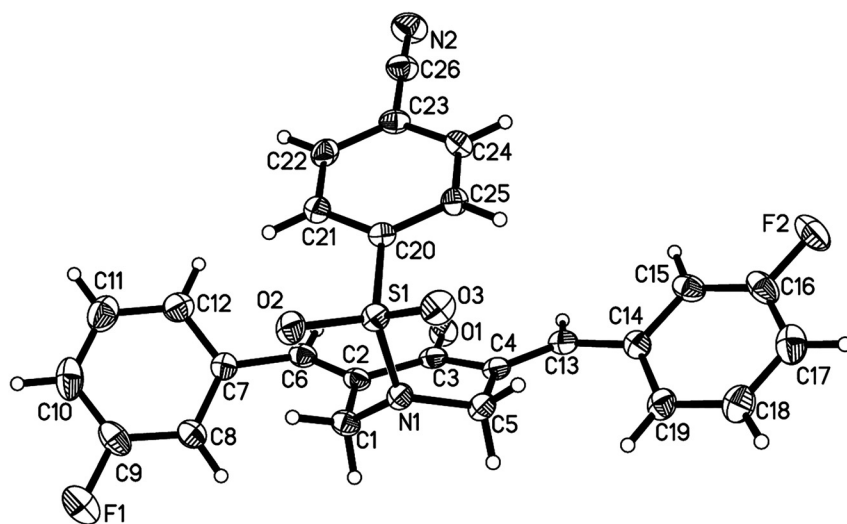


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Crystal structure of (3*E*,5*E*)-1-(4-cyanobenzenesulfonyl)-3,5-bis(3-fluorobenzylidene)piperidin-4-one-dichloromethane (1/1), C₂₇H₂₀Cl₂F₂N₂O₃S



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Abstract

C₂₇H₂₀Cl₂F₂N₂O₃S, triclinic, $P\bar{1}$ (no. 2), $a = 8.7887(4)$ Å, $b = 11.2517(6)$ Å, $c = 13.7609(7)$ Å, $\alpha = 74.962(4)^\circ$, $\beta = 81.084(4)^\circ$, $\gamma = 71.259(4)^\circ$, $V = 1240.68(11)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0582$, $wR_{\text{ref}}(F^2) = 0.1543$, $T = 100.0(1)$ K.

CCDC no.: 2104569

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.15 × 0.13 × 0.11 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.40 mm ⁻¹
Diffractometer, scan mode:	SuperNova
θ_{max} , completeness:	29.6°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	11,635, 5784, 0.033
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 4418
$N(\text{param})_{\text{refined}}$:	350
Programs:	CrysAlis ^{PRO} [1], SHELX [2, 3]

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

Source of material

The title compound was obtained by the Claisen–Schmidt condensation of 4-piperidone and the appropriate aldehyde [4]. A mixture of 4-piperidone hydrochloride (0.68 g, 5 mmol), and 3-fluorobenzaldehyde (1.24 g, 10 mol) was dissolved in acetic acid (10 mL). The reaction was catalyzed

