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## Key indicators

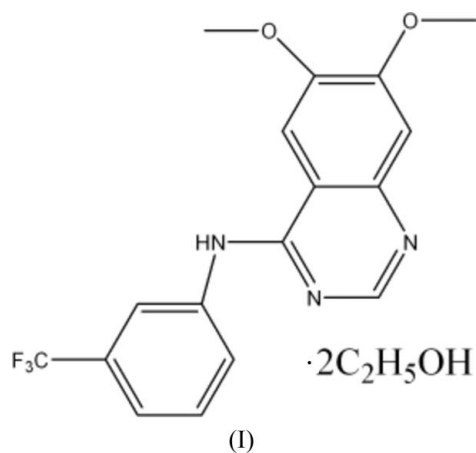
Single-crystal X-ray study  
 $T = 293$  K  
Mean  $\sigma(\text{C}-\text{C}) = 0.004$  Å  
Disorder in main residue  
 $R$  factor = 0.063  
 $wR$  factor = 0.186  
Data-to-parameter ratio = 12.5For details of how these key indicators were  
automatically derived from the article, see  
<http://journals.iucr.org/e>.6,7-Dimethoxy-*N*-[3-(trifluoromethyl)phenyl]-  
quinazolin-4-amine ethanol disolvate

The title compound,  $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2 \cdot 2\text{C}_2\text{H}_5\text{OH}$ , was synthesized by the reaction of 4-chloro-6,7-dimethoxyquinazoline and 3-(trifluoromethyl)aniline at 580 W in a domestic microwave oven and obtained in 93% yield. The bond lengths and angles are normal. Intermolecular  $\text{N}-\text{H} \cdots \text{O}$ ,  $\text{O}-\text{H} \cdots \text{N}$  and  $\text{O}-\text{H} \cdots \text{O}$  hydrogen bonds and  $\pi-\pi$  stacking interactions between the quinazoline rings of neighbouring molecules stabilize the crystal packing.

Received 30 August 2005  
Accepted 16 September 2005  
Online 21 September 2005

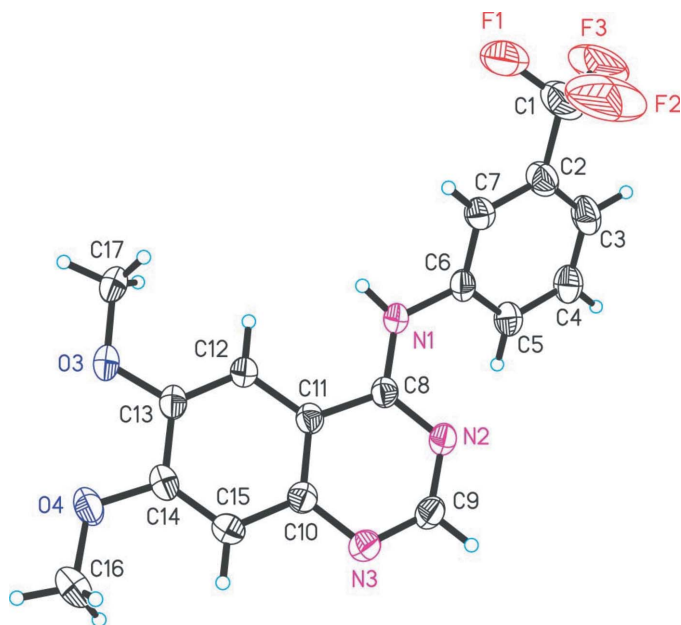
## Comment

Recently, epidermal growth factor receptor (EGFR) has become one of the significant target proteins in medicinal developments (Arteaga, 2002), since its excess always leads to a variety of vicious tumours and cancers. Among the small molecular inhibitors of EGFR, 4-anilinoquinazoline derivatives are clinically confirmed to be among the most effective compounds (Hou *et al.*, 2002). The results of quantitative structure–activity relationship research indicate that electron-donating groups at the 6,7-positions will improve their degree of EGFR inhibition (Bridges *et al.*, 1996). We report here the synthesis and crystal structure of the title compound, (I).



In compound (I) (Fig. 1), the bond lengths and angles are normal (Table 1); two ethanol solvent molecules complete the asymmetric unit. The quinazoline system and non-fused benzene ring make a dihedral angle of  $43.2(1)^\circ$ . Interestingly, atoms N1, C6, C8 and H3 are almost coplanar, with an r.m.s. deviation of  $0.026(8)$  Å, in spite of steric hindrance between the quinazoline system and the non-fused benzene ring.

