Xiao-Fan Zhang, Hui-yun Wang, Jia Song, Lun-Hai Liang, Yang-Rong Xu, Feng-Lan Zhao and Qing-Guo Meng*

Crystal structure of (3*E*,5*E*)-3,5-bis-4-methoxy-3-(trifluoromethyl)benzylidene)-1-methylpiperidin-4-one, C₂₄H₂₁F₆NO₃

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.13 × 0.12 × 0.09 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.13 mm ⁻¹
Diffractometer, scan mode:	SuperNova
$\theta_{\max}$, completeness:	25.5°, >99 %
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	9749, 4139, 0.027
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 3344
$N(\text{param})_{\text{refined}}$:	310
Programs:	CrysAlis ^{PRO} [1], SHELX [2, 3]

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Abstract

C₂₄H₂₁F₆NO₃, monoclinic, $P2_1/c$ (no. 14), $a = 16.6493(9)$ Å, $b = 15.3005(8)$ Å, $c = 8.8554(5)$ Å, $\beta = 99.746(6)^\circ$, $V = 2223.3(2)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0444$, $wR_{\text{ref}}(F^2) = 0.1094$, $T = 100$ 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.

***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: qingguomeng@163.com

Xiao-Fan Zhang, Jia Song, Lun-Hai Liang 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/0000-0003-0674-2008> (X.-F. Zhang)

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

Source of material

N-methyl-4-piperidone (0.3 mL, 3.0 mmol) and 3-(trifluoromethyl)-4-methoxybenzaldehyde (1.08 g, 5.0 mmol) were dissolved in 10 mL acetic acid. Then dry hydrogen chloride gas was flowed continuously into the solution for 45 min. After gas insertion, the reaction system was stirred at room temperature for seven days. The response endpoint was detected by thin layer chromatography (TLC). When the reaction was stopped, the precipitate was filtered from the reaction system, then it was dissolved in distilled water and adjusted to a neutral pH with saturated aqueous Na₂CO₃ solution. The precipitate was filtered from the system and dissolved with dichloromethane. The organic phase was washed successively 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 = 10:1, v/v). Crystals were obtained under ambient conditions *via* solvent evaporation in the mixed solvents of dichloromethane and methanol (1:1, v/v) and drying under vacuo at 333 K for 3 h.

Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with $d(\text{C-H}) = 0.96$ Å (methyl), $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$, and $d(\text{C-H}) = 0.97$ Å

