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Ethyl 4-(4-chloro-3-fluorophenyl)-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carboxylate

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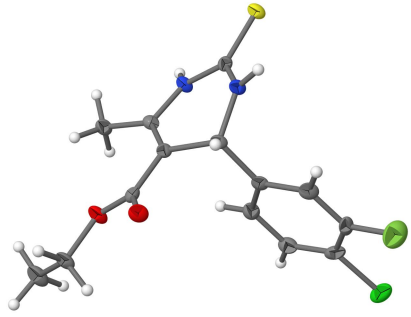
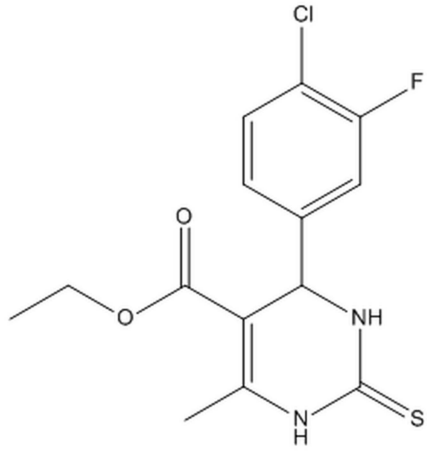
In the title compound, $C_{14}H_{14}ClFN_2O_2S$, the dihydropyrimidine ring adopts a shallow-boat conformation and subtends a dihedral angle of 81.91 (17)° with the phenyl ring. In the crystal, N—H···O, N—H···S and C—H···F hydrogen bonds and C—H···π interactions are found.

3D view



Chemical scheme



Structure description

The title compound is a dihydropyrimidine derivative (Kappe, 2000). Some of these compounds have therapeutic and pharmacological properties, such as anticarcinogenic (Mayer *et al.*, 1999) activity. They have also emerged as integral backbones of several calcium-channel modulators (Jauk *et al.*, 2000). As part of our studies in this area, we now describe the synthesis and structure of the title compound (Fig. 1).

The phenyl ring atttached to chiral atom C4 is positioned axially and bisects the pyrimidine ring with a dihedral angle of 81.91 (17)°. The pyrimidine ring adopts a shallow-boat conformation, with atoms N1 and C4 displaced from the mean plane of the other four atoms (C5/C6/C2/N2) by −0.0982 (7) and −0.0393 (1) Å, respectively. The O atom of the carbonyl group is in an *anti* conformation with respect to the C5—C6 bond.

The crystal structure features pairwise N2—H2···S1^{i} hydrogen bonds (Table 1), resulting in centrosymmetric $R_2^2(8)$ loops and also displays [100] chains linked by N1—H1···O1^{ii} hydrogen bonds (Fig. 2). In addition, the packing is consolidated by a C1—H1*A*···F1^{iii} interaction along the [110] direction (Fig. 3) and a C7—H7*B*···*Cg*^{iv} interaction (*Cg* being the centroid of the C8–C13 ring), with a H···*Cg* distance of 2.62 Å (Fig. 4).

Synthesis and crystallization

A mixture of 4-chloro-3-fluorobenzaldehyde (10 mmol), thiourea (10 mmol), ethyl acetoacetate (10 mmol) and a catalytic amount of concentrated hydrochloric acid in

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

Cg is the centroid of the C8–C13 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···S1^{i}	0.86	2.47	3.301 (1)	163
N1—H1···O1^{ii}	0.86	2.17	2.998 (2)	160
C1—H1*A*···F1^{iii}	0.96	2.60	3.368 (3)	137
C7—H7*B*···*Cg*^{iv}	0.96	2.62	3.577 (1)	168

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

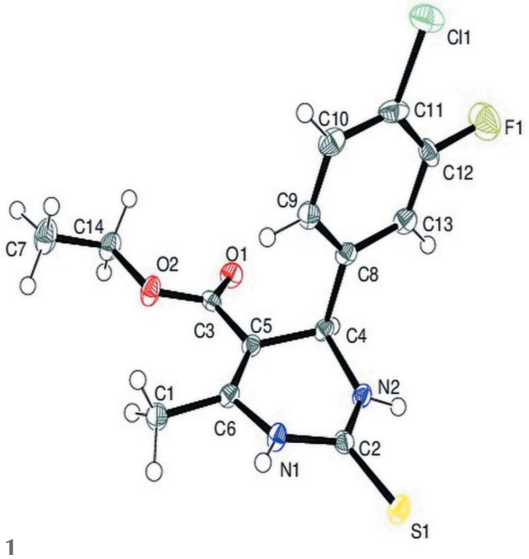


Figure 1
The molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level.

