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# *N*-Cyclopropyl-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-(1*H*-1,2,4-triazol-1-yl)propyl]-2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetamide dichloromethane 0.62-solvate

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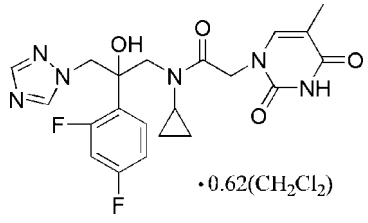
Key indicators: single-crystal X-ray study; $T$ = 298 K; mean $\sigma$(C–C) = 0.008 Å; disorder in solvent or counterion; $R$ factor = 0.092; $wR$ factor = 0.209; data-to-parameter ratio = 11.7.

In the title compound, $C_{21}H_{22}F_2N_6O_4\cdot0.62CH_2Cl_2$, the difluoro-substituted benzene ring forms dihedral angles of 54.6 (3)° with the mean plane of the thymine ring and 50.9 (2)° with the triazole ring. The dihedral angle between the thymine and triazole rings is 7.4 (3)°. In the crystal, intermolecular N—H···N and O—H···O hydrogen bonds link the main molecules into chains along [10$\bar{1}$]. The $CH_2Cl_2$ solvent molecule was refined as partial occupancy over two sets of sites with refined occupancies of 0.308 (9) and 0.310 (8).

## Related literature

For the applications of azole and triazole compounds as antifungal agents, see: Singh (2001); Richardson (2005); Hobson (2003); Slavin *et al.* (2002); Wingard & Leather (2004); Fridkin & Jarvis (1996); Gallis *et al.* (1990); Sheehan *et al.* (1999); Denning (2002); Aoyama *et al.* (1984); Lamb *et al.* (1999).




## Experimental

### Crystal data

$C_{21}H_{22}F_2N_6O_4\cdot0.62CH_2Cl_2$
$M_r$ = 512.93
Triclinic, $P\bar{1}$
$a$ = 8.474 (2) Å
$b$ = 12.464 (3) Å
$c$ = 13.410 (4) Å
$\alpha$ = 62.942 (4)°
$\beta$ = 73.187 (4)°
$\gamma$ = 83.746 (4)°
$V$ = 1207.1 (6) Å$^3$
$Z$ = 2
Mo $K\alpha$ radiation
$\mu$ = 0.24 mm$^{-1}$
$T$ = 298 K
0.30 × 0.16 × 0.14 mm

### Data collection

Bruker SMART APEX diffractometer
6058 measured reflections
4162 independent reflections
3053 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.022

### Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.092
$wR(F^2)$ = 0.209
$S$ = 1.16
4162 reflections
356 parameters
42 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.50 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.34 e Å$^{-3}$

**Table 1**
Hydrogen-bond geometry (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N6—H6···N2$^{i}$ | 0.80 | 2.11 | 2.893 (5) | 167 |
| O1—H1$A$···O2$^{ii}$ | 0.82 | 2.13 | 2.903 (4) | 158 |

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

Data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); 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: LH5302).

## References

Aoyama, Y., Yoshida, Y. & Sato, R. (1984). *J. Biol. Chem.* **259**, 1661–1666.
Bruker (1997). *SMART* and *SAINT*. Bruker AXS, Inc., Madison, Wisconsin, USA.
Denning, D. W. (2002). *J. Antimicrob. Chemother.* **49**, 889–891.
Fridkin, S. K. & Jarvis, W. R. (1996). *Clin. Microbiol. Rev.* **9**, 499-511.
Gallis, H. A., Drew, R. H. & Pickard, W. W. (1990). *Rev. Infect. Dis.* **12**, 308–329.
Hobson, R. P. (2003). *J. Hosp. Infect.* **55**, 159–168.
Lamb, D. C., Kelly, D. E., Venkateswarlu, K., Manning, N. J., Bligh, H. F., Schunck, W. H. & Kelly, S. L. (1999). *Biochemistry.* **38**, 8733–8738.
Richardson, M. D. (2005). *J. Antimicrob. Chemother.* **56**, i5–i11.
Sheehan, D. J., Hitchcock, C. A. & Sibley, C. M. (1999). *Clin. Microbiol. Rev.* **12**, 40–79.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Singh, N. (2001). *Clin. Infect. Dis.* **33**, 1692–1696.
Slavin, M. A. *et al.* (2002). *J. Antimicrob. Chemother.* **49**, 3–6.
Wingard, J. R. & Leather, H. (2004). *Biol. Blood Marrow Transplant.* **10**, 73–90.

