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Crystal structure of (*E*)-7-fluoro-2-(3-fluorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, C₁₇H₁₂F₂O₁

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Abstract

C₁₇H₁₂F₂O₁, monoclinic, $P\bar{1}$ (no. 2), $a = 7.3832(8)$ Å, $b = 8.6467(9)$ Å, $c = 11.3278(11)$ Å, $\alpha = 87.633(8)^\circ$, $\beta = 88.022(8)^\circ$, $\gamma = 65.364(10)^\circ$, $V = 654.88(13)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0369$, $wR_{\text{ref}}(F^2) = 0.0987$, $T = 293(2)$ K.

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The crystal structure is shown in the figure. Displacement ellipsoids are drawn at the 35% 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.

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Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.14 × 0.11 × 0.10 mm
Wavelength:	Mo Kα radiation (0.71073 Å)
μ :	0.10 mm ⁻¹
Diffractometer, scan mode:	XCALIBUR, CCD plate scans
θ_{max} , completeness:	25.5°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	12423, 2433, 0.024
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 1891
$N(\text{param})_{\text{refined}}$:	182
Programs:	CRYSA LIS ^{PRO} [1], SHELX [2, 3]

Source of material

The amounts of 5 ml methanol, 5 ml dichloromethane, 7-fluoro-1-naphthalene ketone and 3-fluorobenzaldehyde were added to a 50 ml flask, stirred in the ice salt bath at -5°C until the system became soluble and clear. Five millilitre (25%) of sodium hydroxide aqueous solution was added dropwise to the mixture and stirred at room temperature for 3 h. The reaction was monitored by silica gel thin layer chromatography (TLC, 254 nm). When the reaction was finished, the precipitate was filtered from the reaction mixture and dissolved with ethyl acetate. The organic phase was washed successively with water and brine in turn and dried with anhydrous sodium sulfate. After filtration, the filtrate was condensed in vacuum to yield a white solid, which was purified by silica-gel column chromatography (petroleum ether: ethyl acetate = 1:2, v/v). Suitable crystals of the title compound were obtained by recrystallization in the dichloromethane and methanol (1:1, v/v) system and dried in a vacuum at 65°C for 3 h.

Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with $d(\text{C}-\text{H}) = 0.97$ Å (methylene), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$, and $d(\text{C}-\text{H}) = 0.93$ Å (aromatic), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

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

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
F1	0.29139 (17)	0.57875 (14)	−0.24594 (9)	0.0833 (4)
F2	−0.1989 (2)	−0.2361 (2)	0.43629 (12)	0.1241 (6)
O1	0.24884 (16)	0.06387 (13)	−0.05141 (9)	0.0550 (3)
C1	0.25997 (19)	0.14906 (17)	0.02942 (12)	0.0418 (3)
C2	0.2600 (2)	0.09233 (17)	0.15540 (12)	0.0422 (3)
C3	0.3449 (2)	0.17173 (19)	0.24109 (13)	0.0503 (4)
H3A	0.488109	0.130181	0.228156	0.060*
H3B	0.320711	0.140288	0.321359	0.060*
C4	0.2471 (2)	0.36500 (19)	0.22417 (13)	0.0512 (4)
H4A	0.108523	0.407188	0.250485	0.061*
H4B	0.313802	0.414192	0.273047	0.061*
C5	0.2493 (2)	0.58209 (18)	0.07057 (15)	0.0527 (4)
H5	0.238161	0.654546	0.131518	0.063*
C6	0.2588 (2)	0.63650 (19)	−0.04364 (16)	0.0563 (4)
H6	0.253793	0.744300	−0.060847	0.068*
C7	0.2760 (2)	0.5271 (2)	−0.13208 (15)	0.0544 (4)
C8	0.2805 (2)	0.36936 (19)	−0.11116 (13)	0.0491 (4)
H8	0.291154	0.298893	−0.173317	0.059*
C9	0.26871 (18)	0.31584 (17)	0.00553 (12)	0.0408 (3)
C10	0.25574 (19)	0.42177 (17)	0.09832 (13)	0.0433 (3)
C11	0.1731 (2)	−0.01351 (17)	0.18075 (12)	0.0458 (4)
H11	0.114476	−0.038397	0.117063	0.055*
C12	0.1557 (2)	−0.09667 (17)	0.29353 (13)	0.0470 (4)
C13	−0.0152 (2)	−0.1248 (2)	0.31512 (14)	0.0579 (4)
H13	−0.118129	−0.086048	0.261061	0.070*
C14	−0.0305 (3)	−0.2099 (3)	0.41639 (16)	0.0719 (5)
C15	0.1148 (3)	−0.2720 (3)	0.49790 (17)	0.0822 (6)
H15	0.099512	−0.329508	0.566053	0.099*
C16	0.2853 (3)	−0.2471 (3)	0.47642 (17)	0.0782 (6)
H16	0.387824	−0.289303	0.530666	0.094*
C17	0.3074 (3)	−0.1604 (2)	0.37551 (15)	0.0608 (4)
H17	0.424065	−0.144812	0.362521	0.073*

