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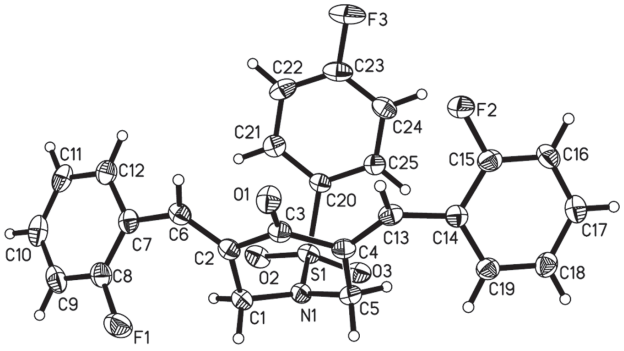
Crystal structure and anti-inflammatory activity of (3*E*,5*E*)-3,5-bis(2-fluorobenzylidene)-1-((4-fluorophenyl)sulfonyl)piperidin-4-one, $C_{25}H_{18}F_3NO_3S$



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Abstract

$C_{25}H_{18}F_3NO_3S$, orthorhombic, $Pca2_1$ (no. 29), $a = 19.1142(7)$ Å, $b = 11.6722(5)$ Å, $c = 9.2390(3)$ Å, $V = 2061.26(13)$ Å^3, $Z = 4$, $R_{gt}(F) = 0.0422$, $wR_{ref}(F^2) = 0.0974$, $T = 100.02(10)$ 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.

Source of material

In a 25 mL beaker, 4-piperidone hydrochloride (0.68 g, 0.005 mol) and 2-fluorobenzaldehyde (1.24 g, 0.01 mol) were dissolved in 10 mL acetic acid, then dry hydrogen chloride gas was injected continuously into the solution for 45 min. After gas insertion, the reaction system was stirred at room

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Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.14 × 0.12 × 0.11 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.21 mm^{-1}
Diffractometer, scan mode:	SuperNova,
θ_{max}, completeness:	29.6°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	17212, 4946, 0.041
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 4413
$N(param)_{refined}$:	298
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.92897(17)	−0.0796(3)	0.0819(3)	0.0237(6)
H1A	0.969086	−0.125161	0.110489	0.028*
H1B	0.904469	−0.120373	0.005714	0.028*
C2	0.88111(16)	−0.0640(3)	0.2093(3)	0.0219(6)
C3	0.90253(15)	0.0227(3)	0.3205(3)	0.0230(6)
C4	0.95125(15)	0.1151(3)	0.2744(3)	0.0220(6)
C5	0.99163(16)	0.1005(3)	0.1344(3)	0.0237(6)
H5A	1.001687	0.175407	0.093997	0.028*
H5B	1.035898	0.063236	0.154919	0.028*
C6	0.81814(16)	−0.1124(3)	0.2243(3)	0.0240(6)
H6	0.792106	−0.089222	0.304170	0.029*
C7	0.78523(16)	−0.1978(3)	0.1296(3)	0.0244(6)
C8	0.81963(17)	−0.2922(3)	0.0738(3)	0.0283(7)
C9	0.7878(2)	−0.3713(3)	−0.0151(4)	0.0343(8)
H9	0.812752	−0.433573	−0.050644	0.041*
C10	0.7183(2)	−0.3567(3)	−0.0505(4)	0.0359(8)
H10	0.696198	−0.408852	−0.111302	0.043*
C11	0.68153(18)	−0.2646(3)	0.0041(3)	0.0320(8)
H11	0.634667	−0.254617	−0.019862	0.038*
C12	0.71449(17)	−0.1869(3)	0.0949(3)	0.0279(7)
H12	0.688959	−0.126346	0.133398	0.033*
C13	0.95049(16)	0.2103(3)	0.3563(3)	0.0237(6)
H13	0.924030	0.206479	0.440661	0.028*
C14	0.98633(15)	0.3198(3)	0.3291(3)	0.0227(6)
C15	0.95304(17)	0.4211(3)	0.3693(3)	0.0272(7)
C16	0.97967(17)	0.5273(3)	0.3421(4)	0.0308(7)
H16	0.955561	0.592710	0.370741	0.037*
C17	1.04345(18)	0.5361(3)	0.2710(3)	0.0304(7)
H17	1.061740	0.607866	0.249059	0.037*
C18	1.07981(17)	0.4382(3)	0.2326(4)	0.0291(7)
H18	1.122988	0.444102	0.186786	0.035*

Table 2 (continued)