# supporting information

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# *N*-Cyclopropyl-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-(1*H*-1,2,4-triazol-1-yl)propyl]-2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetamide dichloromethane 0.62-solvate

**Nan Wang, Huan-Mei Guo, Gui-Ge Hou, Xin-Yue Hu and Qing-Guo Meng**

## S1. Comment

In recent years, fungal infections are prevalent diseases from which a large proportion of the human population suffers (Singh, 2001; Richardson, 2005; Hobson, 2003; Slavin *et al.*, 2002). The increased emergence of both superficial and systemic fungal infections has led to the massive increase in the rate of mortality, especially in immunocompromised individuals i.e. those suffering from tuberculosis, cancer or AIDS (Wingard & Leather, 2004; Fridkin & Jarvis, 1996). There are very few antifungal agents that can be used for life-threatening fungal infections. Several clinical drugs, such as amphotericin *B*,5-fluorocytosine, azoles (such as fluconazole and itraconazole) and echinocandins (such as caspofungin and micafungin) have been developed to reduce the impact of fungal diseases (Gallis *et al.*, 1990; Sheehan *et al.*, 1999; Denning, 2002). Among those, azoles, especially triazole antifungal agents, are used widely and efficiently. For over a decade, azoles have been a mainstay of the antifungal armamentarium. They act by competitive inhibition of the lanosterol 1410 which is the key enzyme in sterol biosynthesis of fungi (Aoyama *et al.*, 1984). Selective inhibition of CYP51 would cause depletion of ergosterol and accumulation of lanosterol and other 14-methyl sterols resulting in the growth inhibition of fungal cells (Lamb *et al.*, 1999). We have attempted to prepare some potential antifungal agents with improved activity and broader spectrum, by sythesizing a series of 1-(1*H*-1,2,4-triazole-1-yl)-(2,4-difluorophenyl)-3-[*N*-n-alkyl-*N*-(1-thyminyl)acetyl]-2-propanol compounds. Herein, we report the crystal structure of the title compound (I).

The molecular structure of the title compound is shown in Fig. 1. The difluoro-substituted benzene ring forms dihedral angles of 54.6 (3)° with the mean plane of the thymine ring and 50.9 (2)° with the triazole ring. The dihedral angle between the thymine and triazole rings is 7.4 (3)°. In the crystal, intermolecular N—H···N and O—H···O hydrogen bonds link the main molecules into one-dimensional chains (Fig. 2) along [$10\bar{1}$].

## S2. Experimental

The synthesis of thymin-1-yl acetic acid: To a solution of thymine (30.00 g, 237.89 mmol) in water (150 ml) was added potassium hydroxide (51.25 g, 903.79 mmol). The solution was heated to 313 K, and then bromoacetic acid (49.58 g, 356.83 mmol) was added dropwise. The resulting solution was allowed to stir for 2 h at the same temperature. The solution was then brought to pH 5 with 36% HCl at 273 K. The white precipitate was filtered off and discarded. Then the filtrate was brought to pH 1 with 36% HCl. Solid was filtered off and dried and obtained in 83.5% yield, m.p 528–530 K.

The synthesis of the title compound: To a solution of 1-(1H-1,2,4-triazole)-2,2-[oxiranyl-(2,4-difluorophenyl)]ethane mesylate (16.75 g, 50 mmol) in ethanol (240 ml) was added triethylamine (16 ml, 110 mmol) and cyclopropylamine (6.93 ml, 100 mmol). The resulting solution was raised to 318 K and stirred for 10 h at the same temperature. Once concentrated to light yellow oil under vacuum, the residue was taken off with ethyl acetate and was treated with 1 M HCl.

The aqueous phase was then brought to pH 8 with sodium carbonate and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. A light yellow oil was obtained in 67.6% yield. A solution of the title compound (9.2 mg,0.02 mmol) in dichloromethane and methanol (4 ml, 1:1, *v*/*v*) was kept at room temperature. Upon slow evaporation of the solvent over about 10 d, colourless block-shaped crystals suitable for X-ray measurements were obtained.

### S3. Refinement

All H atoms were placed in idealized positions and treated as riding,with C—H = 0.97 ($CH_2$), 0.96 ($CH_3$), 0.93 Å ($CH_{aromatic}$), 0.98 Å ($CH_{tertiary\ alkyl}$), N—H = 0.80 Å, O—H = 0.82 Å, and $U_{iso}$(H) = 1.2$U_{eq}$(N, CH and $CH_2$), $U_{iso}$(H) = 1.5$U_{eq}$(OH and $CH_3$). The $CH_2Cl_2$ solvent molecule was refined as partial occupancy over two sets of sites with refined occupancies of 0.308 (9) and 0.310 (8). The precision of this structure is lower than normal and this may be the result of the presence of the disordered solvent in the lattice.

