IUCrData

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1-(3′,6′-Dihydroxy-3-oxo-3*H*-spiro[isobenzofuran-1,9′-xanthen]-5-yl)-3-[4-({4-[1-(4-fluorophenyl)-1*H*-imidazol-5-yl]pyridin-2-yl}amino)phenyl]thiourea methanol monosolvate

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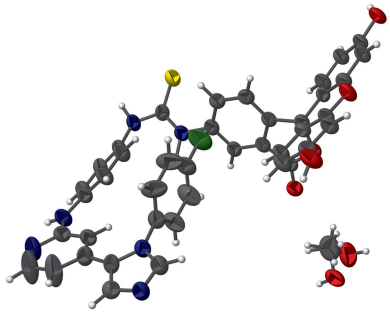
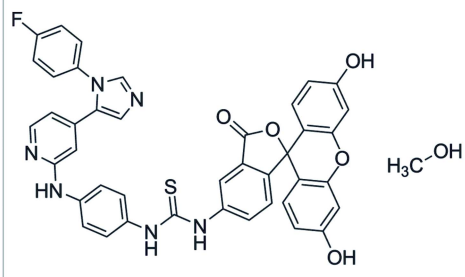
The title compound, which crystallized as a methanol monosolvate, $C_{41}H_{27}FN_6O_5S\cdot CH_3OH$, was synthesized as a probe for a fluorescence polarization-based competition binding assay. The isobenzofuran fused-ring system is close to planar and orientated almost perpendicular to the central ring of the xanthene system. The dihedral angle between the benzene rings of the xanthene system is 10.0 (2)°, indicating a butterfly-like orientation. A short intramolecular C—F$\cdots\pi$ contact [F$\cdots\pi$ = 3.100 (4) Å and C—F$\cdots\pi$ = 139.9 (3)°] to the six-membered ring of the isobenzofuran system may influence the molecular conformation. The methanol solvent molecule is disordered over two orientations in a 0.6:0.4 ratio. In the crystal, the components are linked by numerous hydrogen bonds, generating a three-dimensional network.

3D view



Chemical scheme



Structure description

The title compound was synthesized by reaction of *N*1-{4-[1-(4-fluorophenyl)-1*H*-imidazol-5-yl]pyridin-2-yl}benzene-1,4-diamine and 5(6)-fluorescein-isothiocyanate as a probe for a fluorescence polarization-based competition binding assay. The design and application of similar probes was recently published by our group (Ansideri *et al.*, 2016). As a commercially available isomeric mixture of the 5′- and 6′-isomers of fluorescein-isothiocyanate had been used as a staring material, single-crystal analysis was performed to confirm the isolated isomer. X-ray data confirmed that solely the 5′-isomer was isolated. The title molecule is shown in Fig. 1.

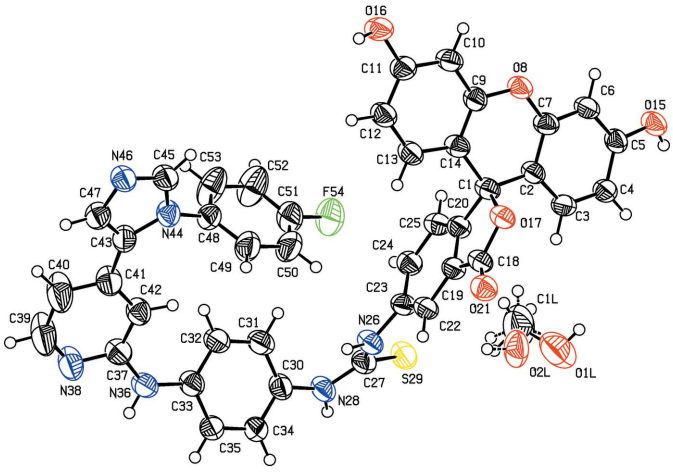


Figure 1
The molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level.

The isobenzofuran fused-ring system is almost planar (r.m.s. deviation = 0.038 Å) and almost perpendicular to the central ring of the xanthene system [dihedral angle = 86.44 (17)°]. The dihedral angle between the benzene rings of the xanthene system is 10.0 (2)°. The thiourea unit of the molecule makes dihedral angles of 53.64 (17)° and 56.3 (2)° with the isobenzofuran ring system and the phenyl ring at the pyridine-C2 position, respectively. The imidazole ring makes a dihedral angle of 14.8 (3)° with the 4-fluorophenyl ring. The pyridine ring is almost perpendicular to the imidazole core, subtending a dihedral angle of 84.9 (3)°. A short intramolecular C—F···π contact [F···π = 3.100 (4) Å and C—F···π = 139.9 (3)°] to the six-membered ring of the isobenzofuran system may influence the molecular conformation.

The crystal packing features numerous hydrogen bonds (Table 1), generating a three-dimensional network, and incorporates one disordered molecule of methanol.

Synthesis and crystallization

A solution of *N*1-{4-[1-(4-fluorophenyl)-1*H*-imidazol-5-yl]-pyridin-2-yl}benzene-1,4-diamine (200 mg, 0.58 mmol) and 5(6)-fluorescein-isothiocyanate (248 mg, 0.77 mmol) in acetone (30 ml) was stirred at 298 K for 48 h with light excluded. The mixture was evaporated to dryness and the residue was purified by flash chromatography (dichloromethane–ethanol 95:05–90:10) obtaining 160 mg of the desired product (yield 37%). Crystals of the title compound suitable for X-ray diffraction were obtained by slow evaporation of a solution of the solid in methanol at 298 K.

