Zhong-Fei Gao, Lei Wang, Gui-Ge Hou and Xiao-Fan Zhang*

Crystal structure of (3*E*,5*E*)-3,5-bis(4-fluorobenzylidene)-1-((4-trifluoromethyl)benzenesulfonyl)piperidin-4-one, C₂₆H₁₈F₅NO₃S

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.14 × 0.12 × 0.10 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.22 mm ⁻¹
Diffractometer, scan mode:	SuperNova,
$\theta_{\max}$, completeness:	29.6°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	12,356, 5294, 0.032
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2\sigma(I_{\text{obs}})$, 4144
$N(\text{param})_{\text{refined}}$:	325
Programs:	CRYSALE ^{PRO} [1], SHELX [2, 3]

Source of material

The synthesis of 3,5-bis(4-fluorobenzylidene)piperidin-4-one was carried out by the Claisen–Schmidt condensation reaction [4]. 4-Piperidone hydrochloride (0.68 g, 5 mmol) and 4-fluorobenzaldehyde (1.24 g, 10 mmol) were added into glacial acetic acid (10 mL). Under a dry HCl flow, the mixture was stirred to obtain a clear solution. Then, the reaction continued to be stirred at room temperature for 24 h. The endpoint of which was determined by thin-layer chromatography (TLC). After the reaction was complete, the above mixture was poured to 100 mL water and adjusted to neutral pH by an aqueous Na₂CO₃ solution. The obtained yellow solids were filtered and washed twice by water. The intermediate 3,5-bis(4-fluorobenzylidene)piperidin-4-one was obtained by the recrystallization of methanol solution. The curcumin analogue and 4-trifluoromethylbenzenesulfonyl chloride (1.22 g, 5 mmol) were dissolved in dichloromethane (100 mL). The solution was stirred under the catalysis of organic pyridine (two drop) and monitored by TLC. After 24 h, the precipitate was collected and dried under vacuum conditions. The resulting product was recrystallized from dichloromethane/petroleum ether (1:1, v/v). Single crystals of the title compound were prepared by slow evaporation of dichloromethane/methanol solutions at room temperature.

Experimental details

The H atoms were positioned geometrically and treated as riding on their parent atoms, with $d(\text{C–H}) = 0.97$ Å

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Abstract

C₂₆H₁₈F₅NO₃S, triclinic, $P\bar{1}$ (no. 2), $a = 7.8831(4)$ Å, $b = 11.9591(7)$ Å, $c = 13.3258(7)$ Å, $\alpha = 69.072(5)^\circ$, $\beta = 88.556(4)^\circ$, $\gamma = 73.730(5)^\circ$, $V = 1122.48(11)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0507$, $wR_{\text{ref}}(F^2) = 0.1216$, $T = 100.0(1)$ 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.

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

Atom	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
C1	0.6245 (3)	0.49568 (19)	0.32766 (16)	0.0204 (4)
H1A	0.672869	0.547280	0.266911	0.025*
H1B	0.714554	0.456990	0.387854	0.025*
C2	0.4638 (3)	0.5783 (2)	0.35755 (16)	0.0219 (4)
C3	0.3133 (3)	0.52704 (19)	0.39938 (15)	0.0208 (4)
C4	0.3200 (2)	0.40041 (19)	0.40027 (15)	0.0193 (4)
C5	0.4951 (3)	0.32090 (19)	0.38201 (16)	0.0210 (4)
H5A	0.570449	0.279806	0.448999	0.025*
H5B	0.474953	0.256714	0.359422	0.025*
C6	0.4407 (3)	0.6995 (2)	0.34183 (16)	0.0234 (4)
H6	0.331586	0.740863	0.358513	0.028*
C7	0.5623 (3)	0.7758 (2)	0.30232 (17)	0.0244 (5)
C8	0.4897 (3)	0.9051 (2)	0.24935 (18)	0.0299 (5)
H8	0.367195	0.939410	0.241474	0.036*
C9	0.5950 (3)	0.9826 (2)	0.20869 (18)	0.0324 (5)
H9	0.545673	1.068166	0.172639	0.039*
C10	0.7745 (3)	0.9294 (2)	0.22313 (17)	0.0282 (5)
C11	0.8548 (3)	0.8037 (2)	0.27762 (16)	0.0240 (4)
H11	0.977686	0.771826	0.287092	0.029*
C12	0.7481 (3)	0.7261 (2)	0.31796 (16)	0.0228 (4)
H12	0.799282	0.640971	0.355439	0.027*
C13	0.1691 (3)	0.36798 (19)	0.40819 (15)	0.0201 (4)
H13	0.066478	0.425800	0.414602	0.024*
C14	0.1518 (2)	0.24925 (19)	0.40759 (16)	0.0204 (4)
C15	0.2630 (3)	0.13494 (19)	0.47520 (17)	0.0247 (5)
H15	0.348292	0.133267	0.523102	0.030*
C16	0.2480 (3)	0.0242 (2)	0.47189 (19)	0.0296 (5)
H16	0.321826	−0.052124	0.517421	0.036*
C17	0.1222 (3)	0.0288 (2)	0.40016 (19)	0.0289 (5)
C18	0.0073 (3)	0.1393 (2)	0.33258 (18)	0.0278 (5)
H18	−0.077816	0.139791	0.285263	0.033*
C19	0.0231 (3)	0.2497 (2)	0.33755 (17)	0.0236 (4)
H19	−0.053694	0.325551	0.293321	0.028*
C20	0.3392 (3)	0.53275 (19)	0.12335 (15)	0.0194 (4)
C21	0.3311 (3)	0.6585 (2)	0.08351 (16)	0.0245 (5)
H21	0.433541	0.682656	0.083388	0.029*
C22	0.1691 (3)	0.7477 (2)	0.04396 (17)	0.0265 (5)
H22	0.161566	0.832345	0.017175	0.032*
C23	0.0178 (3)	0.7096 (2)	0.04463 (16)	0.0229 (4)
C24	0.0264 (3)	0.5838 (2)	0.08493 (16)	0.0236 (4)
H24	−0.075989	0.559595	0.085210	0.028*
C25	0.1881 (3)	0.4946 (2)	0.12467 (16)	0.0219 (4)
H25	0.195541	0.409979	0.151978	0.026*
C26	−0.1567 (3)	0.8044 (2)	−0.00493 (17)	0.0285 (5)
F1	0.88070 (19)	1.00437 (13)	0.18209 (11)	0.0390 (3)
F2	0.10867 (18)	−0.08073 (12)	0.39666 (12)	0.0396 (4)
F3	−0.16273 (17)	0.91979 (13)	−0.01286 (12)	0.0398 (3)
F4	−0.19243 (18)	0.81126 (15)	−0.10532 (11)	0.0454 (4)
F5	−0.29304 (16)	0.77733 (14)	0.05012 (11)	0.0399 (4)
N1	0.5844 (2)	0.39745 (15)	0.29951 (13)	0.0180 (3)
O1	0.18551 (18)	0.58662 (14)	0.43178 (12)	0.0250 (3)
O2	0.67987 (18)	0.47214 (14)	0.11741 (11)	0.0249 (3)
O3	0.53295 (19)	0.30282 (14)	0.17191 (12)	0.0261 (3)
S1	0.54701 (6)	0.41882 (5)	0.17298 (4)	0.01909 (13)