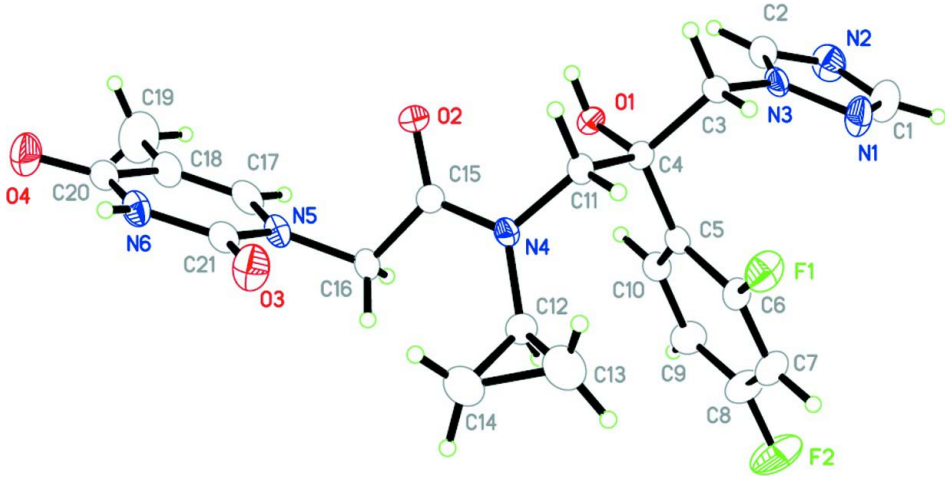


**Figure 1**

The molecular structure of the title compound showing displacement ellipsoids with 30% probability. The solvent molecule is not shown.

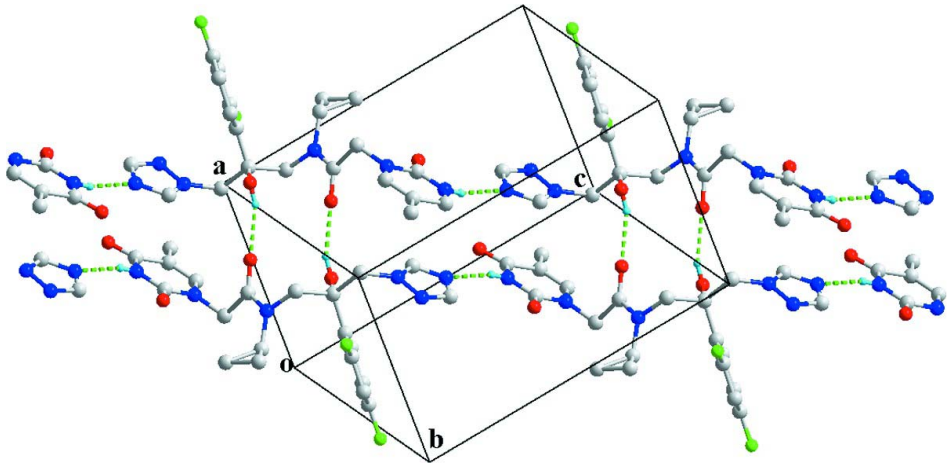


**Figure 2**

Part of the crystal structure of the title compound. Dashed lines indicate hydrogen bonds. Only H atoms involved in hydrogen bonds are shown. The solvent molecules are not shown.

**N-Cyclopropyl-N-[2-(2,4-difluorophenyl)-2-hydroxy- 3-(1H-1,2,4-triazol-1-yl)propyl]-2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetamide dichloromethane 0.62-solvate**

*Crystal data*

$C_{21}H_{22}F_2N_6O_4 \cdot 0.62CH_2Cl_2$
$M_r = 512.93$
Triclinic, $P\overline{1}$
Hall symbol: -P 1
$a = 8.474$ (2) Å
$b = 12.464$ (3) Å
$c = 13.410$ (4) Å
$\alpha = 62.942$ (4)°
$\beta = 73.187$ (4)°
$\gamma = 83.746$ (4)°
$V = 1207.1$ (6) Å$^3$
$Z = 2$
$F(000) = 532.2$
$D_x = 1.411$ Mg m$^{-3}$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 1529 reflections
$\theta = 2.5$–$24.6°$
$\mu = 0.24$ mm$^{-1}$
$T = 298$ K
Block, colourless
0.30 × 0.16 × 0.14 mm

*Data collection*

Bruker SMART APEX diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
$\varphi$ and $\omega$ scans
6058 measured reflections
4162 independent reflections
3053 reflections with $I > 2\sigma(I)$
$R_{int} = 0.022$
$\theta_{max} = 25.0°$, $\theta_{min} = 1.8°$
$h = -10 \rightarrow 8$
$k = -14 \rightarrow 11$
$l = -15 \rightarrow 10$

*Refinement*

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.092$
$wR(F^2) = 0.209$
$S = 1.16$
4162 reflections
356 parameters
42 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
$w = 1/[\sigma^2(F_o^2) + (0.0687P)^2 + 1.6778P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.50$ e Å$^{-3}$
$\Delta\rho_{min} = -0.34$ 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 (Å²)*

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ | Occ. (<1) |
|---|---|---|---|---|---|
| C1 | 0.4568 (7) | 0.7140 (5) | 1.3061 (5) | 0.0602 (15) | |
| H1 | 0.3778 | 0.7522 | 1.3425 | 0.072* | |
| C2 | 0.5856 (6) | 0.5787 (4) | 1.2724 (4) | 0.0416 (11) | |

