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3-(2-Fluorophenyl)-6-(phenoxymethyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole

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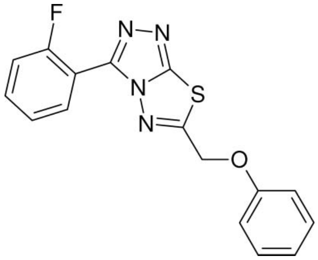
Key indicators: single-crystal X-ray study; T = 193 K; mean σ(C–C) = 0.003 Å; R factor = 0.048; wR factor = 0.136; data-to-parameter ratio = 13.1.

The crystal structure of the title compound, $C_{16}H_{11}FN_4OS$, was synthesized in the course of our studies on 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles as inhibitors of p38 mitogen-activated protein kinase (MAPK). The three-dimensional data obtained were used to generate a three-dimensional pharmacophore model for *in silico* database screening. The dihedral angles between the central heterocylic system and the fluorophenyl and phenyl rings are 20.21 (3) and 5.43 (1)°, respectively; the dihedral angle between the two benzene rings is 15.80 (4)°.

Related literature

Protein kinases (PK) are favoured targets for the development of new drugs (Hopkins & Groon, 2002) because the reversible protein-phosphorylation by PK is an important control mechanism in the signal pathways of a cell (Laufer *et al.*, 2005). The [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole nucleus is associated with diverse biological activities (Malhotra *et al.*, 2003). For the preparation of the title compound, see: Invidiata *et al.* (1997); Malhotra *et al.* (2003).



Experimental

Crystal data

$C_{16}H_{11}FN_4OS$	V = 1442.61 (11) Å^3
M_r = 326.35	Z = 4
Monoclinic, $P2_1/n$	Cu $K\alpha$ radiation
a = 10.8551 (6) Å	μ = 2.19 mm^{-1}
b = 12.1899 (3) Å	T = 193 (2) K
c = 11.6667 (6) Å	0.58 × 0.51 × 0.26 mm
β = 110.857 (5)°	

Data collection

Enraf–Nonius CAD-4 diffractometer	2883 measured reflections
Absorption correction: ψ scan (*CORINC*; Dräger & Gattow, 1971)	2736 independent reflections
T_{min} = 0.61, T_{max} = 0.99 (expected range = 0.348–0.565)	2583 reflections with $I > 2\sigma(I)$
	R_{int} = 0.037
	3 standard reflections frequency: 60 min intensity decay: 4%

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048	209 parameters
$wR(F^2)$ = 0.135	H-atom parameters constrained
S = 1.06	$\Delta\rho_{max}$ = 0.43 e Å^{-3}
2736 reflections	$\Delta\rho_{min}$ = −0.43 e Å^{-3}

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *CORINC* (Dräger & Gattow, 1971); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

We are grateful to BERGHOF Products & Instruments GmbH, Eningen, Germany for the BR-25 high pressure reactor and for technical support.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: BT2678).

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supporting information

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3-(2-Fluorophenyl)-6-(phenoxymethyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole

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S1. Comment

Continued interest in development of small molecule inhibitors of p38 mitogen-activated protein (MAP) kinase is based on the central role of this enzyme in inflammatory cell signalling. Activation of p38 leads to an increase production of pro-inflammatory cytokines such as TNF-alpha and IL-1beta. Many different diseases have their seeds in an overactive immune response. Prominent examples like psoriasis, rheumatoid arthritis and inflammatory bowel disease turn it into a still prominent target for antiinflammatory drug discovery. 3-(2-chlorophenyl)-6-((4-methoxyphenoxy)-methyl)-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole was identified as potential hit in a virtual screening and the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole core therefore chosen as starting point for a medicinal chemistry program. To gain more information about structure-activity relationship, a series of compounds were synthesized and tested.

