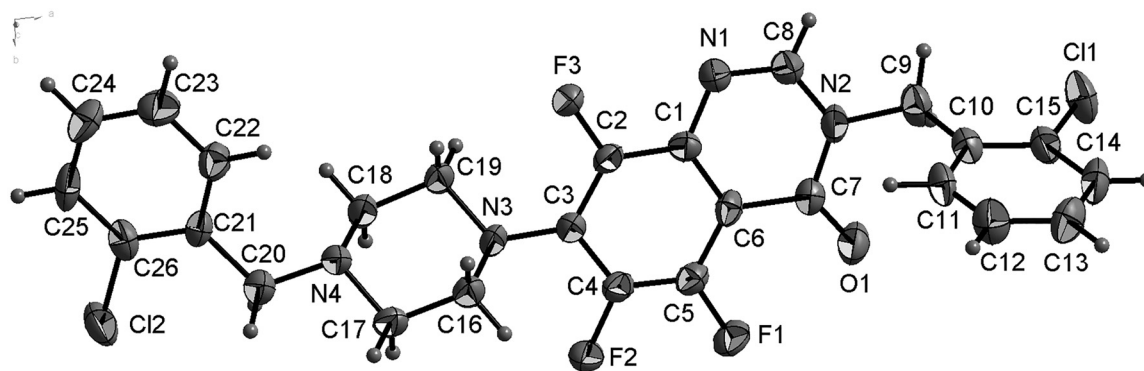


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Crystal structure of 3-(2-chloro-benzyl)-7-[4-(2-chloro-benzyl)-piperazin-1-yl]-5,6,8-trifluoro-3*H*-quinazolin-4-one, $C_{26}H_{21}Cl_2F_3N_4O$



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Abstract

$C_{26}H_{21}Cl_2F_3N_4O$, monoclinic, *Pc* (no. 7), $a = 21.218(6)$ Å, $b = 5.9599(16)$ Å, $c = 9.439(3)$ Å, $\beta = 99.295(3)^\circ$, $V = 1177.9(5)$ Å³, $Z = 2$, $R_{gt}(F) = 0.0471$, $wR_{ref}(F^2) = 0.1282$, $T = 296(2)$ K.

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Table 1: Data collection and handling.

Crystal:	Colourless plate
Size:	0.22 × 0.18 × 0.15 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.33 mm ⁻¹
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
θ_{max} , completeness:	25.5°, 99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int} :	4178, 4178,
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2 \sigma(I_{obs})$, 3955
$N(param)_{refined}$:	326
Programs:	Bruker [1], SHELX [2, 3], Diamond [4]

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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

To a stirred solution of 5,6,8-trifluoro-7-piperazin-1-yl-3*H*-quinazolin-4-one (28.42 g, 0.10 mol) in ethanol (140 mL) was in turn added 1-bromomethyl-2-chloro-benzene (41.10 g, 0.20 mol) and sodium hydroxide (8.00 g, 0.20 mol), and then the reaction mixture was refluxed for about 5 h. After the reaction was found to be completed (monitored by TLC), the ethanol was distilled under reduced pressure to give the

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	0.8915 (2)	0.6189 (9)	0.8761 (6)	0.0331 (12)
C2	0.8280 (3)	0.6519 (9)	0.8191 (6)	0.0331 (11)
C3	0.7920 (2)	0.8327 (9)	0.8544 (6)	0.0331 (12)
C4	0.8257 (3)	0.9890 (9)	0.9485 (7)	0.0365 (13)
C5	0.8876 (3)	0.9633 (9)	1.0078 (6)	0.0366 (12)
C6	0.9234 (2)	0.7797 (10)	0.9737 (6)	0.0326 (11)
C7	0.9902 (3)	0.7459 (10)	1.0329 (6)	0.0378 (13)
C8	0.9818 (3)	0.4122 (10)	0.8826 (7)	0.0429 (14)
H8	1.003084	0.288697	0.853046	0.051*
C9	1.0849 (3)	0.5096 (11)	1.0308 (7)	0.0469 (16)
H9A	1.094702	0.359616	1.000863	0.056*
H9B	1.092800	0.513333	1.134853	0.056*
C10	1.1286 (3)	0.6738 (10)	0.9749 (6)	0.0372 (12)
C11	1.1092 (3)	0.8280 (12)	0.8659 (7)	0.0461 (15)
H11	1.066613	0.829537	0.822217	0.055*
C12	1.1510 (3)	0.9779 (13)	0.8211 (8)	0.0535 (17)
H12	1.136445	1.080749	0.749089	0.064*
C13	1.2146 (3)	0.9760 (13)	0.8827 (8)	0.0555 (18)
H13	1.243109	1.077368	0.853046	0.067*
C14	1.2351 (3)	0.8227 (13)	0.9883 (8)	0.0519 (17)
H14	1.277901	0.819757	1.029972	0.062*
C15	1.1936 (3)	0.6746 (11)	1.0328 (7)	0.0426 (14)
C16	0.7070 (3)	1.0529 (9)	0.7135 (7)	0.0399 (13)
H16A	0.710846	1.011698	0.615798	0.048*
H16B	0.734426	1.181159	0.740717	0.048*
C17	0.6388 (3)	1.1135 (9)	0.7215 (7)	0.0407 (13)
H17A	0.635655	1.162891	0.817990	0.049*
H17B	0.625498	1.236448	0.656166	0.049*
C18	0.6175 (3)	0.7401 (10)	0.7851 (7)	0.0403 (13)
H18A	0.589203	0.612427	0.763563	0.048*
H18B	0.615031	0.789565	0.881969	0.048*
C19	0.6854 (3)	0.6704 (9)	0.7757 (8)	0.0454 (15)
H19A	0.698565	0.549429	0.842749	0.054*
H19B	0.688028	0.617717	0.679637	0.054*
C20	0.5302 (3)	0.9790 (10)	0.6826 (7)	0.0414 (14)
H20A	0.522113	1.126403	0.639999	0.050*
H20B	0.522287	0.987493	0.780903	0.050*
C21	0.4841 (2)	0.8151 (10)	0.6017 (6)	0.0343 (12)
C22	0.5035 (3)	0.6552 (11)	0.5107 (7)	0.0418 (13)
H22	0.546306	0.648783	0.500248	0.050*
C23	0.4610 (4)	0.5058 (12)	0.4354 (8)	0.0569 (18)
H23	0.475146	0.400080	0.375199	0.068*
C24	0.3971 (4)	0.5145 (13)	0.4503 (8)	0.0569 (19)
H24	0.368228	0.413652	0.400428	0.068*
C25	0.3765 (3)	0.6708 (12)	0.5380 (8)	0.0504 (16)
H25	0.333590	0.676770	0.547929	0.061*
C26	0.4193 (3)	0.8193 (10)	0.6117 (6)	0.0390 (13)
N1	0.9225 (2)	0.4344 (8)	0.8302 (6)	0.0385 (11)
N2	1.0166 (2)	0.5573 (8)	0.9795 (6)	0.0399 (11)
N3	0.7270 (2)	0.8641 (8)	0.8104 (6)	0.0401 (12)
N4	0.5969 (2)	0.9218 (8)	0.6840 (5)	0.0360 (10)
O1	1.0225 (2)	0.8669 (9)	1.1194 (5)	0.0544 (12)
Cl1	1.22141 (8)	0.4830 (4)	1.16859 (19)	0.0615 (5)
Cl2	0.39223 (8)	1.0155 (3)	0.72358 (19)	0.0603 (5)
F1	0.91514 (17)	1.1193 (7)	1.0997 (4)	0.0510 (10)