| | | | | |
|---|---|---|---|---|
| H2 | 0.6213 | 0.5044 | 1.2752 | 0.050* |
| C3 | 0.7947 (5) | 0.7116 (4) | 1.0885 (3) | 0.0320 (10) |
| H3A | 0.8887 | 0.6649 | 1.1106 | 0.038* |
| H3B | 0.8256 | 0.7963 | 1.0532 | 0.038* |
| C4 | 0.7508 (5) | 0.6834 (4) | 0.9990 (4) | 0.0296 (9) |
| C5 | 0.5887 (5) | 0.7388 (4) | 0.9760 (3) | 0.0291 (9) |
| C6 | 0.5620 (5) | 0.8613 (4) | 0.9364 (4) | 0.0331 (10) |
| C7 | 0.4170 (6) | 0.9142 (4) | 0.9172 (4) | 0.0481 (12) |
| H7 | 0.4040 | 0.9968 | 0.8914 | 0.058* |
| C8 | 0.2910 (6) | 0.8396 (5) | 0.9378 (5) | 0.0537 (14) |
| C9 | 0.3077 (6) | 0.7182 (4) | 0.9764 (4) | 0.0476 (12) |
| H9 | 0.2210 | 0.6695 | 0.9894 | 0.057* |
| C10 | 0.4563 (5) | 0.6694 (4) | 0.9955 (4) | 0.0349 (10) |
| H10 | 0.4680 | 0.5866 | 1.0227 | 0.042* |
| C11 | 0.8951 (5) | 0.7280 (4) | 0.8885 (4) | 0.0333 (10) |
| H11A | 0.9135 | 0.8136 | 0.8603 | 0.040* |
| H11B | 0.9940 | 0.6873 | 0.9079 | 0.040* |
| C12 | 0.7806 (6) | 0.7963 (4) | 0.7168 (4) | 0.0421 (11) |
| H12 | 0.6619 | 0.7806 | 0.7371 | 0.051* |
| C13 | 0.8329 (10) | 0.9254 (5) | 0.6618 (5) | 0.078 (2) |
| H13A | 0.7476 | 0.9850 | 0.6514 | 0.094* |
| H13B | 0.9264 | 0.9450 | 0.6791 | 0.094* |
| C14 | 0.8650 (8) | 0.8592 (5) | 0.5897 (4) | 0.0644 (16) |
| H14A | 0.9779 | 0.8385 | 0.5633 | 0.077* |
| H14B | 0.7991 | 0.8785 | 0.5357 | 0.077* |
| C15 | 0.9161 (5) | 0.6029 (4) | 0.7912 (4) | 0.0315 (10) |
| C16 | 0.8534 (5) | 0.5732 (4) | 0.7112 (4) | 0.0375 (11) |
| H16A | 0.7435 | 0.5370 | 0.7513 | 0.045* |
| H16B | 0.8459 | 0.6471 | 0.6432 | 0.045* |
| C17 | 0.9241 (6) | 0.3704 (4) | 0.7248 (4) | 0.0440 (12) |
| H17 | 0.8292 | 0.3407 | 0.7861 | 0.053* |
| C18 | 1.0177 (6) | 0.2925 (4) | 0.6907 (4) | 0.0468 (12) |
| C19 | 0.9756 (9) | 0.1617 (5) | 0.7452 (6) | 0.086 (2) |
| H19A | 0.8814 | 0.1425 | 0.8114 | 0.129* |
| H19B | 1.0675 | 0.1158 | 0.7697 | 0.129* |
| H19C | 0.9508 | 0.1422 | 0.6898 | 0.129* |
| C20 | 1.1630 (6) | 0.3403 (4) | 0.5940 (4) | 0.0430 (11) |
| C21 | 1.1004 (5) | 0.5404 (4) | 0.5851 (4) | 0.0376 (10) |
| F1 | 0.6869 (3) | 0.9347 (2) | 0.9153 (3) | 0.0508 (7) |
| F2 | 0.1460 (4) | 0.8888 (3) | 0.9206 (4) | 0.0897 (12) |
| N1 | 0.5731 (5) | 0.7741 (4) | 1.2121 (4) | 0.0512 (11) |
| N2 | 0.4584 (5) | 0.5937 (4) | 1.3470 (3) | 0.0525 (11) |
| N3 | 0.6572 (4) | 0.6839 (3) | 1.1920 (3) | 0.0322 (8) |
| N4 | 0.8680 (4) | 0.7077 (3) | 0.7957 (3) | 0.0298 (8) |
| N5 | 0.9609 (4) | 0.4908 (3) | 0.6742 (3) | 0.0351 (9) |
| N6 | 1.1926 (4) | 0.4609 (3) | 0.5494 (3) | 0.0411 (9) |
| H6 | 1.2754 | 0.4935 | 0.5005 | 0.049* |
| O1 | 0.7269 (3) | 0.5572 (2) | 1.0449 (3) | 0.0351 (7) |