The synthesis of **1** (Figure 1) was started from the substituted hydrazide, which was treated with carbon disulfide. Cyclization followed by reaction with hydrazine. The final product **2** was synthesized by reaction of **1** with 2-phenoxy-acetic acid in presence of phosphorus oxychloride.

Of special interest was the proposed binding mode of disubstituted compound and a crystal structure of compound **2** was prepared (Figure 2).

S2. Experimental

The synthesis of 3-(2-fluorophenyl)-6-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole was started from 2-fluorobenzohydrazide. Carbon disulfide (55.0 mmol) was added slowly to a solution of the hydrazide (36.0 mmol) in absolute ethanol (70 ml) containing potassium hydroxid (55.0 mmol). The resulting mixture was stirred over night at room temperature, then cooled and diluted with ether (100 ml). Potassium 2-(2-fluorobenzoyl)hydrazinecarbodithioate precipitated and was collected by filtration, washed with diethyl ether and dried.

A mixture containing potassium dithiocarbazinate (16.0 mmol) suspended in water (2 ml) and hydrazine hydrate (99%, 32.0 mmol) was heated under gentle reflux for 2 h. It was cooled to room temperature and diluted with water (80 ml) and acidified with concentrated hydrochloric acid. Thick white solid mass separated out. It was collected by filtration, washed with water and recrystallized from ethanol to get 4-amino-5-(2-fluorophenyl)-4*H*-1,2,4-triazole-3-thiol **1**. (Invidiata *et al.*, 1997)

For the preparation of the title compound, a mixture of **1** (5.0 mmol), 2-phenoxyacetic acid (1.0 mmol) and phosphorus oxychloride (10 ml) was refluxed for 6 h, cooled to room temperature and poured onto crushed ice. The solid product separated out and was collected by filtration, washed with aqueous NaOH solution (20 ml, 2 *M*) and then with water, dried and recrystallized from ethanol **2**. (Malhotra *et al.*, 2003)

Crystals of **2** for X-ray analysis precipitated slowly as brown platelets from ethanol at room temperature.

S3. Refinement

Hydrogen atoms were placed at calculated positions with C—H=0.95A% (aromatic) or 0.99 Å (*sp*[3] C-atom). All H atoms were refined with isotropic displacement parameters set at 1.2 times of the U_{eq} of the parent atom.

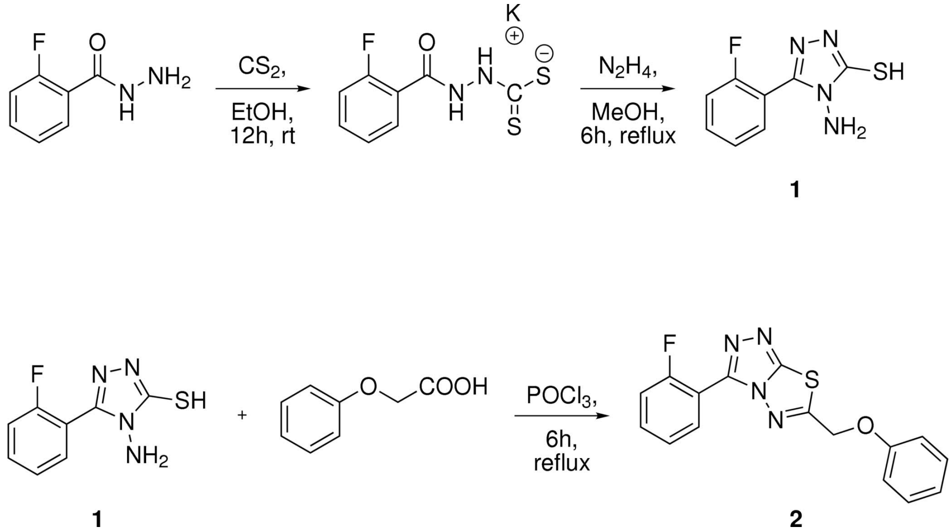

Figure 1

Synthesis of compounds **1** and **2**.

