Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate monohydrate

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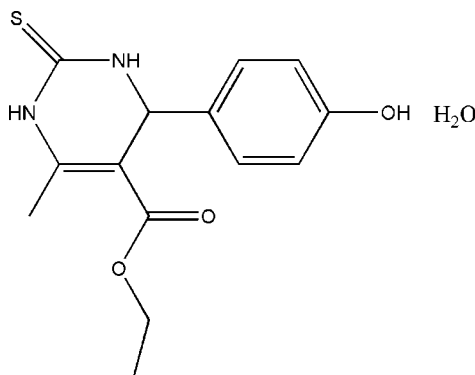
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In the organic molecule of the title compound, $C_{14}H_{16}N_2O_3S \cdot H_2O$, the two rings are oriented at a dihedral angle of 84.31 (2)°. In the crystal structure, intramolecular O—H···O and intermolecular O—H···O, N—H···O, O—H···S and N—H···S hydrogen bonds are found.

Related literature

For general background, see: Atwal *et al.* (1991); Mayer *et al.* (1999). For bond-length data, see: Allen *et al.* (1987).

Experimental

Crystal data

$C_{14}H_{16}N_2O_3S \cdot H_2O$	a = 5.6702 (17) Å
M_r = 310.36	b = 11.212 (3) Å
Triclinic, $P\bar{1}$	c = 12.343 (4) Å
α = 90.406 (5)°	Mo $K\alpha$ radiation
β = 95.251 (5)°	μ = 0.23 mm^{-1}
γ = 104.393 (5)°	T = 294 (2) K
V = 756.5 (4) Å^3	0.22 × 0.16 × 0.16 mm
Z = 2	

Data collection

Bruker SMART CCD area-detector diffractometer	3958 measured reflections
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)	2655 independent reflections
T_{min} = 0.951, T_{max} = 0.964	1741 reflections with $I > 2\sigma(I)$
	R_{int} = 0.025

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.044	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.117	
S = 1.01	$\Delta\rho_{max}$ = 0.20 e Å^{-3}
2655 reflections	$\Delta\rho_{min}$ = −0.21 e Å^{-3}
209 parameters	
5 restraints	

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4B···O1^i	0.855 (10)	1.999 (14)	2.835 (3)	166 (3)
O4—H4A···S1^{ii}	0.87 (3)	2.44 (2)	3.189 (2)	145 (3)
N2—H2A···O3^{iii}	0.892 (10)	2.097 (11)	2.988 (3)	177 (3)
N1—H1A···S1^{iv}	0.895 (10)	2.479 (11)	3.363 (2)	170 (2)
O3—H3···O4	0.82	1.90	2.724 (3)	179

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

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

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supporting information

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S1. Comment

The title compound, (I), is a kind of polyfunctionalized dihydropyrimidines (DHPMs), which represents a heterocyclic system of remarkable pharmacological efficiency and may exhibit antiviral, antitumor, antibacterial, and anti inflammatory properties (Atwal *et al.*, 1991). It is the only cell-permeable molecule currently known to specifically inhibit mitotic kinesis Eg5 and is considered a lead for the development of new anticancer drugs (Mayer *et al.*, 1999).

In the molecule of the title compound, (I), (Fig.1) the bond lengths and angles are within normal ranges (Allen *et al.*, 1987). Rings A (N1/N2/C1—C4) and B (C9—C14) are, of course, planar and they are oriented at a dihedral angle of A/B = 84.31 (2)°.

In the crystal structure, intramolecular O—H···O and intermolecular O—H···O, N—H···O, O—H···S and N—H···S hydrogen bonds (Table 1) link the molecules (Fig. 2), in which they seem to be effective in the stabilization of the structure.

S2. Experimental

For the preparation of the title compound, a solution of ethyl acetoacetate (1.44 g, 10 mmol), 4-hydroxybenzaldehyde (1.38 g, 10 mmol) and thiourea (0.86 g, 10 mmol) in ethanol (5 ml) was heated under reflux in the presence of HCl (three drops) for 2.5 h. After being cooled to room temperature, the reaction mixture was poured onto crushed ice (30 g) and stirred for 5–10 min. The separated solid was filtered under suction (water aspirator), washed with ice-cold water (50 ml), and then recrystallized from hot ethanol to afford the pure product.

