Qin Zhao*, Dong Lin, Yun Hou and Gui-Ge Hou

Crystal structure of (3*E*,5*E*)-1-((4-fluorophenyl)sulfonyl)-3,5-bis(3-nitrobenzylidene)piperidin-4-one – dichloromethane (2/1), C₅₁H₃₈Cl₂F₂N₆O₁₄S₂

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.12 × 0.11 × 0.10 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.31 mm ⁻¹
Diffractometer, scan mode:	SuperNova,
$\theta_{\max}$, completeness:	29.6°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	20754, 11248, 0.028
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 8621
$N(\text{param})_{\text{refined}}$:	694
Programs:	CrysAlis ^{PRO} [1], SHELX [2, 3]

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Abstract

C₅₁H₃₈Cl₂F₂N₆O₁₄S₂, triclinic, $P\bar{1}$ (no. 2), $a = 11.8987(6)$ Å, $b = 14.0939(8)$ Å, $c = 16.1915(9)$ Å, $\alpha = 67.590(5)^\circ$, $\beta = 75.402(5)^\circ$, $\gamma = 77.522(4)^\circ$, $V = 2407.3(2)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0584$, $wR_{\text{ref}}(F^2) = 0.1645$, $T = 100.0(1)$ K.

CCDC no.: 1906806

The asymmetric unit of the title 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

The raw material 3-nitrobenzaldehyde (1.51 mol, 10.0 mmol) and 4-piperidone hydrate hydrochloride (0.77 g, 5.0 mmol)

were added to a solution with 25 mL acetic acid. Dry HCL gas was passed through the solution about 25 min. After stirring at room temperature overnight, the mixture produced a precipitate. The precipitate was filtered and washed by acetone to get a yellow intermediate. Then, the intermediate, 4-fluorobenzenesulfonylchloride (0.62 g, 5.0 mol) and potassium carbonate (2.76 g, 0.02 mol) were added to 50 mL of dichloromethane. The mixture was stirred for about 12 h at room temperature. The precipitate was collected, washed with water and recrystallized from dichloromethane/methanol (2:3, v/v) to get light yellow crystals of the title compound.

Experimental details

All H atoms were placed in idealized positions and treated as riding on their parent atoms, with $d(\text{C}-\text{H}) = 0.97$ Å (methylene), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ and $d(\text{C}-\text{H}) = 0.93$ Å (aromatic), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

Comment

Curcumin, is a yellow pigment extracted from the rhizome of turmeric, which has been extensively investigated for its anti-tumor, anti-inflammatory activity, anti-oxidation and other activities. However, its clinical application was limited due to its poor aqueous solubility, relatively low bioactivities and bioavailability [4]. In order to improve these weakness, many curcumin analogs were previously synthesized as better antitumor and anti-inflammatory agents, such as 3*E*,5*E*-3,5-bis(arylidene)-4-piperidones (BAPs) [5, 6]. In our previous

*Corresponding author: Qin Zhao, College of Food Engineering, Ludong University, Yantai 264025, P. R. China, e-mail: candyffff@163.com

Dong Lin: School of Pharmacy, Binzhou Medical University, Yantai 264003, P. R. China

Yun Hou and Gui-Ge Hou: School of Basic Medical Sciences, Binzhou Medical University, Yantai 264003, P. R. China

