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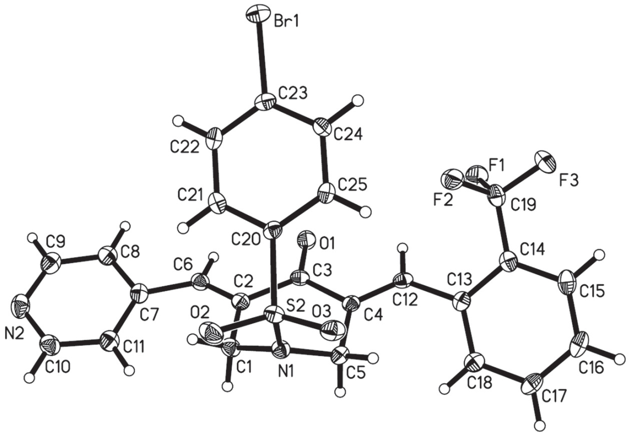
Crystal structure and anti-inflammatory activity of (3*E*,5*E*)-1-((4-bromophenyl)sulfonyl)-3-(pyridin-4-ylmethylene)-5-(2-(trifluoromethyl) benzylidene)piperidin-4-one, $C_{25}H_{18}BrF_3N_2O_3S$



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Abstract

$C_{25}H_{18}BrF_3N_2O_3S$, monoclinic, $P2_1/n$ (no. 14), $a = 9.9295(11)$ Å, $b = 21.755(2)$ Å, $c = 10.2358(11)$ Å, $\beta = 95.022(10)°$, $V = 2202.6(4)$ Å^3, $Z = 4$, $R_{\mathrm{gt}}(F) = 0.0373$, $wR_{\mathrm{ref}}(F^2) = 0.0795$, $T = 100(1)$ 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.

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	$0.13 \times 0.12 \times 0.11$ mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	2.02 mm^{-1}
Diffractometer, scan mode:	SuperNova, ω
$\theta_{\max}$, completeness:	29.6°, >99%
$N(hkl)_{\mathrm{measured}}$, $N(hkl)_{\mathrm{unique}}$, R_{int}:	12079, 5268, 0.033
Criterion for I_{obs}, $N(hkl)_{\mathrm{gt}}$:	$I_{\mathrm{obs}} > 2\ \sigma(I_{\mathrm{obs}})$, 4330
$N(param)_{\mathrm{refined}}$:	316
Programs:	CrysAlis$^{\mathrm{PRO}}$ [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}
Br1	0.94649(2)	0.17973(2)	0.23919(2)	0.02123(8)
C1	0.6314(2)	0.48747(10)	0.2622(2)	0.0189(5)
H1A	0.727700	0.495726	0.267276	0.023*
H1B	0.584372	0.526452	0.251011	0.023*
C2	0.5932(2)	0.44730(10)	0.1443(2)	0.0166(5)
C3	0.4946(2)	0.39606(10)	0.1566(2)	0.0169(5)
C4	0.4248(2)	0.39128(10)	0.2798(2)	0.0157(5)
C5	0.4576(2)	0.43918(10)	0.3829(2)	0.0175(5)
H5A	0.398447	0.474302	0.365971	0.021*
H5B	0.441515	0.422585	0.468075	0.021*
C6	0.6410(2)	0.45364(10)	0.0267(2)	0.0187(5)
H6	0.604942	0.426157	−0.036589	0.022*
C7	0.7400(2)	0.49637(10)	−0.0189(2)	0.0188(5)
C8	0.7997(2)	0.48110(11)	−0.1330(2)	0.0214(5)
H8	0.773329	0.445593	−0.178942	0.026*
C9	0.8969(3)	0.51825(12)	−0.1773(2)	0.0255(6)
H9	0.935452	0.506655	−0.253110	0.031*
C10	0.8800(3)	0.58616(11)	−0.0110(2)	0.0238(5)
H10	0.906776	0.622575	0.031254	0.029*
C11	0.7805(2)	0.55170(11)	0.0408(2)	0.0217(5)
H11	0.741084	0.565297	0.114648	0.026*
C12	0.3408(2)	0.34436(10)	0.2906(2)	0.0171(5)
H12	0.335390	0.315741	0.222880	0.021*
C13	0.2558(2)	0.33301(10)	0.3982(2)	0.0171(5)
C14	0.2337(2)	0.27337(10)	0.4443(2)	0.0177(5)
C15	0.1478(2)	0.26352(11)	0.5412(2)	0.0223(5)
H15	0.133024	0.223741	0.570034	0.027*
C16	0.0837(2)	0.31234(12)	0.5957(2)	0.0244(6)
H16	0.025841	0.305471	0.660897	0.029*
C17	0.1057(2)	0.37105(11)	0.5533(2)	0.0224(5)

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Table 2 (continued)