S3. Refinement

H atoms (for H_2O and NH) were located in difference synthesis and refined isotropicaly [O—H = 0.864 (10) and 0.855 (10) Å, U_{iso}(H) = 0.088 (13) and 0.096 (14) Å^2; N—H = 0.895 (10) and 0.892 (10) Å, U_{iso}(H) = 0.047 (8) and 0.061 (9) Å^2]. The remaining H atoms were positioned geometrically, with O—H = 0.82 Å (for OH) and C—H = 0.93, 0.98, 0.97 and 0.96 Å, for aromatic, methine, methylene and methyl H atoms and constrained to ride on their parent atoms, with U_{iso}(H) = xU_{eq}(C,O), where x = 1.5 for OH H and methyl H, and x = 1.2 for all other H atoms.
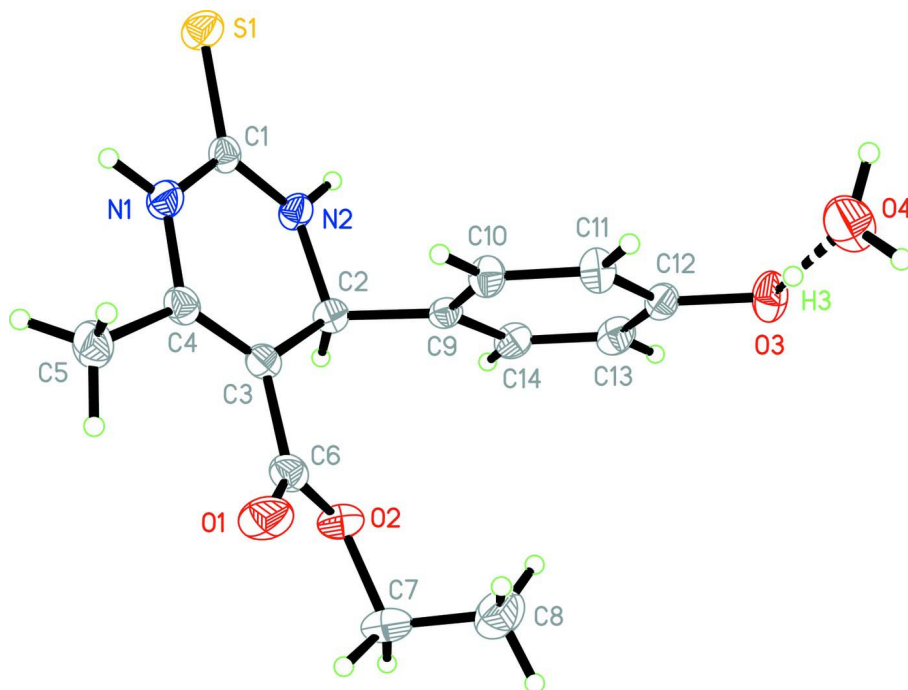
Figure 1