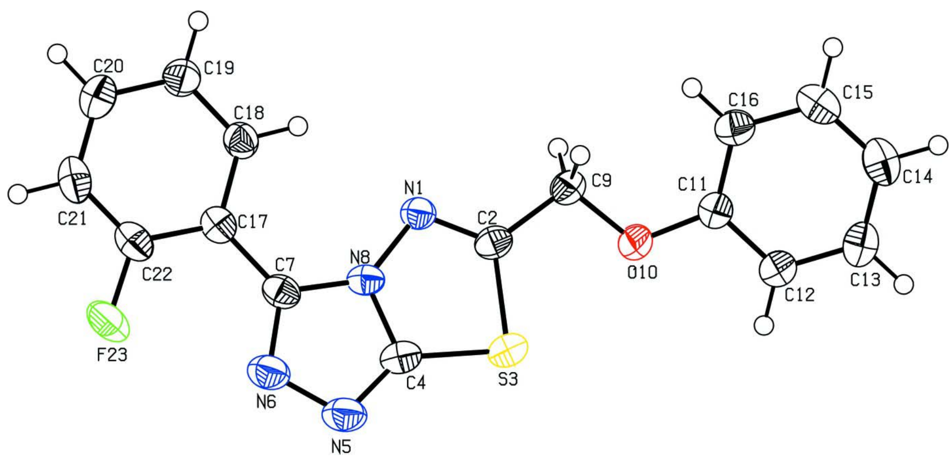

Figure 2

Perspective view of **2**. Displacement ellipsoids are drawn at the 50% probability level. H atoms are depicted as circles of arbitrary size.

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Crystal data

$C_{16}H_{11}FN_4OS$
$M_r = 326.35$
Monoclinic, $P2_1/n$
Hall symbol: -P 2yn
$a = 10.8551$ (6) Å
$b = 12.1899$ (3) Å
$c = 11.6667$ (6) Å
$\beta = 110.857$ (5)°
$V = 1442.61$ (11) Å^3
$Z = 4$
$F(000) = 672$
$D_x = 1.503$ Mg m^{-3}
Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
Cell parameters from 25 reflections

θ = 65–70°
μ = 2.19 mm^{-1}
T = 193 K

Plate, light brown
0.58 × 0.51 × 0.26 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Radiation source: rotating anode
Graphite monochromator
$\omega/2\theta$ scans
Absorption correction: ψ scan (CORINC; Dräger & Gattow, 1971)
T_{min} = 0.61, T_{max} = 0.99
2883 measured reflections

2736 independent reflections
2583 reflections with $I > 2s(I)$
R_{int} = 0.037
θ_{max} = 69.9°, θ_{min} = 4.8°
h = 0→13
k = 0→14
l = −14→13
3 standard reflections every 60 min
intensity decay: 4%

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.135
S = 1.06
2736 reflections
209 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
$w = 1/[\sigma^2(F_o^2) + (0.0847P)^2 + 0.6884P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ < 0.001
$\Delta\rho_{max}$ = 0.43 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 2008), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient: 0.0071 (8)

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}
N1	0.65749 (15)	0.29912 (12)	0.27951 (14)	0.0311 (4)
C2	0.62295 (17)	0.25592 (16)	0.17147 (17)	0.0324 (4)
S3	0.63057 (5)	0.11269 (4)	0.16086 (4)	0.0375 (2)
C4	0.68622 (19)	0.11015 (15)	0.31907 (19)	0.0358 (4)
N5	0.72177 (18)	0.03789 (14)	0.40767 (17)	0.0445 (4)
N6	0.75709 (18)	0.09854 (14)	0.51539 (17)	0.0426 (4)
C7	0.74119 (17)	0.20439 (15)	0.48900 (18)	0.0331 (4)
N8	0.69477 (14)	0.21442 (12)	0.36353 (14)	0.0306 (4)
C9	0.58296 (19)	0.32345 (16)	0.05735 (17)	0.0358 (4)
H9A	0.5190	0.3806	0.0593	0.043*
H9B	0.6607	0.3596	0.0484	0.043*

