of material

To a stirred solution of 6,7,8-trifluoro-4-oxo-1-phenyl-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (34.7 g, 0.1 mol) in ethanol (170 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 (monitored by TLC), the ethanol was distilled under reduced pressure to give a crude product. The crude product was poured into water (30 mL) and extracted with EtOAc (50 mL × 3). The EtOAc solvent was evaporated to provide the title compound in 85.3% yield. ¹H NMR (400 MHz, CDCl₃) δ 1.35–1.39 (t, $J = 8.0$ Hz, 3 H, CH₃), 4.28–4.33 (q, $J = 8.0, 12.0$ Hz, 2 H, OCH₂), 7.40–7.58 (m, 5 H, PhH), 8.05–8.08 (d, $J = 12.0$ Hz, 1 H, ArH), 8.63 (s, 1 H, NCH), 14.40 (br, 1 H, COOH) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 176.04, 165.27, 154.50, 151.79, 149.81, 145.98, 143.50, 142.33, 129.45, 129.19, 129.08, 127.25, 124.92, 120.58, 107.56, 70.35, 14.72 ppm.

*Corresponding authors: Yuan-Zhen Xiong, College of Pharmacy, Nanchang University, Nanchang 330031, P.R. China, e-mail: xiongyuanzhen@yahoo.com.cn; and Jian-Ping Huang, Jiangxi Key Laboratory for Conservation and Utilization of Fungal Resources/Research Center for Engineering Technology of Organic Functional Material and Application/Key Laboratory of Chemical Utilization of Plant Resources of Nanchang, Jiangxi Agricultural University, Nanchang 330045, P.R. China, e-mail: huangchenchuan@126.com. <https://orcid.org/0000-0001-9708-6856>

Jian-Xiong Huang: College of Pharmacy, Nanchang University, Nanchang 330031, P.R. China

Cui-Xin Huang: College of Agronomy, Jiangxi Agricultural University, Nanchang 330045, P.R. China

Guo-Ping Huang: Nanchang Jiangteng Pharmaceutical Ltd/Nanchang Tangteng Science and Technology Ltd, Nanchang 330045, P.R. China

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

Atom	x	y	z	<i>U</i> _{iso} ^a / <i>U</i> _{eq}
C1	0.4506(2)	0.9283(2)	0.22163(18)	0.0471(4)
C2	0.3893(3)	0.9929(2)	0.3322(2)	0.0549(5)
C3	0.4781(3)	1.1266(2)	0.4043(2)	0.0576(5)
C4	0.6346(3)	1.1962(2)	0.3637(2)	0.0602(5)
C5	0.7006(3)	1.1387(2)	0.2587(2)	0.0591(5)
H5	0.8062	1.1886	0.2352	0.071*
C6	0.6092(2)	1.0036(2)	0.18536(19)	0.0486(4)
C7	0.6816(3)	0.9439(2)	0.0716(2)	0.0527(5)
C8	0.5830(3)	0.8058(2)	0.00262(19)	0.0521(5)
C9	0.4304(3)	0.7387(2)	0.0438(2)	0.0551(5)
H9	0.3691	0.6485	−0.0036	0.066*
C10	0.6395(3)	0.7308(3)	−0.1160(2)	0.0659(6)
C11	0.1959(2)	0.7050(2)	0.17521(19)	0.0496(5)
C12	0.0408(3)	0.7171(3)	0.1228(3)	0.0711(7)
H12	0.0394	0.7837	0.0729	0.085*
C13	−0.1147(3)	0.6279(3)	0.1457(3)	0.0766(7)
H13	−0.2218	0.6349	0.1109	0.092*
C14	−0.1135(3)	0.5302(2)	0.2182(2)	0.0649(6)
H14	−0.2190	0.4722	0.2343	0.078*
C15	0.0434(3)	0.5179(3)	0.2671(3)	0.0752(7)
H15	0.0445	0.4496	0.3153	0.090*
C16	0.2005(3)	0.6056(2)	0.2460(2)	0.0660(6)
H16	0.3076	0.5972	0.2795	0.079*
C17 ^a	0.3312(7)	1.2929(8)	0.5078(5)	0.116(2)
H17A ^a	0.3557	1.3628	0.5886	0.139*
H17B ^a	0.3738	1.3419	0.4409	0.139*
C17B ^b	0.2551(17)	1.1689(19)	0.5515(14)	0.084(6)
H17C ^b	0.2633	1.2121	0.6421	0.101*
H17D ^b	0.1958	1.0681	0.5397	0.101*
C18	0.1513(7)	1.2320(7)	0.4809(5)	0.176(2)
H18A	0.1255	1.1736	0.3954	0.265*
H18B	0.0923	1.3059	0.4873	0.265*
H18C	0.1113	1.1742	0.5413	0.265*
F1	0.24205(18)	0.92385(14)	0.37377(14)	0.0829(5)
F2	0.7215(2)	1.32612(14)	0.43496(14)	0.0861(5)
N1	0.3622(2)	0.79323(17)	0.14763(16)	0.0513(4)
O1	0.7907(2)	0.7983(2)	−0.15055(17)	0.0796(5)
H1	0.834(4)	0.889(4)	−0.090(3)	0.119*
O2	0.5548(2)	0.6152(2)	−0.17739(18)	0.0904(6)
O3	0.8214(2)	1.01177(18)	0.03759(16)	0.0755(5)
O4	0.4248(2)	1.18338(19)	0.51602(16)	0.0793(5)

