Xia Zhou, Zhong-Hao Sun, Guang-Zhi Shan and Qing-Guo Meng*

Crystal structure of 3,5-bis((*E*)-4-methoxy-2-(trifluoromethyl)benzylidene)-1-methylpiperidin-4-one, $C_{24}H_{21}F_6NO_3$

<https://doi.org/10.1515/ncrs-2021-0200>

Received May 22, 2021; accepted June 21, 2021;

published online July 20, 2021

Abstract

$C_{24}H_{21}F_6NO_3$, monoclinic, $P2_1/c$ (no. 14), $a = 16.0076(10)$ Å, $b = 7.7424(4)$ Å, $c = 17.3259(11)$ Å, $\beta = 96.161(5)^\circ$, $V = 2134.9(2)$ Å³, $Z = 4$, $R_{gt}(F) = 0.0563$, $wR_{ref}(F^2) = 0.1517$, $T = 100.0(1)$ K.

CCDC no.: 2078210

Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

N-methyl-4-piperidone (0.3 mL, 3.0 mmol) and 4-methoxy-2-(trifluoromethyl) benzaldehyde (880.7 mg, 5.0 mmol) were dissolved in 12 mL acetic acid. Then dry hydrogen

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.11 × 0.10 × 0.08 mm
Wavelength:	Mo $K\alpha$ 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} :	8653, 3958, 0.040
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 3232
$N(param)_{refined}$:	310
Programs:	CrysAlis ^{PRO} [1], SHELX [2, 3]

chloride gas was flowed continuously into the solution for 50 min. After gas insertion, the reaction system was stirred at room temperature for eight days. The response endpoint was detected by thin layer chromatography. When the reaction was finished, the precipitate was filtered from the reaction system, then it was dissolved in distilled water and set to a neutral pH with saturated aqueous Na_2CO_3 solution. The precipitate was filtered from the system and dissolved with dichloromethane. The organic phase was washed with deionized water and brine, dried over anhydrous sodium sulfate and condensed under vacuum. The crude product was purified by silica-gel column chromatography (petroleum ether: ethyl acetate = 8:1, v/v). Crystals were obtained via solvent evaporation in the mixed solvents of dichloromethane and methanol (1:1, v/v) and drying under vacuum at 333 K for 4 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), $U_{iso}(H) = 1.5U_{eq}(C)$, and $d(C-H) = 0.97$ Å (methylene), $U_{iso}(H) = 1.2U_{eq}(C)$, and $d(C-H) = 0.93$ Å (aromatic), $U_{iso}(H) = 1.2U_{eq}(C)$.

Comment

Curcumin has anti-inflammatory, anti-tumor, anti-oxidation and other activities. But its clinical application is limited because of its low stability, poor bioavailability and false positive. So structural

*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

Xia Zhou, 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/0000-0002-2341-6696> (X. Zhou)

Zhong-Hao Sun and Guang-Zhi Shan, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100050, P. R. China

