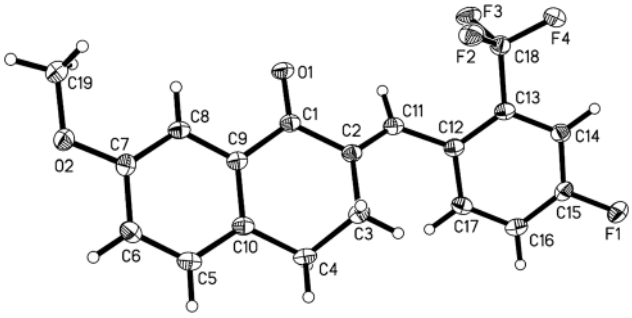
Ming-Zhu Luan, Hui-Yun Wang, Mei Zhang, Jia Song, Yang-Rong Xu, Feng-Lan Zhao and Qing-Guo Meng*

Crystal structure of (*E*)-2-(4-fluoro-2-(trifluoromethyl)benzylidene)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one, $C_{19}H_{14}F_4O_2$



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Abstract

$C_{19}H_{14}F_4O_2$, monoclinic, *C*2/*c* (no. 15), a = 17.1519(13) Å, b = 13.9810(8) Å, c = 15.2299(9) Å, β = 123.031(7)°, V = 3061.9(4) Å^3, Z = 8, $R_{gt}(F)$ = 0.0410, $wR_{ref}(F^2)$ = 0.1010, T = 100(1) 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:	Colourless block
Size:	0.14 × 0.13 × 0.12 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.13 mm^{-1}
Diffractometer, scan mode:	SuperNova, ω
θ_{max}, completeness:	25.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	7328, 2862, 0.027
Criterion for I_{obs}, $N(hkl)_{gt}$:	I_{obs} > 2 σ(I_{obs}), 2364
$N(param)_{refined}$:	227
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

Source of material

7-Methoxy-3,4-dihydronaphthalen-1(2*H*)-one and 4-fluoro-2-(trifluoromethyl)benzaldehyde were dissolved in 10 mL of methanol. After the addition of 5 mL 25% NaOH solution, the mixture was stirred for 3 h at ambient temperature (monitored by TLC, 254 nm). The mixture was filtered and subsequently dissolved with ethyl acetate, and the organic phase was washed with water and brine, and finally dried over anhydrous sodium sulfate. After filtration, the filtrate was evaporated to dryness under vacuum and purified on a silica gel by column chromatography using petroleum ether/EtOAc (2:1, *v*/*v*) as the eluent. The title compound was recrystallized from dichloromethane and methanol (1:1, *v*/*v*) to attain suitable crystals.

Experimental details

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

Comment

Microglial cells function as the immune cells of the central nervous system (CNS), acting as primary mediators of

***Corresponding author: Qing-Guo Meng**, School of Pharmacy, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Yantai University, Yantai, P. R. China, E-mail: qinggmeng@163.com
Ming-Zhu Luan, Mei Zhang, Jia Song and Feng-Lan Zhao, School of Pharmacy, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Yantai University, Yantai, P. R. China. https://orcid.org/0000-0003-0609-9200 (M.-Z. Luan)
Hui-Yun Wang, College of Pharmacy, Jining Medical University, Rizhao, 276826, P. R. China
Yang-Rong Xu, Laboratory of Computer-Aided Drug Design and Discovery, Beijing Institute of Pharmacology and Toxicology, Beijing 100850, P. R. China