^aOccupancy: 0.778(8), ^bOccupancy: 0.222(8).

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

Quinolones are synthetic antibiotics, which are a very important broad-spectrum antibiotic and the most important breakthrough in the synthesis of antibiotics after sulfonamides [5–8]. Quinolones have been widely used in clinic

since the advent of naphthalic acid in the 1960s. Due to the characteristics of 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 the development, production and application in the world [9]. However, quinolones have been used or even abused for a long time, and bacteria have become resistant to some quinolones. Therefore, it is urgent to develop new quinolones effective against drug-resistant bacteria [10]. Recently, an expedient and high-yielding method for the synthesis of fluoroquinolones is explored in our group, and single crystals of several key intermediates are achieved. Herein, we report the synthesis and crystal structure of a key intermediate 7-ethoxyl-6,8-difluoro-4-oxo-1-phenyl-1,4-dihydro-quinoline-3-carboxylic acid, which provides a more efficient synthesis and a more comprehensive understanding for the synthesis of such compounds.

In the molecule of the title compound bond lengths and angles are very similar to those given in the literature for dimethyl 4-oxo-1-phenyl-1,4-dihydroquinoline-2,3-dicarboxylate [11, 12]. The molecule consists of two moieties: quinoline and benzene. The benzene ring is connected to the nitrogen atom (N1) of quinoline ring. The atoms of quinoline and benzene ring are coplanar, and the dihedral angle of quinoline ring and benzene ring is 88.28(8)°.

Acknowledgements: X-ray data were collected at Instrumental Analysis Center Nanchang Hangkong University, Nanchang, 330063, People's Republic of China. This study was supported by grants from Natural Science Foundation of Science and Technology Department of Jiangxi Province (No. 20151BBF60081; 20171BBE50027; 20171BBG70029), Natural Science Foundation of Education Department of Jiangxi Province (No. GJJ170275), Natural Science Foundation of Nanchang City (No. 2014HZZC07, 2018CXTD014), and Natural Science Foundation of Jiangxi Agriculture University (No. 09004634; 09005194; 201910410043).

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. A* **64** (2008) 112–122.
3. Sheldrick, G. M.: Crystal structure refinement with SHELXL. *Acta Crystallogr. C* **71** (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 on Antibiotics* **25** (2004) 138–141.
7. Schellhorn, C.: Classification of quinolones by vadriole. *Infect* **26** (1998) 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 proteome. *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 on Antibiotics* **40** (2019) 171–179.
11. 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.
12. Kuramoto, Y.; Ohshita, Y.; Yoshida, J.; Yazaki, A.; Shiro, M.; Koike, T.: A novel antibacterial 8-chloroquinolone with a distorted orientation of the N^1 -(5-amino-2,4-difluorophenyl) group. *J. Med. Chem.* **46** (2003) 1905–1917.