O10	0.52441 (15)	0.24906 (12)	−0.04087 (12)	0.0433 (4)
C11	0.50482 (17)	0.28429 (16)	−0.15846 (17)	0.0326 (4)
C12	0.45545 (19)	0.20490 (17)	−0.24815 (18)	0.0376 (4)
H12	0.4366	0.1333	−0.2266	0.045*
C13	0.4337 (2)	0.23046 (19)	−0.36915 (19)	0.0436 (5)
H13	0.4012	0.1759	−0.4308	0.052*
C14	0.4591 (2)	0.3350 (2)	−0.40103 (19)	0.0451 (5)
H14	0.4442	0.3524	−0.4843	0.054*
C15	0.5060 (2)	0.41365 (19)	−0.3114 (2)	0.0439 (5)
H15	0.5220	0.4858	−0.3336	0.053*
C16	0.5303 (2)	0.38932 (16)	−0.1887 (2)	0.0378 (5)
H16	0.5637	0.4437	−0.1271	0.045*
C17	0.77445 (17)	0.29576 (16)	0.57653 (17)	0.0323 (4)
C18	0.76314 (19)	0.40498 (16)	0.53692 (18)	0.0345 (4)
H18	0.7312	0.4204	0.4515	0.041*
C19	0.79764 (19)	0.49076 (17)	0.61989 (18)	0.0390 (4)
H19	0.7895	0.5642	0.5909	0.047*
C20	0.8439 (2)	0.47064 (19)	0.74481 (19)	0.0426 (5)
H20	0.8664	0.5297	0.8016	0.051*
C21	0.8569 (2)	0.3633 (2)	0.78588 (19)	0.0451 (5)
H21	0.8895	0.3480	0.8713	0.054*
C22	0.8224 (2)	0.27895 (18)	0.70268 (19)	0.0399 (5)
F23	0.83678 (15)	0.17577 (12)	0.74746 (12)	0.0608 (4)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0311 (7)	0.0273 (8)	0.0325 (8)	0.0000 (6)	0.0082 (6)	0.0011 (6)
C2	0.0281 (8)	0.0299 (9)	0.0381 (10)	−0.0027 (7)	0.0105 (7)	−0.0040 (7)
S3	0.0402 (3)	0.0294 (3)	0.0430 (3)	−0.00168 (17)	0.0147 (2)	−0.00653 (18)
C4	0.0330 (10)	0.0276 (10)	0.0457 (11)	−0.0003 (7)	0.0126 (8)	−0.0033 (8)
N5	0.0482 (10)	0.0293 (9)	0.0522 (10)	0.0041 (7)	0.0134 (8)	0.0039 (7)
N6	0.0453 (10)	0.0317 (9)	0.0464 (10)	0.0027 (7)	0.0111 (8)	0.0066 (7)
C7	0.0283 (8)	0.0320 (10)	0.0375 (10)	0.0007 (7)	0.0099 (7)	0.0059 (7)
N8	0.0279 (7)	0.0244 (7)	0.0375 (8)	0.0009 (6)	0.0092 (6)	0.0011 (6)
C9	0.0390 (10)	0.0318 (10)	0.0325 (10)	−0.0051 (7)	0.0075 (8)	−0.0044 (7)
O10	0.0606 (9)	0.0355 (8)	0.0316 (7)	−0.0147 (6)	0.0137 (6)	−0.0050 (6)
C11	0.0304 (9)	0.0348 (10)	0.0322 (9)	0.0007 (7)	0.0107 (7)	−0.0011 (7)
C12	0.0398 (10)	0.0348 (10)	0.0375 (10)	−0.0024 (8)	0.0129 (8)	−0.0026 (8)
C13	0.0416 (10)	0.0532 (13)	0.0341 (10)	0.0000 (9)	0.0112 (8)	−0.0062 (9)
C14	0.0370 (10)	0.0612 (14)	0.0369 (11)	0.0034 (10)	0.0129 (8)	0.0081 (10)
C15	0.0377 (10)	0.0433 (11)	0.0495 (12)	0.0011 (9)	0.0141 (9)	0.0132 (9)
C16	0.0358 (10)	0.0340 (11)	0.0425 (11)	−0.0018 (7)	0.0125 (8)	−0.0018 (8)
C17	0.0262 (8)	0.0365 (10)	0.0334 (9)	0.0009 (7)	0.0097 (7)	0.0038 (7)
C18	0.0345 (9)	0.0356 (10)	0.0314 (9)	0.0036 (8)	0.0094 (7)	0.0030 (7)
C19	0.0412 (10)	0.0364 (10)	0.0378 (10)	0.0054 (8)	0.0119 (8)	0.0006 (8)
C20	0.0404 (10)	0.0500 (13)	0.0377 (10)	0.0005 (9)	0.0144 (8)	−0.0083 (9)
C21	0.0468 (11)	0.0600 (14)	0.0293 (10)	−0.0021 (10)	0.0144 (8)	0.0045 (9)