The molecular structure of the title molecule, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen bond is shown as dashed lines.
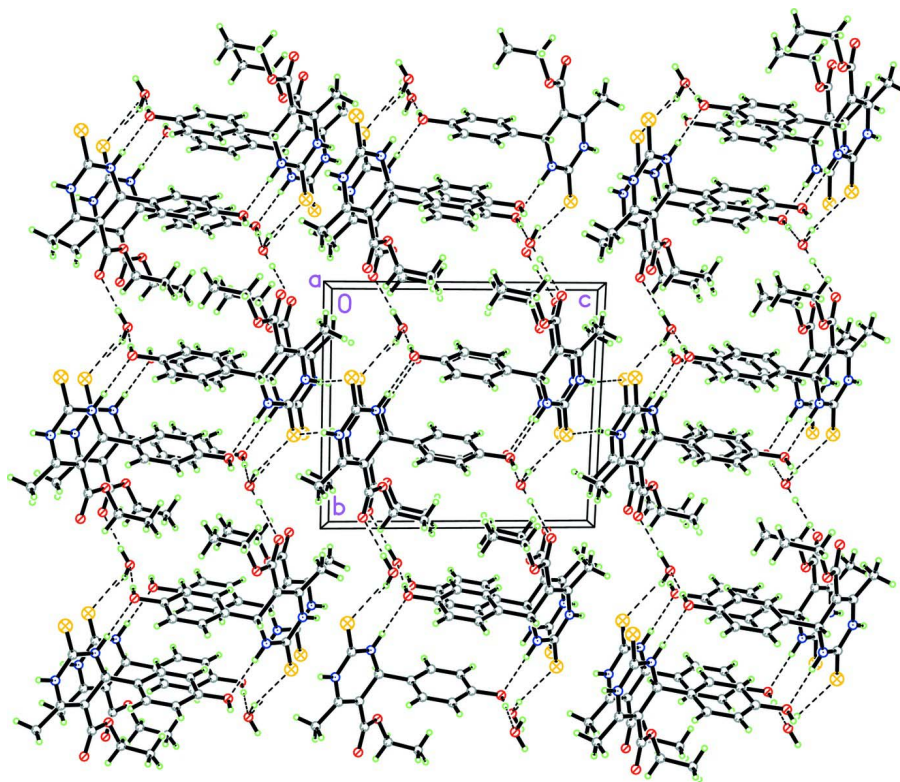
Figure 2

A packing diagram of (I). Hydrogen bonds are shown as dashed lines.

Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate monohydrate

Crystal data

$C_{14}H_{16}N_2O_3S \cdot H_2O$	$Z = 2$
$M_r = 310.36$	$F(000) = 328$
Triclinic, $P\overline{1}$	$D_x = 1.362$ Mg m^{-3}
Hall symbol: -P 1	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 5.6702$ (17) Å	Cell parameters from 1137 reflections
$b = 11.212$ (3) Å	$\theta = 3.3–25.0°$
$c = 12.343$ (4) Å	$\mu = 0.23$ mm^{-1}
$\alpha = 90.406$ (5)°	$T = 294$ K
$\beta = 95.251$ (5)°	Plate, colorless
$\gamma = 104.393$ (5)°	$0.22 \times 0.16 \times 0.16$ mm
$V = 756.5$ (4) Å^3	

Data collection

Bruker SMART CCD area-detector diffractometer	3958 measured reflections
Radiation source: fine-focus sealed tube	2655 independent reflections
Graphite monochromator	1741 reflections with $I > 2\sigma(I)$
φ and ω scans	$R_{int} = 0.025$
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)	$\theta_{max} = 25.0°$, $\theta_{min} = 2.5°$
$T_{min} = 0.951$, $T_{max} = 0.964$	$h = -6 \rightarrow 6$
	$k = -10 \rightarrow 13$
	$l = -14 \rightarrow 14$

