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# 2,4-Dichloro-7-fluoroquinazoline

**Feng Gao,* Yun-Fei Hu and Jin-Long Wang**

Department of Chinese Traditional Herbs, Agromomy College, Sichuan Agricultural University, Chengdu 611130, People's Republic of China
Correspondence e-mail: gaofeng@sicau.edu.cn

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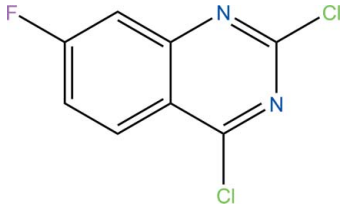
Key indicators: single-crystal X-ray study; $T$ = 293 K; mean $\sigma$(C–C) = 0.003 Å; $R$ factor = 0.038; $wR$ factor = 0.095; data-to-parameter ratio = 12.3.

The molecule of the title compound, $C_8H_3Cl_2FN_2$, is essentially planar, with a maximum deviation of 0.018 (2) Å. In the crystal, $\pi$–$\pi$ stacking is observed between parallel quinazoline moieties of adjacent molecules, the centroid–centroid distance being 3.8476 (14) Å.

## Related literature

For the synthesis of quinazoline derivatives, see: Roberts *et al.* (2011); Gao *et al.* (2010); Li *et al.* (2009); Connolly *et al.* (2005). For the pharmacological properties of quinazoline analogues, see: Koller *et al.* (2011); Garofalo *et al.* (2011); Yang *et al.* (2011). For related structures, see: Jia *et al.* (2011); Ouahrouch *et al.* (2011).




## Experimental

### Crystal data

$C_8H_3Cl_2FN_2$
$M_r$ = 217.02
Monoclinic, $P2_1/n$
$a$ = 3.8257 (3) Å
$b$ = 15.0664 (9) Å
$c$ = 14.3453 (6) Å
$\beta$ = 95.102 (5)°
$V$ = 823.59 (9) Å$^3$
$Z$ = 4
Mo $K\alpha$ radiation
$\mu$ = 0.75 mm$^{-1}$
$T$ = 293 K
0.35 × 0.30 × 0.25 mm

### Data collection

Agilent Xcalibur Eos diffractometer
Absorption correction: multi-scan (*CrysAlis PRO*; Agilent, 2010)
$T_{min}$ = 0.780, $T_{max}$ = 0.835
3156 measured reflections
1452 independent reflections
1120 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.025

### Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.095
$S$ = 1.07
1452 reflections
118 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.20 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.23 e Å$^{-3}$

Data collection: *CrysAlis PRO* (Agilent, 2010); cell refinement: *CrysAlis PRO*; data reduction: *CrysAlis PRO*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: XU5446).

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# supporting information

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## 2,4-Dichloro-7-fluoroquinazoline

**Feng Gao, Yun-Fei Hu and Jin-Long Wang**

### S1. Comment

As the important six-membered heterocycles, quinazoline derivatives have always drawn the attention of organic and medicinal chemists for their various biological activities and significant synthetic materials. Several quinazoline-containing compounds have been approved by FDA, such as EGFR inhibitors Iressa and Tarceva used in the treatment of cancer, as well as alpha adrenergic receptor antagonists Praosin and Alfuzosine, which have been used for anti-hypertensive drugs in clinic. In addition, quinazoline derivatives also have been reported as anti-inflammatory, antibacterial or anticonvulsant agents. Most recently, quinazoline analogues have been found as selective VEGFR-2 receptor tyrosine kinase inhibitors, novel heat shock protein 90 inhibitors, EGFR Tyrosine kinase inhibitors, as well as glucocerebrosidase inhibitors.

