Rong-Kai Li, Chun-Hua Wang, Gui-Ge Hou and Cheng-Bo Li*

Crystal structure of 9-(2-chloroethoxy)-4-(4-methoxy-3-(trifluoromethyl)phenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine, $C_{22}H_{19}ClF_3N_3O_2$

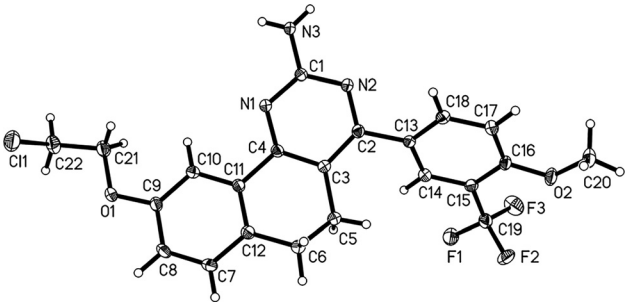

Table 1: Data collection and handling.

Crystal:	Green block
Size :	0.15 × 0.14 × 0.10 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.24 mm^{-1}
Diffractometer, scan mode:	SuperNova
θ_{max}, completeness:	29.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	7817, 4627, 0.022
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 3692
$N(param)_{refined}$:	289
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

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Abstract

$C_{22}H_{19}ClF_3N_3O_2$, triclinic, $P\bar{1}$ (no. 2), a = 9.8138(7) Å, b = 10.9739(7) Å, c = 11.6878(9) Å, α = 62.633(7)°, β = 67.095(7)°, γ = 68.817(6)°, V = 1003.78(14) Å^3, Z = 2, $R_{gt}(F)$ = 0.0454, w$R_{ref}(F^2)$ = 0.1158, T = 293 K.

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The crystal structure is shown in the figure. Displacement ellipsoids are drawn at the 35% probability level. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

Referring to known methods [4, 5], 7-(2-chloroethoxy)-3,4-dihydronaphthalen-1(2*H*)-one, was synthesized with succinic anhydride with the aid of Friedel–Crafts reaction, hydrazine hydrate discount, and dehydration condensation. Dissolve the intermediate (0.67 g, 3.0 mmol) and 4-methoxy-3-(trifluoromethyl)benzaldehyde (0.61 g, 3.0 mmol) in 10 mL of methanol and stir in an ice-salt bathtub at 268 K, then add 5 mL of 25% NaOH solution and stir for 30 min at room temperature. After filtration, the filter residue is directly used for the next reaction. Then, the filter residue, guanidine hydrochloride (1.33 g, 14.00 mmol) and potassium hydroxide (0.79 g, 14.00 mmol) were dissolved with 15 mL of absolute ethanol and 15 mL of 1, 2-dichloroethane. The reaction was monitored by thin-layer chromatography (TLC, petroleum ether:ethyl acetate = 8:1, v/v) after refluxing for 2.5 h at 363 K. The crude product hydrochloride was filtered, concentrated under reduced pressure, and then subjected to silica gel column chromatography (dichloromethane:methanol = 20:1, v/v). Finally, the crude product hydrochloride was dissolved with 20 mL of absolute ethanol, and 5 mL of ammonia was introduced drop by drop. After stirring for 3 h, the mixture was concentrated under reduced pressure. The residue was dissolved in a solution with 30 mL of methylene chloride and 15 mL of methanol and recrystallized at room temperature to get the title compound.

***Corresponding author: Cheng-Bo Li**, School of Pharmacy, The Key Laboratory of Prescription Effect and Clinical Evaluation of State Administration of Traditional Chinese Medicine of China, Binzhou Medical University, Yantai, 264003, P. R. China, E-mail: lichengbo@bzmc.edu.cn
Rong-Kai Li, Chun-Hua Wang and Gui-Ge Hou, School of Pharmacy, The Key Laboratory of Prescription Effect and Clinical Evaluation of State Administration of Traditional Chinese Medicine of China, Binzhou Medical University, Yantai, 264003, P. R. China. https://orcid.org/0000-0002-9493-3981 (G.-G. Hou)

