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Crystal structure of (*E*)-7-fluoro-2-(4-methoxy-2-(trifluoromethyl)benzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, C₁₉H₁₄F₄O₂

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Abstract

C₁₉H₁₄F₄O₂, monoclinic, *P*₂/c (no. 14), *a* = 11.8614(10) Å, *b* = 7.9148(6) Å, *c* = 16.7999(16) Å, β = 99.150(9)°, *V* = 1557.1(2) Å³, *Z* = 4, *R*_{gt}(*F*) = 0.0446, *wR*_{ref}(*F*²) = 0.1150, *T* = 100 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.

Source of material

5 mL of sodium hydroxide aqueous solution (25%) was added dropwise to the mixture of 7-fluoro-3,

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.13 × 0.12 × 0.11 mm
Wavelength:	Mo Kα radiation (0.71073 Å)
μ:	0.13 mm ⁻¹
Diffractometer, scan mode:	SuperNova
θ _{max} , completeness:	25.5°, >99%
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} , <i>R</i> _{int} :	6570, 2891, 0.033
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2σ(<i>I</i> _{obs}), 2362
<i>N</i> (<i>param</i>) _{refined} :	227
Programs:	CRYSTALIS ^{PRO} [1], SHELX [2, 3]

4-dihydronaphthalen-1(2*H*)-one (700 mg, 4.26 mmol) and 4-methoxy-2-(trifluoromethyl)benzaldehyde (870 mg, 4.26 mmol) in 10 mL methanol and stirred at room temperature for 4 h. The in process-control was monitored by silica gel thin layer chromatography (TLC, 254 nm). When the reaction was finished, the precipitate was suction filtered out, and a 50% methanol aqueous solution was added dropwise to wash, and the filter cake was vacuum dried at 65 °C to obtain a light yellow solid. Suitable crystals of the title compound were obtained by recrystallization in dichloromethane and methanol (1:1, v/v) system and dried under vacuum at 65 °C for 5 h.

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) = 1.5 *U*_{eq}(C), and *d*(C–H) = 0.97 Å (methylene), *U*_{iso}(H) = 1.2 *U*_{eq}(C), and *d*(C–H) = 0.93 Å (aromatic), *U*_{iso}(H) = 1.2 *U*_{eq}(C). Displacement ellipsoids are drawn at the 40% probability level.

Comment

Studies have shown that the development of an anti-inflammatory and low toxic NF-κB inhibitor is of great significance for the treatment of inflammatory neurodegenerative CNS diseases [4–6].

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

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
C1	0.28309 (15)	0.5351 (2)	0.78121 (11)	0.0242 (4)
C2	0.27811 (15)	0.5544 (2)	0.86916 (11)	0.0236 (4)
C3	0.36931 (15)	0.6621 (2)	0.91647 (11)	0.0284 (4)
H3A	0.367680	0.648498	0.973661	0.034*
H3B	0.354869	0.779988	0.902764	0.034*
C4	0.48686 (16)	0.6116 (3)	0.89791 (11)	0.0327 (5)
H4A	0.543716	0.689546	0.924611	0.039*
H4B	0.505830	0.499491	0.919318	0.039*
C5	0.59270 (16)	0.6416 (2)	0.77932 (12)	0.0323 (5)
H5	0.658930	0.662887	0.815598	0.039*
C6	0.59774 (17)	0.6400 (2)	0.69787 (12)	0.0322 (5)
H6	0.666504	0.657909	0.679216	0.039*
C7	0.49842 (17)	0.6113 (2)	0.64475 (11)	0.0287 (4)
C8	0.39622 (16)	0.5805 (2)	0.67011 (11)	0.0269 (4)
H8	0.330568	0.560696	0.633021	0.032*
C9	0.39252 (15)	0.5795 (2)	0.75310 (11)	0.0236 (4)
C10	0.49092 (15)	0.6120 (2)	0.80877 (11)	0.0262 (4)
C11	0.19726 (15)	0.4668 (2)	0.89900 (11)	0.0255 (4)
H11	0.151055	0.397381	0.862845	0.031*
C12	0.17339 (14)	0.4679 (2)	0.98250 (11)	0.0237 (4)
C13	0.14704 (14)	0.3193 (2)	1.02263 (11)	0.0222 (4)
C14	0.12003 (14)	0.3241 (2)	1.09972 (11)	0.0236 (4)
H14	0.103418	0.224366	1.124732	0.028*
C15	0.11756 (14)	0.4778 (2)	1.14019 (11)	0.0239 (4)
C16	0.14380 (15)	0.6255 (2)	1.10272 (11)	0.0256 (4)
H16	0.143609	0.728480	1.129337	0.031*
C17	0.17037 (15)	0.6187 (2)	1.02523 (11)	0.0268 (4)
H17	0.186882	0.719063	1.000702	0.032*
C18	0.0905 (2)	0.6203 (2)	1.26099 (12)	0.0370 (5)
H18A	0.166907	0.663892	1.271356	0.056*
H18B	0.064546	0.597491	1.311225	0.056*
H18C	0.041027	0.701959	1.231018	0.056*
C19	0.15198 (15)	0.1506 (2)	0.98292 (11)	0.0268 (4)
F1	0.50222 (10)	0.61374 (15)	0.56421 (7)	0.0421 (3)
F2	0.25497 (9)	0.11891 (13)	0.96276 (8)	0.0411 (3)
F3	0.07742 (10)	0.13620 (13)	0.91407 (7)	0.0377 (3)
F4	0.12968 (10)	0.02243 (12)	1.02984 (7)	0.0356 (3)
O1	0.20172 (11)	0.48343 (16)	0.73312 (8)	0.0323 (3)
O2	0.08882 (11)	0.46776 (15)	1.21546 (8)	0.0307 (3)