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

Comment

Curcumin, acknowledged as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, has attracted extensive attentions because of their potential applications in the aspect of anti-inflammatory, anti-proliferative and antiangiogenic therapies [5–7]. As an α,β -unsaturated polyphenol compound, it can be considered as one kind of chemopreventive and anticancer agent [8, 9]. Just because of the presence of a diketone group, curcumin becomes unstable at physiological pH. Rapid metabolism and deficient absorption affect its pharmacokinetics and hinder its clinical application [10]. In order to overcome the defect, it is important to modify its structure with mono ketone instead of the β -diketone group. Liu's group synthesized novel curcumin analogues by the deletion of a methylene and the β -diketone moiety groups. Among these compounds, 5,7-dimethoxy-3-(3-(2-((1*E*,4*E*)-3-oxo-5-(pyridin-2-yl)penta-1,4-dien-1-yl)phenoxy)propoxy)-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-4-one could induce gastric cancer cells apoptosis by inhibiting the TrxR activity [11]. Li's group reported that curcumin analogues based on a cyclohexanone moiety possess anti-inflammatory properties [12]. It was found that heterocyclic compounds often exhibit a wide range of biological activities such as antimicrobial, antitumor and antimalarial properties [13]. A piperidone ring was introduced to curcumin analogues and a set of 3,5-bis(arylidene)-4-piperidones were designed [14, 15]. Previous results indicated that fluorine-containing substituents in the aromatic rings usually imparted some distinctive properties to medicines including enhanced binding interactions, metabolic stability, and selective reactivity of compounds [16]. Additionally, it was reported that the phenylsulfonyl moiety in 3,5-bis(arylidene)-4-piperidones could significantly improve the bioactivity of anti-inflammatory [17]. As a part of our continuing study on anti-neuroinflammatory agents, one new curcumin analogue containing the piperidone ring, a fluorine atom and phenylsulfonyl moiety was synthesized by the Claisen–Schmidt condensation reaction and *N*-benzenesulfonylation reaction.

Single-crystal structure analysis shows that the asymmetric unit consists of a 3,5-bis(arylidene)-4-piperidinone molecule (cf. Figure). All bond lengths and bond angles were found to be consistent with the values reported in the literature [18–21]. Both 4-fluorobenzylidene moieties are symmetrically arranged on the both sides of the central

piperidone scaffold. In the title molecule, the torsion angles of C3–C2–C6–C7 and C3–C4–C13–C14 bonds are $179.84(19)^\circ$ and $178.45(17)^\circ$, respectively. It means that the title molecule is in the *E* stereochemistry of the exocyclic olefinic double bonds. The piperidone ring displays a half-chair conformation with the N1 atom deviating by $0.594(2)$ Å from the least-squares plane through the ring. The title compound is obviously not planar with the dihedral angle between the fluorophenyl and piperidone rings being $31.97(6)^\circ$ and $63.87(6)^\circ$, respectively. The dihedral angle between fluorophenyl rings is $48.21(7)^\circ$. The phenylsulfonyl moiety adopts a pseudo-axial conformation with respect to the piperidone ring, meaning that the molecule as a whole forms a “organic click” in the direction of the carbonyl group. No classic hydrogen bonds were found. Neighbouring molecules are linked via weak C–H $\cdots$ F hydrogen bonds to a two-dimensional sheet in the *ab* plane. Molecules containing as a group the α,β -unsaturated ketone and peripheric heteroatoms (such as O and F) may have anticancer, anti-bacterial and antifungal activities [22].

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