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

Atom	x	y	z	<i>U</i> _{iso} */ <i>U</i> _{eq}
C1	0.1551 (3)	0.9503 (2)	0.0751 (2)	0.0231 (5)
H1A	0.053606	0.946082	0.113060	0.028*
H1B	0.138444	1.035979	0.032045	0.028*
C2	0.2801 (3)	0.9266 (2)	0.14703 (19)	0.0211 (5)
C3	0.4535 (3)	0.8806 (2)	0.11010 (19)	0.0224 (5)
C4	0.4932 (3)	0.8431 (2)	0.01056 (19)	0.0216 (5)
C5	0.3562 (3)	0.8590 (3)	−0.05079 (19)	0.0229 (5)
H5A	0.337563	0.940722	−0.099644	0.027*
H5B	0.387138	0.791133	−0.087740	0.027*
C6	0.2456 (3)	0.9336 (2)	0.2438 (2)	0.0232 (5)
H6	0.333216	0.913422	0.281584	0.028*
C7	0.0857 (3)	0.9695 (2)	0.2973 (2)	0.0238 (5)
C8	−0.0427 (3)	1.0723 (2)	0.2554 (2)	0.0262 (6)
H8	−0.029744	1.123116	0.191414	0.031*
C9	−0.1893 (3)	1.0961 (3)	0.3118 (2)	0.0336 (7)
C10	−0.2155 (4)	1.0239 (3)	0.4065 (3)	0.0407 (8)
H10	−0.316448	1.041989	0.441692	0.049*
C11	−0.0890 (4)	0.9245 (3)	0.4474 (2)	0.0413 (8)
H11	−0.103849	0.874866	0.511599	0.050*
C12	0.0604 (4)	0.8970 (3)	0.3947 (2)	0.0315 (6)
H12	0.145164	0.829689	0.424156	0.038*
C13	0.6496 (3)	0.7909 (2)	−0.0172 (2)	0.0224 (5)
H13	0.722333	0.782780	0.028225	0.027*
C14	0.7205 (3)	0.7452 (2)	−0.1090 (2)	0.0232 (5)
C15	0.8672 (3)	0.6468 (2)	−0.1046 (2)	0.0285 (6)
H15	0.916736	0.611916	−0.044300	0.034*
C16	0.9377 (3)	0.6020 (3)	−0.1897 (3)	0.0334 (7)
C17	0.8708 (4)	0.6518 (3)	−0.2816 (2)	0.0354 (7)
H17	0.920296	0.620270	−0.338356	0.043*
C18	0.7281 (4)	0.7500 (3)	−0.2858 (2)	0.0341 (7)
C19	0.6523 (3)	0.7978 (3)	−0.2023 (2)	0.0277 (6)
H19	0.556304	0.864538	−0.207821	0.033*
C20	0.3020 (3)	0.6245 (2)	0.15259 (18)	0.0201 (5)
C21	0.2511 (3)	0.6259 (2)	0.25291 (19)	0.0240 (5)
H21	0.146134	0.671444	0.270636	0.029*
C22	0.3575 (3)	0.5591 (2)	0.3264 (2)	0.0259 (6)
H22	0.324655	0.558935	0.393970	0.031*
C23	0.5147 (3)	0.4918 (2)	0.29827 (19)	0.0238 (5)
C24	0.5653 (3)	0.4900 (2)	0.1975 (2)	0.0241 (5)
H24	0.669891	0.443777	0.179727	0.029*
C25	0.4586 (3)	0.5575 (2)	0.12419 (19)	0.0221 (5)
H25	0.491249	0.558129	0.056509	0.026*
C26	0.6296 (4)	0.4243 (3)	0.3735 (2)	0.0301 (6)
C27	0.7397 (4)	0.7305 (3)	0.3522 (2)	0.0403 (8)
H27A	0.764444	0.810790	0.321723	0.048*
H27B	0.727871	0.693610	0.298449	0.048*
Cl1	0.55934 (10)	0.76047 (12)	0.42894 (7)	0.0659 (3)
Cl2	0.89824 (9)	0.62350 (7)	0.42406 (6)	0.0384 (2)
F1	−0.3130 (2)	1.19405 (18)	0.27309 (15)	0.0469 (5)
F2 ^a	1.0812 (4)	0.5073(3)	−0.1850 (3)	0.0429 (10)
H18 ^a	0.687 (11)	0.775 (9)	−0.349 (3)	0.052*
F2 ^b	0.6617 (8)	0.8121 (6)	−0.3704 (4)	0.0425 (18)
H16 ^b	1.027 (11)	0.531 (9)	−0.173 (11)	0.051*
N1	0.2053 (2)	0.8547 (2)	0.01211 (15)	0.0203 (4)
N2	0.7232 (3)	0.3712 (2)	0.43143 (19)	0.0394 (6)

Table 2: (continued)

Atom	x	y	z	<i>U</i> _{iso} */ <i>U</i> _{eq}
O1	0.5608 (2)	0.87332 (18)	0.16111(13)	0.0270(4)
O2	0.0085 (2)	0.74401 (18)	0.10387(14)	0.0279(4)
O3	0.2126 (2)	0.65024 (18)	−0.02404 (14)	0.0279 (4)
S1	0.16951 (7)	0.71565 (6)	0.05705 (5)	0.02108 (16)

^aOccupancy: 0.643(5), ^bOccupancy: 0.357(5).

by dry hydrogen chloride for 45 min. Then, the mixture was stirred continually at room temperature and monitored by thin layer chromatography (TLC). After the end of reaction, the solvent was removed by filtration and the residue was redissolved in water. The solution was adjusted to a neutral pH value with saturated Na₂CO₃ solution. Yellow precipitates were obtained and purified by silica gel column chromatography (methanol/petroleum ether/ethyl acetate = 1:10:10, v/v/v). The intermediate product (3,5-bis(3-fluorobenzylidene)piperidin-4-one) was dissolved in dichloromethane (100 mL). 4-Cyanobenzene-sulfonyl chloride (0.98 g, 5 mmol) and three drops of pyridine were added to the above solution. The mixture was stirred at room temperature (monitored by TLC). After 10 h, the reaction solution was concentrated under reduced pressure. The yellow solid was washed twice by distilled water and recrystallized from dichloromethane/methanol (1:1, v/v). Crystals were obtained by slow evaporation from the solution of dichloromethane and methanol (1:1, v/v) at room temperature.