^{1}H NMR (250 MHz, DMSO-d_6): δ 6.45 (*dd*, J_1 = 5.3 Hz, J_2 = 1.4 Hz, 1H), 6.53–6.63 (*m*, 5H), 6.67 (*d*, J = 2.0 Hz, 2H), 7.18 (*d*, J = 8.4 Hz, 1H), 7.27 (*d*, J = 8.9 Hz, 2H), 7.35–7.45 (*m*, 5H), 7.47 (*d*, J = 9.0 Hz, 2H), 7.82 (*dd*, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 8.00 (*d*, J = 1.0 Hz, 1H), 8.05 (*d*, J = 5.4 Hz, 1H), 8.17 (*d*, J = 1.9 Hz, 1H), 9.06 (*br s*, 1H), 9.94 (*br s*, 1H), 10.00 (*s*, 1H), 10.17 (*s*, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 83.6, 102.9, 108.3, 111.4, 113.3, 113.4, 117.3 (*d*, J = 22.9 Hz), 118.4, 119.1, 124.6, 125.7, 127.2, 128.7 (*d*, J = 8.8 Hz), 129.8, 130.8, 131.3, 132.7, 133.3 (*d*, J = 2.4 Hz), 138.4, 139.6, 141.8, 142.3, 148.5, 148.7, 152.8, 156.9, 160.5, 162.6 (*d*, J = 245.6 Hz), 169.6, 180.8. HPLC: t = 11.54 min, purity: 98% (λ = 254 nm).

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

D—H···A	D—H	H···A	D···A	D—H···A
O15—H15···N46^{i}	0.84	1.84	2.667 (5)	168
O16—H16···O21^{ii}	0.84	2.04	2.808 (5)	153
C22—H22···O15^{iii}	0.95	2.59	3.315 (5)	133
C24—H24···S29^{iv}	0.95	2.99	3.804 (5)	145
N26—H26···O15^{iii}	1.09	2.17	3.061 (5)	138
N28—H28···N38^{v}	1.17	1.94	3.069 (6)	162
C34—H34···O1L^{vi}	0.95	2.46	3.334 (9)	154
N36—H36···S29^{vii}	0.88	2.64	3.437 (4)	152
C40—H40···O2L^{viii}	0.95	2.32	3.103 (12)	139
C45—H45···O17^{ii}	0.95	2.49	3.379 (6)	155
C53—H53···S29^{ix}	0.95	2.87	3.743 (6)	153
C1L—H2M···O21	0.98	2.56	3.267 (7)	129
O1L—H1L···S29^{x}	0.84	2.46	3.202 (8)	147

Symmetry codes: (i) $x, y-1, z$; (ii) $-x+\frac{3}{2}, -y+\frac{1}{2}, -z+1$; (iii) $x-\frac{1}{2}, y+\frac{1}{2}, z$; (iv) $-x+1, y, -z+\frac{1}{2}$; (v) $-x+\frac{1}{2}, y-\frac{1}{2}, -z+\frac{1}{2}$; (vi) $-x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (vii) $-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{2}$; (viii) $-x+1, -y+1, -z+1$; (ix) $x+\frac{1}{2}, y+\frac{1}{2}, z$; (x) $-x+1, -y, -z+1$.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{41}H_{27}FN_6O_5S\cdot CH_4O$
M_r	766.79
Crystal system, space group	Monoclinic, *C*2/*c*
Temperature (K)	193
a, *b*, *c* (Å)	15.1825 (8), 17.7557 (7), 26.2236 (13)
β (°)	92.283 (4)
V (Å^3)	7063.6 (6)
Z	8
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.16
Crystal size (mm)	0.09 × 0.08 × 0.07
Data collection	
Diffractometer	Stoe *IPDS* 2T
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	23065, 8960, 3244
R_{int}	0.085
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.674
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.070, 0.240, 0.92
No. of reflections	8960
No. of parameters	516
No. of restraints	2
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.35, −0.38

Computer programs: *X-AREA* and *X-RED* (Stoe & Cie, 2011, *SIR2004* (Burla *et al.*, 2005) and *SHELXL2014* (Sheldrick, 2015).

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. The methanol solvent molecule is disordered over two orientations in a 0.6:0.4 ratio.

References

Ansideri, F., Lange, A., El-Gokha, A., Boeckler, F. M. & Koch, P. (2016). *Anal. Biochem.* **503**, 28–40.
Burla, M. C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G. L., De Caro, L., Giacovazzo, C., Polidori, G. & Spagna, R. (2005). *J. Appl. Cryst.* **38**, 381–388.
Sheldrick, G. M. (2015). *Acta Cryst.* C**71**, 3–8.
Stoe & Cie (2011). *X-RED* and *X-AREA*. Stoe & Cie, Darmstadt, Darmstadt, Germany.

full crystallographic data

IUCrData (2016). **1**, x160840 [doi:10.1107/S2414314616008403]

1-(3′,6′-Dihydroxy-3-oxo-3*H*-spiro[isobenzofuran-1,9′-xanthen]-5-yl)-3-[4-({4-[1-(4-fluorophenyl)-1*H*-imidazol-5-yl]pyridin-2-yl}amino)phenyl]-thiourea methanol monosolvate

Francesco Ansideri, Dieter Schollmeyer and Pierre Koch

1-(3′,6′-Dihydroxy-3-oxo-3*H*-spiro[isobenzofuran-1,9′-xanthen]-5-yl)-3-[4-({4-[1-(4-fluorophenyl)-1*H*-imidazol-5-yl]pyridin-2-yl}amino)phenyl]thiourea; methanol

Crystal data

$C_{41}H_{27}FN_6O_5S·CH_4O$
M_r = 766.79
Monoclinic, *C*2/*c*
a = 15.1825 (8) Å
b = 17.7557 (7) Å
c = 26.2236 (13) Å
β = 92.283 (4)°
V = 7063.6 (6) Å^3
Z = 8
F(000) = 3184
D_x = 1.442 Mg m^{-3}
Mo *Kα* radiation, *λ* = 0.71073 Å
Cell parameters from 7245 reflections
θ = 2.3–27.9°
μ = 0.16 mm^{-1}
T = 193 K
Block, colourless
0.09 × 0.08 × 0.07 mm