Comment

Central nervous system degenerative disease refers to a group of diseases are caused by chronic progressive degeneration of the central nervous system. Pathologically, degeneration and loss of neurons occurred in the brain and/or spinal cord [4]. Inflammation in the brain is induced by activated microglia and reactive astrocytes [5]. Potential drugs should be able to cross the blood-brain barrier and activate the increase of circulating inflammatory markers of microglia, resulting in the production of cellular inflammation [6]. The cytotoxicity and anti-inflammatory activity of such compounds were evaluated. It is found that they can inhibit tumor growth and has anti-inflammatory activity. Some piperidones may inhibit the expression of NF-κB and make activated microglia produce an anti-inflammatory effect [7–9]. Combined with the data of cytotoxicity,

cytocompatibility and anti-inflammatory activity, some of these compounds may be a new NF KB inhibitor with anti-inflammatory and anti hepatoma activities, which is expected to be further developed into a multifunctional drug for clinical treatment of liver cancer and inflammatory diseases [10, 11]. However, DHN derivatives are rarely developed as anti-neuroinflammatory drugs. Our group also synthesized some of these compounds, and studied their anti-neuroinflammatory activity [12, 13]. In this paper, we report on a benzylidene-substituted DHN derivative which was designed and synthesized through Claisen–Schmidt condensation reactions (see the figure) [14]. Single crystal of the title compound were prepared under ambient conditions, with crystallization obtained via solvent evaporation in the mixed solution of methanol and dichloromethane (1:1, v/v) [15].

There is one molecule in the asymmetric unit of the title structure (see the Figure). Bond lengths and angles are all in the expected ranges [16]. Because of the disto 3,4-dihydronaphthalen-1(2*H*)-one, the 7-fluorophenyl and 3-fluorophenyl groups are not coplanar with each other, with a dihedral angle of approximately 65°. This twisted configuration may increase likelihood of interactions with bioactive molecules, for the purposes of creating more potent biological activity [17, 18].

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References

1. Rigaku OD. CrysAlis^{PRO}; Rigaku Oxford Diffraction Ltd: Yarnton, Oxfordshire, England, 2017.
2. Sheldrick G. M. A short history of *SHELX*. *Acta Crystallogr.* 2008, *A64*, 112–122.
3. Sheldrick G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Stephenson J., Nutma E., van der Valk P., Amor S. Inflammation in CNS neurodegenerative diseases. *Immunology* 2018, *154*, 204–219.
5. Goldmann T., Prinz M. Role of microglia in CNS autoimmunity. *Clin. Dev. Immunol.* 2013, *2013*, 208093.
6. Gao C. L., Hou G. G., Liu J., Ru T., Xu Y. Z., Zhao S. Y., Ye H., Zhang L. Y., Chen K. X., Guo Y. W., Pang T., Li X. W. Synthesis and target identification of benzoxepane derivatives as potential anti-neuroinflammatory agents for ischemic stroke. *Angew. Chem. Int. Ed.* 2020, *59*, 2429–2439.