Existing studies have used 3,4-dihydronaphthalen-1(2*H*)-one (DHN) derivatives with anti-tumor and anti-inflammatory activities as novel allergic and inflammatory responses modifiers [7] and as potential retinoic acid (RA)-metabolizing enzymes inhibitors to treat skin diseases and cancer. However, there are few studies on DHN derivatives as anti-neuroinflammatory drugs. Therefore, it is of great significance to study the synthesis and crystal structure of novel benzylidene-substituted DHN derivatives with anti-neuroinflammatory activity. Our group also synthesized some of these compounds in the early

stage, and studied their anti-neuroinflammatory activity. The results showed that the fluorine-substituted compounds had better activity [8–10]. In this study, a new benzylidene-substituted DHN derivative was designed and synthesized through Claisen–Schmidt condensation reactions (see the Figure).

Single-crystal structure analysis revealed that the title compound crystallized in the monoclinic space group *P*₂₁/*c*. The ORTEP diagram is presented in the Figure. Bond lengths and angles are all in the expected ranges [11–13]. There is only one molecule in the asymmetric unit. The molecule adopts the *E* stereochemistry [14]. The 3,4-dihydronaphthalen-1(2*H*)-one, the 7-fluorophenyl and 4-methoxy-2-(trifluoromethyl) phenyl groups are not coplanar. This twisted configuration may increase likelihood of interactions with bioactive molecules, for the purposes of creating more potent biological activity [15].

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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 Crystallogr.* 2008, *A64*, 112–122.
3. Sheldrick G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Zeng K. W., Wang S., Dong X., Jiang Y., Tu P. F. Sesquiterpene dimer (DSF-52) from *Artemisia argyi* inhibits microglia-mediated neuroinflammation via suppression of NF-κB, JNK/p38 MAPKs and Jak2/Stat3 signaling pathways. *Phytomedicine* 2014, *21*, 298–306.
5. Zhang J. Q., Zhang Q., Xu Y. R., Li H. X., Zhao F. L., Wang C. M., Liu Z., Liu P., Liu Y. N., Meng Q. G., Zhao F. Synthesis and in vitro anti-inflammatory activity of C20 epimeric ocotillol-type triterpenes and protopanaxadiol. *Planta Med.* 2019, *85*, 292–301.
6. Wang C. M., Liu J., Deng J. Q., Wang J. Z., Weng W. Z., Chu H. X., Meng Q. G. Advances in the chemistry, pharmacological diversity, and metabolism of 20(*R*)-ginseng saponins. *J. Ginseng. Res.* 2020, *44*, 14–23.
7. Kirby A. J., Le L. R., Maharlouie F., Mason P., Nicholls P. J., Smith H. J., Simons C. Inhibition of retinoic acid metabolising enzymes by 2-(4-aminophenylmethyl)-6-hydroxy-3,4-dihydronaphthalen-1(2*H*)-one and related compounds. *J. Enzym. Inhib. Med. Chem.* 2003, *18*, 27–33.

8. Sun Y., Zhou Y. Q., Liu Y. K., Zhang H. Q., Hou G. G., Meng Q. G., Hou Y. Potential anti-neuroinflammatory NF- κ B inhibitors based on 3,4-dihydronaphthalen-1(2H)-one derivatives. *J. Enzym. Inhib. Med. Chem.* 2020, 35, 1631–1640.
9. Su C. M., Hou G. H., Wang C. H., Zhang H. Q., Cheng Y., Liu M., Hou Y. Potential multifunctional agents with anti-hepatoma and anti-inflammation properties by inhibiting NF- κ B activation. *J. Enzym. Inhib. Med. Chem.* 2019, 34, 1287–1297.
10. 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.
11. 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(2H)-one, $C_{20}H_{14}F_6O_2$. *Z. Kristallogr. N. Cryst. Struct.* 2021, 236, 61–63.
12. Zhang X.-F., Wang H.-Y., Zhao S.-N., Zhang S.-N., Zhao F.-L., Meng Q.-G. Crystal structure of (E)-2-(4-fluoro-3(trifluoromethyl)benzylidene)-7-methoxy-3,4-dihydronaphthalen-1(2H)-one, $C_{19}H_{14}F_4O_2$. *Z. Kristallogr. N. Cryst. Struct.* 2021, 236, 47–49.
13. Zhang X.-F., Meng Q.-G. Crystal structure of (E)-2-((2-methoxy-3-pyridyl)methylene)-7-fluoro-3,4-dihydronaphthalen-1(2H)-one, $C_{17}H_{14}FNO_2$. *Z. Kristallogr. N. Cryst. Struct.* 2021, 236, 507–509.
14. 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.
15. 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.