Atom	x	y	z	U_{iso}*/U_{eq}
C19	1.05177(16)	0.3312(3)	0.2626(3)	0.0260(7)
H19	1.076896	0.265832	0.238014	0.031*
C20	0.84272(15)	0.1839(2)	−0.0002(3)	0.0208(6)
C21	0.77656(16)	0.1383(3)	0.0258(3)	0.0261(7)
H21	0.764816	0.066093	−0.009261	0.031*
C22	0.72859(17)	0.2015(3)	0.1041(4)	0.0313(7)
H22	0.683907	0.173226	0.121841	0.038*
C23	0.74856(19)	0.3071(3)	0.1550(4)	0.0310(7)
C24	0.81335(17)	0.3537(3)	0.1305(3)	0.0282(7)
H24	0.824879	0.425619	0.166656	0.034*
C25	0.86106(17)	0.2912(3)	0.0506(3)	0.0245(6)
H25	0.905181	0.321069	0.031193	0.029*
F1	0.88669(11)	−0.31159(18)	0.1142(2)	0.0385(5)
F2	0.89017(9)	0.41300(17)	0.4371(2)	0.0347(5)
F3	0.70209(11)	0.3690(2)	0.2336(2)	0.0468(6)
N1	0.95296(13)	0.0322(2)	0.0267(3)	0.0230(5)
O1	0.87751(12)	0.02028(19)	0.4428(2)	0.0288(5)
O2	0.86955(12)	0.0150(2)	−0.1752(2)	0.0311(5)
O3	0.95212(12)	0.1790(2)	−0.1632(2)	0.0318(5)
S1	0.90554(4)	0.10069(6)	−0.09250(8)	0.02328(17)

temperature for 8 h. The 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 regulated to a neutral pH with a dilute sodium hydroxide solution. The collected precipitate was recrystallized from the 70% methanol solution to attain the intermediate BAP-H that was used directly for next reaction. BAP-H and 4-fluorobenzenesulfonyl chloride (0.89 g, 0.005 mol) were dissolved in 100 mL of dichloromethane. After adding 3 drops of pyridine, the reaction system was stirred at room temperature overnight. The reaction solution was washed twice with 2 mol/L hydrochloric acid, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the yellow solid which was recrystallized from dichloromethane/methanol (1:1, *v*/*v*) to get yellow crystals.

Process of anti-inflammatory activity test: Anti-inflammatory activity was evaluated by ELISA method, which can detect NO secretion changes in LPS-induced inflammatory model of RAW264.7. The target compound had no significant toxicity to RAW264.7 cells at 6.0 μM. Firstly, RAW264.7 cells in log phase were collected then the cells were added into a 96-well plate at 100 μL per well. After 12 h of incubation, drug was added. After 2 h of incubation, 10 μL of LPS (concentration: 1 μg/mL) was added. Each group had 6 parallel duplicate wells. After 24 h of incubation, the cell supernatants in 96-well plates were collected then NO secretion was detected by ELISA with an ELISA kit (eBioScience, San Diego, CA). Pyrrolidine dithiocarbamate (PDTC) was regarded as a positive control.

Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with 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). Displacement ellipsoids are drawn at the 50% probability level.

Comment

Curcumin is a yellow phenolic pigment, which exists in rhizomes of turmeric and other Zingiberaceaes. Curcumin is highly valued because of its multiple effects of anti-inflammatory, antibacterial, anti-tumor, and anti-senile dementia, etc [4]. Nevertheless, curcumin is restricted in clinic due to its poor water solubility, unsteady structure, low bioavailability and other limits [5]. Therefore, (3*E*,5*E*)-3,5-bis(arylidene)-4-piperidone derivatives (BAPs) are transformed from curcumin in order to ameliorate above disadvantages. As curcumin analogs, BAPs possess potential specific cytotoxic anti-tumor activity, in whose structure, double α,β-unsaturated ketones are the main pharmacophores and show selective affinity to tumor's mercapto groups but perform poor affinity to active groups in nucleic acid, such as amino-groups and hydroxyl groups [6–9]. BAPs display prominently activities on tumor cells and inflammatory cells [10]. The title compound was synthesized by Claisen-Schmidt condensation reaction and *N*-benzenesulfonylation reaction then its anti-inflammatory was initially studied.

Single-crystal structure analysis reveals that there is only one drug molecule in the asymmetric unit of the title crystal structure (*cf*. the figure). Bond lengths and angles are all in the expected ranges. In the solid state, 2-fluorobenzylidene groups on both sides of central piperidone adopt the *E* stereochemistry of the olefinic double bonds [11–14]. The dihedral angles between 2-fluorobenzylidenes and central piperidone ring are 42.1(4)° and 60.6(3)°, respectively. The *N*-phenylsulfonyl group extends in the same direction as the carbonyl group of central piperidone, which looks like an "organic clip" [15]. The dihedral angles between 4-fluorobenzenesulfonyl group and central piperidone is 30.9(2)°.

Based on literatures, the pro-inflammatory cytokines, such as NO, TNF-α and IL-6 can trigger inflammation resulting in various diseases. If the secretion of these pro-inflammatory cytokines can be effectively suppressed, it can play a role in inhibiting inflammation [16, 17]. In this study, the effect of the title compound on NO production in mouse RAW264.7 cells induced by LPS was examined by ELISA. Pyrrolidine dithiocarbamate (PDTC) was as a positive control. After

treatment with PDTC for RAW264.7 cells, the express rate for NO production could reach $66.42 \pm 1.83\%$. If we treat RAW264.7 cells with the title compound, the express rate of NO production could reach $42.37 \pm 0.69\%$. The result showed that title compound displayed potential inhibitory effects on LPS-induced NO secretion compared with PDTC.