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.15858 (12)	0.32258 (13)	0.34683 (13)	0.0216 (4)
C2	0.13311 (12)	0.40869 (13)	0.38473 (12)	0.0216 (4)
C3	0.06355 (12)	0.39118 (13)	0.41445 (13)	0.0244 (4)
H3A	0.002668	0.379568	0.351814	0.029*
H3B	0.059398	0.447392	0.449029	0.029*
C4	0.09287 (12)	0.30525 (13)	0.48741 (13)	0.0252 (4)
H4A	0.151509	0.318790	0.552337	0.030*
H4B	0.046523	0.293022	0.503856	0.030*
C5	0.08278 (12)	0.12699 (14)	0.45434 (14)	0.0271 (4)
H5	0.063827	0.119032	0.500627	0.033*
C6	0.09002 (12)	0.04824 (14)	0.40523 (14)	0.0275 (4)
H6	0.076345	−0.012150	0.418954	0.033*
C7	0.11778 (11)	0.05825 (13)	0.33484 (13)	0.0232 (4)
C8	0.14015 (11)	0.14734 (13)	0.31668 (13)	0.0226 (4)
H8	0.160090	0.154448	0.271197	0.027*
C9	0.13271 (11)	0.22752 (13)	0.36722 (12)	0.0211 (4)
C10	0.10321 (12)	0.21842 (13)	0.43627 (13)	0.0226 (4)
C11	0.17173 (12)	0.49206 (13)	0.38675 (13)	0.0234 (4)
H11	0.211379	0.491860	0.362846	0.028*
C12	0.15803 (11)	0.58469 (13)	0.42303 (13)	0.0224 (4)
C13	0.13661 (11)	0.66879 (13)	0.36431 (13)	0.0217 (4)
C14	0.12213 (11)	0.75452 (14)	0.39928 (13)	0.0239 (4)
H14	0.107828	0.810213	0.359957	0.029*
C15	0.12959 (12)	0.75459 (13)	0.49395 (14)	0.0243 (4)
C16	0.15281 (12)	0.67566 (14)	0.55613 (14)	0.0270 (4)
H16	0.158728	0.678664	0.620505	0.032*
C17	0.16721 (12)	0.59111 (14)	0.52000 (13)	0.0248 (4)
H17	0.183564	0.536638	0.561494	0.030*
C18	0.12763 (12)	0.66818 (13)	0.26046 (14)	0.0251 (4)
C19	0.15224 (14)	−0.01821 (14)	0.21971 (15)	0.0314 (5)
H19A	0.110912	0.021932	0.161285	0.047*
H19B	0.153713	−0.080884	0.194888	0.047*
H19C	0.213632	0.008756	0.256636	0.047*
F1	0.11301 (8)	0.83847 (8)	0.52698 (8)	0.0353 (3)
F2	0.06892 (7)	0.60081 (8)	0.19533 (8)	0.0320 (3)
F3	0.20967 (7)	0.65053 (8)	0.27124 (8)	0.0339 (3)
F4	0.09746 (8)	0.75128 (8)	0.20967 (8)	0.0329 (3)
O1	0.19860 (9)	0.33000 (9)	0.30076 (10)	0.0296 (3)
O2	0.12024 (9)	−0.02482 (9)	0.28854 (10)	0.0289 (3)

inflammation. Neuroinflammation in the CNS mediated by overactivated microglia plays a key role in many neurodegenerative diseases [4–6]. M1 type microglial activation leads to proinflammatory effects by producing numerous cyto-mediators, such as proteases, proinflammatory cytokines and reactive oxygen species (ROS) [7]. Studies have shown that the inhibition of NF-κB signal pathway in microglia can reduce the expression of pro-inflammatory cytokines such as nitric oxide (NO), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6, and play an anti-neuroinflammatory effect [8–11]. Therefore, developing an NF-κB inhibitor with anti-neuroinflammatory activities and low toxicity is a potential therapeutic strategy for treating inflammatory neurodegenerative CNS diseases [12].

3,4–Dihydronaphthalen-1(2*H*)-one (DHN) derivatives with anti-inflammatory activities have been investigated as potential Bcl-2 inhibitors and as anti-inflammatory agents that stabilize mast cells [13–15]. However, DHN derivatives have rarely been developed as anti-neuroinflammatory drugs. Therefore, our group designed and synthesized a new benzylidene-substituted DHN derivative which may have anti-neuroinflammatory activity. The synthesis succeeded by a Claisen–Schmidt condensation reaction.