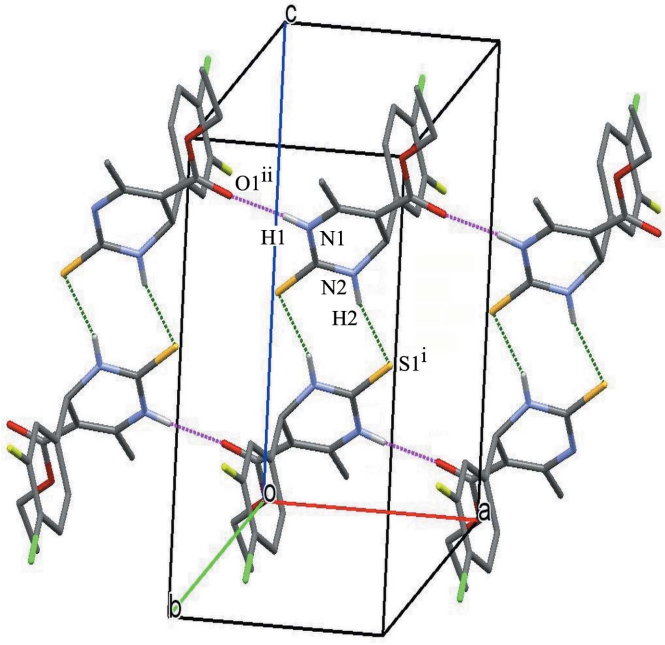


Figure 2
Unit-cell packing of the title compound, showing N—H···O and N—H···S interactions as dotted lines. H atoms not involved in hydrogen bonding have been excluded. See Table 1 for symmetry codes.

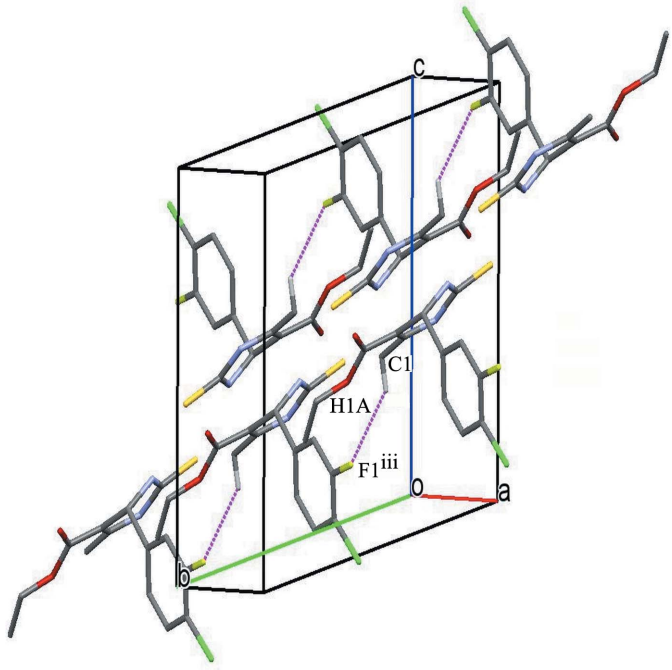


Figure 3
Unit-cell packing of the title compound, showing C—H···F interactions with dotted lines. H atoms not involved in hydrogen bonding have been excluded. See Table 1 for symmetry code.