C22	0.0384 (10)	0.0428 (11)	0.0384 (10)	−0.0014 (8)	0.0136 (8)	0.0110 (9)
F23	0.0822 (10)	0.0482 (8)	0.0443 (7)	−0.0076 (7)	0.0128 (7)	0.0186 (6)

Geometric parameters (Å, º)

N1—C2	1.292 (2)	C13—C14	1.382 (3)
N1—N8	1.381 (2)	C13—H13	0.9500
C2—C9	1.492 (3)	C14—C15	1.376 (3)
C2—S3	1.7544 (19)	C14—H14	0.9500
S3—C4	1.726 (2)	C15—C16	1.392 (3)
C4—N5	1.307 (3)	C15—H15	0.9500
C4—N8	1.363 (2)	C16—H16	0.9500
N5—N6	1.389 (3)	C17—C22	1.391 (3)
N6—C7	1.324 (2)	C17—C18	1.400 (3)
C7—N8	1.373 (2)	C18—C19	1.383 (3)
C7—C17	1.467 (3)	C18—H18	0.9500
C9—O10	1.422 (2)	C19—C20	1.384 (3)
C9—H9A	0.9900	C19—H19	0.9500
C9—H9B	0.9900	C20—C21	1.384 (3)
O10—C11	1.380 (2)	C20—H20	0.9500
C11—C16	1.382 (3)	C21—C22	1.371 (3)
C11—C12	1.385 (3)	C21—H21	0.9500
C12—C13	1.381 (3)	C22—F23	1.349 (2)
C12—H12	0.9500		
C2—N1—N8	107.31 (15)	C12—C13—H13	119.8
N1—C2—C9	122.45 (17)	C14—C13—H13	119.8
N1—C2—S3	118.02 (15)	C15—C14—C13	119.5 (2)
C9—C2—S3	119.48 (13)	C15—C14—H14	120.2
C4—S3—C2	87.12 (9)	C13—C14—H14	120.2
N5—C4—N8	111.49 (18)	C14—C15—C16	121.1 (2)
N5—C4—S3	138.59 (15)	C14—C15—H15	119.4
N8—C4—S3	109.92 (14)	C16—C15—H15	119.4
C4—N5—N6	105.39 (16)	C11—C16—C15	118.55 (19)
C7—N6—N5	109.71 (16)	C11—C16—H16	120.7
N6—C7—N8	107.62 (17)	C15—C16—H16	120.7
N6—C7—C17	126.80 (18)	C22—C17—C18	116.43 (19)
N8—C7—C17	125.48 (17)	C22—C17—C7	122.11 (18)
C4—N8—C7	105.78 (16)	C18—C17—C7	121.42 (17)
C4—N8—N1	117.63 (15)	C19—C18—C17	121.19 (18)
C7—N8—N1	136.59 (15)	C19—C18—H18	119.4
O10—C9—C2	105.77 (15)	C17—C18—H18	119.4
O10—C9—H9A	110.6	C18—C19—C20	120.62 (19)
C2—C9—H9A	110.6	C18—C19—H19	119.7
O10—C9—H9B	110.6	C20—C19—H19	119.7
C2—C9—H9B	110.6	C21—C20—C19	119.1 (2)
H9A—C9—H9B	108.7	C21—C20—H20	120.4
C11—O10—C9	117.99 (15)	C19—C20—H20	120.4