7. Troubat R., Barone P., Leman S., Desmidt T., Cressant A., Atanasova B., Brizard B., El Hage W., Surget A., Belzung C., Camus V. Neuroinflammation and depression: a review. *Eur. J. Neurosci.* 2021, 154, 151–171.
8. Li N., Xin W. Y., Yao B. R., Cong W., Wang C. H., Hou G. G. N-phenylsulfonyl-3,5-bis(arylidene)-4-piperidone derivatives as activation NF-kappaB inhibitors in hepatic carcinoma cell lines. *Eur. J. Med. Chem.* 2018, 155, 531–544.
9. Yao B. R., Sun Y., Chen S. L., Suo H. D., Zhang Y. L., Wei H., Wang C. H., Zhao F., Cong W., Xin W. Y., Hou G. G. Dissymmetric pyridyl-substituted 3,5-bis(arylidene)-4-piperidones as anti-hepatoma agents by inhibiting NF-κB pathway activation. *Eur. J. Med. Chem.* 2019, 167, 187–199.
10. Sun Y., Gao Z. F., Yan W. B., Yao B. R., Xin W. Y., Wang C. H., Meng Q. G., Hou G. G. Discovery of novel NF-κB inhibitor based on scaffold hopping: 1,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidine. *Eur. J. Med. Chem.* 2020, 198, 112366.
11. 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, 75, 1157–1165.
12. 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(2H)-one derivatives. *J. Enzym. Inhib. Med. Chem.* 2020, 35, 1631–1640.
13. Li N., Xin W. Y., Yao B. R., Wang C. H., Cong W., Zhao F., Li H. J., Hou Y., Meng Q. G., Hou G. G. Novel dissymmetric 3,5-bis(arylidene)-4-piperidones as potential antitumor agents with biological evaluation *in vitro* and *in vivo*. *Eur. J. Med. Chem.* 2018, 147, 21–33.
14. Li N., Yao B. Y., Wang C. H., Meng Q. G., Hou G. G. Synthesis, crystal structure and activity evaluation of novel 3,4-dihydro-1-benzoxepin-5(2H)-one derivatives as protein-tyrosine kinase (PTK) inhibitors. *Acta Crystallogr.* 2017, C73, 1003–1009.
15. Xiong C. L., Lan Y. D., Song X. Y., Xiong W. M., Nie X. L. Crystal structure of methyl 4-acetoxy-3,5-dimethoxybenzoate, $C_{12}H_{14}O_6$. *Z. Kristallogr. N. Cryst. Struct.* 2021, 236, 573–575;.
16. Luan M.-Z., Meng Q.-G. Crystal structure of (E)-7-methoxy-2-((5-methoxypyridin-3-yl)methylene)-3,4-dihydronaphthalen-1(2H)-one, $C_{18}H_{17}NO_3$. *Z. Kristallogr. N. Cryst. Struct.* 2021, 236, 387–389.
17. Sun Y., Liu Y. K., Li J. D., Meng Q. G., Hou G. G. Crystal structure and anti-inflammatory activity of (3E,5E)-3-(2-fluorobenzylidene)-1-((4-fluorophenyl)sulfonyl)-5-(pyridin-3-ylmethylene)piperidin-4-one, $C_{24}H_{18}F_2N_2O_3S$. *Z. Kristallogr. N. Cryst. Struct.* 2020, 235, 377–379.
18. Zhou Y. Q., Hou G. G., Meng Q. G., Hou Y. Crystal structure and anti-inflammatory activity of (3E,5E)-1-((4-chlorophenyl)sulfonyl)-3-(pyridin-4-ylmethylene)-5-(2-(trifluoromethyl) benzylidene) piperidin-4-one, $C_{25}H_{18}ClF_3N_2O_3S$. *Z. Kristallogr. N. Cryst. Struct.* 2020, 235, 411–413.