

Marília S. Costa,^a Nubia Boechat,^a Vitor F. Ferreira,^b Solange M. S. V. Wardell^a and Janet M. S. Skakle^{c*}

^aFundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos, Departamento de Síntese Orgânica, Manguinhos, CEP 21041-250 Rio de Janeiro, RJ, Brazil, ^bUniversidade Federal Fluminense, Departamento de Química Orgânica, Instituto de Química, Outeiro de São João Baptista, CEP 24020-150 Niterói, RJ, Brazil, and ^cDepartment of Chemistry, College of Physical Sciences, University of Aberdeen, Meston Walk, Aberdeen AB24 3UE, Scotland

Correspondence e-mail: j.skakle@abdn.ac.uk

Key indicators

Single-crystal X-ray study
 $T = 120\text{ K}$
 Mean $\sigma(\text{C}-\text{C}) = 0.004\text{ \AA}$
 R factor = 0.062
 wR factor = 0.160
 Data-to-parameter ratio = 15.2

For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

4-Difluoromethyl-1-(4-methylphenyl)-1H-1,2,3-triazole

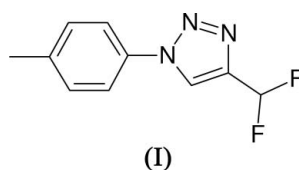
In the crystal structure of the title compound, $\text{C}_{10}\text{H}_9\text{F}_2\text{N}_3$, weak hydrogen bonding involving the triazole and difluoromethyl groups leads to the formation of chains along [010]. The benzene and triazole rings are essentially coplanar, with an angle of $0.34(17)^\circ$ between the planes defined by the two rings.

Received 11 April 2006

Accepted 11 April 2006

Comment

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a leading cause of mortality worldwide. The World Health Organization estimates that about one-third of the world's population harbours latent infection of TB. Among such infected individuals, approximately eight million develop active TB, and almost two million of these die from the disease each year. 95% of new TB cases occur in developing countries. The current human immunodeficiency virus (AIDS) pandemic and resistance to the currently available drugs are proving major obstacles to the control of tuberculosis (Tewari *et al.*, 2004; World Health Organization, 2005; Tripathi *et al.*, 2005). Chemotherapy of TB started in the 1940s. Various drugs have been used against TB, including *para*-aminosalicylic acid, isoniazid, pyrazinamide, cycloserine, ethionamide, rifampicin and ethambutol. However, six decades have passed without any significant development of new chemical treatments of tuberculosis. TB really can be classed as a neglected disease.



In pursuit of new drugs for TB, we have synthesized a series of 1-aryl-4-difluoromethyl-1,2,3-triazole derivatives and evaluated their inhibitory activities against *Mycobacterium tuberculosis*. All derivatives exhibited tuberculosis inhibitory activity; a full description of biological tests will be reported elsewhere (Costa, Boechat, Rangel *et al.*, 2006). The structure of 1-(4-methylphenyl)-4-difluoromethyl-1H-1,2,3-triazole, which exhibited 87% of inhibition at a concentration of $40.0\text{ }\mu\text{g ml}^{-1}$, is reported here.

The geometry of the title molecular structure (Fig. 1) was analysed with the aid of *PLATON* (Spek, 2003). The methyl group is almost coplanar with the aryl ring, with a torsion angle $\text{C}7-\text{C}8-\text{C}9-\text{C}91 = 178.2(3)^\circ$. Excluding the difluoromethyl group, the molecule is planar, with an angle between the planes defined by the triazole and aryl rings of

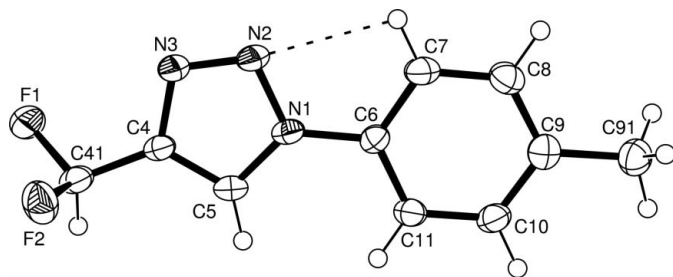


Figure 1
The molecular structure of the title compound, showing displacement ellipsoids at the 50% probability level. H atoms are shown as circles of arbitrary radii and the dashed line indicates a weak hydrogen bond.