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	0.34239 (10)	0.51961 (12)	1.0154 (2)	0.0209 (4)
H1A	0.358800	0.474316	0.950240	0.025*
H1B	0.354762	0.499579	1.120683	0.025*
C2	0.38918 (10)	0.60199 (12)	0.9979 (2)	0.0198 (4)
C3	0.35617 (11)	0.66182 (12)	0.8690 (2)	0.0213 (4)
C4	0.27457 (10)	0.64132 (12)	0.7777 (2)	0.0192 (4)
C5	0.23427 (10)	0.55702 (12)	0.8111 (2)	0.0212 (4)
H5A	0.175645	0.562691	0.782357	0.025*
H5B	0.252142	0.510311	0.750505	0.025*
C6	0.45786 (10)	0.62848 (12)	1.0886 (2)	0.0211 (4)
H6	0.476439	0.682892	1.062865	0.025*
C7	0.50871 (10)	0.58754 (12)	1.2203 (2)	0.0192 (4)
C8	0.55976 (11)	0.64270 (12)	1.3201 (2)	0.0234 (4)
H8	0.558054	0.702582	1.301795	0.028*
C9	0.61256 (11)	0.61061 (13)	1.4450 (2)	0.0244 (4)
C10	0.61713 (10)	0.52027 (12)	1.4723 (2)	0.0215 (4)
C11	0.56644 (10)	0.46473 (12)	1.3759 (2)	0.0217 (4)
H11	0.568168	0.404860	1.394203	0.026*
C12	0.51311 (10)	0.49823 (12)	1.2520 (2)	0.0211 (4)
H12	0.479396	0.460126	1.188472	0.025*
C13	0.24251 (10)	0.70065 (12)	0.6724 (2)	0.0203 (4)
H13	0.272410	0.751910	0.671175	0.024*
C14	0.16736 (10)	0.69634 (12)	0.5593 (2)	0.0189 (4)
C15	0.13748 (10)	0.61818 (12)	0.4899 (2)	0.0190 (4)
H15	0.163908	0.566004	0.520758	0.023*
C16	0.06948 (10)	0.61682 (11)	0.3762 (2)	0.0194 (4)
C17	0.02792 (10)	0.69454 (12)	0.3303 (2)	0.0209 (4)
C18	0.05735 (11)	0.77299 (12)	0.3972 (2)	0.0247 (4)
H18	0.030395	0.825076	0.367775	0.030*
C19	0.12680 (11)	0.77333 (12)	0.5077 (2)	0.0229 (4)
H19	0.147087	0.826407	0.548900	0.028*
C20	0.20988 (11)	0.45674 (13)	1.0058 (2)	0.0297 (5)
H20A	0.225946	0.408296	0.948814	0.045*
H20B	0.152430	0.466695	0.976415	0.045*
H20C	0.221957	0.443889	1.113385	0.045*
C21	0.66475 (14)	0.67136 (14)	1.5514 (3)	0.0385 (5)
C22	0.67636 (11)	0.40334 (13)	1.6317 (2)	0.0271 (4)
H22A	0.624135	0.384305	1.651251	0.041*
H22B	0.716670	0.393967	1.721448	0.041*
H22C	0.690694	0.370673	1.547642	0.041*
C23	0.04149 (12)	0.53290 (12)	0.2988 (2)	0.0269 (4)
C24	−0.08211 (13)	0.76389 (14)	0.1662 (3)	0.0378 (5)
H24A	−0.102170	0.792175	0.249185	0.057*
H24B	−0.127054	0.749226	0.087295	0.057*
H24C	−0.045761	0.802582	0.125398	0.057*
F1	0.65144 (9)	0.66507 (8)	1.69672 (14)	0.0517 (4)
F2	0.74447 (8)	0.65660 (10)	1.55706 (18)	0.0601 (4)
F3	0.65177 (9)	0.75566 (8)	1.51230 (16)	0.0562 (4)
F4	0.03826 (7)	0.53547 (8)	0.14683 (13)	0.0370 (3)
F5	−0.03341 (7)	0.50918 (8)	0.32096 (14)	0.0401 (3)
F6	0.09103 (8)	0.46619 (7)	0.34974 (15)	0.0435 (4)
N1	0.25459 (8)	0.53509 (10)	0.97355 (17)	0.0211 (3)
O1	0.39569 (8)	0.72479 (9)	0.83720 (16)	0.0313 (3)
O2	0.67275 (8)	0.49435 (9)	1.59430 (15)	0.0277 (3)
O3	−0.03947 (8)	0.68600 (8)	0.22099 (16)	0.0289 (3)

(methylene), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$, and $d(\text{C}-\text{H}) = 0.93 \text{ \AA}$ (aromatic), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

Comment

During inflammatory neurodegenerative diseases in central nervous system (CNS), the resident microglia become activated and polarized to a pro-inflammatory M1 phenotype [4], which can produce pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1b (IL-1b), and interleukin-6 (IL-6) [5–7]. These pro-inflammatory cytokines disrupt blood-brain barrier (BBB) by activating the nuclear factor kappa B (NF- κ B) signaling pathway [8]. In addition, activated microglia can produce reactive oxygen species (ROS), which may indirectly induce neuroinflammation by activating NF- κ B [9]. Therefore, developing an NF- κ B inhibitor with anti-neuroinflammatory activity and low toxicity may be a therapeutic option for the treatment of inflammatory CNS neurodegenerative diseases [10].

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. Structural modification based on curcumin was carried out and different curcumin analogues have been reported. Therein, (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- κ B dependent signaling pathways [11]. Some symmetric and dissymmetric BAPs had been designed and synthesized as anti-tumor and anti-inflammatory agents [12–18]. However, BAPs have rarely been developed as anti-neuroinflammatory drugs. In our recent study, a series of new BAPs were designed and synthesized through Claisen–Schmidt condensation reactions.

Single-crystal structure analysis reveals that the title compound contains one drug molecule in the asymmetric unit (cf. the figure). Bond lengths and angles are all in the expected ranges [20]. The arylidene moieties on both sides of central piperidone adopt the *E* stereochemistry [19]. The dihedral angles between the two-fluorobenzylidenes and the central piperidone ring are 36.05(2)° and 26.86(3)°, respectively. In the title compound, the peripheric heteroatoms (such as F, N, O, S) can act as hydrogen bonding acceptors for bioactive molecules with the aim of creating more potent antitumor activities and anti-inflammatory activity [21].

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