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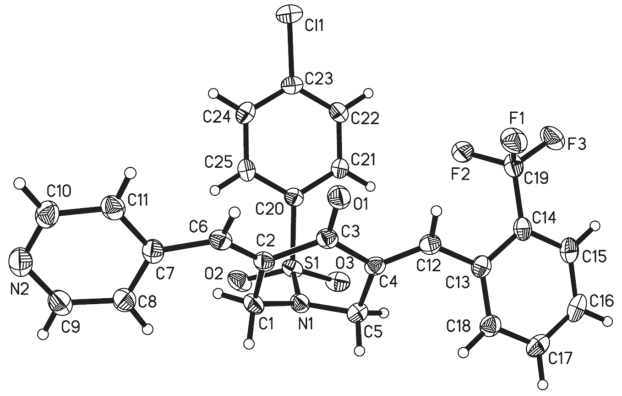
Crystal structure and anti-inflammatory activity of (3*E*,5*E*)-1-((4-chlorophenyl)sulfonyl)-3-(pyridin-4-ylmethylene)-5-(2-(trifluoromethyl) benzylidene)piperidin-4-one, $C_{25}H_{18}ClF_3N_2O_3S$



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Abstract

$C_{25}H_{18}ClF_3N_2O_3S$, monoclinic, $P2_1/n$ (no. 14), $a = 9.9087(5)$ Å, $b = 21.7843(10)$ Å, $c = 10.2512(6)$ Å, $\beta = 94.749(5)°$, $V = 2205.2(2)$ Å^3, $Z = 4$, $R_{gt}(F) = 0.0448$, $wR_{ref}(F^2) = 0.1028$, $T = 100$ 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:	0.14 × 0.12 × 0.11 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.33 mm^{-1}
Diffractometer, scan mode:	SuperNova, ω
θ_{max}, completeness:	29.6°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	19019, 5362, 0.040
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 4204
$N(param)_{refined}$:	316
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

Source of material

2-(Trifluoromethy)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 about 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 then aqueous Na_2CO_3 solution was added until the pH value was adjusted to about 7. The precipitates were filtered, subsequently washed by water, and purified on silica gel by column using methanol/petroleum ether/EtOAc (1:10:10, *v*/*v*/*v*) as the eluent to afford a yellow intermediate. Next, the intermediate (0.69 g, 2.0 mmol), and 4-chlorobenzenesulfonyl chloride (0.46 g, 2.2 mmol) were dissolved in dichloromethane (50 mL). Two drops of pyridine were added. After stirring for about 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 the 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 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 h 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

