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Crystal structure of 2-amino-4-(2-fluoro-3-(trifluoromethyl)phenyl)-9-methoxy-1,4,5,6-tetrahydrobenzo[*h*]quinazolin-3-ium chloride, C₂₀H₁₈ClF₄N₃O

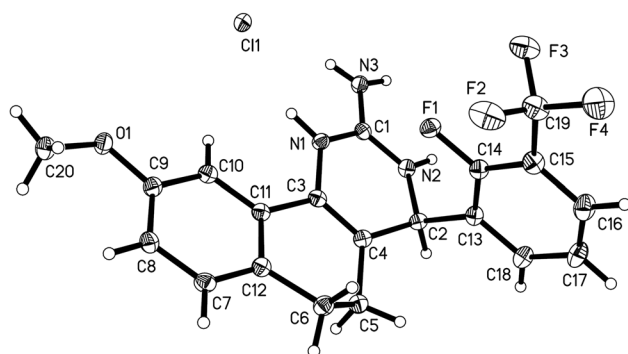


Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.15 × 0.14 × 0.12 mm
Wavelength:	Cu Kα radiation (1.54178 Å)
μ:	2.27 mm ⁻¹
Diffractometer, scan mode:	XtaLAB AFC12 (RINC)
θ _{max} , completeness:	73.9°, >99 %
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} , <i>R</i> _{int} :	15,274, 3805, 0.054
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2 σ(<i>I</i> _{obs}), 3361
<i>N</i> (<i>param</i>) _{refined} :	267
Programs:	CrysAlis ^{PRO} [1], SHELX [2, 3]

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Abstract

C₂₀H₁₈ClF₄N₃O, orthorhombic, *Pbca* (no. 61), *a* = 12.5254(4) Å, *b* = 12.6845(5) Å, *c* = 24.1490(11) Å, *V* = 3836.8(3) Å³, *Z* = 8, *R*_{gt}(*F*) = 0.0485, *wR*_{ref}(*F*²) = 0.1343, *T* = 293 K.

CCDC no.: 2272279

The crystal structure is shown in the Figure. Displacement ellipsoids are drawn at the 30 % probability level.

Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

1 Source of material

Based on literature synthetic techniques [4, 5], using 20 % sodium hydroxide solution (5.0 mL) as a catalyst, 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (0.70 g, 4.00 mmol) was

mixed with 2-fluoro-3-(trifluoromethyl)benzaldehyde (0.77 g, 4.00 mmol) in 25 mL of methanol with stirring for 3 h at room temperature to produce a yellow precipitate. Filtration gave an intermediate: (*E*)-2-(2-fluoro-3-(trifluoromethyl)benzylidene)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. The intermediate (0.830 g, 2.37 mmol), guanidine hydrochloride (1.58 g, 16.59 mmol) and potassium hydroxide (0.931 g, 16.59 mmol) were added to a mixture of anhydrous ethanol (10 mL) and dichloroethane (10 mL), and the reaction was carried out at 90 °C for 2 h. The reaction was monitored by Thin-Layer Chromatography (TLC, PE:EA = 8:1, v/v). The filtered filtrate is depressurized to remove the solvent. Dichloromethane/methanol (20:1, v/v) was used as eluent to separate and purify by the silica gel column. The obtained product was dissolved in a solution of dichloromethane (5 mL) and methanol (5 mL), and slowly evaporated at room temperature to achieve appropriate yellow crystals.

2 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) = 1.5*U*_{eq}(C), and *d*(C–H) = 0.97 Å (methylene), *U*_{iso}(H) = 1.2*U*_{eq}(C), and *d*(C–H) = 0.98 Å (methyne), *U*_{iso}(H) = 1.2*U*_{eq}(C), and *d*(C–H) = 0.93 Å (aromatic), *U*_{iso}(H) = 1.2*U*_{eq}(C). H atoms on N atom were located in different maps and treated as riding.