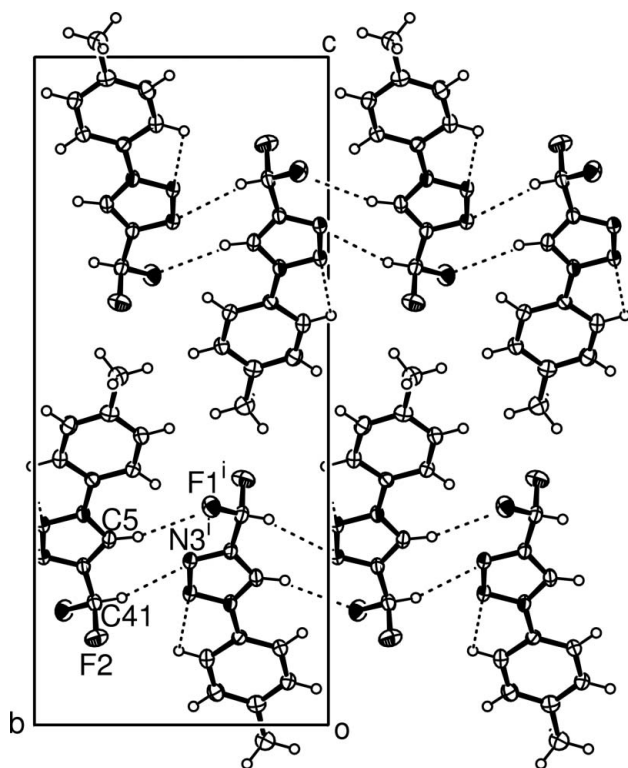


Figure 2
Part of the structure of the title compound, showing the formation of hydrogen-bonded (dashed lines) chains along [010]. Ellipsoids and H atoms are shown as in Fig. 1. [Symmetry code: (i) $\frac{3}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z$].

0.34 (17) Å. This is in marked contrast to the orientations in 1-(2,5-dimethoxyphenyl)-4-difluoromethyl-1*H*-1,2,3-triazole (Costa, Boechat, Ferreira, Wardell & Skakle, 2006), in which the substituent methoxy groups on the aryl ring cause a marked deviation from planarity.

With no scope for strong hydrogen bonding in the structure, weak hydrogen bonds exist (Table 1); an intramolecular hydrogen bond provides additional support between the triazole and aryl ring (C7–H7···N2). All other hydrogen bonds involve donors and acceptors within the triazole–difluoromethyl unit, and lead to the formation of chains along [010] (Fig. 2).

Experimental

A solution of diazomalonaldehyde (5.0 mmol) in water (30 ml) was added dropwise to a stirred solution of 4-aminotoluene hydrochloride (4.5 mmol) in water (5 ml). The reaction mixture was stirred for 24 h at room temperature; the solid was collected, washed with cold water and crystallized from aqueous ethanol. The title compound was obtained in 93% yield as colourless solid, m.p. 351–352 K. Analysis calculated for C₁₀H₉F₂N₃: C 57.41, H 4.34, N 20.09%; found: C 57.45, H 4.37, N 19.97%. Full spectroscopic data are given in the CIF.

Crystal data

C ₁₀ H ₉ F ₂ N ₃	Z = 4
<i>M_r</i> = 209.20	<i>D_x</i> = 1.492 Mg m ⁻³
Monoclinic, <i>P</i> 2 ₁ / <i>n</i>	Mo <i>K</i> α radiation
<i>a</i> = 4.6055 (6) Å	<i>μ</i> = 0.12 mm ⁻¹
<i>b</i> = 9.4285 (9) Å	<i>T</i> = 120 (2) K
<i>c</i> = 21.459 (3) Å	Cut blade, colourless
<i>β</i> = 92.136 (5)°	0.22 × 0.11 × 0.03 mm
<i>V</i> = 931.2 (2) Å ³	