| | | | | | |
|---|---|---|---|---|---|
| H1A | 0.8101 | 0.5229 | 1.0622 | 0.053* | |
| O2 | 0.9993 (4) | 0.5299 (3) | 0.8517 (3) | 0.0455 (8) | |
| O3 | 1.1376 (4) | 0.6464 (3) | 0.5414 (3) | 0.0573 (10) | |
| O4 | 1.2549 (5) | 0.2801 (3) | 0.5518 (3) | 0.0655 (11) | |
| C1A | 0.332 (3) | 0.799 (2) | 0.626 (4) | 0.104 (10) | 0.308 (9) |
| H1AA | 0.2307 | 0.7586 | 0.6801 | 0.125* | 0.308 (9) |
| H1AB | 0.3205 | 0.8252 | 0.5492 | 0.125* | 0.308 (9) |
| Cl1 | 0.4739 (16) | 0.7045 (11) | 0.6375 (13) | 0.193 (7) | 0.308 (9) |
| Cl2 | 0.350 (3) | 0.920 (2) | 0.633 (2) | 0.371 (15) | 0.308 (9) |
| C1B | 0.401 (4) | 0.803 (2) | 0.5671 (15) | 0.103 (9) | 0.310 (8) |
| H1BA | 0.3007 | 0.7941 | 0.5521 | 0.123* | 0.310 (8) |
| H1BB | 0.4728 | 0.7448 | 0.5497 | 0.123* | 0.310 (8) |
| Cl1′ | 0.3513 (16) | 0.7336 (13) | 0.7053 (12) | 0.177 (6) | 0.310 (8) |
| Cl2′ | 0.477 (3) | 0.9237 (19) | 0.453 (2) | 0.340 (13) | 0.310 (8) |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| C1 | 0.051 (3) | 0.067 (4) | 0.056 (4) | 0.010 (3) | 0.005 (3) | −0.036 (3) |
| C2 | 0.045 (3) | 0.046 (3) | 0.030 (2) | 0.003 (2) | −0.003 (2) | −0.017 (2) |
| C3 | 0.028 (2) | 0.041 (2) | 0.032 (2) | 0.0028 (18) | −0.0105 (18) | −0.019 (2) |
| C4 | 0.027 (2) | 0.030 (2) | 0.032 (2) | 0.0003 (17) | −0.0059 (18) | −0.0146 (18) |
| C5 | 0.027 (2) | 0.036 (2) | 0.024 (2) | −0.0010 (18) | −0.0036 (17) | −0.0159 (18) |
| C6 | 0.027 (2) | 0.034 (2) | 0.043 (3) | −0.0028 (18) | −0.0070 (19) | −0.021 (2) |
| C7 | 0.047 (3) | 0.038 (3) | 0.059 (3) | 0.010 (2) | −0.016 (2) | −0.022 (2) |
| C8 | 0.035 (3) | 0.054 (3) | 0.074 (4) | 0.009 (2) | −0.022 (3) | −0.027 (3) |
| C9 | 0.033 (3) | 0.050 (3) | 0.062 (3) | −0.006 (2) | −0.015 (2) | −0.024 (3) |
| C10 | 0.033 (2) | 0.037 (2) | 0.034 (2) | −0.0029 (19) | −0.0070 (19) | −0.016 (2) |
| C11 | 0.025 (2) | 0.044 (3) | 0.038 (3) | 0.0033 (18) | −0.0082 (19) | −0.026 (2) |
| C12 | 0.048 (3) | 0.040 (3) | 0.036 (3) | 0.008 (2) | −0.012 (2) | −0.016 (2) |
| C13 | 0.137 (6) | 0.041 (3) | 0.054 (4) | 0.002 (3) | −0.031 (4) | −0.015 (3) |
| C14 | 0.093 (4) | 0.051 (3) | 0.037 (3) | 0.001 (3) | −0.014 (3) | −0.011 (3) |
| C15 | 0.020 (2) | 0.042 (2) | 0.029 (2) | 0.0004 (18) | −0.0021 (18) | −0.016 (2) |
| C16 | 0.035 (2) | 0.050 (3) | 0.035 (2) | 0.005 (2) | −0.009 (2) | −0.026 (2) |
| C17 | 0.048 (3) | 0.052 (3) | 0.031 (2) | −0.013 (2) | −0.005 (2) | −0.017 (2) |
| C18 | 0.058 (3) | 0.043 (3) | 0.044 (3) | −0.001 (2) | −0.012 (2) | −0.025 (2) |
| C19 | 0.107 (5) | 0.048 (3) | 0.094 (5) | −0.012 (3) | −0.007 (4) | −0.034 (4) |
| C20 | 0.050 (3) | 0.051 (3) | 0.046 (3) | 0.012 (2) | −0.023 (2) | −0.032 (2) |
| C21 | 0.042 (3) | 0.040 (3) | 0.033 (2) | −0.001 (2) | −0.011 (2) | −0.017 (2) |
| F1 | 0.0455 (16) | 0.0343 (14) | 0.075 (2) | −0.0060 (12) | −0.0167 (14) | −0.0245 (14) |
| F2 | 0.0437 (18) | 0.082 (2) | 0.143 (4) | 0.0242 (17) | −0.048 (2) | −0.041 (2) |
| N1 | 0.057 (3) | 0.048 (2) | 0.049 (3) | 0.008 (2) | −0.002 (2) | −0.030 (2) |
| N2 | 0.050 (3) | 0.060 (3) | 0.036 (2) | −0.005 (2) | 0.003 (2) | −0.019 (2) |
| N3 | 0.0328 (19) | 0.043 (2) | 0.0258 (19) | 0.0026 (16) | −0.0049 (15) | −0.0214 (17) |
| N4 | 0.0309 (19) | 0.036 (2) | 0.0232 (18) | 0.0019 (15) | −0.0046 (15) | −0.0153 (15) |
| N5 | 0.036 (2) | 0.043 (2) | 0.030 (2) | −0.0042 (16) | −0.0038 (16) | −0.0212 (17) |
| N6 | 0.039 (2) | 0.050 (2) | 0.033 (2) | −0.0022 (18) | −0.0007 (17) | −0.0214 (18) |
| O1 | 0.0352 (17) | 0.0327 (16) | 0.0405 (18) | 0.0086 (13) | −0.0139 (14) | −0.0183 (14) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O2 | 0.0464 (19) | 0.057 (2) | 0.047 (2) | 0.0239 (16) | −0.0270 (16) | −0.0315 (17) |
| O3 | 0.060 (2) | 0.045 (2) | 0.054 (2) | −0.0065 (17) | 0.0030 (18) | −0.0210 (18) |
| O4 | 0.071 (3) | 0.071 (2) | 0.074 (3) | 0.018 (2) | −0.018 (2) | −0.052 (2) |
| C1A | 0.102 (13) | 0.108 (13) | 0.095 (12) | −0.001 (9) | −0.034 (9) | −0.034 (9) |
| Cl1 | 0.178 (9) | 0.167 (9) | 0.210 (10) | 0.003 (6) | 0.005 (7) | −0.096 (7) |
| Cl2 | 0.363 (17) | 0.382 (18) | 0.371 (18) | 0.015 (10) | −0.130 (10) | −0.153 (11) |
| C1B | 0.073 (11) | 0.102 (12) | 0.104 (13) | 0.007 (8) | −0.023 (9) | −0.022 (9) |
| Cl1′ | 0.162 (9) | 0.207 (9) | 0.181 (9) | −0.023 (6) | −0.020 (6) | −0.112 (7) |
| Cl2′ | 0.310 (15) | 0.319 (15) | 0.367 (16) | 0.024 (9) | −0.121 (10) | −0.119 (10) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| C1—N1 | 1.306 (6) | C15—O2 | 1.226 (5) |
| C1—N2 | 1.342 (6) | C15—N4 | 1.348 (5) |
| C1—H1 | 0.9300 | C15—C16 | 1.519 (6) |
| C2—N2 | 1.304 (6) | C16—N5 | 1.460 (5) |
| C2—N3 | 1.326 (5) | C16—H16A | 0.9700 |
| C2—H2 | 0.9300 | C16—H16B | 0.9700 |
| C3—N3 | 1.455 (5) | C17—C18 | 1.345 (6) |
| C3—C4 | 1.541 (6) | C17—N5 | 1.364 (6) |
| C3—H3A | 0.9700 | C17—H17 | 0.9300 |
| C3—H3B | 0.9700 | C18—C20 | 1.444 (7) |
| C4—O1 | 1.418 (5) | C18—C19 | 1.487 (7) |
| C4—C5 | 1.517 (6) | C19—H19A | 0.9600 |
| C4—C11 | 1.533 (6) | C19—H19B | 0.9600 |
| C5—C10 | 1.383 (6) | C19—H19C | 0.9600 |
| C5—C6 | 1.386 (6) | C20—O4 | 1.222 (5) |
| C6—F1 | 1.356 (4) | C20—N6 | 1.362 (6) |
| C6—C7 | 1.364 (6) | C21—O3 | 1.211 (5) |
| C7—C8 | 1.376 (7) | C21—N6 | 1.366 (6) |
| C7—H7 | 0.9300 | C21—N5 | 1.370 (5) |
| C8—F2 | 1.346 (5) | N1—N3 | 1.355 (5) |
| C8—C9 | 1.364 (7) | N6—H6 | 0.8013 |
| C9—C10 | 1.378 (6) | O1—H1A | 0.8200 |
| C9—H9 | 0.9300 | C1A—Cl1 | 1.580 (12) |
| C10—H10 | 0.9300 | C1A—Cl2 | 1.581 (12) |
| C11—N4 | 1.460 (5) | C1A—H1AA | 0.9600 |
| C11—H11A | 0.9700 | C1A—H1AB | 0.9601 |
| C11—H11B | 0.9700 | C1A—H1BA | 1.1262 |
| C12—N4 | 1.448 (5) | Cl1—H1BB | 1.0513 |
| C12—C13 | 1.489 (7) | C1B—Cl1′ | 1.590 (12) |
| C12—C14 | 1.495 (7) | C1B—Cl2′ | 1.599 (12) |
| C12—H12 | 0.9800 | C1B—H1AB | 0.7735 |
| C13—C14 | 1.488 (8) | C1B—H1BA | 0.9600 |
| C13—H13A | 0.9700 | C1B—H1BB | 0.9601 |
| C13—H13B | 0.9700 | Cl1′—H1AA | 1.1355 |
| C14—H14A | 0.9700 | Cl2′—H1AB | 1.6877 |
| C14—H14B | 0.9700 | | |

