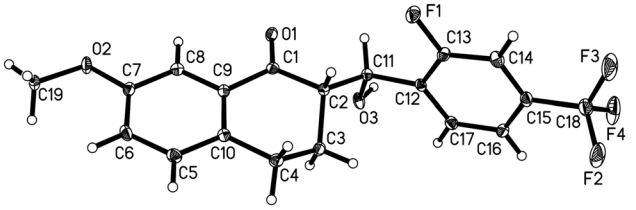
Yu-Lun Li, Qing-Guo Meng, Gui-Ge Hou and Zi-Kai Geng*

Crystal structure of 2-((2-fluoro-4-(trifluoromethyl)phenyl)(hydroxy)methyl)-7-methoxy-3,4-dihydronaphthalen-1((2*H*))-one, $C_{19}H_{16}F_4O_3$



https://doi.org/10.1515/ncrs-2023-0373
Received August 16, 2023; accepted September 27, 2023;
published online October 10, 2023

Abstract

$C_{19}H_{16}F_4O_3$, monoclinic, $P2_1/n$ (no. 14), a = 9.5792(5) Å, b = 9.5542(4) Å, c = 17.6986(9) Å, β = 99.508(5)°, V = 1597.55(14) Å^3, Z = 4, $R_{gt}(F)$ = 0.0481, $wR_{ref}(F^2)$ = 0.1153, T = 293 K.

CCDC no.: 2272259

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.12 × 0.12 × 0.10 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.13 mm^{-1}
Diffractometer, scan mode:	SuperNova,
θ_{max}, completeness:	25.5°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	7486, 2984, 0.028
Criterion for I_{obs}, $N(hkl)_{gt}$:	I_{obs} > 2 σ(I_{obs}), 2502
$N(param)_{refined}$:	237
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

The crystal structure is shown in the Figure. Displacement ellipsoids are drawn at the 40 % probability level.

Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

1 Source of material

The raw material 7-methoxy-3,4-dihydronaphthalene-1(2*H*)-one was obtained according to a literature [4]. The raw material (0.53 g, 3.0 mmol) and 2-fluoro-4-(trifluoromethyl) benzaldehyde (0.58 g, 3.0 mmol) were dissolved in 15 mL of methanol. About 5.0 mL of 20 % NaOH solution was added dropwise. The mixture was stirred at room temperature for about 1 h, and detected the reaction process by Thin-Layer Chromatography (TLC). The solvent was then removed by pouring, and the residues were purified on a silica gel by column chromatography using petroleum ether/EtOAc (2:1, v/v) as the eluent to obtain the light yellow solid of the title compound in 82.2 % yield.

2 Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with d(C–H) = 0.96 Å(methyl), U_{iso}(H) = 1.5U_{eq}(C); d(C–H) = 0.97 Å(methylene), U_{iso}(H) = 1.2U_{eq}(C); U_{iso}(H) = 1.2U_{eq}(C); d(C–H) = 0.93 Å(aromatic), U_{iso}(H) = 1.2U_{eq}(C); and d(O–H) = 0.82 Å(hydroxyl), U_{iso}(H) = 1.5U_{eq}(O), respectively.

3 Comment

3,4-Dihydronaphthalen-1(2*H*)-one is an active fragment with potential for the treatment of allergies and inflammatory phenomena among others [5]. In our previous study, we demonstrated that compounds with 3,4-dihydronaphthalen-1(2*H*)-one fragment could have inhibitory effects on the NF-**κ**B signaling pathway [6], so we introduced electron-withdrawing groups fluorine atoms and trifluoromethyl side chains based on the original compounds with aromatic aldehydes through the Claisen–Schmidt reaction because their lipophilicity could enhance the membrane permeability of the drug, the

***Corresponding author: Zi-Kai Geng**, School of Pharmacy, Binzhou Medical University, Yantai, 264003, P.R. China, E-mail: gengzikai@126.com
Yu-Lun Li, Qing-Guo Meng and Gui-Ge Hou, School of Pharmacy, Binzhou Medical University, Yantai, 264003, P.R. China. https://orcid.org/0000-0002-9493-3981 (G.-G. Hou)