ethanol (20 ml) was refluxed for 8 h. The reaction mixture was allowed to stand overnight at room temperature. The solid thus separated was neutralized using an aqueous sodium carbonate solution and the obtained precipitate was filtered off and washed with a mixture of ethanol and water (1:1 *v*/*v*), and recrystallized from ethyl–acetate solution, yielding colourless blocks of the title compound (yield 80%; m.p. 422—425 °C). IR (KBr) (cm^{-1}): 3321 (CH), 1667 (C═O), 1572 (ester), 1487 (NH). ^{1}H NMR ($CDCl_3$): δ 1.2 (*t*, 3H), 2.5 (*s*, 3H),

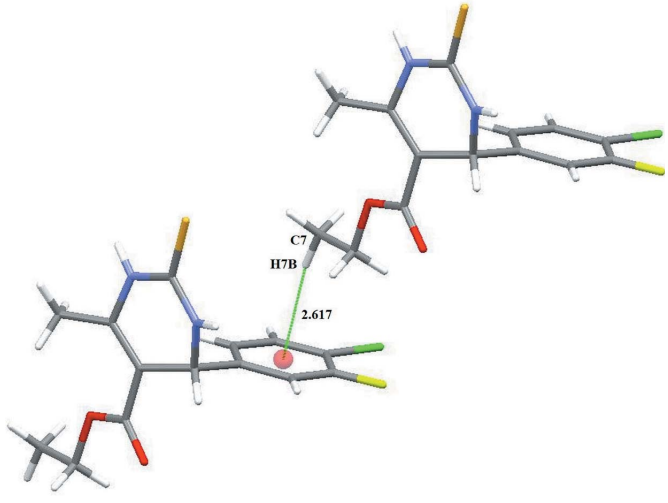


Figure 4
Unit-cell packing depicting the C—H···π interaction as a dotted line.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{14}H_{14}ClFN_2O_2S$
M_r	328.78
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	446
a, b, c (Å)	7.2599 (5), 9.4979 (7), 11.9596 (8)
α, β, γ (°)	106.149 (2), 90.236 (2), 108.939 (2)
V (Å^3)	745.18 (9)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.41
Crystal size (mm)	0.18 × 0.16 × 0.15
Data collection	
Diffractometer	Bruker SMART APEX CCD
Absorption correction	Multi-scan (*SADABS*; Bruker, 1998)
T_{min}, T_{max}	0.930, 0.941
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	9007, 2630, 2087
R_{int}	0.042
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.595
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.054, 0.158, 1.03
No. of reflections	2630
No. of parameters	192
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.72, −0.58

Computer programs: *SMART* and *SAINT* (Bruker, 1998), *SHELXS97* (Sheldrick, 2008), *SHELXL2018* (Sheldrick, 2015) and *ORTEP-3 for Windows* (Farrugia, 2012).

4 (*q*, 3H), 5.3 (*s*, 1H), 7.05 (*dd*, 1H), 7.15 (*dd*, 1H), 7.52–7.60 (*t*, 3H). *m*/*z*: 328.086, (*M* + 2) 330.086, 331.06.

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. H atoms were placed at calculated positions in the riding-model approximation, with C—H = 0.95, 1.00 and 0.96 Å for aromatic, methine and methyl H atoms, respectively, and with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H atoms and $1.2U_{eq}(C)$ otherwise.

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full crystallographic data

IUCrData (2019). **4**, x190960 [https://doi.org/10.1107/S241431461900960X]

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Crystal data

$C_{14}H_{14}ClFN_2O_2S$
M_r = 328.78
Triclinic, $P\overline{1}$
a = 7.2599 (5) Å
b = 9.4979 (7) Å
c = 11.9596 (8) Å
α = 106.149 (2)°
β = 90.236 (2)°
γ = 108.939 (2)°
V = 745.18 (9) Å^3
Z = 2
$F(000)$ = 340
D_x = 1.465 Mg m^{-3}
Melting point: 696 K
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 2630 reflections
θ = 2.4–25.0°
μ = 0.41 mm^{-1}
T = 446 K
Block, colorless
0.18 × 0.16 × 0.15 mm

Data collection

Bruker SMART APEX CCD diffractometer
Radiation source: fine-focus sealed tube
ω scans
Absorption correction: multi-scan (SADABS; Bruker, 1998)
T_{min} = 0.930, T_{max} = 0.941
9007 measured reflections
2630 independent reflections
2087 reflections with $I > 2\sigma(I)$
R_{int} = 0.042
θ_{max} = 25.0°, θ_{min} = 2.4°
h = −8→8
k = −11→11
l = −14→14