### S2. Experimental

2,4-Dichloro-7-fluoroquinazoline was synthesized presently through two steps reactions implying 2-amino-4-fluoro-benzoic acid as the starting material: 1. Acetic acid (80 ml) was added to a suspension of **2-amino-4-fluorobenzoic acid** (100 g, 0.645 mol) in water (2*L*), a solution of NaOCN (105 g, 1.616 mol) in water (800 ml) was added dropwise under vigorous stirring with a mechanical stirrer. The reaction mixture was stirred at room temperature for 30 min, and NaOH (480 g, 12 mol) was added in small portions, and the mixture was cooled to room temperature. Then concentrated HCl (~1.2*L*) was added dropwise to the reaction mixture to attain pH ~4 (strong foaming!). The formed precipitate was separated by filtration, washed with water, and air-dried to give compound **7-fluoroquinazoline-2,4(1*H*,3*H*)-dione** (yield 82%, 95 g). It was used in the next step without any purification. 2. A mixture of compound **7-fluoro-quinazoline-2,4(1*H*,3*H*)-dione** (150 g, 0.83 mol), *N*,*N*-diethylaniline (125 g, 0.84 mol), and $POCl_3$ (500 ml) was refluxed for overnight. Most of $POCl_3$ was removed by rotary vapor. The residue was poured into the mixture water/ice (~4*L*), and the formed precipitate was separated by filtration, washed with water, and vacuum-dried to give compound **2,4-di-chloro-7-fluoroquinazoline** (yield 94%, 170 g). Single crystals of 2,4-dichloro-7-fluoroquinazoline, $C_8H_3Cl_2FN_2$, were recrystallized from acetone, mounted in inert oil and transferred to the cold gas stream of the diffractometer.

### S3. Refinement

H atoms were placed in calculated positions and treated as riding atoms [C—H = 0.93–0.96 Å], with $U_{iso}$(H) = 1.5$U_{eq}$(C) for methyl H atoms and 1.2$U_{eq}$(C) for others.

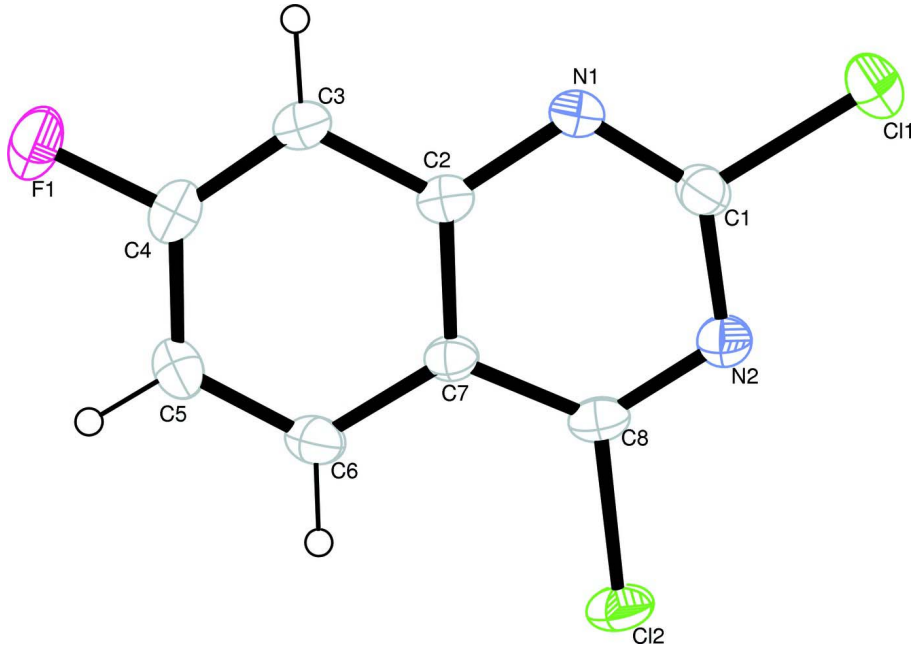


**Figure 1**

Molecular structure of showing 30% probability displacement ellipsoids.