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.8667 (2)	0.21441 (18)	1.00450 (16)	0.0185 (4)
C2	0.80976 (19)	0.26815 (18)	0.81204 (16)	0.0183 (4)
C3	0.7408 (2)	0.40652 (18)	0.80431 (16)	0.0190 (4)
C4	0.74371 (19)	0.43893 (18)	0.90630 (16)	0.0176 (3)
C5	0.6681 (2)	0.5203 (2)	0.69572 (18)	0.0261 (4)
H5A	0.635205	0.477206	0.657658	0.031*
H5B	0.742543	0.572368	0.625033	0.031*
C6	0.5331 (2)	0.62104 (19)	0.74914 (17)	0.0225 (4)
H6A	0.501114	0.701439	0.674660	0.027*
H6B	0.449382	0.574212	0.803560	0.027*
C7	0.4962 (2)	0.80384 (19)	0.83955 (17)	0.0218 (4)
H7	0.427037	0.864026	0.789789	0.026*
C8	0.5253 (2)	0.84683 (19)	0.92065 (17)	0.0225 (4)
H8	0.475132	0.934798	0.925823	0.027*
C9	0.6296 (2)	0.75805 (18)	0.99418 (16)	0.0205 (4)
C10	0.7029 (2)	0.62601 (18)	0.98889 (17)	0.0199 (4)
H10	0.772298	0.566693	1.038561	0.024*
C11	0.6715 (2)	0.58235 (18)	0.90777 (16)	0.0180 (4)
C12	0.5691 (2)	0.67143 (18)	0.83135 (16)	0.0189 (4)
C13	0.8173 (2)	0.21622 (18)	0.71182 (16)	0.0186 (4)
C14	0.8646 (2)	0.29219 (19)	0.57519 (17)	0.0205 (4)
H14	0.895340	0.374951	0.545889	0.025*
C15	0.8664 (2)	0.24580 (18)	0.48218 (17)	0.0201 (4)
C16	0.8194 (2)	0.12214 (19)	0.52508 (17)	0.0203 (4)
C17	0.7749 (2)	0.04470 (19)	0.66096 (17)	0.0220 (4)
H17	0.745148	−0.038687	0.690670	0.026*
C18	0.7749 (2)	0.09211 (19)	0.75237 (17)	0.0212 (4)
H18	0.745623	0.039117	0.843297	0.025*
C19	0.9123 (2)	0.3312 (2)	0.33596 (18)	0.0267 (4)
C20	0.7547 (2)	−0.0286 (2)	0.4673 (2)	0.0316 (5)
H20A	0.811140	−0.112979	0.520732	0.047*
H20B	0.758717	−0.039677	0.389111	0.047*
H20C	0.651041	−0.010868	0.518494	0.047*
C21	0.7581 (2)	0.7215 (2)	1.14599 (19)	0.0275 (4)
H21A	0.857986	0.700062	1.087696	0.033*
H21B	0.726238	0.633818	1.205866	0.033*
C22	0.7640 (2)	0.7944 (2)	1.2256 (2)	0.0313 (5)
H22A	0.774409	0.889969	1.167444	0.038*
H22B	0.852042	0.745611	1.260622	0.038*
Cl1	0.59680 (6)	0.79796 (6)	1.36069 (5)	0.03925 (16)
F1	0.95667 (15)	0.44491 (12)	0.31196 (10)	0.0339 (3)
F2	0.79864 (16)	0.37828 (13)	0.27954 (11)	0.0389 (3)
F3	1.02787 (16)	0.25873 (13)	0.26686 (11)	0.0440 (4)
H3A	0.932 (3)	0.142 (2)	1.160 (2)	0.033 (6)*
H3B	0.985 (3)	0.039 (3)	1.101 (2)	0.039 (7)*
N1	0.80815 (17)	0.34519 (15)	1.00443 (14)	0.0192 (3)
N2	0.87066 (17)	0.17029 (15)	0.91274 (13)	0.0190 (3)
N3	0.9257 (2)	0.11606 (18)	1.10729 (16)	0.0265 (4)
O1	0.65381 (16)	0.81141 (13)	1.06887 (13)	0.0260 (3)
O2	0.81910 (16)	0.08711 (14)	0.42774 (12)	0.0281 (3)

Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with *d*(C—H) = 0.96 Å (methyl), U_{iso}(H) = 1.5U_{eq}(C), *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

Some 3,4-dihydronaphthyl 1 (2*H*)-ketone (DHN) derivatives with antitumor and anti-inflammatory activities have been reported [6]. In order to optimize its water solubility and toxicity, 5,6-dihydrobenzo[*h*]quinazolin-2-amine (BQA) derivatives were obtained by condensation of DHN with guanidine hydrochloride [7]. Some fluoro- or trifluoromethyl-substituted benzo[*h*] quinazoline derivatives were synthesized and they showed excellent anti-neuroinflammatory effects. Recently, we just reported a BQA derivative, 9-bromo-4-(6-methoxypyridin-2-yl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine [8]. Herein, the raw material 6-methoxypicolinaldehyde was replaced by 4-methoxy-3-(trifluoromethyl)benzaldehyde, while the 9-bromo substituent group is replaced by the 2-chloroethoxy group.

Single-crystal structure analysis reveals that there is one BQA molecule in the asymmetric unit (*cf*. Figure 1). Bond lengths and angles are all in the expected ranges [8–12]. Under the pull of the two methyl groups, –C(5)–C(6)-, the (2-chloroethoxy)phenyl ring has better coplanarity with the central pyrimidine ring, whose dihedral angle is only 17.15(3)°. Due to the space effect of the title compound, the 4-methoxy-3-(trifluoromethyl)phenyl ring is not coplanar with the central pyrimidine ring, with the dihedral angle of about 47.86(3)°. The twisted configuration is similar to that of reported BQA compound (50.83(8)°) [8]. In title compound, the 9-substituent is 2-chloroethoxy group, which torsion angle of O(1)–C(21)–C(22)–Cl(1) is 73.47(19)°. Compared with DHN derivatives [9, 10], the substituents in BQA derivatives are more comprehensive. There are $–NH_2$, $–CF_3$, –OMe, –Cl groups as hydrogen bond acceptor and donor, which are easy to extend through hydrogen bonding to form three-dimensional structures [12].

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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