Data collection

Bruker–Nonius KappaCCD diffractometer	8742 measured reflections
<i>φ</i> and <i>ω</i> scans	2112 independent reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2003)	1262 reflections with <i>I</i> > 2σ(<i>I</i>)
<i>T_{min}</i> = 0.636, <i>T_{max}</i> = 1.000	<i>R_{int}</i> = 0.071
	<i>θ_{max}</i> = 27.7°

Refinement

Refinement on <i>F</i> ²	$w = 1/[\sigma^2(F_o^2) + (0.0577P)^2 + 0.6473P]$
$R[F^2 > 2\sigma(F^2)] = 0.062$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.160$	(Δ/σ) _{max} < 0.001
<i>S</i> = 1.03	$\Delta\rho_{max} = 0.24 \text{ e } \text{Å}^{-3}$
2112 reflections	$\Delta\rho_{min} = -0.32 \text{ e } \text{Å}^{-3}$
139 parameters	
H-atom parameters constrained	

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

<i>D</i> –H··· <i>A</i>	<i>D</i> –H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> –H··· <i>A</i>
C7–H7···N2	0.95	2.45	2.780 (3)	100
C5–H5···F1 ⁱ	0.93	2.52	3.421 (3)	164
C41–H41···N2 ⁱ	1.00	2.46	3.458 (3)	173
C41–H41···N3 ⁱ	1.00	2.47	3.403 (3)	155

Symmetry code: (i) $-x + \frac{3}{2}, y - \frac{1}{2}, -z + \frac{1}{2}$.

All H atoms were located in difference maps and then treated as riding atoms, with C–H distances of 0.93 Å (triazole), 0.95 Å (aryl), 1.00 Å (tertiary –CHF₂) and 0.98 Å (methyl). *U*_{iso} values for the triazole and tertiary H were freely refined; otherwise *U*_{iso}(H) values were set at 1.2*U*_{eq}(aryl C) or 1.5*U*_{eq}(methyl C).

Data collection: COLLECT (Hooft, 1998); cell refinement: DENZO (Otwinowski & Minor, 1997) and COLLECT; data reduction: DENZO and COLLECT; program(s) used to solve structure: OSCAIL (McArdle, 2003) and SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: OSCAIL and SHELXL97 (Sheldrick, 1997); molecular graphics: ORTEP-3 for Windows (Farrugia, 1997); software used to prepare material for publication: CIFTAB (Sheldrick, 1997).

We are indebted to the EPSRC for the use of both the Chemical Database Service at Daresbury, England, primarily for access to the Cambridge Structural Database (Fletcher *et*

al., 1996), and the X-ray service at the University of Southampton, England, for data collection.

References

- Costa, M. S., Boechat, N., Ferreira, V. F., Wardell, S. M. V. & Skakle, J. M. S. (2006). *Acta Cryst.* **E62**, o2048–o2050.
- Costa, M. S., Boechat, N., Rangel, E. A., Ferreira, V. F., Junior, I. N., Lourenço, M. C. S. & Wardell, S. M. S. V. (2006). *Eur. J. Med. Chem.* In preparation.
- Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
- Fletcher, D. A., McMeeking, R. F. & Parkin, D. (1996). *J. Chem. Inf. Comput. Sci.* **36**, 746–749.
- Hooft, R. W. W. (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
- McArdle, P. (2003). *OSCAIL for Windows*. Version 10. Crystallography Centre, Chemistry Department, National University of Ireland, Galway, Ireland.
- Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
- Sheldrick, G. M. (1997). *SHELXS97*, *SHELXL97* and *CIFTAB*. University of Göttingen, Germany.
- Sheldrick, G. M. (2003). *SADABS*. Version 2.10. University of Göttingen, Germany.
- Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
- Tewari, N., Tiwari, V. K., Tripathi, R. P., Chaturvedi, V., Srivastava, A., Srivastava, R., Shukla, P. K., Chaturvedi, A. K., Gaikwad, A., Sinha, S. & Srivastava, B. S. (2004). *Bioorg. Med. Chem. Lett.* **14**, 329–332.
- Tripathi, R. P., Tewari, N., Dwivedi, N. & Tiwari, V. K. (2005). *Med. Res. Rev.* **25**, 93–131.
- World Health Organization (2005). Report WHO/HTM/TB/2005. *Global Tuberculosis Control – Surveillance, Planning, Financing*. <http://www.who.int/tb>.