The solvent molecules play an important role in the crystal formation, participating in a number of hydrogen bonds with the quinazolin-4-amine molecules (Table 2). These hydrogen bonds stabilize the crystal packing (Fig. 2), along with  $\pi-\pi$



**Figure 1**  
View of (I), showing the atom-labelling scheme and displacement ellipsoids at the 40% probability level. The two ethanol solvent molecules and the minor component of the disordered  $\text{CF}_3$  group have been omitted for clarity. H atoms are represented by circles of arbitrary size.

stacking interactions between the quinazoline rings of neighbouring molecules; the interplanar distance to the symmetry-related molecule at  $(1 - x, 2 - y, 2 - z)$  is 3.356 (8) Å.

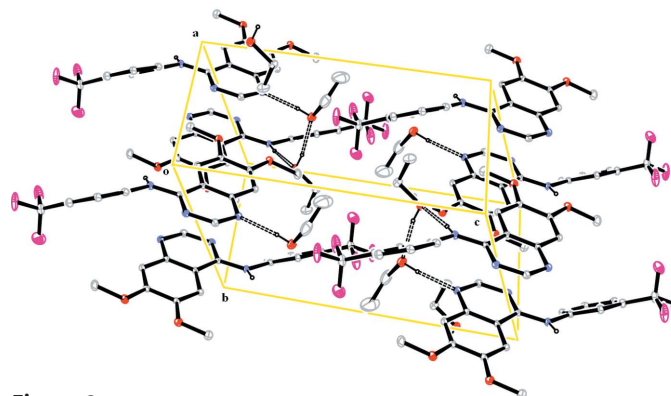
## Experimental

At room temperature, basic alumina (2 g) was added to a solution of 4-chloro-6,7-dimethoxyquinazoline (1 mmol) and 3-(trifluoromethyl)aniline (1 mmol) in diethyl ether (10 ml). After removal of the ether, the solid was poured into an open vessel and irradiated for 3 min at 580 W in a domestic microwave oven. After cooling to room temperature, ethanol (15 ml) was added and the filtrate was concentrated on a rotary evaporator. The residue was isolated by silica column chromatography with  $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$  (5:3 *v/v*) as the eluent in 93% yield. Suitable crystals were obtained by evaporation of an ethanol-water (1:1 *v/v*) mixed solution (m.p. 442–443 K).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  4.01(*s*, 3H), 4.03(*s*, 3H), 7.08 (*s*, 1H), 7.27 (*d*, 1H,  $J = 7.5$  Hz), 7.38–7.50 (*m*, 2H), 7.51 (*t*, 1H,  $J = 8.0$  Hz), 8.70 (*s*, 1H). IR (KBr,  $\nu$   $\text{cm}^{-1}$ ): 3448, 2925, 2851, 1625, 1584, 1516, 1449, 1332, 1242, 1166, 1123, 1069, 993, 793, 700. Analysis calculated for  $\text{C}_{21}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_4$ : C 57.14, H 5.94, N 9.52%; found C 57.39, H 5.78, N 9.67%.

### Crystal data

$\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2 \cdot 2\text{C}_2\text{H}_6\text{O}$   
 $M_r = 441.45$   
 Triclinic,  $P\bar{1}$   
 $a = 8.7035$  (7) Å  
 $b = 9.7426$  (8) Å  
 $c = 14.5212$  (9) Å  
 $\alpha = 70.652$  (4)°  
 $\beta = 89.493$  (1)°  
 $\gamma = 77.484$  (3)°  
 $V = 1131.52$  (15) Å<sup>3</sup>

$Z = 2$   
 $D_x = 1.296$  Mg m<sup>-3</sup>  
 Mo  $K\alpha$  radiation  
 Cell parameters from 4851 reflections  
 $\theta = 2.3\text{--}27.4^\circ$   
 $\mu = 0.11$  mm<sup>-1</sup>  
 $T = 293$  (2) K  
 Prism, colourless  
 $0.48 \times 0.35 \times 0.30$  mm



**Figure 2**  
The molecular packing, showing the hydrogen-bonding interactions (dashed lines). C-bound H atoms have been omitted for clarity.