Data collection

Stoe IPDS 2T diffractometer
Radiation source: sealed X-ray tube, 12 x 0.4 mm long-fine focus
Detector resolution: 6.67 pixels mm^{-1}
rotation method scans
23065 measured reflections
8960 independent reflections
3244 reflections with $I > 2\sigma(I)$
R_{int} = 0.085
θ_{max} = 28.6°, θ_{min} = 2.3°
h = −20→20
k = −21→23
l = −35→35

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.070
$wR(F^2)$ = 0.240
S = 0.92
8960 reflections
516 parameters
2 restraints
Hydrogen site location: mixed
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.110P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.35 e Å^{-3}
$\Delta\rho_{min}$ = −0.38 e Å^{-3}
Extinction correction: *SHELXL2014* (Sheldrick, 2015), $Fc^* = kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient: 0.00101 (19)

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}	Occ. (<1)
C1	0.7146 (3)	0.0416 (2)	0.45826 (18)	0.0456 (10)	
C2	0.7446 (3)	−0.0387 (2)	0.45478 (17)	0.0438 (9)	
C3	0.6854 (3)	−0.0980 (2)	0.45158 (19)	0.0491 (11)	
H3	0.6242	−0.0874	0.4526	0.059*	
C4	0.7120 (3)	−0.1717 (2)	0.44691 (18)	0.0485 (10)	
H4	0.6698	−0.2113	0.4457	0.058*	
C5	0.8021 (3)	−0.1878 (2)	0.44396 (18)	0.0466 (10)	
C6	0.8623 (3)	−0.1298 (2)	0.44888 (19)	0.0503 (11)	
H6	0.9237	−0.1402	0.4484	0.060*	
C7	0.8333 (3)	−0.0563 (2)	0.45448 (18)	0.0469 (10)	
O8	0.89947 (18)	−0.00298 (16)	0.45973 (14)	0.0535 (8)	
C9	0.8766 (3)	0.0723 (2)	0.45771 (19)	0.0467 (10)	
C10	0.9461 (3)	0.1221 (3)	0.45871 (19)	0.0519 (11)	
H10	1.0050	0.1041	0.4617	0.062*	
C11	0.9296 (3)	0.1988 (3)	0.4553 (2)	0.0525 (11)	
C12	0.8432 (3)	0.2243 (3)	0.4504 (2)	0.0578 (12)	
H12	0.8314	0.2767	0.4469	0.069*	
C13	0.7748 (3)	0.1734 (2)	0.45061 (19)	0.0523 (11)	
H13	0.7158	0.1915	0.4481	0.063*	
C14	0.7897 (3)	0.0962 (2)	0.45448 (18)	0.0454 (10)	
O15	0.83304 (19)	−0.25782 (16)	0.43631 (13)	0.0548 (8)	
H15	0.7917	−0.2856	0.4254	0.082*	
O16	0.99968 (19)	0.24600 (18)	0.45616 (15)	0.0636 (9)	
H16	0.9845	0.2883	0.4672	0.095*	
O17	0.67552 (18)	0.05307 (17)	0.51047 (12)	0.0470 (7)	
C18	0.5937 (3)	0.0830 (2)	0.50544 (18)	0.0453 (10)	
C19	0.5674 (3)	0.0866 (2)	0.45147 (18)	0.0453 (10)	
C20	0.6358 (3)	0.0599 (2)	0.42341 (18)	0.0441 (10)	
O21	0.5539 (2)	0.10267 (18)	0.54287 (13)	0.0541 (8)	
C22	0.4891 (3)	0.1127 (2)	0.42833 (18)	0.0462 (10)	
H22	0.4421	0.1305	0.4479	0.055*	
C23	0.4827 (3)	0.1116 (2)	0.37583 (18)	0.0470 (10)	
C24	0.5513 (3)	0.0831 (2)	0.34715 (19)	0.0488 (11)	
H24	0.5447	0.0814	0.3110	0.059*	
C25	0.6285 (3)	0.0575 (3)	0.37110 (19)	0.0487 (11)	
H25	0.6753	0.0387	0.3518	0.058*	
N26	0.4075 (2)	0.1462 (2)	0.35115 (15)	0.0497 (9)	
H26	0.3989	0.2001	0.3703	0.060*	
C27	0.3620 (3)	0.1219 (3)	0.30850 (18)	0.0491 (11)	