supporting information

Acta Cryst. (2006). E62, o1925–o1927 [https://doi.org/10.1107/S1600536806013286]

4-Difluoromethyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole

Marilia S. Costa, Nubia Boechat, Vitor F. Ferreira, Solange M. S. V. Wardell and Janet M. S. Skakle

4-Difluoromethyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole*Crystal data*

$C_{10}H_9F_2N_3$

$M_r = 209.20$

Monoclinic, $P2_1/n$

Hall symbol: -P 2yn

$a = 4.6055$ (6) Å

$b = 9.4285$ (9) Å

$c = 21.459$ (3) Å

$\beta = 92.136$ (5)°

$V = 931.2$ (2) Å³

$Z = 4$

$F(000) = 432$

$D_x = 1.492$ Mg m⁻³

Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å

Cell parameters from 1891 reflections

$\theta = 2.9$ – 27.5 °

$\mu = 0.12$ mm⁻¹

$T = 120$ K

Cut blade, colourless

$0.22 \times 0.11 \times 0.03$ mm

Data collection

Bruker–Nonius KappaCCD
diffractometer

Radiation source: Bruker–Nonius FR591
rotating anode

10 cm confocal mirrors monochromator

Detector resolution: 9.091 pixels mm⁻¹

φ and ω scans

Absorption correction: multi-scan
(SADABS; Sheldrick, 2003)

$T_{\min} = 0.636$, $T_{\max} = 1.000$

8742 measured reflections

2112 independent reflections

1262 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.071$

$\theta_{\max} = 27.7$ °, $\theta_{\min} = 3.6$ °

$h = -5 \rightarrow 6$

$k = -10 \rightarrow 12$

$l = -27 \rightarrow 18$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.062$

$wR(F^2) = 0.160$

$S = 1.03$

2112 reflections

139 parameters

0 restraints

Primary atom site location: structure-invariant
direct methods

Secondary atom site location: difference Fourier
map

Hydrogen site location: difference Fourier map

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0577P)^2 + 0.6473P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} < 0.001$

$\Delta\rho_{\max} = 0.24$ e Å⁻³

$\Delta\rho_{\min} = -0.32$ e Å⁻³

Special details

Experimental. IR (KBr, ν_{\max} , cm^{-1}): 3162, 1031, 3152, 1043. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{Me}_4\text{Si}$): δ 2.43 (s, 1H, CH_3), 6.94 (t, 1H, CF_2H , $J = 54.5$ Hz), 7.31 (d, 2H, $J = 8.8$ Hz, arom.), 7.60 (d, 2H, $J = 8.8$ Hz, arom.), 8.18 (s, 1H, triazole); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{Me}_4\text{Si}$): δ 20.5 (CH_3), 109.5 (t, CF_2H , $J = 233.4$ Hz), 119.9, 139.1, 133.6, 129.8, 120.1, 142.7 (t, $J = 28.5$ Hz); ^{19}F NMR (376.0 MHz, $\text{CDCl}_3/\text{CFCl}_3$): δ -112.3 (2 F, CHF_2); EIMS (m/z): 209 (M^+ , 42%), 180 (M^+ -29, 68%), 162 (M^+ -47, 40%), 130 (M^+ -79, 42%), 91 (M^+ -118, 100%).