### Data collection

Rigaku R-Axis RAPID  
 diffractometer  
 $\omega$  scans  
 Absorption correction: multi-scan  
 (ABSCOR; Higashi, 1995)  
 $T_{\text{min}} = 0.956$ ,  $T_{\text{max}} = 0.969$   
 8371 measured reflections

3972 independent reflections  
 3264 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.058$   
 $\theta_{\text{max}} = 25.2^\circ$   
 $h = -10 \rightarrow 10$   
 $k = -11 \rightarrow 11$   
 $l = -17 \rightarrow 17$

### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.063$   
 $wR(F^2) = 0.186$   
 $S = 1.08$   
 3972 reflections  
 318 parameters  
 H atoms treated by a mixture of  
 independent and constrained  
 refinement

$w = 1/[\sigma^2(F_o^2) + (0.0909P)^2 + 0.4785P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\text{max}} = 0.001$   
 $\Delta\rho_{\text{max}} = 0.48$  e Å<sup>-3</sup>  
 $\Delta\rho_{\text{min}} = -0.44$  e Å<sup>-3</sup>  
 Extinction correction: SHELXL97  
 Extinction coefficient: 0.028 (5)

**Table 1**

Selected geometric parameters (Å, °).

F1—C1	1.282 (6)	N1—H3	0.86 (3)
F2—C1	1.320 (7)	N2—C8	1.328 (3)
F3—C1	1.307 (6)	N2—C9	1.341 (3)
N1—C8	1.362 (3)	N3—C9	1.319 (3)
N1—C6	1.409 (3)	N3—C10	1.371 (3)
C13—O3—C17	116.34 (17)	C9—N3—C10	115.86 (19)
C14—O4—C16	117.31 (19)	F1—C1—C2	114.1 (3)
C8—N1—C6	126.92 (18)	F3—C1—C2	113.4 (4)
C8—N1—H3	119.6 (16)	F2—C1—C2	111.1 (4)
C6—N1—H3	112.5 (16)		

**Table 2**

Hydrogen-bond geometry (Å, °).

$D\text{—}H\cdots A$	$D\text{—}H$	$H\cdots A$	$D\cdots A$	$D\text{—}H\cdots A$
N1—H3 $\cdots$ O1	0.86 (3)	2.12 (3)	2.965 (3)	169 (2)
O2—H2 $\cdots$ N3 <sup>i</sup>	0.82	1.93	2.745 (3)	173
O1—H1 $\cdots$ O2 <sup>ii</sup>	0.82	1.90	2.690 (3)	162

Symmetry codes: (i)  $-x + 1, -y + 1, -z + 2$ ; (ii)  $x, y + 1, z$ .

All H atoms were initially located in a difference Fourier map. All methyl H atoms were then constrained to an ideal geometry, with

C—H distances of 0.96 Å and  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ , but each group was allowed to rotate freely about the C—C bond. The aromatic and hydroxyl H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H = 0.93 Å, O—H = 0.82 Å, and  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$  or  $1.5U_{\text{eq}}(\text{O})$ . The amine H atom was refined isotropically. The  $\text{CF}_3$  group is disordered and the major and minor orientations have refined occupancies of 0.70 (1) and 0.30 (1), respectively. The atomic displacement parameters of one ethanol solvent molecule (O2/C20/C21) are significantly higher than those of the other solvent molecule, indicating a possible partial disorder of the former residue.

Data collection: *RAPID-AUTO* (Rigaku, 1998); cell refinement: *RAPID-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC, 2002); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

We are grateful for financial support from the Analysis and Determination Fund of Zhejiang Province (04103)

## References

- Arteaga, C. L. (2002). *Oncologist*, **7** (Suppl. 4), 31–39.
- Bridges, A. J., Zhou, H., Cody, D. R., Rewcastle, G. W., McMichael, A., Showalter, H. D. H., Fry, D. W., Kraker, A. J. & Denny, W. A. (1996). *J. Med. Chem.* **39**, 267–276.
- Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
- Higashi, T. (1995). *ABSCOR*. Rigaku Corporation, Tokyo, Japan.
- Hou, T. J., Zhu, L. L., Chen, L. R. & Xu, X. J. (2002). *Acta Chim. Sinica*, **60**, 1023–1028.
- Rigaku (1998). *RAPID-AUTO*. Rigaku Corporation, Tokyo, Japan.
- Rigaku/MSC (2002). *CrystalStructure*. Rigaku/MSC, 9009 New Trails Drive, The Woodlands, TX 77381-5209, USA.
- Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.