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	0.3285(2)	0.59236(19)	0.62774(17)	0.0171(5)
H1A	0.406713	0.557480	0.613515	0.020*
H1B	0.273239	0.542990	0.647586	0.020*
C2	0.3219(2)	0.63555(19)	0.70138(17)	0.0158(5)
C3	0.2338(2)	0.72859(19)	0.70366(18)	0.0170(5)
C4	0.1496(2)	0.76505(19)	0.63950(18)	0.0163(5)
C5	0.1757(2)	0.7245(2)	0.56201(18)	0.0164(5)
H5A	0.126611	0.671592	0.575997	0.020*
H5B	0.158350	0.780313	0.507114	0.020*
C6	0.3921(2)	0.59859(19)	0.76293(18)	0.0167(5)
H6	0.382410	0.634951	0.802138	0.020*
C7	0.4828(2)	0.50708(19)	0.77592(17)	0.0157(5)
C8	0.5844(2)	0.5122(2)	0.80113(18)	0.0172(5)
H8	0.593025	0.570908	0.810904	0.021*
C9	0.6723(2)	0.4286(2)	0.81140(18)	0.0187(5)
C10	0.6615(2)	0.3368(2)	0.80315(18)	0.0199(6)
H10	0.721193	0.281203	0.811996	0.024*
C11	0.5585(2)	0.3309(2)	0.78125(18)	0.0190(5)
H11	0.548005	0.269839	0.776401	0.023*
C12	0.4709(2)	0.4150(2)	0.76648(17)	0.0168(5)
H12	0.403396	0.410330	0.750076	0.020*
C13	0.0548(2)	0.83261(19)	0.65495(18)	0.0172(5)
H13	0.049903	0.851452	0.705019	0.021*
C14	−0.0418(2)	0.88096(19)	0.60503(17)	0.0162(5)
C15	−0.0682(2)	0.8488(2)	0.54095(18)	0.0176(5)
H15	−0.023425	0.792140	0.527102	0.021*
C16	−0.1622(2)	0.9030(2)	0.49853(18)	0.0190(5)
C17	−0.2337(2)	0.9871(2)	0.5168(2)	0.0208(6)
H17	−0.295272	1.022347	0.486330	0.025*
C18	−0.2096(2)	1.0163(2)	0.5819(2)	0.0215(6)
H18	−0.257034	1.071198	0.597151	0.026*
C19	−0.1157(2)	0.9650(2)	0.62506(19)	0.0182(5)
H19	−0.100992	0.986762	0.668396	0.022*
C20	0.2633(2)	0.5944(2)	0.43145(17)	0.0166(5)
C21	0.2977(2)	0.4880(2)	0.45398(19)	0.0207(6)
H21	0.366107	0.457178	0.476839	0.025*
C22	0.2287(3)	0.4293(2)	0.4418(2)	0.0261(6)
H22	0.250149	0.358288	0.455516	0.031*
C23	0.1275(3)	0.4777(3)	0.4090(2)	0.0274(7)
C24	0.0912(3)	0.5828(3)	0.3868(2)	0.0276(7)
H24	0.021818	0.612626	0.365150	0.033*
C25	0.1608(2)	0.6423(2)	0.39769(19)	0.0225(6)
H25	0.139532	0.713452	0.382660	0.027*
C26	0.6508(2)	0.77958(19)	0.99781(18)	0.0166(5)
H26A	0.644556	0.769370	1.061441	0.020*
H26B	0.733265	0.776675	0.970130	0.020*
C27	0.6019(2)	0.6920(2)	0.99134(17)	0.0156(5)
C28	0.4854(2)	0.7147(2)	0.96240(18)	0.0166(5)
C29	0.4122(2)	0.81629(19)	0.96007(17)	0.0157(5)
C30	0.4627(2)	0.8900(2)	0.98407(18)	0.0170(5)
H30A	0.427253	0.960309	0.955797	0.020*
H30B	0.444176	0.873815	1.049433	0.020*
C31	0.6539(2)	0.59328(19)	1.01301(17)	0.0153(5)
H31	0.615877	0.548453	1.003232	0.018*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
C32	0.7614(2)	0.54555(19)	1.04973(17)	0.0155(5)
C33	0.8092(2)	0.44626(19)	1.04741(17)	0.0165(5)
H33	0.773522	0.413815	1.022385	0.020*
C34	0.9094(2)	0.3968(2)	1.08246(18)	0.0181(5)
C35	0.9648(2)	0.4394(2)	1.12283(19)	0.0216(6)
H35	1.031483	0.403905	1.146765	0.026*
C36	0.9175(2)	0.5370(2)	1.1263(2)	0.0231(6)
H36	0.952992	0.567959	1.152760	0.028*
C37	0.8177(2)	0.5890(2)	1.09093(19)	0.0191(5)
H37	0.787260	0.654219	1.094454	0.023*
C38	0.3091(2)	0.83801(19)	0.93303(18)	0.0172(5)
H38	0.289568	0.788308	0.916321	0.021*
C39	0.2232(2)	0.93215(19)	0.92683(18)	0.0164(5)
C40	0.1564(2)	0.9673(2)	0.85843(18)	0.0174(5)
H40	0.165495	0.931887	0.818536	0.021*
C41	0.0766(2)	1.0559(2)	0.85170(18)	0.0183(5)
C42	0.0588(2)	1.1118(2)	0.90948(19)	0.0203(6)
H42	0.005800	1.172217	0.901918	0.024*
C43	0.1227(2)	1.0746(2)	0.97870(19)	0.0194(6)
H43	0.111660	1.109531	1.019223	0.023*
C44	0.2034(2)	0.9851(2)	0.98795(18)	0.0175(5)
H44	0.244768	0.960199	1.035374	0.021*
C45	0.6177(2)	0.8921(2)	0.77609(18)	0.0187(5)
C46	0.6962(2)	0.8088(2)	0.76228(18)	0.0198(5)
H46	0.760629	0.783261	0.790874	0.024*
C47	0.6767(3)	0.7642(2)	0.70494(19)	0.0222(6)
H47	0.727432	0.707831	0.694857	0.027*
C48	0.5812(3)	0.8049(2)	0.6634(2)	0.0253(6)
C49	0.5014(3)	0.8866(2)	0.6773(2)	0.0272(6)
H49	0.436530	0.910984	0.649180	0.033*
C50	0.5207(2)	0.9317(2)	0.73432(19)	0.0240(6)
H50	0.469207	0.987761	0.744461	0.029*
C51	0.6996(3)	0.7302(3)	0.3190(3)	0.0393(8)
H51A	0.638414	0.688575	0.357481	0.047*
H51B	0.718445	0.765757	0.353578	0.047*
Cl1	0.64805(8)	0.82089(7)	0.22466(7)	0.0446(2)
Cl2	0.82525(8)	0.64819(7)	0.28940(7)	0.0454(2)
F1	0.06066(17)	0.41963(16)	0.39576(14)	0.0409(5)
F2	0.56466(17)	0.76282(15)	0.60517(13)	0.0364(5)
N1	0.29952(18)	0.68065(16)	0.54724(15)	0.0157(4)
N2	0.7835(2)	0.43892(19)	0.82920(17)	0.0250(5)
N3	−0.1891(2)	0.86664(19)	0.43283(18)	0.0257(5)
N4	0.59040(19)	0.88264(16)	0.95335(15)	0.0166(4)
N5	0.0046(2)	1.09108(18)	0.78081(17)	0.0232(5)
N6	0.9613(2)	0.29491(17)	1.07519(16)	0.0213(5)
O1	0.22913(17)	0.77193(15)	0.75744(13)	0.0219(4)
O2	0.33192(17)	0.77294(14)	0.38099(13)	0.0215(4)
O3	0.46790(15)	0.61664(14)	0.44778(13)	0.0188(4)
O4	0.8588(2)	0.36308(18)	0.84322(19)	0.0411(6)
O5	0.79632(19)	0.52369(17)	0.82756(17)	0.0329(5)
O6	−0.13104(19)	0.78789(15)	0.42119(15)	0.0289(5)
O7	−0.2704(2)	0.91683(19)	0.39251(17)	0.0386(6)
O8	0.45046(17)	0.65123(14)	0.94342(14)	0.0233(4)
O9	0.76788(17)	0.93781(16)	0.84201(14)	0.0253(4)
O10	0.57626(19)	1.04971(14)	0.82985(14)	0.0259(5)