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.5783 (2)	0.2291 (2)	0.90120 (11)	0.0129 (4)
C2	0.4323 (2)	0.2717 (2)	0.91677 (11)	0.0126 (4)
H2	0.443743	0.361583	0.943790	0.015*
C3	0.3316 (2)	0.2974 (2)	0.84093 (12)	0.0152 (5)
H3A	0.323081	0.212900	0.810155	0.018*
H3B	0.238366	0.322276	0.851173	0.018*
C4	0.3905 (2)	0.4162 (2)	0.79752 (12)	0.0160 (5)
H4A	0.330365	0.428978	0.748260	0.019*
H4B	0.389467	0.502565	0.826261	0.019*
C5	0.5940 (2)	0.4459 (2)	0.72495 (12)	0.0175 (5)
H5	0.536793	0.505706	0.691771	0.021*
C6	0.7316 (2)	0.4195 (2)	0.71239 (12)	0.0171 (5)
H6	0.765118	0.460905	0.671324	0.021*
C7	0.8182 (2)	0.3306 (2)	0.76195 (12)	0.0146 (4)
C8	0.7667 (2)	0.2699 (2)	0.82302 (11)	0.0137 (4)
H8	0.824690	0.211162	0.856419	0.016*
C9	0.6285 (2)	0.2962 (2)	0.83480 (11)	0.0121 (4)
C10	0.5396 (2)	0.3859 (2)	0.78526 (11)	0.0131 (4)
C11	0.3767 (2)	0.1676 (2)	0.97036 (11)	0.0139 (4)
H11	0.451738	0.150908	1.014224	0.017*
C12	0.2467 (2)	0.2205 (2)	1.00053 (11)	0.0126 (4)
C13	0.2563 (2)	0.3275 (2)	1.05421 (12)	0.0155 (4)
C14	0.1444 (2)	0.3740 (2)	1.08781 (12)	0.0178 (5)
H14	0.156028	0.445362	1.124055	0.021*
C15	0.0140 (2)	0.3102 (2)	1.06534 (12)	0.0160 (5)
C16	−0.0024 (2)	0.2048 (2)	1.01059 (12)	0.0168 (5)
H16	−0.090617	0.163869	0.995184	0.020*
C17	0.1134 (2)	0.1609 (2)	0.97897 (12)	0.0159 (5)
H17	0.101724	0.089981	0.942492	0.019*
C18	−0.1117 (2)	0.3531 (2)	1.09992 (13)	0.0217 (5)
C19	1.0140 (2)	0.3652 (3)	0.69570 (12)	0.0216 (5)
H19A	0.955676	0.347368	0.647115	0.032*
H19B	1.107654	0.330063	0.695010	0.032*
H19C	1.018278	0.464145	0.705200	0.032*
F1	0.38489 (13)	0.38979 (13)	1.07585 (7)	0.0224 (3)
F2	−0.21041 (16)	0.41932 (17)	1.05058 (9)	0.0416 (4)
F3	−0.07929 (17)	0.4326 (2)	1.16122 (10)	0.0587 (6)
F4	−0.18188 (16)	0.24189 (16)	1.12227 (9)	0.0406 (4)
O1	0.65304 (15)	0.14541 (15)	0.94221 (8)	0.0171 (3)
O2	0.95477 (16)	0.29652 (16)	0.75505 (8)	0.0194 (4)
O3	0.34839 (16)	0.03904 (15)	0.92984 (8)	0.0167 (3)
H3	0.345647	−0.024889	0.960473	0.025*

stabilized C–F bond could improve the metabolic stability and prolong the duration of *in vivo* action. It is well known that fluorine atoms are the strongly electronegative that can form hydrogen bonds with the target proteins, thus enhancing the inhibitory effect of the drug against NF-κB [7]. Previously, we reported a series of condensation products with electron-donoring and electron-withdrawing groups, which were obtained by Claisen–Schmidt condensation reaction between aromatic aldehydes and 3,4-dihydronaphthalen-1(2*H*)-one [8–11]. The common structural features is the formation of *α,β*-unsaturated ketones. In this study, we still expected the compound containing the *α,β*-unsaturated ketone, but our structural analysis of the title compound revealed that there is *β*-hydroxyketone unit [12] but not *β*-unsaturated ketone unit.