O10—C11—C16	124.62 (17)	C22—C21—C20	119.70 (19)
O10—C11—C12	114.51 (17)	C22—C21—H21	120.2
C16—C11—C12	120.87 (18)	C20—C21—H21	120.2
C13—C12—C11	119.58 (19)	F23—C22—C21	117.38 (19)
C13—C12—H12	120.2	F23—C22—C17	119.7 (2)
C11—C12—H12	120.2	C21—C22—C17	122.9 (2)
C12—C13—C14	120.3 (2)		

N8—N1—C2—C9	−176.82 (15)	C9—O10—C11—C12	175.96 (17)
N8—N1—C2—S3	0.50 (19)	O10—C11—C12—C13	−179.06 (17)
N1—C2—S3—C4	0.04 (15)	C16—C11—C12—C13	1.2 (3)
C9—C2—S3—C4	177.45 (15)	C11—C12—C13—C14	−1.0 (3)
C2—S3—C4—N5	179.1 (2)	C12—C13—C14—C15	−0.1 (3)
C2—S3—C4—N8	−0.59 (14)	C13—C14—C15—C16	1.0 (3)
N8—C4—N5—N6	−0.9 (2)	O10—C11—C16—C15	179.97 (18)
S3—C4—N5—N6	179.41 (19)	C12—C11—C16—C15	−0.4 (3)
C4—N5—N6—C7	0.4 (2)	C14—C15—C16—C11	−0.8 (3)
N5—N6—C7—N8	0.2 (2)	N6—C7—C17—C22	−3.4 (3)
N5—N6—C7—C17	−176.25 (17)	N8—C7—C17—C22	−179.30 (17)
N5—C4—N8—C7	1.0 (2)	N6—C7—C17—C18	174.60 (19)
S3—C4—N8—C7	−179.19 (12)	N8—C7—C17—C18	−1.2 (3)
N5—C4—N8—N1	−178.73 (15)	C22—C17—C18—C19	−0.3 (3)
S3—C4—N8—N1	1.1 (2)	C7—C17—C18—C19	−178.43 (17)
N6—C7—N8—C4	−0.7 (2)	C17—C18—C19—C20	−0.3 (3)
C17—C7—N8—C4	175.79 (17)	C18—C19—C20—C21	0.9 (3)
N6—C7—N8—N1	178.96 (18)	C19—C20—C21—C22	−0.8 (3)
C17—C7—N8—N1	−4.5 (3)	C20—C21—C22—F23	−179.92 (18)
C2—N1—N8—C4	−1.0 (2)	C20—C21—C22—C17	0.2 (3)
C2—N1—N8—C7	179.34 (19)	C18—C17—C22—F23	−179.53 (17)
N1—C2—C9—O10	−167.07 (16)	C7—C17—C22—F23	−1.4 (3)
S3—C2—C9—O10	15.6 (2)	C18—C17—C22—C21	0.3 (3)
C2—C9—O10—C11	−165.85 (15)	C7—C17—C22—C21	178.45 (19)
C9—O10—C11—C16	−4.3 (3)		