N28	0.3064 (2)	0.1732 (2)	0.28696 (16)	0.0525 (9)	
H28	0.2590	0.1411	0.2583	0.063*	
S29	0.36943 (8)	0.03475 (7)	0.28470 (5)	0.0582 (4)	
C30	0.3108 (3)	0.2532 (2)	0.29427 (19)	0.0511 (11)	
C31	0.3902 (3)	0.2919 (3)	0.2939 (2)	0.0591 (12)	
H31	0.4438	0.2645	0.2924	0.071*	
C32	0.3928 (3)	0.3699 (3)	0.2956 (2)	0.0576 (12)	
H32	0.4477	0.3955	0.2953	0.069*	
C33	0.3145 (3)	0.4108 (3)	0.29767 (19)	0.0513 (11)	
C34	0.2351 (3)	0.3715 (3)	0.29846 (19)	0.0527 (11)	
H34	0.1812	0.3986	0.2995	0.063*	
C35	0.2338 (3)	0.2942 (3)	0.29771 (19)	0.0526 (11)	
H35	0.1792	0.2684	0.2996	0.063*	
N36	0.3091 (2)	0.4896 (2)	0.29414 (17)	0.0570 (10)	
H36	0.2562	0.5064	0.2850	0.068*	
C37	0.3706 (3)	0.5452 (3)	0.30223 (19)	0.0532 (11)	
N38	0.3436 (3)	0.6124 (3)	0.2834 (2)	0.0799 (15)	
C39	0.3977 (5)	0.6696 (4)	0.2922 (4)	0.126 (4)	
H39	0.3783	0.7182	0.2815	0.151*	
C40	0.4795 (5)	0.6642 (4)	0.3158 (3)	0.115 (3)	
H40	0.5173	0.7068	0.3177	0.138*	
C41	0.5070 (3)	0.5962 (3)	0.3369 (2)	0.0607 (13)	
C42	0.4508 (3)	0.5361 (3)	0.32982 (19)	0.0528 (11)	
H42	0.4663	0.4882	0.3437	0.063*	
C43	0.5906 (3)	0.5970 (3)	0.36659 (19)	0.0534 (11)	
N44	0.6417 (2)	0.5368 (2)	0.38405 (15)	0.0509 (9)	
C45	0.7124 (3)	0.5661 (3)	0.4102 (2)	0.0561 (12)	
H45	0.7584	0.5368	0.4257	0.067*	
N46	0.7097 (2)	0.6401 (2)	0.41169 (16)	0.0534 (9)	
C47	0.6355 (3)	0.6593 (3)	0.38449 (19)	0.0548 (11)	
H47	0.6168	0.7097	0.3785	0.066*	
C48	0.6348 (3)	0.4580 (3)	0.37468 (19)	0.0523 (11)	
C49	0.5898 (4)	0.4127 (3)	0.4064 (2)	0.0721 (16)	
H49	0.5584	0.4341	0.4335	0.087*	
C50	0.5895 (4)	0.3352 (3)	0.3992 (3)	0.0799 (18)	
H50	0.5583	0.3030	0.4211	0.096*	
C51	0.6341 (4)	0.3071 (3)	0.3607 (2)	0.0675 (15)	
C52	0.6814 (5)	0.3505 (3)	0.3291 (3)	0.091 (2)	
H52	0.7139	0.3286	0.3027	0.109*	
C53	0.6807 (5)	0.4272 (3)	0.3365 (2)	0.084 (2)	
H53	0.7127	0.4590	0.3147	0.101*	
F54	0.6336 (3)	0.23112 (17)	0.35271 (16)	0.0939 (11)	
C1L	0.5122 (6)	0.1316 (5)	0.6625 (3)	0.123 (3)	
H1M	0.4629	0.1554	0.6435	0.185*	0.6
H2M	0.5428	0.0971	0.6401	0.185*	0.6
H3M	0.5534	0.1705	0.6752	0.185*	0.6
H4M	0.5767	0.1337	0.6620	0.185*	0.4
H5M	0.4867	0.1573	0.6323	0.185*	0.4

H6M	0.4930	0.0789	0.6625	0.185*	0.4
O1L	0.4803 (5)	0.0914 (5)	0.7038 (3)	0.111 (3)	0.6
H1L	0.5221	0.0681	0.7188	0.166*	0.6
O2L	0.4841 (7)	0.1673 (5)	0.7067 (3)	0.081 (3)	0.4
H2L	0.4341	0.1864	0.7008	0.122*	0.4