Experimental details

The H atoms were positioned geometrically and treated as riding on their parent atoms, with *d* (C–H) = 0.97 Å (methylene) and *U*_{iso}(H) = 1.2*U*_{eq}(C); *d*(C–H) = 0.93 Å (aromatic) and *U*_{iso}(H) = 1.2*U*_{eq}(C).

Comment

As one of the most widespread tumors, colorectal cancer has become the second leading cause of death among all cancers [5]. The low incidence of colorectal cancer in South and Southeast Asia receives intensive attention. It was found that curcumin was generally utilized as an element of dietary supplements in those countries. Curcumin, known as 1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione, is a lipophilic polyphenol from the rhizome of *Curcuma longa* [6]. Due to the

pharmacophore of α , β -unsaturated ketone, curcumin can work as anti-inflammatory, antibacterial and anti-oxidant agent [7, 8]. However, poor aqueous solubility, rapid metabolic degradation and low bioavailability limit its therapeutic usage. In order to ameliorate these defects, structural modification based on curcumin was necessary and large amounts of curcumin analogs have been synthesized. For example, 3,5-bis(arylidene)-4-piperidone derivatives exhibited anticancer, antioxidant and anti-cholinesterase properties [9]. 4-Boc-piperidone chalcones have the potential against highly-metastatic cancer cells [10]. 3,5-Bis(3-alkylamino-methyl-4-hydroxybenzylidene)-4-piperidones can be considered as a novel class of potent tumor-selective cytotoxins [11]. The 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore of these curcumin analogs has a selective affinity for cellular thiols with little or no affinity for hydroxyl and amino groups in nucleic acids [12]. In the previous study, it was found that 3,5-bis(arylidene)-4-piperidones bearing strong electron-withdrawing substituents in the aromatic rings possess moderate antitumor properties [13]. Additionally, it was reported that many compounds containing phenylsulfonyl moiety had significant anti-inflammatory activity [14, 15]. Based on the above consideration, the title compound was synthesized by Claisen–Schmidt condensation reaction and N-benzenesulfonylation reaction.

X-ray crystallographic analysis shows that there are a 3,5-bis(arylidene)-4-piperidinone molecule and a dichloromethane in the asymmetric unit (*cf.* the figure). For clarity, the responding solvent molecule was omitted. All bond lengths and bond angles are all in the close agreement with those values reported previously [16–20]. In the title molecule, the 3-fluorobenzylidene moieties are symmetrically arranged on the both sides of the central piperidone scaffold. Due to the arrangement of the aromatic rings and carbonyl group around the C=C olefinic bonds, the title compound adopts the *E* stereochemistry. The piperidone ring shows a half-chair conformation, which can be attributed to the conjugated relationship of the carbonyl group with adjacent double bonds. Due to the rotation of C6–C7 and C13–C14 single bonds, the aromatic rings and the carbonyl group of the central piperidone are co-planar to each other. The dihedral angles between them are 55.24(13) and 34.60(18)°, respectively. For the further observation, it was found that the dihedral angle between the fluorophenyl rings is 38.40(9)°. The *N*-phenylsulfonyl substituent of the title molecule is extended in the direction of the carbonyl group, which can be attributed to the π – π interaction between the benzene ring of the phenylsulfonyl moiety and the carbonyl group.

No classic hydrogen bonds were found in the crystal, but solvent CH_2Cl_2 molecules are connected to 3,5-bis(arylidene)-4-piperidinone molecules through weak C27–H27B...O1 hydrogen bonds. It's worth noting that the heterocycle piperidonyl moiety and peripheric heteroatoms (such as N and F can serve as the potential hydrogen bonding donor/acceptor to improve binding affinity of target protein. Therefore, molecules containing these fragments may exhibit potential biological activity in the aspect of anticancer, anti-bacterial and antifungal activities [21].

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