Single-crystal structure analysis revealed that the title compound crystallized in the monoclinic space group *C*2/*c*. The ORTEP diagram is presented in Figure. Bond lengths and angles are all in the expected ranges [16]. There is one drug molecule in the asymmetric unit (see the Figure). According to the configuration at the C(2) = C(11) olefinic bond, the title molecule adopts the E stereochemistry [17]. Because of the distorting effect of 3,4-dihydronaphthalen-1(2*H*)-one, the 7-methoxyphenyl and 4-fluoro-2-(trifluoromethyl)phenyl groups are not coplanar with each other, with a dihedral angle of 29.37(3)°. This twist may increase the likelihood of interactions with bio molecules with the aim of creating more potent anti-neuroinflammatory activity [18].

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

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. Hong Z. Y., Shi X. R., Zhu K., Wu T. T., Zhu Y. Z. SCM-198 inhibits microglial overactivation and attenuates Aβ_{1-40}-induced cognitive impairments in rats via JNK and NF-κB pathways. *J. Neuroinflamm.* 2014, *11*, 147.

5. Lee D. S., Kwon K. H., Cheong S. H. Taurine chloramine suppresses LPS-induced neuroinflammatory responses through Nrf2-mediated heme oxygenase-1 expression in mouse BV2 microglial cells. *Adv. Exp. Med. Biol.* 2017, *975*, 131–143.
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. Su P., Zhang J., Wang D., Zhao F., Cao Z., Aschner M., Luo W. The role of autophagy in modulation of neuroinflammation in microglia. *Neuroscience* 2016, *319*, 155–167.
8. Cho K. H., Kim D. C., Yoon C. S., Ko W. M., Lee S. J., Sohn J. H., Jang J. H., Ahn J. S., Kim Y. C., Oh H. Anti-neuroinflammatory effects of citreohybridonol involving TLR4–MyD88-mediated inhibition of NF-κB and MAPK signaling pathways in lipopolysaccharide-stimulated BV2 cells. *Neurochem. Int.* 2016, *95*, 55–62.
9. 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.
10. 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.
11. Liu J., Xu Y. R., Yang J. J., Wang W. Z., Zhang J. Q., Zhang R. Z., Meng Q. G. Discovery, semisynthesis, biological activities, and metabolism of ocotillol-type saponins. *J. Ginseng Res.* 2017, *41*, 373–378.
12. Srinivasan M., Lahiri D. K. Significance of NF-κB as a pivotal therapeutic target in the neurodegenerative pathologies of Alzheimer's disease and multiple sclerosis. *Expert Opin. Ther. Targets* 2015, *19*, 471–487.
13. Wang F. L., Zhang R. X., Cui Y., Sheng L. P., Sun Y. P., Tian W., Liu X., Liang S. Z. Design, synthesis and biological evaluation of 3,4-dihydronaphthalen-1(2*H*)-one derivatives as Bcl-2 inhibitors. *Res. Chem. Intermed.* 2017, *43*, 5933–5942.
14. Barlow J. W., Walsh J. J. Synthesis and evaluation of 4-amino-3,4-dihydro-2*H*-naphthalen-1-one derivatives as mast cell stabilising and anti-inflammatory compounds. *Eur. J. Med. Chem.* 2008, *43*, 2891–2900.
15. 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. Enzym. Inhib. Med. Chem.* 2020, *35*, 1631–1640.
16. El-Sayed N. E., Almaneai N. M., Ghabbour H. A., Alafeefy A. M. Crystal structure of (E)-2-(4-hydroxy-3-methoxybenzylidene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one, $C_{19}H_{18}O_4$. *Z. Kristallogr. N. Cryst. Struct.* 2017, *232*, 203–205.
17. 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.
18. 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(2*H*)-one derivatives as protein-tyrosine kinase (PTK) inhibitors. *Acta Crystallogr.* 2017, *C73*, 1003–1009.