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.044$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.117$	
$S = 1.01$	$w = 1/[\sigma^2(F_o^2) + (0.0529P)^2 + 0.1375P]$ where $P = (F_o^2 + 2F_c^2)/3$
2655 reflections	
209 parameters	$(\Delta/\sigma)_{max} = 0.003$
5 restraints	$\Delta\rho_{max} = 0.20$ e Å^{-3}
Primary atom site location: structure-invariant direct methods	$\Delta\rho_{min} = -0.21$ 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*	$U_{iso}*/U_{eq}$
S1	0.30417 (14)	0.38411 (6)	0.11066 (6)	0.0509 (3)
O1	0.1221 (4)	0.95058 (17)	0.15444 (17)	0.0588 (6)
O2	−0.2131 (3)	0.83224 (15)	0.21777 (15)	0.0464 (5)
O3	0.1542 (4)	0.70709 (18)	0.67773 (14)	0.0520 (5)
H3	0.2977	0.7438	0.6934	0.078*
O4	0.6317 (5)	0.8288 (2)	0.72788 (18)	0.0688 (7)
H4A	0.700 (6)	0.7722 (19)	0.753 (3)	0.088 (13)*
H4B	0.681 (6)	0.8966 (17)	0.765 (2)	0.096 (14)*
N1	0.2842 (4)	0.61232 (19)	0.06966 (18)	0.0417 (6)
H1A	0.385 (4)	0.602 (2)	0.0205 (16)	0.047 (8)*
N2	0.0298 (4)	0.51470 (18)	0.19204 (17)	0.0376 (5)
H2A	−0.020 (5)	0.4483 (17)	0.231 (2)	0.061 (9)*
C1	0.1972 (5)	0.5103 (2)	0.12598 (19)	0.0343 (6)
C2	−0.0549 (5)	0.6237 (2)	0.2218 (2)	0.0351 (6)
H2	−0.2327	0.6050	0.2044	0.042*
C3	0.0627 (4)	0.7321 (2)	0.1543 (2)	0.0334 (6)
C4	0.2179 (5)	0.7224 (2)	0.0817 (2)	0.0378 (6)
C5	0.3300 (6)	0.8169 (2)	0.0035 (2)	0.0521 (8)
H5A	0.2437	0.8805	−0.0010	0.078*
H5B	0.3197	0.7784	−0.0671	0.078*
H5C	0.4986	0.8521	0.0286	0.078*
C6	−0.0012 (5)	0.8494 (2)	0.1737 (2)	0.0401 (6)
C7	−0.2762 (6)	0.9417 (2)	0.2582 (3)	0.0563 (8)
H7A	−0.4527	0.9281	0.2532	0.068*
H7B	−0.2115	1.0112	0.2139	0.068*
C8	−0.1728 (7)	0.9697 (3)	0.3736 (3)	0.0710 (10)
H8A	−0.2140	0.8963	0.4147	0.106*
H8B	−0.2398	1.0318	0.4038	0.106*
H8C	0.0018	0.9990	0.3766	0.106*
C9	0.0011 (4)	0.6489 (2)	0.34304 (19)	0.0319 (6)
C10	0.2363 (5)	0.7051 (2)	0.3872 (2)	0.0388 (6)
H10	0.3597	0.7294	0.3413	0.047*
C11	0.2911 (5)	0.7258 (2)	0.4978 (2)	0.0410 (6)
H11	0.4501	0.7639	0.5259	0.049*
C12	0.1096 (5)	0.6899 (2)	0.5672 (2)	0.0371 (6)
C13	−0.1259 (5)	0.6333 (2)	0.5247 (2)	0.0428 (7)
H13	−0.2488	0.6088	0.5708	0.051*
C14	−0.1787 (5)	0.6130 (2)	0.4140 (2)	0.0392 (6)
H14	−0.3377	0.5747	0.3862	0.047*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0668 (5)	0.0371 (4)	0.0559 (5)	0.0198 (4)	0.0232 (4)	0.0093 (3)
O1	0.0698 (14)	0.0296 (11)	0.0781 (15)	0.0097 (10)	0.0198 (12)	0.0033 (10)