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|---|---|---|---|
| N1—C1—N2 | 115.8 (4) | N5—C16—C15 | 112.0 (3) |
| N1—C1—H1 | 122.1 | N5—C16—H16A | 109.2 |
| N2—C1—H1 | 122.1 | C15—C16—H16A | 109.2 |
| N2—C2—N3 | 110.8 (4) | N5—C16—H16B | 109.2 |
| N2—C2—H2 | 124.6 | C15—C16—H16B | 109.2 |
| N3—C2—H2 | 124.6 | H16A—C16—H16B | 107.9 |
| N3—C3—C4 | 111.7 (3) | C18—C17—N5 | 123.5 (4) |
| N3—C3—H3A | 109.3 | C18—C17—H17 | 118.3 |
| C4—C3—H3A | 109.3 | N5—C17—H17 | 118.3 |
| N3—C3—H3B | 109.3 | C17—C18—C20 | 117.6 (4) |
| C4—C3—H3B | 109.3 | C17—C18—C19 | 123.2 (5) |
| H3A—C3—H3B | 107.9 | C20—C18—C19 | 119.2 (5) |
| O1—C4—C5 | 106.0 (3) | C18—C19—H19A | 109.5 |
| O1—C4—C11 | 109.8 (3) | C18—C19—H19B | 109.5 |
| C5—C4—C11 | 112.6 (3) | H19A—C19—H19B | 109.5 |
| O1—C4—C3 | 109.4 (3) | C18—C19—H19C | 109.5 |
| C5—C4—C3 | 111.1 (3) | H19A—C19—H19C | 109.5 |
| C11—C4—C3 | 107.9 (3) | H19B—C19—H19C | 109.5 |
| C10—C5—C6 | 115.5 (4) | O4—C20—N6 | 120.5 (5) |
| C10—C5—C4 | 121.8 (4) | O4—C20—C18 | 124.1 (5) |
| C6—C5—C4 | 122.7 (4) | N6—C20—C18 | 115.3 (4) |
| F1—C6—C7 | 117.1 (4) | O3—C21—N6 | 123.1 (4) |
| F1—C6—C5 | 118.6 (4) | O3—C21—N5 | 122.3 (4) |
| C7—C6—C5 | 124.4 (4) | N6—C21—N5 | 114.5 (4) |
| C6—C7—C8 | 116.9 (4) | C1—N1—N3 | 101.6 (4) |
| C6—C7—H7 | 121.6 | C2—N2—C1 | 102.3 (4) |
| C8—C7—H7 | 121.6 | C2—N3—N1 | 109.6 (3) |
| F2—C8—C9 | 119.3 (4) | C2—N3—C3 | 130.1 (4) |
| F2—C8—C7 | 118.3 (4) | N1—N3—C3 | 120.2 (3) |
| C9—C8—C7 | 122.3 (4) | C15—N4—C12 | 122.2 (3) |
| C8—C9—C10 | 118.4 (4) | C15—N4—C11 | 118.4 (3) |
| C8—C9—H9 | 120.8 | C12—N4—C11 | 119.2 (3) |
| C10—C9—H9 | 120.8 | C17—N5—C21 | 121.4 (4) |
| C9—C10—C5 | 122.6 (4) | C17—N5—C16 | 121.9 (4) |
| C9—C10—H10 | 118.7 | C21—N5—C16 | 116.7 (4) |
| C5—C10—H10 | 118.7 | C20—N6—C21 | 127.5 (4) |
| N4—C11—C4 | 113.4 (3) | C20—N6—H6 | 121.9 |
| N4—C11—H11A | 108.9 | C21—N6—H6 | 110.3 |
| C4—C11—H11A | 108.9 | C4—O1—H1A | 109.5 |
| N4—C11—H11B | 108.9 | Cl1—C1A—Cl2 | 122 (2) |
| C4—C11—H11B | 108.9 | Cl1—C1A—H1AA | 108.7 |
| H11A—C11—H11B | 107.7 | Cl2—C1A—H1AA | 108.8 |
| N4—C12—C13 | 118.6 (4) | Cl1—C1A—H1AB | 104.8 |
| N4—C12—C14 | 119.8 (4) | Cl2—C1A—H1AB | 104.5 |
| C13—C12—C14 | 59.8 (3) | H1AA—C1A—H1AB | 107.3 |
| N4—C12—H12 | 115.7 | Cl1—C1A—H1BA | 96.4 |
| C13—C12—H12 | 115.7 | Cl2—C1A—H1BA | 124.6 |