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.158
S = 1.03
2630 reflections
192 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
$w = 1/[\sigma^2(F_o^2) + (0.0909P)^2 + 1.0474P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 1.72 e Å^{-3}
$\Delta\rho_{min}$ = −0.58 e Å^{-3}

Special details

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

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
S1	0.80640 (12)	0.09215 (10)	0.95796 (7)	0.0197 (3)
Cl1	0.03066 (14)	−0.26657 (11)	0.39379 (8)	0.0338 (3)
O2	0.4590 (3)	0.5730 (3)	0.7799 (2)	0.0226 (6)
F1	−0.0960 (3)	−0.2780 (3)	0.6204 (2)	0.0425 (6)
O1	0.1990 (3)	0.4448 (3)	0.8562 (2)	0.0208 (5)
N2	0.4864 (4)	0.1580 (3)	0.9215 (2)	0.0170 (6)
H2	0.431451	0.099667	0.964027	0.020*
N1	0.7687 (4)	0.3128 (3)	0.8740 (2)	0.0167 (6)
H1	0.888114	0.327771	0.858940	0.020*
C13	0.1221 (5)	−0.0377 (4)	0.7349 (3)	0.0209 (8)
H13	0.068725	−0.053984	0.802681	0.025*
C8	0.2770 (5)	0.0978 (4)	0.7412 (3)	0.0169 (7)
C3	0.3659 (5)	0.4668 (4)	0.8320 (3)	0.0166 (7)
C4	0.3629 (5)	0.2150 (4)	0.8609 (3)	0.0153 (7)
H4	0.254875	0.225653	0.907590	0.018*
C2	0.6770 (5)	0.1905 (4)	0.9151 (3)	0.0162 (7)
C1	0.8217 (5)	0.5621 (4)	0.8419 (3)	0.0212 (8)
H1A	0.838551	0.549769	0.760558	0.032*
H1B	0.945410	0.584707	0.884459	0.032*
H1C	0.772705	0.646242	0.872113	0.032*
C7	0.4830 (6)	0.7615 (5)	0.6824 (4)	0.0304 (9)
H7A	0.607619	0.821085	0.727304	0.046*
H7B	0.423767	0.830729	0.664819	0.046*
H7C	0.501190	0.692882	0.610805	0.046*
C5	0.4835 (5)	0.3742 (4)	0.8520 (3)	0.0153 (7)
C10	0.2735 (5)	0.0099 (4)	0.5308 (3)	0.0233 (8)
H10	0.322306	0.027342	0.462235	0.028*
C14	0.3523 (5)	0.6672 (4)	0.7517 (3)	0.0229 (8)
H14A	0.326826	0.734864	0.822577	0.027*
H14B	0.228463	0.601271	0.705837	0.027*
C6	0.6797 (5)	0.4153 (4)	0.8551 (3)	0.0167 (7)
C9	0.3514 (5)	0.1203 (4)	0.6382 (3)	0.0211 (8)
H9	0.454970	0.210554	0.641312	0.025*
C12	0.0481 (5)	−0.1471 (4)	0.6293 (3)	0.0223 (8)
C11	0.1241 (5)	−0.1249 (4)	0.5265 (3)	0.0245 (8)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0175 (5)	0.0224 (5)	0.0247 (5)	0.0090 (4)	0.0040 (3)	0.0128 (4)
Cl1	0.0348 (6)	0.0350 (6)	0.0249 (5)	0.0135 (5)	−0.0060 (4)	−0.0033 (4)
O2	0.0191 (13)	0.0245 (13)	0.0328 (14)	0.0114 (11)	0.0069 (10)	0.0173 (11)
F1	0.0379 (14)	0.0399 (14)	0.0399 (13)	0.0011 (12)	0.0066 (11)	0.0109 (11)
O1	0.0150 (13)	0.0251 (13)	0.0251 (13)	0.0092 (11)	0.0039 (10)	0.0090 (10)
N2	0.0165 (15)	0.0187 (14)	0.0180 (14)	0.0052 (12)	0.0029 (11)	0.0098 (12)
N1	0.0134 (14)	0.0196 (14)	0.0226 (14)	0.0080 (12)	0.0079 (11)	0.0121 (12)
C13	0.0156 (17)	0.0267 (19)	0.0230 (17)	0.0080 (16)	0.0036 (14)	0.0106 (15)
C8	0.0132 (17)	0.0203 (17)	0.0203 (17)	0.0090 (15)	0.0009 (13)	0.0070 (14)
C3	0.0161 (18)	0.0151 (16)	0.0144 (15)	0.0029 (14)	−0.0010 (13)	0.0008 (13)
C4	0.0135 (17)	0.0198 (17)	0.0163 (16)	0.0077 (14)	0.0032 (13)	0.0084 (14)
C2	0.0182 (18)	0.0153 (16)	0.0134 (15)	0.0037 (14)	0.0013 (13)	0.0037 (13)
C1	0.0159 (18)	0.0209 (18)	0.0291 (19)	0.0063 (15)	0.0019 (14)	0.0112 (15)
C7	0.026 (2)	0.031 (2)	0.046 (2)	0.0152 (18)	0.0095 (18)	0.0225 (19)
C5	0.0171 (18)	0.0161 (16)	0.0130 (15)	0.0057 (14)	0.0018 (13)	0.0048 (13)
C10	0.027 (2)	0.028 (2)	0.0184 (17)	0.0147 (17)	0.0047 (15)	0.0075 (15)
C14	0.0226 (19)	0.0244 (19)	0.0305 (19)	0.0149 (16)	0.0040 (15)	0.0134 (16)
C6	0.0176 (17)	0.0194 (17)	0.0158 (16)	0.0075 (15)	0.0032 (13)	0.0076 (14)
C9	0.0189 (18)	0.0210 (18)	0.0245 (18)	0.0070 (15)	0.0026 (14)	0.0083 (15)
C12	0.0126 (17)	0.0141 (17)	0.036 (2)	0.0019 (15)	−0.0038 (15)	0.0046 (15)
C11	0.024 (2)	0.032 (2)	0.0192 (17)	0.0168 (18)	−0.0049 (15)	0.0010 (15)