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References

1. Rigaku OD: CrysAlis^{PRO}. Rigaku Oxford Diffraction Ltd, Yarnton, Oxfordshire, England (2017).
2. Sheldrick, G. M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
3. Sheldrick, G. M.: Crystal structure refinement with SHELXL. Acta Crystallogr. **C71** (2015) 3–8.
4. Anand, P.; Kunnumakkara, A. B.; Newman, R. A.; Aggarwal, B. B.: Bioavailability of curcumin: problems and promises. Mol. Pharmaceutics **4** (2007) 807–818.
5. Nelson, K. M.; Dahlin, J. L.; Bisson, J.; Graham, J.; Pauli, G. F.; Walters, M. A.: The essential medicinal chemistry of curcumin. J. Med. Chem. **60** (2017) 1620–1637.
6. Thakur, A.; Manohar, S.; Gerena, C. E. V.; Zayas, B.; Kumar, V.; Malhotra, S. V.; Rawat, D. S.: Novel 3,5-bis(arylidiene)-4-piperidone based monocarbonyl analogs of curcumin: anticancer activity evaluation and mode of action study. Med. Chem. Commun. **5** (2014) 576–586.
7. Gao, C. L.; Hou, G. G.; Liu, J.; Ru, T.; Xu, Y. Z.; Zhao, S. Y.; Ye, H.; Zhang, L. Y.; Chen, K. X.; Guo, Y. W.; Pang, T.; Li, X. W.: Synthesis and target identification of benzoxepane derivatives as potential anti-neuroinflammatory agents for ischemic stroke. MedChemComm **59** (2020) 2429–2439.
8. Li, N.; Xin, W. Y.; Yao, B. R.; Wang, C. H.; Cong, W.; Zhao, F.; Li, H. J.; Hou, Y.; Meng, Q. G.; Hou, G. G.: Novel dissymmetric 3,5-bis(arylidene)-4-piperidones as potential antitumor agents with biological evaluation *in vitro* and *in vivo*. Eur. J. Med. Chem. **147** (2018) 21–33.
9. Li, N.; Xin, W. Y.; Yao, B. R.; Cong, W.; Wang, C. H.; Hou, G. G.: **N**-Phenylsulfonyl-3,5-bis(arylidene)-4-piperidone derivatives as activation NF-κB inhibitors in hepatic carcinoma cell lines. Eur. J. Med. Chem. **155** (2018) 531–544.
10. Zhang, L. S.; Chen, Q.; Hou, G. G.; Zhao, W.; Hou, Y.: Hydroxyl-substituted double Schiff-base condensed 4-piperidone/cyclohexanones as potential anticancer agents with biological evaluation. J. Enzyme Inhib. Med. Chem. **34** (2019) 264–271.
11. Yao, B. R.; Sun, Y.; Chen, S. L.; Suo, H. D.; Zhang, Y. L.; Wei, H.; Wang, C. H.; Zhao, F.; Cong, W.; Xin, W. Y.; Hou, G. G.: Dissymmetric pyridyl-substituted 3,5-bis(arylidene)-4-piperidones as anti-hepatoma agents by inhibiting NF-κB pathway activation. Eur. J. Med. Chem. **167** (2019) 187–199.
12. Liu, L. D.; Liu, S. L.; Hou, G. G.: Crystal structure of 4-((*E*)-((*E*)-5-(2-fluorobenzylidene)-1-((4-fluorophenyl)sulfonyl)-4-oxopiperidin-3-ylidene)methyl)benzonitrile, $C_{26}H_{18}F_2N_2O_3S$. Z. Kristallogr. NCS **233** (2018) 1063–1065.
13. Li, X. Y.; Meng, Q. G.; Hou, G. G.: Crystal structure of (3*E*,5*E*)-3,5-bis(4-cyanobenzylidene)-1-((4-fluorophenyl) sulfonyl)piperidin-4-one, $C_{27}H_{18}FN_3O_3S$. Z. Kristallogr. NCS **234** (2019) 771–773.
14. Sun, Y.; Wang, S. X.; Hou, G. G.: Crystal structure of (3*E*,5*E*)-3,5-bis(3-nitrobenzylidene)-1-((4-(trifluoromethyl)phenyl)sulfonyl) piperidin-4-one-dichloromethane (2/1), $C_{53}H_{38}Cl_2F_6N_6O_{14}S_2$. Z. Kristallogr. NCS **234** (2019) 1047–1049.
15. Hou, G. G.; Zhao, H. J.; Sun, J. F.; Lin, D.; Dai, X. P.; Han, J. T.; Zhao, H.: Synthesis, structure and luminescence of Co-crystals with hexagonal channels: arranging disposition and π-π interactions. CrystEngComm **15** (2013) 577–585.
16. Zhang, L.; Shi, L.; Soars, S. M.; Kamps, J.; Yin, H.: Discovery of novel small-molecule inhibitors of NF-κB signaling with antiinflammatory and anticancer properties. J. Med. Chem. **61** (2018) 5881–5899.
17. 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. Enzyme Inhib. Med. Chem. **34** (2019) 1287–1297.