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0352 (19)	0.044 (2)	0.057 (3)	0.0036 (17)	−0.0048 (18)	−0.006 (2)
C2	0.0364 (19)	0.042 (2)	0.052 (3)	0.0047 (17)	−0.0059 (17)	−0.002 (2)
C3	0.0342 (19)	0.043 (2)	0.070 (3)	0.0017 (17)	0.0030 (19)	−0.002 (2)
C4	0.039 (2)	0.038 (2)	0.068 (3)	−0.0018 (17)	−0.0038 (19)	−0.003 (2)
C5	0.044 (2)	0.034 (2)	0.061 (3)	0.0040 (17)	−0.003 (2)	−0.0025 (19)
C6	0.035 (2)	0.043 (2)	0.072 (3)	0.0047 (17)	−0.003 (2)	−0.003 (2)
C7	0.036 (2)	0.045 (2)	0.059 (3)	−0.0005 (17)	−0.0040 (19)	−0.006 (2)
O8	0.0363 (14)	0.0361 (15)	0.087 (2)	0.0002 (12)	−0.0070 (15)	−0.0041 (15)
C9	0.043 (2)	0.035 (2)	0.062 (3)	−0.0002 (17)	−0.005 (2)	−0.005 (2)
C10	0.035 (2)	0.047 (2)	0.073 (3)	0.0026 (18)	−0.004 (2)	−0.009 (2)
C11	0.043 (2)	0.045 (2)	0.069 (3)	−0.0048 (19)	−0.002 (2)	−0.006 (2)
C12	0.045 (2)	0.042 (2)	0.085 (4)	0.0045 (19)	−0.005 (2)	−0.004 (2)
C13	0.041 (2)	0.040 (2)	0.075 (3)	0.0040 (18)	−0.008 (2)	−0.005 (2)
C14	0.038 (2)	0.041 (2)	0.056 (3)	0.0026 (17)	−0.0028 (18)	−0.010 (2)
O15	0.0430 (15)	0.0361 (15)	0.085 (2)	0.0058 (13)	−0.0048 (15)	−0.0086 (16)
O16	0.0409 (15)	0.0425 (17)	0.107 (3)	−0.0043 (13)	0.0025 (17)	−0.0120 (18)
O17	0.0389 (14)	0.0475 (17)	0.0541 (19)	0.0063 (12)	−0.0050 (13)	−0.0031 (14)
C18	0.037 (2)	0.043 (2)	0.055 (3)	0.0050 (17)	−0.0051 (19)	−0.006 (2)
C19	0.037 (2)	0.041 (2)	0.058 (3)	0.0024 (17)	0.0013 (19)	−0.001 (2)
C20	0.038 (2)	0.040 (2)	0.054 (3)	0.0023 (17)	0.0015 (18)	−0.0023 (19)
O21	0.0514 (17)	0.0521 (19)	0.059 (2)	0.0047 (15)	0.0018 (15)	−0.0044 (16)
C22	0.037 (2)	0.046 (2)	0.055 (3)	0.0064 (17)	−0.0010 (18)	−0.002 (2)
C23	0.0340 (19)	0.045 (2)	0.061 (3)	0.0011 (17)	−0.0048 (18)	−0.002 (2)
C24	0.044 (2)	0.046 (2)	0.056 (3)	−0.0010 (18)	−0.003 (2)	−0.005 (2)
C25	0.038 (2)	0.051 (3)	0.057 (3)	0.0035 (18)	0.0034 (19)	−0.006 (2)
N26	0.0429 (18)	0.046 (2)	0.060 (2)	0.0064 (16)	−0.0094 (17)	−0.0054 (18)
C27	0.042 (2)	0.048 (2)	0.056 (3)	−0.0002 (18)	−0.0078 (19)	0.002 (2)
N28	0.046 (2)	0.041 (2)	0.069 (3)	0.0028 (16)	−0.0160 (17)	−0.0009 (18)
S29	0.0543 (6)	0.0454 (6)	0.0736 (9)	0.0011 (5)	−0.0144 (6)	−0.0027 (6)
C30	0.050 (2)	0.039 (2)	0.063 (3)	0.0015 (19)	−0.010 (2)	0.001 (2)
C31	0.044 (2)	0.051 (3)	0.082 (4)	0.004 (2)	−0.007 (2)	0.000 (3)
C32	0.044 (2)	0.044 (2)	0.084 (4)	0.0012 (19)	−0.005 (2)	−0.003 (2)
C33	0.049 (2)	0.041 (2)	0.063 (3)	0.0012 (19)	−0.006 (2)	−0.005 (2)
C34	0.044 (2)	0.044 (2)	0.070 (3)	−0.0028 (18)	−0.006 (2)	0.004 (2)
C35	0.045 (2)	0.048 (3)	0.064 (3)	−0.0009 (19)	−0.005 (2)	0.009 (2)
N36	0.043 (2)	0.044 (2)	0.083 (3)	0.0023 (16)	−0.0078 (19)	−0.006 (2)
C37	0.050 (2)	0.046 (3)	0.063 (3)	−0.002 (2)	−0.009 (2)	−0.010 (2)
N38	0.079 (3)	0.051 (3)	0.107 (4)	−0.006 (2)	−0.039 (3)	0.014 (3)
C39	0.119 (6)	0.058 (4)	0.192 (9)	−0.034 (4)	−0.103 (6)	0.041 (5)

C40	0.108 (5)	0.062 (4)	0.170 (8)	−0.029 (4)	−0.081 (5)	0.039 (4)
C41	0.063 (3)	0.050 (3)	0.068 (3)	−0.006 (2)	−0.022 (2)	0.001 (2)
C42	0.056 (3)	0.040 (2)	0.062 (3)	0.001 (2)	−0.007 (2)	−0.004 (2)
C43	0.055 (3)	0.047 (2)	0.057 (3)	−0.004 (2)	−0.007 (2)	0.009 (2)
N44	0.054 (2)	0.0402 (19)	0.058 (2)	−0.0027 (17)	−0.0079 (17)	0.0009 (18)
C45	0.048 (2)	0.047 (3)	0.073 (3)	−0.004 (2)	−0.012 (2)	−0.001 (2)
N46	0.049 (2)	0.045 (2)	0.065 (3)	−0.0013 (17)	−0.0119 (18)	−0.0027 (19)
C47	0.056 (3)	0.047 (3)	0.061 (3)	−0.006 (2)	−0.007 (2)	−0.002 (2)
C48	0.051 (2)	0.043 (2)	0.062 (3)	−0.007 (2)	−0.003 (2)	0.004 (2)
C49	0.077 (3)	0.049 (3)	0.092 (4)	0.005 (3)	0.027 (3)	0.010 (3)
C50	0.080 (4)	0.046 (3)	0.116 (5)	−0.005 (3)	0.029 (4)	0.011 (3)
C51	0.074 (3)	0.036 (2)	0.092 (4)	−0.005 (2)	−0.004 (3)	−0.007 (3)
C52	0.138 (6)	0.053 (3)	0.085 (5)	−0.015 (4)	0.036 (4)	−0.016 (3)
C53	0.133 (6)	0.053 (3)	0.069 (4)	−0.027 (3)	0.033 (4)	−0.011 (3)
F54	0.110 (3)	0.0416 (17)	0.130 (3)	−0.0085 (17)	0.003 (2)	−0.0046 (18)
C1L	0.151 (8)	0.113 (6)	0.108 (7)	0.029 (6)	0.026 (6)	0.039 (5)
O1L	0.099 (6)	0.122 (7)	0.111 (7)	0.036 (5)	−0.006 (5)	0.026 (6)
O2L	0.108 (8)	0.052 (6)	0.086 (7)	0.018 (5)	0.027 (6)	0.007 (5)

Geometric parameters (Å, º)