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
F2	0.79463 (16)	1.1701 (6)	0.9887 (4)	0.0493 (9)
F3	0.79970 (16)	0.5028 (6)	0.7220 (4)	0.0437 (8)

crude product. The crude product was poured into water (30 mL) and extracted with EtOAc (50 mL * 3). The EtOAc solvent was evaporated to provide the title compound as crystals suitable for X-ray diffraction analysis in 95.3% yield. ¹H NMR (400 MHz, CDCl₃) δ 2.44–2.468 (t, *J* = 4.8 Hz, 4 H, PhN(CH₂)₂), 3.230–3.254 (t, *J* = 4.8, Hz, 4 H, BnN(CH₂)₂), 3.476 (s, 2 H, NCH₂), 5.014 (s, 2 H, OCNCH₂), 6.987–7.298 (m, 8 H, PhH), 7.934 (s, 1 H, NCHN) ppm. ¹³C NMR (100 MHz, CDCl₃) δ = 156.30, 146.58, 133.77, 132.98, 131.80, 130.58, 130.22, 129.19, 128.84, 127.73, 126.69, 125.99, 101.28, 58.52, 52.67, 49.97, 46.74, 28.97 ppm.

Experimental details

All H atoms were included in calculated positions and refined as riding atoms, with O–H = 0.82 Å with *U*_{iso}(H) = 1.2 *U*_{eq}(O), C–H = 0.93–0.98 Å with *U*_{iso}(H) = 1.2–1.5 *U*_{eq}(C) [3].

Comment

KRAS mutations have been ubiquitous in human cancers [5]. Because of the missense mutation of KRAS at codon 12, the protein are aberrantly activated into a hyperexcitable state by attenuating its GTPase activity resulting in accretion of GTP-bound activated KRAS and activation of downstream signaling pathways [6–9]. KRAS p.G12C mutations are dominant in NSCLC and existent in 11–16% of lung adenocar-cinomas (45–50% of mutant KRAS is p.G12C), as well as 1–4% of pancreatic and colorectal adenocarcinomas respectively [10–13]. KRAS G12C was recently identified to be potentially druggable by allele-specific covalent targeting of Cys-12 in vicinity to an inducible allosteric switch II pocket (S–IIP). As accessibility of the S–IIP being restricted only to the GDP-bound state, the success of abovementioned approach requires active cycling of KRAS G12C between its active–GTP and inactive–GDP conformations [14]. The active cycling has been realized by these compounds, which possess a quinazoline core as a versatile lead scaffold following systematic optimization of substituent around the scaffold to achieve rapid and sustained *in vitro* and *in vivo* target occupancy to induce tumor regression [14, 15]. Recently, an impactful and high-yielding method for the

synthesis of quinazolines is developed in our group, and crystals of several key compounds have been achieved. Herein, the synthesis and crystal structure of a key compound 3-(2-chloro-benzyl)-7-(4-(2-chloro-benzyl)-piperazin-1-yl)-5,6,8-trifluoro-3*H*-quinazolin-4-one is disclosed.

There is one molecule in the asymmetric unit (shown in the figure). In the crystal structure of the title compound bond lengths and angles are very similar to those given in the literature for 3-benzyl-7-chloro-2-isobutylquinazolin-4(3*H*)-one [16].

The molecule consists of four moieties: quinoline, piperazin ring and two chlorobenzyl groups. The quinoline ring is connected to the nitrogen atom (N3) of piperazin ring. Two benzyls are connected to the nitrogen atom (N4) of piperazin ring and the nitrogen atom (N2) of the quinoline ring, respectively. The atoms of the quinoline and the two chlorobenzyl moieties are coplanar, and piperazin ring is in a typical chair configuration. The torsion angles of C21–C20–N4–C18 and C20–N4–C18–C19 are $76.6(6)^\circ$ and $175.3(5)^\circ$, respectively.

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