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

Atom	x	y	z	U _{iso} */U _{eq}
C1	0.58995 (13)	0.3371 (3)	0.09157 (12)	0.0189 (5)
H1A	0.605963	0.421036	0.132044	0.023*
H1B	0.626498	0.237557	0.100498	0.023*
C2	0.49983 (13)	0.2824 (3)	0.09579 (12)	0.0188 (5)
C3	0.45205 (13)	0.2146 (3)	0.02408 (12)	0.0183 (5)
C4	0.49522 (13)	0.2158 (3)	−0.04905 (12)	0.0178 (5)
C5	0.58385 (13)	0.2841 (3)	−0.04460 (12)	0.0196 (5)
H5A	0.622935	0.188860	−0.035028	0.024*
H5B	0.592958	0.335375	−0.094098	0.024*
C6	0.46004 (14)	0.2882 (3)	0.16050 (12)	0.0201 (5)
H6	0.403223	0.260128	0.154364	0.024*
C7	0.49564 (13)	0.3334 (3)	0.23924 (12)	0.0198 (5)
C8	0.44807 (13)	0.4112 (3)	0.29482 (12)	0.0200 (5)
C9	0.48440 (14)	0.4547 (3)	0.36771 (13)	0.0239 (5)
H9	0.452093	0.506695	0.402739	0.029*
C10	0.56946 (14)	0.4216 (3)	0.38967 (12)	0.0219 (5)
C11	0.61603 (14)	0.3357 (3)	0.33852 (12)	0.0226 (5)
H11	0.671741	0.306240	0.353469	0.027*
C12	0.57907 (13)	0.2947 (3)	0.26552 (12)	0.0209 (5)
H12	0.611366	0.238054	0.231831	0.025*
C13	0.45160 (13)	0.1566 (3)	−0.11345 (12)	0.0199 (5)
H13	0.397470	0.118478	−0.107950	0.024*
C14	0.47775 (13)	0.1436 (3)	−0.19215 (12)	0.0187 (5)
C15	0.41857 (14)	0.1618 (3)	−0.25854 (12)	0.0211 (5)
C16	0.44102 (14)	0.1459 (3)	−0.33253 (13)	0.0242 (5)
H16	0.400995	0.160780	−0.375031	0.029*
C17	0.52404 (14)	0.1073 (3)	−0.34380 (12)	0.0236 (5)
C18	0.58299 (14)	0.0865 (3)	−0.28080 (13)	0.0232 (5)
H18	0.638223	0.059735	−0.288162	0.028*
C19	0.56019 (13)	0.1053 (3)	−0.20603 (12)	0.0212 (5)
H19	0.600988	0.092037	−0.164012	0.025*
C20	0.68703 (13)	0.4750 (3)	0.01643 (13)	0.0218 (5)
H20A	0.725461	0.380431	0.026475	0.033*
H20B	0.698107	0.560944	0.056145	0.033*
H20C	0.694110	0.524731	−0.033198	0.033*
C21	0.35576 (14)	0.4435 (3)	0.27449 (13)	0.0245 (5)
C22	0.69049 (15)	0.4672 (3)	0.47956 (14)	0.0319 (6)
H22A	0.707049	0.348018	0.482764	0.048*
H22B	0.706336	0.522605	0.528516	0.048*
H22C	0.717879	0.523495	0.439804	0.048*
C23	0.32754 (14)	0.1935 (3)	−0.24898 (13)	0.0230 (5)
C24	0.62044 (16)	0.0421 (4)	−0.43534 (15)	0.0403 (7)
H24A	0.661283	0.121630	−0.411280	0.061*
H24B	0.623326	0.041165	−0.490398	0.061*
H24C	0.631866	−0.071604	−0.414813	0.061*
F1	0.33702 (8)	0.52726 (17)	0.20745 (7)	0.0280 (3)
F2	0.31109 (8)	0.29569 (18)	0.26835 (8)	0.0346 (4)
F3	0.32217 (8)	0.53810 (19)	0.32878 (8)	0.0350 (4)
F4	0.28055 (8)	0.22091 (19)	−0.31646 (7)	0.0352 (4)
F5	0.29317 (8)	0.05606 (16)	−0.21648 (8)	0.0294 (4)
F6	0.31521 (8)	0.32848 (15)	−0.20345 (7)	0.0249 (3)
N1	0.60094 (11)	0.4123 (2)	0.01625 (10)	0.0187 (4)
O1	0.38112 (9)	0.15587 (19)	0.02407 (8)	0.0219 (4)
O2	0.60103 (10)	0.4784 (2)	0.46102 (8)	0.0292 (4)
O3	0.53849 (10)	0.0945 (2)	−0.41980 (9)	0.0342 (4)

modification based on curcumin was carried out and large amounts of curcumin analogues have been reported. There in, (3*E*, 5*E*)-3,5-bis(arylene)-4-piperidones (BAPs) was a very distinguished class because they could inhibit tumor growth by anti-inflammatory and inhibiting NF-κB dependent signaling pathways [4]. Some symmetric and asymmetric BAPs had been designed as anti-tumor and anti-inflammatory agents [5, 6]. However, BAPs have rarely been developed as anti-neuroinflammatory drugs, so the synthesis of novel BAPs with anti-neuroinflammatory activities are of great significance.

Single-crystal structure analysis reveals that the title compound contains one molecule in the asymmetric unit (cf. the figure). Bond lengths and angles are all in the expected ranges. Arylidene moieties on both sides of piperidone adopt the *E* stereochemistry [7]. The dihedral angles between the benzylidene moieties and piperidone ring are 44.82° and 40.62°, respectively. In title compound, the peripheric heteroatoms (such as F, N, O, S) may act as hydrogen bonding acceptors for bioactive molecules with the aim of creating more anti-inflammatory activity [8].

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

Research funding: Science and Technology Innovation Development Plan of Yantai (No. 2020XDRH105) and the National Natural Science Foundation of China (No. 81473104).

Conflict of interest statement: 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 Crystallogr.* 2008, *A64*, 112–122.
3. Sheldrick G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Su C. M., Hou G. G., Wang C. H., Zhang H. Q., Yang C., Liu M., Hou Y. Potential multifunctional agents with anti-hepatoma and anti-inflammation properties by inhibiting NF-κB activation. *J. Enzym. Inhib. Med. Chem.* 2019, *34*, 1287–1297.
5. Xiong C. L., Lan Y. D., Song X. Y., Xiong W. M., Nie X. L. Crystal structure of methyl 4-acetoxy 3,5-dimethoxybenzoate, C₁₂H₁₄O₆. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 573–575.
6. Zhang X. F., Meng Q. G. Crystal structure of (3*E*,5*E*)-2-((2-methoxy-3-pyridyl) methylene)-7-fluoro-3,4-dihydronaphthalen-1(2*H*)-one, C₁₇H₁₄FNO₂. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 507–509.

7. Sun Y., Liu Y. K., Li J. D., Meng Q. G., Hou G. G. Crystal structure and anti-inflammatory activity of (3*E*,5*E*)-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.
8. Zhou Y. Q., Hou G. G., Meng Q. G., Hou Y. Crystal structure and anti-inflammatory activity of (3*E*,5*E*)-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.