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 (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
N1	0.3195 (5)	0.8343 (2)	0.31724 (10)	0.0260 (5)
N2	0.3710 (5)	0.9715 (2)	0.30179 (11)	0.0310 (6)
N3	0.5439 (5)	0.9707 (2)	0.25457 (10)	0.0295 (6)
C4	0.6035 (5)	0.8331 (3)	0.24014 (12)	0.0250 (6)
C41	0.7803 (6)	0.7957 (3)	0.18634 (13)	0.0302 (7)
H41	0.8804	0.7028	0.1939	0.039 (8)*
F1	0.9784 (3)	0.89866 (16)	0.17542 (8)	0.0393 (5)
F2	0.6082 (3)	0.78929 (19)	0.13270 (8)	0.0431 (5)
C5	0.4641 (5)	0.7459 (3)	0.27948 (12)	0.0255 (6)
H5	0.4614	0.6481	0.2836	0.020 (7)*
C6	0.1326 (5)	0.8032 (3)	0.36744 (12)	0.0237 (6)
C7	0.0059 (6)	0.9134 (3)	0.39883 (13)	0.0308 (7)
H7	0.0411	1.0089	0.3872	0.037*
C8	-0.1735 (6)	0.8830 (3)	0.44753 (13)	0.0331 (7)
H8	-0.2600	0.9591	0.4692	0.040*
C9	-0.2305 (5)	0.7448 (3)	0.46568 (13)	0.0295 (7)
C91	-0.4185 (6)	0.7151 (3)	0.51982 (14)	0.0363 (7)
H91A	-0.3959	0.6157	0.5324	0.047*
H92B	-0.6221	0.7335	0.5076	0.047*
H93C	-0.3601	0.7768	0.5549	0.047*
C10	-0.1033 (6)	0.6371 (3)	0.43229 (13)	0.0308 (7)
H10	-0.1404	0.5414	0.4433	0.037*
C11	0.0768 (6)	0.6648 (3)	0.38327 (12)	0.0279 (6)
H11	0.1605	0.5890	0.3609	0.033*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0313 (12)	0.0172 (11)	0.0294 (13)	-0.0014 (9)	-0.0006 (10)	0.0012 (10)
N2	0.0445 (14)	0.0177 (12)	0.0309 (14)	-0.0011 (10)	0.0047 (12)	0.0025 (10)
N3	0.0411 (14)	0.0194 (12)	0.0283 (13)	-0.0006 (10)	0.0045 (11)	0.0014 (10)

C4	0.0294 (14)	0.0180 (13)	0.0274 (15)	-0.0021 (11)	-0.0009 (12)	0.0012 (11)
C41	0.0373 (16)	0.0207 (14)	0.0323 (17)	-0.0031 (12)	-0.0006 (13)	0.0034 (12)
F1	0.0369 (9)	0.0341 (10)	0.0475 (11)	-0.0100 (7)	0.0101 (8)	-0.0035 (8)
F2	0.0420 (10)	0.0563 (12)	0.0311 (10)	-0.0080 (8)	0.0021 (8)	-0.0078 (8)
C5	0.0270 (13)	0.0177 (14)	0.0314 (16)	0.0002 (11)	-0.0036 (12)	-0.0013 (11)
C6	0.0254 (13)	0.0229 (14)	0.0226 (14)	-0.0026 (11)	-0.0012 (11)	0.0017 (11)
C7	0.0342 (15)	0.0213 (14)	0.0370 (17)	0.0008 (12)	0.0008 (13)	-0.0006 (12)
C8	0.0315 (15)	0.0303 (15)	0.0375 (17)	0.0046 (12)	0.0021 (13)	-0.0037 (13)
C9	0.0223 (13)	0.0363 (17)	0.0297 (16)	-0.0014 (12)	-0.0035 (12)	0.0003 (13)
C91	0.0312 (15)	0.0401 (17)	0.0377 (18)	-0.0033 (13)	0.0037 (13)	-0.0010 (14)
C10	0.0387 (16)	0.0235 (14)	0.0302 (16)	-0.0047 (12)	0.0005 (13)	0.0022 (12)
C11	0.0335 (15)	0.0225 (14)	0.0276 (15)	0.0006 (11)	0.0000 (12)	-0.0023 (12)

Geometric parameters (Å, °)