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| C14—C12—H12 | 115.7 | H1AA—C1A—H1BA | 92.2 |
| C14—C13—C12 | 60.3 (3) | H1AB—C1A—H1BA | 21.3 |
| C14—C13—H13A | 117.7 | C1A—Cl1—H1BB | 73.9 |
| C12—C13—H13A | 117.7 | Cl1′—C1B—Cl2′ | 147 (2) |
| C14—C13—H13B | 117.7 | Cl1′—C1B—H1AB | 106.6 |
| C12—C13—H13B | 117.7 | Cl2′—C1B—H1AB | 82.9 |
| H13A—C13—H13B | 114.9 | Cl1′—C1B—H1BA | 100.4 |
| C13—C14—C12 | 59.9 (3) | Cl2′—C1B—H1BA | 100.3 |
| C13—C14—H14A | 117.8 | H1AB—C1B—H1BA | 25.2 |
| C12—C14—H14A | 117.8 | Cl1′—C1B—H1BB | 99.5 |
| C13—C14—H14B | 117.8 | Cl2′—C1B—H1BB | 100.0 |
| C12—C14—H14B | 117.8 | H1AB—C1B—H1BB | 125.7 |
| H14A—C14—H14B | 114.9 | H1BA—C1B—H1BB | 104.4 |
| O2—C15—N4 | 123.6 (4) | C1B—Cl1′—H1AA | 74.3 |
| O2—C15—C16 | 119.6 (4) | C1B—Cl2′—H1AB | 27.0 |
| N4—C15—C16 | 116.7 (4) | | |