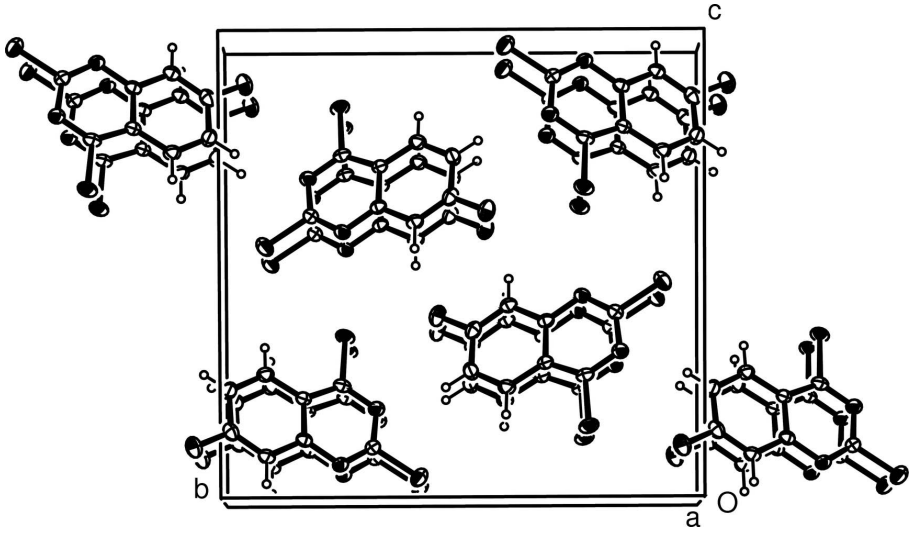


**Figure 2**

The packing viewed along *c* axis with $\pi\cdots\pi$ interactions, indicating the dimer.

### 2,4-Dichloro-7-fluoroquinazoline

*Crystal data*

$C_8H_3Cl_2FN_2$
$M_r = 217.02$
Monoclinic, $P2_1/n$
$a = 3.8257\ (3)$ Å
$b = 15.0664\ (9)$ Å
$c = 14.3453\ (6)$ Å
$\beta = 95.102\ (5)°$
$V = 823.59\ (9)$ Å$^3$
$Z = 4$
$F(000) = 432$
$D_x = 1.750$ Mg m$^{-3}$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 1033 reflections
$\theta = 3.0–25.0°$

$\mu$ = 0.75 mm$^{-1}$
$T$ = 293 K

Block, brown
0.35 × 0.30 × 0.25 mm

*Data collection*

Agilent Xcalibur Eos diffractometer
Radiation source: Enhance (Mo) X-ray Source
Graphite monochromator
Detector resolution: 10.0 pixels mm$^{-1}$
$\omega$ scans
Absorption correction: multi-scan (*CrysAlis PRO*; Agilent, 2010)
$T_{min}$ = 0.780, $T_{max}$ = 0.835

3156 measured reflections
1452 independent reflections
1120 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.025
$\theta_{max}$ = 25.0°, $\theta_{min}$ = 3.1°
$h$ = −4→4
$k$ = −15→17
$l$ = −16→16

*Refinement*

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.095
$S$ = 1.07
1452 reflections
118 parameters
0 restraints
Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0389P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.20 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.23 e Å$^{-3}$

*Special details*

**Geometry**. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

**Refinement**. Refinement of $F^2$ against ALL reflections. The weighted $R$-factor $wR$ and goodness of fit $S$ are based on $F^2$, conventional $R$-factors $R$ are based on $F$, with $F$ set to zero for negative $F^2$. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating $R$-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. $R$-factors based on $F^2$ are statistically about twice as large as those based on $F$, and $R$- factors based on ALL data will be even larger.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$)*

| | $x$ | $y$ | $z$ | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| Cl1 | 0.18763 (19) | 0.24582 (4) | 0.86579 (4) | 0.0500 (3) |
| Cl2 | 0.2734 (2) | 0.09054 (5) | 0.54819 (5) | 0.0628 (3) |
| F1 | 0.8584 (4) | 0.55046 (10) | 0.60324 (11) | 0.0652 (5) |
| N1 | 0.2491 (5) | 0.17987 (14) | 0.70176 (14) | 0.0416 (5) |
| N2 | 0.4812 (5) | 0.25290 (13) | 0.57255 (14) | 0.0389 (5) |
| C1 | 0.3448 (6) | 0.18701 (17) | 0.61375 (17) | 0.0392 (6) |
| C2 | 0.3050 (6) | 0.25134 (16) | 0.75263 (17) | 0.0360 (6) |
| C3 | 0.4494 (6) | 0.33043 (16) | 0.72000 (16) | 0.0331 (6) |
| C4 | 0.5323 (6) | 0.32793 (16) | 0.62626 (16) | 0.0327 (6) |
| C5 | 0.6758 (7) | 0.40354 (16) | 0.58670 (16) | 0.0389 (6) |
| H5 | 0.7365 | 0.4030 | 0.5253 | 0.047* |
| C6 | 0.7228 (7) | 0.47677 (17) | 0.64004 (19) | 0.0428 (7) |
| C7 | 0.6403 (7) | 0.48233 (17) | 0.73259 (19) | 0.0455 (7) |