O2	0.0440 (11)	0.0348 (10)	0.0620 (13)	0.0132 (9)	0.0048 (10)	−0.0021 (9)
O3	0.0695 (14)	0.0479 (12)	0.0334 (11)	0.0024 (11)	0.0112 (9)	0.0031 (8)
O4	0.0863 (18)	0.0457 (14)	0.0663 (16)	0.0087 (14)	−0.0142 (12)	0.0029 (12)
N1	0.0536 (15)	0.0357 (13)	0.0396 (14)	0.0141 (11)	0.0160 (12)	0.0062 (10)
N2	0.0493 (14)	0.0279 (12)	0.0361 (13)	0.0082 (11)	0.0112 (11)	0.0007 (10)
C1	0.0404 (15)	0.0317 (14)	0.0288 (14)	0.0062 (12)	0.0006 (12)	−0.0015 (11)
C2	0.0342 (14)	0.0324 (14)	0.0376 (15)	0.0064 (12)	0.0038 (11)	0.0005 (11)
C3	0.0369 (15)	0.0274 (13)	0.0339 (14)	0.0062 (11)	−0.0022 (12)	−0.0007 (10)
C4	0.0474 (17)	0.0305 (14)	0.0332 (15)	0.0077 (12)	−0.0014 (12)	0.0015 (11)
C5	0.073 (2)	0.0400 (16)	0.0440 (17)	0.0119 (15)	0.0150 (15)	0.0102 (13)
C6	0.0445 (17)	0.0357 (16)	0.0386 (16)	0.0103 (13)	−0.0045 (13)	0.0004 (12)
C7	0.058 (2)	0.0427 (17)	0.075 (2)	0.0245 (15)	0.0114 (16)	0.0012 (15)
C8	0.090 (3)	0.052 (2)	0.072 (2)	0.0149 (19)	0.019 (2)	−0.0077 (16)
C9	0.0351 (15)	0.0277 (13)	0.0350 (14)	0.0106 (11)	0.0067 (11)	0.0014 (10)
C10	0.0349 (15)	0.0436 (16)	0.0366 (15)	0.0048 (13)	0.0110 (12)	0.0047 (12)
C11	0.0376 (15)	0.0446 (16)	0.0358 (16)	0.0010 (13)	0.0032 (12)	0.0015 (12)
C12	0.0518 (18)	0.0289 (14)	0.0321 (15)	0.0098 (13)	0.0115 (13)	0.0038 (11)
C13	0.0444 (17)	0.0397 (15)	0.0460 (17)	0.0082 (13)	0.0206 (13)	0.0061 (12)
C14	0.0323 (15)	0.0397 (15)	0.0451 (17)	0.0069 (12)	0.0076 (12)	−0.0018 (12)

Geometric parameters (Å, º)

S1—C1	1.688 (2)	C5—H5A	0.9600
O1—C6	1.213 (3)	C5—H5B	0.9600
O2—C6	1.335 (3)	C5—H5C	0.9600
O2—C7	1.458 (3)	C7—C8	1.489 (4)
O3—C12	1.368 (3)	C7—H7A	0.9700
O3—H3	0.8200	C7—H7B	0.9700
O4—H4A	0.87 (3)	C8—H8A	0.9600
O4—H4B	0.855 (10)	C8—H8B	0.9600
N1—C1	1.353 (3)	C8—H8C	0.9600
N1—C4	1.387 (3)	C9—C10	1.385 (3)
N1—H1A	0.895 (10)	C9—C14	1.390 (3)
N2—C1	1.316 (3)	C10—C11	1.377 (3)
N2—C2	1.476 (3)	C10—H10	0.9300
N2—H2A	0.892 (10)	C11—C12	1.384 (4)
C2—C9	1.510 (3)	C11—H11	0.9300
C2—C3	1.526 (3)	C12—C13	1.381 (4)
C2—H2	0.9800	C13—C14	1.376 (4)
C3—C4	1.333 (3)	C13—H13	0.9300
C3—C6	1.472 (3)	C14—H14	0.9300
C4—C5	1.500 (4)		
C6—O2—C7	117.0 (2)	O2—C7—C8	110.0 (2)
C12—O3—H3	109.5	O2—C7—H7A	109.7
C1—N1—C4	124.1 (2)	C8—C7—H7A	109.7
C1—N1—H1A	114.2 (17)	O2—C7—H7B	109.7
C4—N1—H1A	121.6 (17)	C8—C7—H7B	109.7