Geometric parameters (Å, º)

S1—C2	1.688 (3)	C4—C5	1.515 (4)
Cl1—C11	1.732 (3)	C4—H4	0.9800
O2—C3	1.331 (4)	C1—C6	1.491 (5)
O2—C14	1.460 (4)	C1—H1A	0.9600
F1—C12	1.316 (4)	C1—H1B	0.9600
O1—C3	1.211 (4)	C1—H1C	0.9600
N2—C2	1.324 (4)	C7—C14	1.502 (5)
N2—C4	1.467 (4)	C7—H7A	0.9600
N2—H2	0.8600	C7—H7B	0.9600
N1—C2	1.361 (4)	C7—H7C	0.9600
N1—C6	1.395 (4)	C5—C6	1.347 (5)
N1—H1	0.8600	C10—C11	1.371 (5)
C13—C12	1.365 (5)	C10—C9	1.390 (5)
C13—C8	1.391 (5)	C10—H10	0.9300
C13—H13	0.9300	C14—H14A	0.9700
C8—C9	1.390 (5)	C14—H14B	0.9700
C8—C4	1.527 (4)	C9—H9	0.9300
C3—C5	1.470 (5)	C12—C11	1.391 (5)
C3—O2—C14	117.4 (3)	C14—C7—H7A	109.5
C2—N2—C4	124.3 (3)	C14—C7—H7B	109.5