| | | | | |
|---|---|---|---|---|
| H7 | 0.6783 | 0.5346 | 0.7665 | 0.055* |
| C8 | 0.5030 (7) | 0.40973 (16) | 0.77230 (17) | 0.0426 (7) |
| H8 | 0.4443 | 0.4122 | 0.8338 | 0.051* |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| Cl1 | 0.0595 (5) | 0.0612 (5) | 0.0313 (4) | 0.0047 (4) | 0.0158 (3) | 0.0092 (3) |
| Cl2 | 0.0870 (6) | 0.0476 (5) | 0.0541 (5) | −0.0111 (4) | 0.0086 (4) | −0.0150 (4) |
| F1 | 0.0783 (13) | 0.0466 (10) | 0.0717 (12) | −0.0159 (9) | 0.0123 (10) | 0.0132 (9) |
| N1 | 0.0454 (14) | 0.0428 (13) | 0.0367 (12) | −0.0035 (11) | 0.0043 (10) | 0.0014 (11) |
| N2 | 0.0455 (13) | 0.0404 (13) | 0.0314 (11) | −0.0004 (11) | 0.0074 (10) | −0.0032 (10) |
| C1 | 0.0433 (16) | 0.0373 (15) | 0.0369 (14) | 0.0015 (13) | 0.0029 (12) | −0.0033 (12) |
| C2 | 0.0330 (14) | 0.0469 (16) | 0.0285 (12) | 0.0071 (12) | 0.0045 (11) | 0.0052 (12) |
| C3 | 0.0320 (14) | 0.0385 (14) | 0.0286 (12) | 0.0057 (12) | 0.0022 (11) | 0.0039 (11) |
| C4 | 0.0301 (14) | 0.0365 (14) | 0.0315 (13) | 0.0033 (12) | 0.0019 (11) | 0.0037 (11) |
| C5 | 0.0427 (16) | 0.0437 (16) | 0.0311 (13) | 0.0022 (13) | 0.0074 (12) | 0.0037 (12) |
| C6 | 0.0389 (15) | 0.0397 (16) | 0.0493 (16) | −0.0033 (13) | 0.0008 (13) | 0.0123 (14) |
| C7 | 0.0504 (17) | 0.0370 (15) | 0.0485 (16) | 0.0004 (13) | 0.0013 (13) | −0.0069 (13) |
| C8 | 0.0469 (17) | 0.0478 (16) | 0.0336 (14) | 0.0060 (14) | 0.0066 (12) | −0.0037 (13) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| Cl1—C2 | 1.724 (2) | C3—C8 | 1.416 (3) |
| Cl2—C1 | 1.739 (3) | C4—C5 | 1.406 (3) |
| F1—C6 | 1.352 (3) | C5—C6 | 1.346 (3) |
| N1—C2 | 1.308 (3) | C5—H5 | 0.9300 |
| N1—C1 | 1.350 (3) | C6—C7 | 1.394 (4) |
| N2—C1 | 1.289 (3) | C7—C8 | 1.360 (3) |
| N2—C4 | 1.372 (3) | C7—H7 | 0.9300 |
| C2—C3 | 1.411 (3) | C8—H8 | 0.9300 |
| C3—C4 | 1.409 (3) | | |
| | | | |
| C2—N1—C1 | 114.3 (2) | C5—C4—C3 | 119.5 (2) |
| C1—N2—C4 | 114.9 (2) | C6—C5—C4 | 118.2 (2) |
| N2—C1—N1 | 130.1 (2) | C6—C5—H5 | 120.9 |
| N2—C1—Cl2 | 116.50 (18) | C4—C5—H5 | 120.9 |
| N1—C1—Cl2 | 113.36 (19) | C5—C6—F1 | 119.2 (2) |
| N1—C2—C3 | 124.0 (2) | C5—C6—C7 | 124.1 (2) |
| N1—C2—Cl1 | 116.25 (18) | F1—C6—C7 | 116.7 (2) |
| C3—C2—Cl1 | 119.70 (18) | C8—C7—C6 | 118.6 (2) |
| C4—C3—C2 | 115.0 (2) | C8—C7—H7 | 120.7 |
| C4—C3—C8 | 119.6 (2) | C6—C7—H7 | 120.7 |
| C2—C3—C8 | 125.4 (2) | C7—C8—C3 | 120.0 (2) |
| N2—C4—C5 | 118.8 (2) | C7—C8—H8 | 120.0 |
| N2—C4—C3 | 121.7 (2) | C3—C8—H8 | 120.0 |