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Crystal structure of (*E*)-2-(3,5-bis(trifluoromethyl) benzylidene)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one, $C_{20}H_{14}F_6O_2$

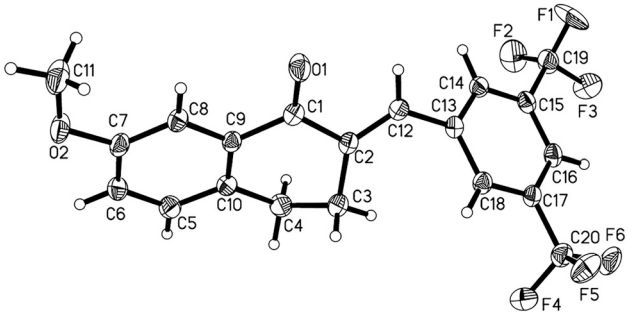

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.13 × 0.12 × 0.10 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.14 mm^{-1}
Diffractometer, scan mode:	SuperNova, Ω
θ_{max}, completeness:	25.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	8090, 3297, 0.027
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 2189
$N(param)_{refined}$:	282
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

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Abstract

$C_{20}H_{14}F_6O_2$, monoclinic, $P2_1/c$ (no. 14), a = 14.791(2) Å, b = 8.5303(9) Å, c = 15.531(3) Å, β = 115.474(19)°, V = 1769.1(5) Å^3, Z = 4, $R_{gt}(F)$ = 0.0574, $wR_{ref}(F^2)$ = 0.1451, T = 100 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.

Source of material

An amount of 5 mL (25%) of sodium hydroxide aqueous solution was added dropwise to the mixture of 7-methoxy-1-tetralone and 3,5-bis(trifluoromethyl)benzaldehyde in 10 mL methanol and stirred at room temperature for 3 h. The in process-control was monitored by silica gel thin layer chromatography (TLC, 254 nm). When the reaction was stopped, the precipitate was filtered from the reaction and dissolved with ethyl acetate. The organic phase was washed successively by water and brine, and dried over anhydrous sodium sulfate. After filtration, the ethyl acetate was condensed in vacuo 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 dichloromethane and methanol (1:1, *v/v*) system and dried under vacuo 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(C–H) = 0.97 Å

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.47461 (19)	0.1153 (3)	0.1241 (2)	0.0519 (7)
C2	0.36909 (17)	0.0798 (3)	0.10808 (19)	0.0502 (6)
C3	0.28942 (19)	0.1754 (4)	0.0325 (2)	0.0656 (8)
H3A	0.291862	0.282213	0.054855	0.079*
H3B	0.224084	0.132339	0.019421	0.079*
C4	0.30470 (19)	0.1750 (4)	−0.0585 (2)	0.0683 (8)
H4A	0.294702	0.069663	−0.084519	0.082*
H4B	0.255408	0.242855	−0.105403	0.082*
C5	0.4261 (2)	0.3093 (4)	−0.1090 (2)	0.0648 (8)
H5	0.373400	0.328156	−0.168287	0.078*
C6	0.5207 (2)	0.3600 (3)	−0.0913 (2)	0.0632 (8)
H6	0.531200	0.413260	−0.138502	0.076*
C7	0.60023 (19)	0.3324 (3)	−0.0040 (2)	0.0554 (7)
C8	0.58468 (18)	0.2523 (3)	0.06519 (19)	0.0523 (7)
H8	0.638189	0.231863	0.123758	0.063*
C9	0.48839 (17)	0.2014 (3)	0.04756 (18)	0.0467 (6)
C10	0.40796 (18)	0.2302 (3)	−0.03959 (19)	0.0530 (7)
C11	0.7751 (2)	0.3566 (5)	0.0911 (3)	0.0959 (12)
H11A	0.765592	0.399739	0.143713	0.144*
H11B	0.833515	0.402354	0.089219	0.144*
H11C	0.783664	0.245171	0.098772	0.144*
C12	0.35570 (18)	−0.0359 (3)	0.15895 (19)	0.0520 (7)
H12	0.413263	−0.086342	0.201750	0.062*
C13	0.25978 (17)	−0.0934 (3)	0.15514 (18)	0.0492 (6)
C14	0.24401 (19)	−0.2546 (3)	0.15445 (19)	0.0536 (7)
H14	0.294294	−0.323454	0.158182	0.064*
C15	0.1539 (2)	−0.3130 (3)	0.14822 (19)	0.0552 (7)
C16	0.0797 (2)	−0.2134 (3)	0.14618 (19)	0.0566 (7)
H16	0.019643	−0.253201	0.142653	0.068*
C17	0.09560 (18)	−0.0542 (3)	0.14942 (19)	0.0507 (6)
C18	0.18432 (18)	0.0053 (3)	0.15334 (19)	0.0533 (7)
H18	0.193578	0.113288	0.154787	0.064*
C19	0.1377 (3)	−0.4860 (4)	0.1444 (3)	0.0774 (9)
C20	0.0177 (2)	0.0556 (4)	0.1499 (3)	0.0663 (8)
F1[a]	0.1920 (7)	−0.5559 (10)	0.2203 (7)	0.125 (3)
F3[a]	0.0422 (5)	−0.5177 (10)	0.1291 (7)	0.101 (3)
F6[a]	−0.0607 (8)	−0.0103 (14)	0.1545 (10)	0.112 (4)
F1′[a]	0.2287 (7)	−0.5661 (10)	0.1883 (8)	0.134 (3)
F3′[a]	0.0819 (10)	−0.5374 (12)	0.1776 (10)	0.191 (6)
F6′[a]	−0.0677 (6)	−0.0156 (16)	0.1276 (11)	0.129 (5)
F2	0.1286 (2)	−0.5476 (2)	0.06383 (19)	0.1223 (9)
F4	−0.00985 (15)	0.1597 (3)	0.07954 (16)	0.1039 (7)
F5	0.04895 (15)	0.1423 (3)	0.22760 (16)	0.1035 (7)
O1	0.54603 (13)	0.0733 (3)	0.19655 (15)	0.0733 (6)
O2	0.69088 (14)	0.3898 (3)	0.00556 (15)	0.0751 (6)