C1—C2	1.501 (6)	C31—H31	0.9500
C1—C14	1.503 (6)	C32—C33	1.395 (6)
C1—C20	1.511 (6)	C32—H32	0.9500
C1—O17	1.527 (5)	C33—C34	1.394 (6)
C2—C7	1.383 (5)	C33—N36	1.404 (6)
C2—C3	1.385 (6)	C34—C35	1.374 (6)
C3—C4	1.376 (6)	C34—H34	0.9500
C3—H3	0.9500	C35—H35	0.9500
C4—C5	1.403 (6)	N36—C37	1.371 (6)
C4—H4	0.9500	N36—H36	0.8800
C5—O15	1.347 (5)	C37—N38	1.348 (6)
C5—C6	1.380 (6)	C37—C42	1.400 (6)
C6—C7	1.386 (6)	N38—C39	1.322 (7)
C6—H6	0.9500	C39—C40	1.368 (9)
C7—O8	1.383 (5)	C39—H39	0.9500
O8—C9	1.382 (5)	C40—C41	1.385 (8)
C9—C10	1.377 (6)	C40—H40	0.9500
C9—C14	1.385 (6)	C41—C42	1.375 (6)
C10—C11	1.387 (6)	C41—C43	1.462 (7)
C10—H10	0.9500	C42—H42	0.9500
C11—O16	1.354 (5)	C43—C47	1.373 (6)
C11—C12	1.389 (6)	C43—N44	1.388 (6)
C12—C13	1.378 (6)	N44—C45	1.354 (6)
C12—H12	0.9500	N44—C48	1.423 (6)
C13—C14	1.393 (6)	C45—N46	1.314 (6)
C13—H13	0.9500	C45—H45	0.9500
O15—H15	0.8400	N46—C47	1.353 (6)

O16—H16	0.8400	C47—H47	0.9500
O17—C18	1.354 (5)	C48—C53	1.358 (7)
C18—O21	1.223 (5)	C48—C49	1.360 (7)
C18—C19	1.456 (7)	C49—C50	1.389 (7)
C19—C20	1.381 (6)	C49—H49	0.9500
C19—C22	1.392 (6)	C50—C51	1.333 (8)
C20—C25	1.372 (7)	C50—H50	0.9500
C22—C23	1.376 (6)	C51—C52	1.358 (8)
C22—H22	0.9500	C51—F54	1.365 (6)
C23—C24	1.402 (6)	C52—C53	1.376 (8)
C23—N26	1.429 (5)	C52—H52	0.9500
C24—C25	1.384 (6)	C53—H53	0.9500
C24—H24	0.9500	C1L—O1L	1.3998 (10)
C25—H25	0.9500	C1L—O2L	1.4009 (10)
N26—C27	1.362 (6)	C1L—H1M	0.9800
N26—H26	1.0913	C1L—H2M	0.9800
C27—N28	1.350 (6)	C1L—H3M	0.9800
C27—S29	1.675 (5)	C1L—H4M	0.9800
N28—C30	1.434 (6)	C1L—H5M	0.9800
N28—H28	1.1665	C1L—H6M	0.9800
C30—C35	1.383 (6)	O1L—H1L	0.8400
C30—C31	1.389 (6)	O2L—H2L	0.8400
C31—C32	1.386 (7)		

C2—C1—C14	112.1 (3)	C32—C31—C30	121.3 (4)
C2—C1—C20	113.8 (4)	C32—C31—H31	119.4
C14—C1—C20	113.9 (4)	C30—C31—H31	119.4
C2—C1—O17	108.1 (4)	C31—C32—C33	119.8 (4)
C14—C1—O17	107.2 (3)	C31—C32—H32	120.1
C20—C1—O17	100.8 (3)	C33—C32—H32	120.1
C7—C2—C3	117.3 (4)	C34—C33—C32	118.6 (4)
C7—C2—C1	120.9 (4)	C34—C33—N36	116.8 (4)
C3—C2—C1	121.8 (3)	C32—C33—N36	124.3 (4)
C4—C3—C2	122.4 (4)	C35—C34—C33	120.7 (4)
C4—C3—H3	118.8	C35—C34—H34	119.6
C2—C3—H3	118.8	C33—C34—H34	119.6
C3—C4—C5	119.2 (4)	C34—C35—C30	121.1 (4)
C3—C4—H4	120.4	C34—C35—H35	119.5
C5—C4—H4	120.4	C30—C35—H35	119.5
O15—C5—C6	118.0 (4)	C37—N36—C33	132.1 (4)
O15—C5—C4	122.8 (4)	C37—N36—H36	114.0
C6—C5—C4	119.2 (4)	C33—N36—H36	114.0
C5—C6—C7	120.0 (4)	N38—C37—N36	112.7 (4)
C5—C6—H6	120.0	N38—C37—C42	122.5 (4)
C7—C6—H6	120.0	N36—C37—C42	124.7 (4)
O8—C7—C2	123.3 (4)	C39—N38—C37	116.0 (5)
O8—C7—C6	115.0 (3)	N38—C39—C40	124.8 (6)
C2—C7—C6	121.8 (4)	N38—C39—H39	117.6