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{iso}^*/U_{eq}
O11	0.91975(18)	0.26238(15)	1.03116(15)	0.0276(5)
O12	1.04559(18)	0.24864(16)	1.11218(15)	0.0305(5)
O13	0.02287(19)	1.04271(16)	0.72889(15)	0.0280(5)
O14	−0.0694(2)	1.16705(18)	0.77640(17)	0.0391(6)
S1	0.35120(5)	0.67091(5)	0.44594(4)	0.01573(15)
S2	0.64384(6)	0.94941(5)	0.84852(4)	0.01867(15)

study, we found BAPs have greater predilection or sequential interaction for bio-thiols resulting in a greater activity to tumors rather than with normal cells [7].

In order to improve its biological activity, strong electron-withdrawing substituent groups (Such as $-NO_2$, $-CN$, $-CF_3$) were introduced on both sides of BAPs. While some electron-withdrawing trifluoromethyl groups (Such as $-F$, $-NO_2$, $-CN$, $-CF_3$) were introduced into *N*-benzenesulfonyl substituents of BAPs. By introducing these groups, the antitumor and anti-inflammatory activity of BAPs should be improved, while toxicity should be reduced to different degrees [8].

Crystal structure and bioactivity of 4-((*E*)-((*E*)-5-(2-fluorobenzylidene)-1-((4-fluorophenyl)sulfonyl)-4-oxopiperidin-3-ylidene)methyl)benzonitrile (BAP-1) and (3*E*, 5*E*)-3,5-bis(4-cyanobenzylidene)-1-((4-fluorophenyl)sulfonyl)piperidin-4-one (BAP-2) were reported by our group [9, 10]. Recently, we found that the antitumor and anti-inflammatory activity were improved when fluorine was substituted on *N*-benzenesulfonyl substituents of BAPs. Herein, the crystal structure of (3*E*, 5*E*)-1-((4-fluorophenyl)sulfonyl)-3,5-bis(3-nitrobenzylidene)piperidin-4-one-dichloromethane(2/1) will be reported.

There are two BAP molecules and a dichloromethane molecule in the asymmetric unit of the title compound (*cf.* the figure). Bond lengths and angles are all in the expected ranges. Single-crystal structure analysis reveals that configurations of the two BAPs molecules are different. In a molecule, two 3-nitro phenyl groups on both sides of BAP take the *trans*-configuration compared with the central piperidin-4-one. And the two 3-nitro phenyl groups adopt the *E* stereochemistry of olefinic double bonds, which was the same as those reported in literature [10]. In the other molecule, two 3-nitro phenyl groups are symmetric compared with central piperidin-4-one, which also adopt the *E* stereochemistry of the double bond. The dihedral angles between two 4-nitro phenyl groups in both molecules are $32.61(6)^\circ$ and $26.36(3)^\circ$, respectively. Interestingly, the 4-trifluoromethylphenyl group bend towards the side of carbonyl group in one molecule, which looks like an “organic clip” [10], however, 4-trifluoromethylphenyl group stretch in

the other direction of carbonyl group in another molecule. 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 biological activity [11, 12].

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