N1—C5	1.355 (3)	C7—C8	1.386 (4)
N1—N2	1.358 (3)	C7—H7	0.9500
N1—C6	1.434 (3)	C8—C9	1.388 (4)
N2—N3	1.312 (3)	C8—H8	0.9500
N3—C4	1.364 (3)	C9—C10	1.385 (4)
C4—C5	1.357 (4)	C9—C91	1.501 (4)
C4—C41	1.480 (4)	C91—H91A	0.9800
C41—F1	1.358 (3)	C91—H92B	0.9800
C41—F2	1.374 (3)	C91—H93C	0.9800
C41—H41	1.0000	C10—C11	1.388 (4)
C5—H5	0.9262	C10—H10	0.9500
C6—C11	1.375 (4)	C11—H11	0.9500
C6—C7	1.380 (4)		
C5—N1—N2	110.2 (2)	C6—C7—H7	120.4
C5—N1—C6	130.2 (2)	C8—C7—H7	120.4
N2—N1—C6	119.6 (2)	C7—C8—C9	122.0 (2)
N3—N2—N1	107.44 (19)	C7—C8—H8	119.0
N2—N3—C4	108.3 (2)	C9—C8—H8	119.0
C5—C4—N3	109.3 (2)	C10—C9—C8	117.0 (2)
C5—C4—C41	128.9 (2)	C10—C9—C91	122.1 (2)
N3—C4—C41	121.7 (2)	C8—C9—C91	120.9 (2)
F1—C41—F2	104.9 (2)	C9—C91—H91A	109.5
F1—C41—C4	110.9 (2)	C9—C91—H92B	109.5
F2—C41—C4	110.3 (2)	H91A—C91—H92B	109.5
F1—C41—H41	110.2	C9—C91—H93C	109.5
F2—C41—H41	110.2	H91A—C91—H93C	109.5
C4—C41—H41	110.2	H92B—C91—H93C	109.5
N1—C5—C4	104.7 (2)	C9—C10—C11	122.0 (2)
N1—C5—H5	123.2	C9—C10—H10	119.0
C4—C5—H5	132.1	C11—C10—H10	119.0
C11—C6—C7	120.5 (2)	C6—C11—C10	119.2 (2)
C11—C6—N1	120.2 (2)	C6—C11—H11	120.4

C7—C6—N1	119.3 (2)	C10—C11—H11	120.4
C6—C7—C8	119.1 (2)		
C5—N1—N2—N3	0.5 (3)	N2—N1—C6—C11	179.5 (2)
C6—N1—N2—N3	-179.3 (2)	C5—N1—C6—C7	-179.1 (3)
N1—N2—N3—C4	-0.3 (3)	N2—N1—C6—C7	0.6 (4)
N2—N3—C4—C5	-0.1 (3)	C11—C6—C7—C8	1.5 (4)
N2—N3—C4—C41	176.5 (2)	N1—C6—C7—C8	-179.7 (2)
C5—C4—C41—F1	-153.8 (3)	C6—C7—C8—C9	-0.2 (4)
N3—C4—C41—F1	30.4 (4)	C7—C8—C9—C10	-0.9 (4)
C5—C4—C41—F2	90.4 (3)	C7—C8—C9—C91	178.2 (3)
N3—C4—C41—F2	-85.4 (3)	C8—C9—C10—C11	0.8 (4)
N2—N1—C5—C4	-0.5 (3)	C91—C9—C10—C11	-178.2 (3)
C6—N1—C5—C4	179.3 (3)	C7—C6—C11—C10	-1.5 (4)
N3—C4—C5—N1	0.3 (3)	N1—C6—C11—C10	179.6 (2)
C41—C4—C5—N1	-175.8 (3)	C9—C10—C11—C6	0.4 (4)
C5—N1—C6—C11	-0.2 (4)		

Hydrogen-bond geometry (Å, °)

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
C7—H7...N2	0.95	2.45	2.780 (3)	100
C5—H5...F1 ⁱ	0.93	2.52	3.421 (3)	164
C41—H41...N2 ⁱ	1.00	2.46	3.458 (3)	173
C41—H41...N3 ⁱ	1.00	2.47	3.403 (3)	155

Symmetry code: (i) $-x+3/2, y-1/2, -z+1/2$.