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.36719(19)	0.01360(9)	0.7383(2)	0.0243(4)
H1A	0.413494	−0.025556	0.748411	0.029*
H1B	0.270601	0.005736	0.734639	0.029*
C2	0.40727(18)	0.05309(8)	0.8558(2)	0.0223(4)
C3	0.50729(18)	0.10386(8)	0.8421(2)	0.0221(4)
C4	0.57578(18)	0.10822(8)	0.71815(19)	0.0209(4)
C5	0.54113(18)	0.06107(9)	0.6148(2)	0.0240(4)
H5A	0.556707	0.077951	0.529763	0.029*
H5B	0.599724	0.025681	0.630095	0.029*
C6	0.36069(18)	0.04677(9)	0.9741(2)	0.0232(4)
H6	0.397797	0.073965	1.037188	0.028*
C7	0.26083(18)	0.00403(9)	1.0204(2)	0.0244(4)
C8	0.2181(2)	−0.05078(9)	0.9602(2)	0.0283(4)
H8	0.256554	−0.064371	0.885603	0.034*
C9	0.1176(2)	−0.08473(10)	1.0129(2)	0.0316(5)
H9	0.088942	−0.120678	0.970164	0.038*
C10	0.1033(2)	−0.01748(10)	1.1811(2)	0.0321(5)
H10	0.065378	−0.005962	1.257398	0.039*
C11	0.2019(2)	0.01939(9)	1.1356(2)	0.0277(4)
H11	0.229448	0.054657	1.181523	0.033*
C12	0.66212(18)	0.15485(9)	0.7062(2)	0.0228(4)
H12	0.669478	0.183350	0.773987	0.027*
C13	0.74629(18)	0.16552(9)	0.59708(19)	0.0229(4)
C14	0.77123(18)	0.22534(9)	0.5521(2)	0.0238(4)
C15	0.85715(19)	0.23483(10)	0.4541(2)	0.0284(5)
H15	0.873237	0.274488	0.425613	0.034*
C16	0.91924(19)	0.18544(10)	0.3985(2)	0.0318(5)
H16	0.977437	0.191946	0.333205	0.038*
C17	0.89461(19)	0.12670(10)	0.4401(2)	0.0303(5)
H17	0.934948	0.093482	0.401686	0.036*
C18	0.80987(18)	0.11691(9)	0.5392(2)	0.0257(4)
H18	0.795292	0.077073	0.567437	0.031*
C19	0.69965(19)	0.27899(9)	0.6051(2)	0.0271(4)
C20	0.23114(18)	0.14497(8)	0.59438(19)	0.0211(4)
C21	0.27440(18)	0.20120(9)	0.54837(19)	0.0220(4)
H21	0.336383	0.202740	0.485108	0.026*
C22	0.22374(18)	0.25479(9)	0.5982(2)	0.0244(4)
H22	0.250678	0.292787	0.568148	0.029*
C23	0.13269(18)	0.25123(9)	0.6932(2)	0.0229(4)
C24	0.09139(19)	0.19570(9)	0.7407(2)	0.0254(4)
H24	0.030997	0.194371	0.805445	0.030*
C25	0.14094(18)	0.14205(9)	0.6909(2)	0.0246(4)
H25	0.114026	0.104213	0.721750	0.029*
Cl1	0.06547(5)	0.31803(2)	0.75425(5)	0.03149(14)
F1	0.73106(12)	0.28836(6)	0.73354(12)	0.0363(3)
F2	0.56353(11)	0.27187(5)	0.59193(13)	0.0320(3)
F3	0.72490(13)	0.33172(5)	0.54540(13)	0.0385(3)
N1	0.39938(15)	0.04171(7)	0.61467(16)	0.0228(3)
N2	0.05926(17)	−0.06926(8)	1.12081(19)	0.0342(4)
O1	0.53350(14)	0.14026(6)	0.93125(14)	0.0284(3)
O2	0.16749(14)	0.03602(6)	0.51482(15)	0.0321(4)
O3	0.34327(14)	0.09227(6)	0.40400(14)	0.0299(3)
S1	0.28177(5)	0.07630(2)	0.52095(5)	0.02351(12)

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, USA). 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(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).

Comment

Because of low bioactivities, poor aqueous solubility and false positive problem of curcumin, it is rarely used in clinical practice [4]. In order to improve these aspects of the problem, lots of curcumin analogues were synthesized through structural modification, such as (3*E*,5*E*)-3,5-bis(arylidene)-4-piperidone derivatives (BAPs). In this class of compounds, two α,β-unsaturated keto groups cause greater predilection or sequential interaction for bio-thiols in tumors rather than normal cells [5, 6]. In our group, some BAPs with better antitumor and anti-inflammatory properties were reported [7–9]. They involve some strong electron-withdrawing substituent groups (Such as -NO_2, -CN, -CF_3) and great electron-donating substitutes (Such as -NHAc, -OMe, -CMe_3) resulting in improving antitumor and anti-inflammatory activity to different extent [10–12].

Changing one side of BAPs to 4-pyridine substituents, while on the other side of BAPs a 2-CF_3 group is added, asymmetric BAPs could be generated [8]. Our interests lie in incorporation of different substituent groups on the end of *N*-phenylsulfonyl substituent, and find the desired and improved antitumor and anti-inflammatory activities in contrast to symmetric derivatives.

Single-crystal structure analysis reveals that the title structure contains one drug molecule in the asymmetric unit (*cf*. the figure 1). Bond lengths and angles are all in the expected ranges. The central 3,5-bis(arylidene)-4-piperidone expand both sides in a linear fashion, and pyridyl and arylidene on both sides of central piperidone adopt the *E* stereochemistry [13, 14]. The dihedral angle between the mean planes of the pyridyl and central piperidone is 11.9(2)°, while the dihedral angle between the mean planes of the arylidene and central piperidone is 45.7(3)°. In addition, the *N*-phenylsulfonyl substituents are going to stretch in the direction of the carbonyl group of central piperidone. It looks like an “organic clip” [15]. The dihedral angle between *N*-phenylsulfonyl group and piperidone ring is 42.6(3)°.

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 used 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 52.19 ± 0.37%. The result showed that title compound displayed potential inhibitory effect on LPS-induced NO secretion than PDTC [8, 16, 17].

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