[a]Occupancy: 0.5.

(methylene), U_{iso}(H) = 1.2U_{eq}(C), and *d*(C–H) = 0.93 Å (aromatic), U_{iso}(H) = 1.2U_{eq}(C).

Comment

During inflammatory neurodegenerative diseases in the central nervous system (CNS), microglia are activated and polarized into pro-inflammatory M1 phenotype, which mediate neuroinflammation and play a key role in the progression of brain diseases [4, 5]. The inflammatory process may lead to excessive release of inflammatory mediators or cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and so on [6]. The activation of NF-κB is a result of underlying inflammation and the expression of the inflammatory cytokines, including IL-6 and TNF-α can be down-regulated by inhibiting the activation of NF-κB, and play an anti-inflammatory role [7–9]. Furthermore, inhibiting the activation of NF-κB can produce anti-neuroinflammatory effects on activated microglial cells [10]. Therefore, the study of NF-κB inhibitors with anti-neuroinflammatory properties and low toxicity is of great significance in the treatment of inflammatory neurodegenerative CNS diseases [11].

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 [12, 13] and as potential retinoic acid (RA)-metabolizing enzymes inhibitors to treat skin diseases and cancer. However, DHN derivatives are rarely developed as anti-neuroinflammatory drugs, so the synthesis of novel benzylidene-substituted DHN derivatives with anti-neuroinflammatory activities are of great significance. 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 higher activities [14, 15]. In this study, a new benzylidene-substituted DHN was designed and synthesized through Claisen–Schmidt condensation reaction.

The crystal structure analysis revealed that the title compound crystallized in the monoclinic space group $P2_1/c$. The ORTEP diagram is presented in the Figure. There is only a drug molecule in the asymmetric unit. The configuration at the C(2)=C(11) olefinic 3,5-bis(trifluoromethyl)phenyl and carbonyl moiety showed an *E* stereochemistry [7, 16]. Because of the distorting effect of 3,4-dihydronaphthalen-1(2*H*)-one, the 7-methoxyphenyl and 3,5-bis(trifluoromethyl) phenyl groups are not coplanar with each other, with a dihedral angle of approximately 70°. This twisted configuration may increase likelihood of interactions with bioactive molecules, for the purposes of creating more potent

biological activity [17]. Bond lengths and angles are all in the expected ranges [17, 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. Goldmann T., Prinz M. Role of microglia in CNS autoimmunity. Clin. Dev. Immunol. 2013, *2013*, 208093.
5. 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.
6. 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.
7. 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.
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-κB inhibitors in hepatic carcinoma cell lines. *Eur. J. Med. Chem.* 2018, *155*, 531–544.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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. Enzyme Inhib. Med. Chem.* 2003, *18*, 27–33.
14. 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.
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. Enzyme Inhib. Med. Chem.* 2020, *35*, 1631–1640.
16. 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.
17. 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.
18. 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, C19H18O4. *Z. Kristallogr. NCS* 2017, *232*, 203–205.