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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	0.30840 (16)	0.12858 (17)	0.96703 (8)	0.0246 (4)
C2	0.23258 (17)	−0.03005 (17)	0.92281 (9)	0.0254 (4)
H2	0.196956	−0.087685	0.942537	0.031*
C3	0.42679 (17)	0.00620 (16)	0.92360 (8)	0.0242 (4)
C4	0.34727 (17)	−0.06157 (17)	0.91374 (8)	0.0255 (4)
C5	0.37032 (17)	−0.17070 (18)	0.89178 (9)	0.0288 (5)
H5A	0.307908	−0.197654	0.872669	0.035*
H5B	0.386304	−0.217742	0.922342	0.035*
C6	0.46457 (17)	−0.16732 (19)	0.85214 (10)	0.0300 (5)
H6A	0.486494	−0.238748	0.843386	0.036*
H6B	0.442855	−0.133391	0.817949	0.036*
C7	0.66270 (18)	−0.13206 (18)	0.86310 (10)	0.0303 (5)
H7	0.676359	−0.191188	0.841456	0.036*
C8	0.74780 (17)	−0.07028 (18)	0.88084 (9)	0.0295 (5)
H8	0.817419	−0.088135	0.871275	0.035*
C9	0.72789 (17)	0.01795 (18)	0.91283 (9)	0.0272 (5)
C10	0.62408 (17)	0.04198 (17)	0.92874 (9)	0.0267 (4)
H10	0.611432	0.099480	0.951717	0.032*
C11	0.53901 (16)	−0.01928 (17)	0.91057 (8)	0.0243 (4)
C12	0.55823 (17)	−0.10792 (18)	0.87679 (9)	0.0270 (4)
C13	0.17654 (16)	−0.01599 (18)	0.86689 (9)	0.0262 (4)
C14	0.20727 (17)	0.06165 (17)	0.82983 (9)	0.0269 (5)
C15	0.16062 (19)	0.07353 (19)	0.77779 (9)	0.0330 (5)
C16	0.0802 (2)	0.0040 (2)	0.76248 (10)	0.0407 (6)
H16	0.047463	0.010721	0.728103	0.049*
C17	0.0488 (2)	−0.0752 (2)	0.79826 (11)	0.0405 (6)
H17	−0.004475	−0.122119	0.787646	0.049*
C18	0.09643 (18)	−0.0851 (2)	0.85013 (9)	0.0326 (5)
H18	0.074436	−0.138563	0.873875	0.039*
C19	0.2015 (2)	0.1571 (2)	0.73930 (10)	0.0400 (6)
C20	0.90917 (17)	0.07421 (19)	0.90861 (10)	0.0318 (5)
H20A	0.939270	0.008785	0.921084	0.048*
H20B	0.953645	0.131551	0.920490	0.048*
H20C	0.904789	0.074016	0.868927	0.048*
Cl1	0.53974 (4)	0.31046 (4)	0.97499 (2)	0.02830 (16)
F1	0.28703 (10)	0.12832 (10)	0.84377 (5)	0.0310 (3)
F2	0.30268 (14)	0.13926 (13)	0.72382 (7)	0.0561 (5)
F3	0.20003 (13)	0.25397 (12)	0.76144 (6)	0.0452 (4)
F4	0.14390 (17)	0.16261 (15)	0.69268 (6)	0.0643 (5)
N1	0.40529 (14)	0.10538 (14)	0.94739 (7)	0.0251 (4)
H1A	0.458166	0.152892	0.953256	0.033 (7)*
N2	0.22689 (14)	0.06415 (14)	0.95774 (7)	0.0261 (4)
H2A	0.164557	0.082781	0.970729	0.031 (7)*
N3	0.29398 (14)	0.21691 (15)	0.99561 (8)	0.0279 (4)
H3A	0.347756	0.251484	1.003201	0.045 (8)*
H3B	0.229409	0.229185	1.008687	0.042 (8)*
O1	0.80455 (12)	0.08656 (13)	0.93148 (7)	0.0316 (4)

3 Comment

3,4-Dihydronaphthalene-1(2*H*)-one derivatives have been used in previous studies as formulations and inhibitors of

novel anti-allergic, anti-inflammatory drugs and retinoic acid metabolic enzymes [6]. It contains two pharmacophores: 3,4-dihydronaphthalene-1(2*H*)-one and an α,β -unsaturated token. These two pharmacophores can be used as the main binding sites [4]. The 1,4,5,6-tetrahydrobenzo[*h*]quinazoline-2-amine skeleton structure formed by the condensation of α,β -unsaturated ketones with guanidinium chloride that can effectively improve the water solubility [7]. The substitution of the trifluoromethyl group can transform the substituent into a powerful electron-withdrawing group, which can slightly increase lipophilicity [8]. In this study, the Claisen–Schmidt reaction of 7-methoxy-3,4-dihydronaphthalene-1(2*H*)-one with 2-fluoro-3-(trifluoromethyl)benzaldehyde to form the intermediate (*E*)-2-(2-fluoro-3-(trifluoromethyl)benzylidene)-7-methoxy-3,4-dihydronaphthalene-1(2*H*)-one was investigated. The target product: 4-(2-fluoro-4-(trifluoromethyl)phenyl)-9-methoxy-1,4,5,6-tetrahydrobenzo[*h*]quinazolin-2-amine was obtained by the condensation of the intermediate with guanidinium chloride hydrochloride.

Single crystals were obtained by evaporation from dichloromethane/methanol solution at room temperature. The single crystal structure analysis shows that 2-fluoro-4-(trifluoromethyl)phenyl and carbonyl groups adopt *E* stereochemistry. There is a chiral C(2) atom at the bridgehead position of 1,4,5,6-tetrahydrobenzo[*h*]quinazoline-2-amine. In the solid state, the molecules crystallize in an orthorhombic group *Pbca*, and the whole does not show chiral properties. However, the crystal generates two isomers, which one is the *S* configuration and the other is the *R* configuration [9]. The benzene ring at C(2) atom is substituted by electron-withdrawing substituents (−F and −CF₃). Because of the chiral structural characteristics and the substituent effect, there is a large dihedral angle between the central parent nucleus and the substituted benzene ring, with the dihedral angle of about 84.98(3)°. This twisting structure may increase the possibility of interaction with bioactive molecules [10]. In addition, the pyrimidine ring is non-aromatic ring, which is different from aromatic pyrimidine ring in 5,6-dihydrobenzo[*h*]quinazolin-2-amine derivatives [11, 12]. In this study, the non-aromatic pyrimidine ring has different bond lengths, *i.e.* bond lengths of C(1)–N(1), C(1)–N(2), C(2)–N(2), C(2)–C(4), C(3)–C(4), C(3)–N(1) are 1.336(3), 1.327(3), 1.464(3), 1.507(3), 1.337(3) and 1.409(3) Å, respectively. Interestingly, 1,4,5,6-tetrahydro-benzo[*h*]quinazoline-2-amine has a positive charge and forms a stable structure with a chloride ion [13, 14]. The chloride ion, as a hydrogen-bond acceptor, was stabilized by three groups of hydrogen bonds, *viz.* N(1)–H(1A)⋯Cl(1), N(3)–H(3A)⋯Cl(1) and C(10)–H(10)⋯Cl(1) bonds.

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

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