C2—N2—H2	117.8	H7A—C7—H7B	109.5
C4—N2—H2	117.8	C14—C7—H7C	109.5
C2—N1—C6	123.6 (3)	H7A—C7—H7C	109.5
C2—N1—H1	118.2	H7B—C7—H7C	109.5
C6—N1—H1	118.2	C6—C5—C3	126.0 (3)
C12—C13—C8	120.1 (3)	C6—C5—C4	119.9 (3)
C12—C13—H13	119.9	C3—C5—C4	113.9 (3)
C8—C13—H13	119.9	C11—C10—C9	119.5 (3)
C9—C8—C13	118.7 (3)	C11—C10—H10	120.2
C9—C8—C4	122.2 (3)	C9—C10—H10	120.2
C13—C8—C4	119.1 (3)	O2—C14—C7	105.4 (3)
O1—C3—O2	123.5 (3)	O2—C14—H14A	110.7
O1—C3—C5	123.5 (3)	C7—C14—H14A	110.7
O2—C3—C5	113.0 (3)	O2—C14—H14B	110.7
N2—C4—C5	108.9 (3)	C7—C14—H14B	110.7
N2—C4—C8	109.9 (2)	H14A—C14—H14B	108.8
C5—C4—C8	112.3 (3)	C5—C6—N1	118.7 (3)
N2—C4—H4	108.5	C5—C6—C1	127.9 (3)
C5—C4—H4	108.5	N1—C6—C1	113.3 (3)
C8—C4—H4	108.5	C10—C9—C8	121.0 (3)
N2—C2—N1	116.3 (3)	C10—C9—H9	119.5
N2—C2—S1	123.4 (2)	C8—C9—H9	119.5
N1—C2—S1	120.2 (2)	F1—C12—C13	121.7 (3)
C6—C1—H1A	109.5	F1—C12—C11	117.3 (3)
C6—C1—H1B	109.5	C13—C12—C11	121.0 (3)
H1A—C1—H1B	109.5	C10—C11—C12	119.6 (3)
C6—C1—H1C	109.5	C10—C11—Cl1	120.2 (3)
H1A—C1—H1C	109.5	C12—C11—Cl1	120.3 (3)
H1B—C1—H1C	109.5		

C12—C13—C8—C9	1.1 (5)	N2—C4—C5—C3	−159.6 (2)
C12—C13—C8—C4	−177.4 (3)	C8—C4—C5—C3	78.4 (3)
C14—O2—C3—O1	0.3 (5)	C3—O2—C14—C7	−173.6 (3)
C14—O2—C3—C5	177.6 (3)	C3—C5—C6—N1	−179.4 (3)
C2—N2—C4—C5	−32.1 (4)	C4—C5—C6—N1	−4.0 (4)
C2—N2—C4—C8	91.4 (4)	C3—C5—C6—C1	1.3 (5)
C9—C8—C4—N2	−102.3 (3)	C4—C5—C6—C1	176.7 (3)
C13—C8—C4—N2	76.1 (4)	C2—N1—C6—C5	−15.2 (5)
C9—C8—C4—C5	19.2 (4)	C2—N1—C6—C1	164.2 (3)
C13—C8—C4—C5	−162.4 (3)	C11—C10—C9—C8	−1.6 (5)
C4—N2—C2—N1	16.7 (4)	C13—C8—C9—C10	−0.1 (5)
C4—N2—C2—S1	−165.0 (2)	C4—C8—C9—C10	178.4 (3)
C6—N1—C2—N2	9.3 (4)	C8—C13—C12—F1	178.7 (3)
C6—N1—C2—S1	−169.1 (2)	C8—C13—C12—C11	−0.6 (5)
O1—C3—C5—C6	−162.2 (3)	C9—C10—C11—C12	2.2 (5)
O2—C3—C5—C6	20.5 (5)	C9—C10—C11—Cl1	−177.9 (3)
O1—C3—C5—C4	22.2 (4)	F1—C12—C11—C10	179.6 (3)
O2—C3—C5—C4	−155.2 (3)	C13—C12—C11—C10	−1.1 (5)

N2—C4—C5—C6	24.5 (4)	F1—C12—C11—Cl1	−0.4 (4)
C8—C4—C5—C6	−97.6 (3)	C13—C12—C11—Cl1	179.0 (3)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···S1^{i}	0.86	2.47	3.301 (1)	163
N1—H1···O1^{ii}	0.86	2.17	2.998 (2)	160
C1—H1*A*···F1^{iii}	0.96	2.60	3.368 (3)	137
C7—H7*B*···*Cg*^{iv}	0.96	2.62	3.577 (1)	168

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