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|---|---|---|---|
| N3—C3—C4—O1 | −66.7 (4) | C17—C18—C20—N6 | 2.0 (7) |
| N3—C3—C4—C5 | 50.0 (4) | C19—C18—C20—N6 | −179.9 (5) |
| N3—C3—C4—C11 | 173.9 (3) | N2—C1—N1—N3 | −0.6 (6) |
| O1—C4—C5—C10 | −2.4 (5) | N3—C2—N2—C1 | 0.6 (6) |
| C11—C4—C5—C10 | 117.7 (4) | N1—C1—N2—C2 | 0.1 (7) |
| C3—C4—C5—C10 | −121.1 (4) | N2—C2—N3—N1 | −1.0 (5) |
| O1—C4—C5—C6 | 176.4 (4) | N2—C2—N3—C3 | −175.6 (4) |
| C11—C4—C5—C6 | −63.5 (5) | C1—N1—N3—C2 | 1.0 (5) |
| C3—C4—C5—C6 | 57.7 (5) | C1—N1—N3—C3 | 176.2 (4) |
| C10—C5—C6—F1 | −179.9 (4) | C4—C3—N3—C2 | 65.9 (6) |
| C4—C5—C6—F1 | 1.3 (6) | C4—C3—N3—N1 | −108.2 (4) |
| C10—C5—C6—C7 | 0.3 (6) | O2—C15—N4—C12 | 175.1 (4) |
| C4—C5—C6—C7 | −178.5 (4) | C16—C15—N4—C12 | −8.5 (5) |
| F1—C6—C7—C8 | 179.4 (4) | O2—C15—N4—C11 | −9.3 (6) |
| C5—C6—C7—C8 | −0.8 (7) | C16—C15—N4—C11 | 167.1 (3) |
| C6—C7—C8—F2 | 179.5 (5) | C13—C12—N4—C15 | −135.1 (5) |
| C6—C7—C8—C9 | 0.5 (8) | C14—C12—N4—C15 | −65.5 (6) |
| F2—C8—C9—C10 | −178.8 (5) | C13—C12—N4—C11 | 49.3 (6) |
| C7—C8—C9—C10 | 0.2 (8) | C14—C12—N4—C11 | 118.9 (5) |
| C8—C9—C10—C5 | −0.7 (7) | C4—C11—N4—C15 | −89.6 (4) |
| C6—C5—C10—C9 | 0.4 (6) | C4—C11—N4—C12 | 86.1 (5) |
| C4—C5—C10—C9 | 179.3 (4) | C18—C17—N5—C21 | −1.3 (7) |
| O1—C4—C11—N4 | 61.5 (4) | C18—C17—N5—C16 | 178.0 (4) |
| C5—C4—C11—N4 | −56.3 (5) | O3—C21—N5—C17 | −177.8 (4) |
| C3—C4—C11—N4 | −179.4 (3) | N6—C21—N5—C17 | 2.6 (6) |
| N4—C12—C13—C14 | 109.7 (5) | O3—C21—N5—C16 | 2.8 (6) |
| N4—C12—C14—C13 | −107.7 (5) | N6—C21—N5—C16 | −176.7 (4) |
| O2—C15—C16—N5 | −27.8 (6) | C15—C16—N5—C17 | 100.4 (5) |
| N4—C15—C16—N5 | 155.7 (3) | C15—C16—N5—C21 | −80.3 (5) |
| N5—C17—C18—C20 | −1.1 (7) | O4—C20—N6—C21 | 178.6 (4) |
| N5—C17—C18—C19 | −179.2 (5) | C18—C20—N6—C21 | −0.6 (7) |

| | | | |
|---|---|---|---|
| C17—C18—C20—O4 | −177.2 (5) | O3—C21—N6—C20 | 178.8 (5) |
| C19—C18—C20—O4 | 0.9 (8) | N5—C21—N6—C20 | −1.7 (6) |

*Hydrogen-bond geometry (Å, º)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N6—H6···N2$^{i}$ | 0.80 | 2.11 | 2.893 (5) | 167 |
| O1—H1*A*···O2$^{ii}$ | 0.82 | 2.13 | 2.903 (4) | 158 |

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