C1—N2—C2	127.1 (2)	H7A—C7—H7B	108.2
C1—N2—H2A	116.3 (18)	C7—C8—H8A	109.5
C2—N2—H2A	115.7 (18)	C7—C8—H8B	109.5
N2—C1—N1	117.3 (2)	H8A—C8—H8B	109.5
N2—C1—S1	122.54 (19)	C7—C8—H8C	109.5
N1—C1—S1	120.1 (2)	H8A—C8—H8C	109.5
N2—C2—C9	108.85 (18)	H8B—C8—H8C	109.5
N2—C2—C3	109.3 (2)	C10—C9—C14	117.9 (2)
C9—C2—C3	113.4 (2)	C10—C9—C2	120.7 (2)
N2—C2—H2	108.4	C14—C9—C2	121.4 (2)
C9—C2—H2	108.4	C11—C10—C9	121.3 (2)
C3—C2—H2	108.4	C11—C10—H10	119.3
C4—C3—C6	121.1 (2)	C9—C10—H10	119.3
C4—C3—C2	122.1 (2)	C10—C11—C12	120.0 (2)
C6—C3—C2	116.7 (2)	C10—C11—H11	120.0
C3—C4—N1	119.6 (2)	C12—C11—H11	120.0
C3—C4—C5	127.9 (2)	O3—C12—C13	118.0 (2)
N1—C4—C5	112.4 (2)	O3—C12—C11	122.5 (2)
C4—C5—H5A	109.5	C13—C12—C11	119.5 (2)
C4—C5—H5B	109.5	C14—C13—C12	120.0 (2)
H5A—C5—H5B	109.5	C14—C13—H13	120.0
C4—C5—H5C	109.5	C12—C13—H13	120.0
H5A—C5—H5C	109.5	C13—C14—C9	121.3 (2)
H5B—C5—H5C	109.5	C13—C14—H14	119.4
O1—C6—O2	122.9 (2)	C9—C14—H14	119.4
O1—C6—C3	125.3 (3)	H4A—O4—H4B	112.8 (17)
O2—C6—C3	111.7 (2)		
C2—N2—C1—N1	−7.7 (4)	C2—C3—C6—O1	156.6 (2)
C2—N2—C1—S1	171.99 (18)	C4—C3—C6—O2	158.4 (2)
C4—N1—C1—N2	3.7 (4)	C2—C3—C6—O2	−22.3 (3)
C4—N1—C1—S1	−176.06 (19)	C6—O2—C7—C8	−88.3 (3)
C1—N2—C2—C9	−118.3 (3)	N2—C2—C9—C10	77.4 (3)
C1—N2—C2—C3	6.0 (3)	C3—C2—C9—C10	−44.5 (3)
N2—C2—C3—C4	−0.5 (3)	N2—C2—C9—C14	−100.6 (3)
C9—C2—C3—C4	121.1 (3)	C3—C2—C9—C14	137.5 (2)
N2—C2—C3—C6	−179.8 (2)	C14—C9—C10—C11	−0.4 (4)
C9—C2—C3—C6	−58.2 (3)	C2—C9—C10—C11	−178.4 (2)
C6—C3—C4—N1	176.6 (2)	C9—C10—C11—C12	0.2 (4)
C2—C3—C4—N1	−2.8 (4)	C10—C11—C12—O3	179.4 (2)
C6—C3—C4—C5	−6.3 (4)	C10—C11—C12—C13	0.0 (4)
C2—C3—C4—C5	174.4 (2)	O3—C12—C13—C14	−179.4 (2)
C1—N1—C4—C3	1.4 (4)	C11—C12—C13—C14	0.0 (4)
C1—N1—C4—C5	−176.2 (2)	C12—C13—C14—C9	−0.2 (4)
C7—O2—C6—O1	−9.2 (4)	C10—C9—C14—C13	0.4 (4)
C7—O2—C6—C3	169.7 (2)	C2—C9—C14—C13	178.4 (2)
C4—C3—C6—O1	−22.8 (4)		

Hydrogen-bond geometry (Å, º)

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4B···O1[i]	0.86 (1)	2.00 (1)	2.835 (3)	166 (3)
O4—H4A···S1[ii]	0.87 (3)	2.44 (2)	3.189 (2)	145 (3)
N2—H2A···O3[iii]	0.89 (1)	2.10 (1)	2.988 (3)	177 (3)
N1—H1A···S1[iv]	0.90 (1)	2.48 (1)	3.363 (2)	170 (2)
O3—H3···O4	0.82	1.90	2.724 (3)	179

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