Atom	x	y	z	U_{iso}*/U_{eq}
H17	0.063638	0.404017	0.590919	0.027*
C18	0.1897(2)	0.38142(11)	0.4553(2)	0.0193(5)
H18	0.202515	0.421392	0.426703	0.023*
C19	0.3092(2)	0.22032(11)	0.3935(2)	0.0214(5)
C20	0.7680(2)	0.35671(10)	0.4060(2)	0.0152(5)
C21	0.8570(2)	0.36054(10)	0.3094(2)	0.0187(5)
H21	0.882209	0.398706	0.278679	0.022*
C22	0.9082(2)	0.30734(10)	0.2590(2)	0.0178(5)
H22	0.967692	0.309318	0.193888	0.021*
C23	0.8701(2)	0.25173(10)	0.3062(2)	0.0169(5)
C24	0.7802(2)	0.24705(10)	0.4012(2)	0.0179(5)
H24	0.755130	0.208683	0.431049	0.021*
C25	0.7277(2)	0.30013(10)	0.4517(2)	0.0164(5)
H25	0.666416	0.297897	0.515205	0.020*
F1	0.28225(14)	0.21058(6)	0.26410(12)	0.0271(3)
F2	0.44372(13)	0.22854(6)	0.41137(13)	0.0261(3)
F3	0.28415(16)	0.16732(6)	0.45231(14)	0.0305(3)
N1	0.59818(19)	0.45915(8)	0.38476(17)	0.0166(4)
N2	0.9401(2)	0.57049(10)	−0.11773(19)	0.0270(5)
O1	0.47048(17)	0.35949(7)	0.06761(14)	0.0217(4)
O2	0.82831(16)	0.46570(7)	0.48795(15)	0.0231(4)
O3	0.65387(17)	0.40849(7)	0.59584(14)	0.0214(4)
S2	0.71535(6)	0.42498(2)	0.47970(5)	0.01684(13)

Source of material

The title compound was prepared in a two step protocol of a Claisen-Schmidt condensation followed by a *N*-sulfonylation. Firstly, 2-(trifluoromethyl)benzaldehyde (1.74 g, 10.0 mmol), 4-pyridinecarboxaldehyde (1.07 g, 10.0 mmol) and 4-piperidone hydrate hydrochloride (1.35 g, 10.0 mmol) were dissolved in dilute acetic acid (25 mL). This mixture was passed through by dry HCL gas for 30 min. After stirring at room temperature for 24 h (monitored by thin-layer chromatography (TLC)), the precipitate was collected and washed with cold acetone. The precipitates were added into 100 mL water, and the pH value was adjusted to 7 by aqueous Na_2CO_3 solution. The precipitates were filtered and washed by water. The crude product was purified on silica gel by column using methanol/petroleum ether/EtOAc (1:10:10, *v*/*v*/*v*) as the eluent to afford intermediates. Secondly, the intermediate (0.69 g, 2.0 mmol), and 4-bromobenzenesulfonyl chloride (0.46 g, 2.2 mmol) were dissolved in dichloromethane (50 mL). Two drops of pyridine were added. After stirring for 6 h at room temperature, the precipitate was collected, washed with water and recrystallized from dichloromethane/methanol (1:1, *v*/*v*) to get light yellow crystals of title compound.

The anti-inflammatory activities of title compound were evaluated by inhibition of LPS-induced NO secretion on mouse RAW264.7 macrophages. Pyrrolidine dithiocarbamate (PDTC) was used as a reference standard. When the concentration of the title compound was 6.0 μM, it had no significant toxicity on experimental RAW264.7 cells. Firstly, RAW264.7 cells were pretreated for 2.0 hours with 30 μM of PDTC or 6.0 μM of title compound, respectively. Secondly, the cells were treated with LPS (1.0 μg/mL) for 22 h, and then the collected culture media were centrifuged at 1000 rpm for 10 min. The expression levels of NO secretion in the media were determined by ELISA with an ELISA kit (eBioScience, San Diego, CA). The experiment was carried out in triplicate.

Experimental details

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

Comment

Curcumin analogues, like the 3,5-bis(arylidene)-4-piperidone (BAPs), contain two α,β-unsaturated keto groups, and have greater predilection or sequential interaction for bio-thiols in tumors rather than normal cells [4, 5]. Some BAPs with antitumor and anti-inflammatory properties better than curcumin [6] were reported by our group [7–9]. They involve some strong electron-withdrawing groups (-NO_2, -CN, -CF_3) and electron-donating substitutes (-NHAc, -OMe, -CMe_3) improving antitumor and anti-inflammatory activity to different extent [10–12].

An asymmetric BAP is obtained by the use of a 4-pyridine substituent, and a trifluoromethylphenyl substituent, respectively (see the figure) [8]. Our interests lie in incorporation of different substituents on the end of *N*-phenylsulfonyl substituent, and find the desired and improved antitumor and anti-inflammatory activities.

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. The pyridyl and arylidene moieties on both sides of central piperidone adopt the *E* stereochemistry [13, 14]. The dihedral angle between the mean plane of the pyridyl and the mean plane of the piperidone moiety is 12°, while the dihedral angle between the mean plane of the aryl and the mean plane of the piperidone moiety is 46°. In addition, the *N*-phenylsulfonyl substituents are going to stretch in the direction of the carbonyl group of the central piperidone. The title compound looks like an “organic clip” [15, 16]. The dihedral angle between the mean plane of the *N*-phenylsulfonyl and the mean plane of the piperidone ring is 42°.

In our study, the effect of title compound on pro-inflammatory cytokine (NO) production in mouse RAW264.7

cells induced by LPS was examined by ELISA. PDTC was as a reference standard. After treatment with PDTC, the expression rate for NO production in RAW264.7 cells was 68.32 ± 2.69%. For title compound, the expression rate of NO production could reach 55.39 ± 0.91%. The result showed that title compound displayed potential inhibitory effect on LPS-induced NO secretion than PDTC [8, 17].

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