Single-crystal structure analysis reveals that there is only a title molecule in the asymmetric unit (*cf.* the Figure). The bond lengths and bond angles of the title compound are within the normal range and are in agreement with previous reports [7, 9, 11, 13]. The parent nucleus of this compound is 3,4-dihydronaphthalen-1(2*H*)-one with a methoxy group attached to C(7), while a 2-fluoro-4-(trifluoromethyl)phenyl substituted β-hydroxyketone attached to C(2). Interestingly, C(11) is a chiral carbon atom. In the solid state, the molecules crystallize in a centrosymmetric space group, $P2_1/n$, and the whole does not show chiral properties. In addition, the benzene ring is substituted with electron-withdrawing substituents (–F and $–CF_3$), and the substituted benzene ring is not coplanar with the parent nucleus with a big dihedral angle of about 85.20(2)°. The C(11)-substituted hydroxyl group and C(1)=O(1) group did not form the intramolecular hydrogen bond, and the torsion angle of C(1)–C(2)–C(1)–O(3) is about −68.3(2)°, and the torsion angle of O(1)=C(1)–C(2)–C(11) is about −17.7(3)°, respectively. The C(11)-substituted hydroxyl group and the C(13)-substituted fluorine atom are in the trans structure, so that the torsion angle of O(3)–C(11)–C(12)–C(13) is about 166.92(17)°, and the torsion angle of C(11)–C(12)–C(13)–F(1) is about 3.8(3)°, respectively.

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

Research funding: Shandong Provincial Natural Science Foundation (No. ZR2023MH190).

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

References

1. Rigaku O. D. CrysAlis^{PRO}; Rigaku Oxford Diffraction Ltd: Yarnton, Oxfordshire, England, 2017.
2. Sheldrick G. M. A short history of *SHELX*. *Acta Cryst* 2008, *A64*, 112–122.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Cryst* 2015, *C71*, 3–8.
4. Sun Y., Gao Z. F., Wang C. H., Hou G. G. Synthesis, crystal structures and anti-inflammatory activity of fluorine-substituted 1,4,5,6-tetrahydrobenzo[*h*]quinazolin-2-amine derivatives. *Acta Crystallogr*. 2019, *C75*, 1157–1165.
5. Barlow J. W., Zhang T., Woods O., Byrne A. J., Walsh J. J. Novel mast cell-stabilising amine derivatives of 3,4-dihydronaphthalen-1(2*H*)-one and 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one. *Med. Chem.* 2011, *7*, 213–223.
6. Kirby A. J., Le L. R., Maharlouie F., Mason P., Nicholls P. J., Smith H. J. Inhibition of retinoic acid metabolising enzymes by 2-(4-aminophenyl

methyl)-6-hydroxy-3,4-dihydronaphthalen-1(2*H*)-one and related compounds. *J. Enzyme Inhib. Med. Chem.* 2003, *18*, 27–33.
7. Luan M. Z., Wang H. Y., Zhang M., Song J., Hou G. G., Zhao F. L., Meng Q. G. Crystal structure of (*E*)-2-(3,5-bis(trifluoromethyl) benzylidene)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one, $C_{20}H_{14}F_6O_2$. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 61–63.
8. Sun Y., Zhou Y. Q., Liu Y. K., Zhang H. Q., Hou G. G., Meng Q. G., Hou Y. Potential anti-neuroinflammatory NF-κB inhibitors based on 3,4-dihydronaphthalen-1(2*H*)-one derivatives. *J. Enzyme Inhib. Med. Chem.* 2020, *35*, 1631–1640.
9. Zhang Y. L., Liu S. L., Hou G. G., Zhang X. F., Wang L., Xin W. Y. Crystal structure of (*E*)-7-bromo-2-(4-methoxybenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, $C_{18}H_{15}BrO_2$. *Z. Kristallogr. N. Cryst. Struct.* 2022, *237*, 945–947.
10. Zhang X. F., Luan M. Z., Yan W. B., Zhao F. L., Hou Y., Hou G. G., Meng Q. G. Anti-neuroinflammatory effects of novel 5,6-dihydrobenzo [*h*]quinazolin-2-amine derivatives in lipopolysaccharide-stimulated BV2 microglial cells. *Eur. J. Med. Chem.* 2022, *235*, 114322.
11. Qi Q. B., Li W. X., Hou G. G., Li C. B. Crystal structure of (*E*)-7-bromo-2-(4-(4-methylpiperazin-1-yl)benzylidene)-3,4-dihydronaphthalen-1(2H)-one, $C_{22}H_{23}BrN_2O$. *Z. Kristallogr. N. Cryst. Struct.* 2023, *238*, 235–237.
12. Yang Y., Gao Z. F., Hou G. G., Meng Q. G., Hou Y. Discovery of anti-neuroinflammatory agents from 1,4,5,6-tetrahydrobenzo[2,3]oxepino [*4,5-d*]pyrimidin-2-amine derivatives by regulating microglia polarization. *Eur. J. Med. Chem.* 2023, *259*, 115688.
13. Dai Z.-Y., Nong Z.-S., Wang P.-S. Light-mediated asymmetric aliphatic C–H alkylation with hydrogen atom transfer catalyst and chiral phosphoric acid. *ACS Catal*. 2020, *10*, 4786–4790.