C9—O8—C7	118.5 (3)	C40—C39—H39	117.6
C10—C9—O8	115.4 (4)	C39—C40—C41	119.7 (6)
C10—C9—C14	122.2 (4)	C39—C40—H40	120.1
O8—C9—C14	122.5 (4)	C41—C40—H40	120.1
C9—C10—C11	119.5 (4)	C42—C41—C40	116.5 (5)
C9—C10—H10	120.2	C42—C41—C43	126.9 (4)
C11—C10—H10	120.2	C40—C41—C43	116.5 (4)
O16—C11—C12	122.6 (4)	C41—C42—C37	120.1 (4)
O16—C11—C10	117.8 (4)	C41—C42—H42	119.9
C12—C11—C10	119.6 (4)	C37—C42—H42	119.9
C13—C12—C11	119.7 (4)	C47—C43—N44	104.1 (4)
C13—C12—H12	120.2	C47—C43—C41	126.7 (4)
C11—C12—H12	120.2	N44—C43—C41	129.1 (4)
C12—C13—C14	121.7 (4)	C45—N44—C43	107.0 (4)
C12—C13—H13	119.1	C45—N44—C48	121.2 (4)
C14—C13—H13	119.1	C43—N44—C48	131.5 (4)
C9—C14—C13	117.3 (4)	N46—C45—N44	112.0 (4)
C9—C14—C1	121.4 (4)	N46—C45—H45	124.0
C13—C14—C1	121.2 (4)	N44—C45—H45	124.0
C5—O15—H15	109.5	C45—N46—C47	105.2 (4)
C11—O16—H16	109.5	N46—C47—C43	111.6 (4)
C18—O17—C1	110.7 (3)	N46—C47—H47	124.2
O21—C18—O17	120.9 (4)	C43—C47—H47	124.2
O21—C18—C19	130.0 (4)	C53—C48—C49	119.9 (5)
O17—C18—C19	109.1 (4)	C53—C48—N44	119.1 (4)
C20—C19—C22	122.0 (4)	C49—C48—N44	120.8 (5)
C20—C19—C18	108.7 (4)	C48—C49—C50	120.2 (5)
C22—C19—C18	129.4 (4)	C48—C49—H49	119.9
C25—C20—C19	120.7 (4)	C50—C49—H49	119.9
C25—C20—C1	129.0 (4)	C51—C50—C49	118.3 (5)
C19—C20—C1	110.2 (4)	C51—C50—H50	120.9
C23—C22—C19	117.1 (4)	C49—C50—H50	120.9
C23—C22—H22	121.4	C50—C51—C52	123.1 (5)
C19—C22—H22	121.4	C50—C51—F54	119.1 (5)
C22—C23—C24	121.2 (4)	C52—C51—F54	117.8 (5)
C22—C23—N26	118.0 (4)	C51—C52—C53	118.0 (6)
C24—C23—N26	120.6 (4)	C51—C52—H52	121.0
C25—C24—C23	120.5 (5)	C53—C52—H52	121.0
C25—C24—H24	119.7	C48—C53—C52	120.6 (5)
C23—C24—H24	119.7	C48—C53—H53	119.7
C20—C25—C24	118.5 (4)	C52—C53—H53	119.7
C20—C25—H25	120.7	O1L—C1L—H1M	109.5
C24—C25—H25	120.7	O1L—C1L—H2M	109.5
C27—N26—C23	127.3 (4)	H1M—C1L—H2M	109.5
C27—N26—H26	126.1	O1L—C1L—H3M	109.5
C23—N26—H26	106.1	H1M—C1L—H3M	109.5
N28—C27—N26	114.8 (4)	H2M—C1L—H3M	109.5
N28—C27—S29	121.2 (4)	O2L—C1L—H4M	109.5

N26—C27—S29	124.0 (3)	O2L—C1L—H5M	109.5
C27—N28—C30	125.9 (4)	H4M—C1L—H5M	109.5
C27—N28—H28	107.4	O2L—C1L—H6M	109.5
C30—N28—H28	126.4	H4M—C1L—H6M	109.5
C35—C30—C31	118.4 (4)	H5M—C1L—H6M	109.5
C35—C30—N28	119.6 (4)	C1L—O1L—H1L	109.5
C31—C30—N28	121.8 (4)	C1L—O2L—H2L	109.5

C14—C1—C2—C7	7.2 (6)	C22—C23—C24—C25	−2.0 (7)
C20—C1—C2—C7	138.2 (4)	N26—C23—C24—C25	172.5 (4)
O17—C1—C2—C7	−110.7 (4)	C19—C20—C25—C24	0.7 (7)
C14—C1—C2—C3	−172.6 (4)	C1—C20—C25—C24	−174.6 (4)
C20—C1—C2—C3	−41.6 (6)	C23—C24—C25—C20	0.7 (7)
O17—C1—C2—C3	69.5 (5)	C22—C23—N26—C27	−142.2 (5)
C7—C2—C3—C4	−1.7 (7)	C24—C23—N26—C27	43.1 (7)
C1—C2—C3—C4	178.1 (5)	C23—N26—C27—N28	−166.0 (4)
C2—C3—C4—C5	−1.6 (8)	C23—N26—C27—S29	16.3 (7)
C3—C4—C5—O15	−175.9 (5)	N26—C27—N28—C30	20.6 (7)
C3—C4—C5—C6	3.8 (7)	S29—C27—N28—C30	−161.7 (4)
O15—C5—C6—C7	177.1 (4)	C27—N28—C30—C35	−141.9 (5)
C4—C5—C6—C7	−2.7 (7)	C27—N28—C30—C31	43.5 (7)
C3—C2—C7—O8	−177.0 (4)	C35—C30—C31—C32	−1.6 (8)
C1—C2—C7—O8	3.2 (7)	N28—C30—C31—C32	173.1 (5)
C3—C2—C7—C6	2.9 (7)	C30—C31—C32—C33	−0.1 (9)
C1—C2—C7—C6	−176.9 (5)	C31—C32—C33—C34	0.6 (8)
C5—C6—C7—O8	179.2 (4)	C31—C32—C33—N36	−173.1 (5)
C5—C6—C7—C2	−0.7 (8)	C32—C33—C34—C35	0.6 (8)
C2—C7—O8—C9	−9.8 (7)	N36—C33—C34—C35	174.7 (5)
C6—C7—O8—C9	170.3 (4)	C33—C34—C35—C30	−2.4 (8)
C7—O8—C9—C10	−174.6 (4)	C31—C30—C35—C34	2.8 (8)
C7—O8—C9—C14	4.9 (7)	N28—C30—C35—C34	−172.0 (5)
O8—C9—C10—C11	178.0 (5)	C34—C33—N36—C37	165.4 (5)
C14—C9—C10—C11	−1.5 (8)	C32—C33—N36—C37	−20.9 (9)
C9—C10—C11—O16	−179.7 (4)	C33—N36—C37—N38	165.5 (5)
C9—C10—C11—C12	−0.6 (8)	C33—N36—C37—C42	−18.5 (9)
O16—C11—C12—C13	−178.9 (5)	N36—C37—N38—C39	176.4 (7)
C10—C11—C12—C13	2.0 (8)	C42—C37—N38—C39	0.3 (9)
C11—C12—C13—C14	−1.5 (8)	C37—N38—C39—C40	4.4 (14)
C10—C9—C14—C13	2.0 (7)	N38—C39—C40—C41	−6.7 (16)
O8—C9—C14—C13	−177.5 (4)	C39—C40—C41—C42	4.0 (12)
C10—C9—C14—C1	−174.3 (5)	C39—C40—C41—C43	−173.0 (8)
O8—C9—C14—C1	6.2 (7)	C40—C41—C42—C37	0.3 (9)
C12—C13—C14—C9	−0.5 (8)	C43—C41—C42—C37	176.9 (5)
C12—C13—C14—C1	175.8 (5)	N38—C37—C42—C41	−2.5 (8)
C2—C1—C14—C9	−11.7 (6)	N36—C37—C42—C41	−178.2 (5)
C20—C1—C14—C9	−142.7 (4)	C42—C41—C43—C47	−162.3 (5)
O17—C1—C14—C9	106.7 (5)	C40—C41—C43—C47	14.3 (9)
C2—C1—C14—C13	172.1 (4)	C42—C41—C43—N44	16.3 (9)

C20—C1—C14—C13	41.2 (6)	C40—C41—C43—N44	−167.1 (6)
O17—C1—C14—C13	−69.4 (5)	C47—C43—N44—C45	−0.4 (5)
C2—C1—O17—C18	−127.2 (4)	C41—C43—N44—C45	−179.2 (5)
C14—C1—O17—C18	111.8 (4)	C47—C43—N44—C48	−173.9 (5)
C20—C1—O17—C18	−7.6 (4)	C41—C43—N44—C48	7.3 (9)
C1—O17—C18—O21	−173.6 (4)	C43—N44—C45—N46	1.1 (6)
C1—O17—C18—C19	6.0 (5)	C48—N44—C45—N46	175.4 (4)
O21—C18—C19—C20	178.0 (5)	N44—C45—N46—C47	−1.3 (6)
O17—C18—C19—C20	−1.5 (5)	C45—N46—C47—C43	1.1 (6)
O21—C18—C19—C22	−0.8 (8)	N44—C43—C47—N46	−0.4 (6)
O17—C18—C19—C22	179.6 (4)	C41—C43—C47—N46	178.5 (5)
C22—C19—C20—C25	−0.7 (7)	C45—N44—C48—C53	−79.0 (7)
C18—C19—C20—C25	−179.6 (4)	C43—N44—C48—C53	93.6 (7)
C22—C19—C20—C1	175.4 (4)	C45—N44—C48—C49	94.7 (6)
C18—C19—C20—C1	−3.6 (5)	C43—N44—C48—C49	−92.6 (7)
C2—C1—C20—C25	−62.3 (6)	C53—C48—C49—C50	−1.1 (9)
C14—C1—C20—C25	67.8 (6)	N44—C48—C49—C50	−174.8 (5)
O17—C1—C20—C25	−177.8 (4)	C48—C49—C50—C51	0.0 (10)
C2—C1—C20—C19	122.1 (4)	C49—C50—C51—C52	1.6 (11)
C14—C1—C20—C19	−107.8 (4)	C49—C50—C51—F54	−179.2 (6)
O17—C1—C20—C19	6.6 (4)	C50—C51—C52—C53	−2.0 (11)
C20—C19—C22—C23	−0.6 (6)	F54—C51—C52—C53	178.8 (6)
C18—C19—C22—C23	178.1 (4)	C49—C48—C53—C52	0.7 (10)
C19—C22—C23—C24	1.9 (6)	N44—C48—C53—C52	174.5 (6)
C19—C22—C23—N26	−172.8 (4)	C51—C52—C53—C48	0.7 (11)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O15—H15···N46^{i}	0.84	1.84	2.667 (5)	168
O16—H16···O21^{ii}	0.84	2.04	2.808 (5)	153
C22—H22···O15^{iii}	0.95	2.59	3.315 (5)	133
C24—H24···S29^{iv}	0.95	2.99	3.804 (5)	145
N26—H26···O15^{iii}	1.09	2.17	3.061 (5)	138
N28—H28···N38^{v}	1.17	1.94	3.069 (6)	162
C34—H34···O1*L*^{vi}	0.95	2.46	3.334 (9)	154
N36—H36···S29^{vii}	0.88	2.64	3.437 (4)	152
C40—H40···O2*L*^{viii}	0.95	2.32	3.103 (12)	139
C45—H45···O17^{ii}	0.95	2.49	3.379 (6)	155
C53—H53···S29^{ix}	0.95	2.87	3.743 (6)	153
C1*L*—H2*M*···O21	0.98	2.56	3.267 (7)	129
O1*L*—H1*L*···S29^{x}	0.84	2.46	3.202 (8)	147

Symmetry codes: (i) *x*, *y*−1, *z*; (ii) −*x*+3/2, −*y*+1/2, −*z*+1; (iii) *x*−1/2, *y*+1/2, *z*; (iv) −*x*+1, *y*, −*z*+1/2; (v) −*x*+1/2, *y*−1/2, −*z*+1/2; (vi) −*x*+1/2, −*y*+1/2, −*z*+1; (vii) −*x*+1/2, *y*+1/2, −*z*+1/2; (viii) −*x*+1, −*y*+1, −*z*+1; (ix) *x*+1/2, *y*+1/2, *z*; (x) −*x*+1, −*y*, −*z*+1.