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Crystal structure and Hirshfeld surface analysis of ethyl 5-phenylisoxazole-3-carboxylate

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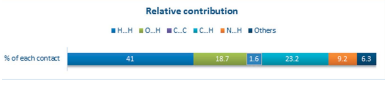
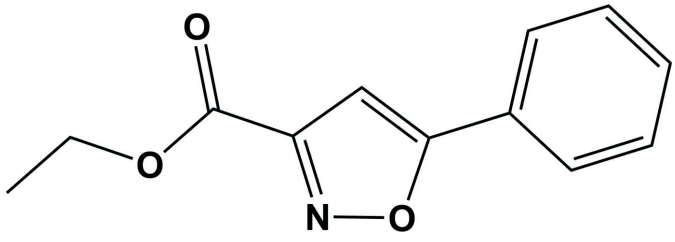
The title compound, $C_{12}H_{11}NO_3$, is an intermediate used in the synthesis of many drug-like molecules. The molecule is almost planar, with the phenyl ring inclined to the isoxazole ring by 0.5 (1)°. The ester moiety has an extended conformation and is almost in the same plane with respect to the isoxazole ring, as indicated by the O—C—C—N torsion angle of −172.86 (18)°. In the crystal, molecules are linked *via* pairs of C—H···O hydrogen bonds with the same acceptor atom, forming inversion dimers with two $R_2^1(7)$ ring motifs. The molecules stack in layers lying parallel to $(10\overline{3})$. Analysis using Hirshfeld surface generation and two-dimensional fingerprint plots explores the distribution of weak intermolecular interactions in the crystal structure.

1. Chemical context

Nitrogen-containing heterocyclic rings are of great importance in medicinal and organic chemistry (Dou *et al.*, 2013). Isoxazole derivatives are important heterocyclic pharmaceuticals having a broad spectrum of biological activity, which includes antagonism of the NMDA receptor, anti-inflammatory (Panda *et al.*, 2009), anti-tumour, anticonvulsant, anti-psychotic, antidepressant and anti HIV activity (Conti *et al.*, 2005; Srivastava *et al.*, 1999). Considerable attention has been paid to isoxazole derivatives as a result of their prominent biological properties (Dou *et al.*, 2013). Valdecoxib (Bextra), a selective cyclooxygenase-2 (COX-2) inhibitor used in the treatment of arthritis, contains an isoxazole moiety which is responsible for its biological activity (Waldo & Larock, 2007; Dadiboyena & Nefzi, 2010). In addition, isoxazole derivatives are also important intermediates in the preparation of various heterocyclic biologically active drugs (Dou *et al.*, 2013). As part of our ongoing studies on isoxazole derivatives as kinase inhibitors, we have synthesized the title compound, and report herein on its crystal structure and the quantitative analysis of intermolecular interactions using the Hirshfeld surface and 2D fingerprint plot analysis.





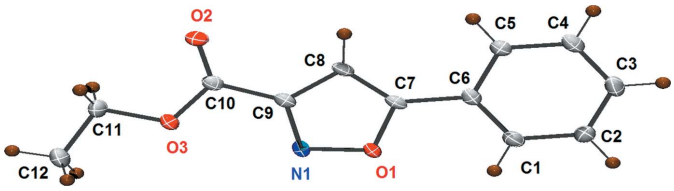


Figure 1
The molecular structure of compound (I), with the atom labelling and displacement ellipsoid drawn at the 50% probability level.

2. Structural commentary

The molecular structure of the title compound, (I), is illustrated in Fig. 1. The molecule consists of three almost flat units: the phenyl ring, the isoxazole ring and the ester. The phenyl (C1–C6) and isoxazole (O1/N1/C7–C9) rings are almost coplanar, as indicated by the torsion angle C5—C6—C7—O1 = 0.1 (3)°. The ester unit has an extended conformation and is almost in the same plane as the isoxazole ring, as indicated by the torsion angle O2—C10—C9—N1 = −172.86 (18)°.

3. Supramolecular features

In the crystal of (I), molecules are linked *via* pairs of C—H···O hydrogen bonds, both involving atom O2 as acceptor, forming inversion dimers with two $R_2^1(7)$ ring motifs (Table 1 and Fig. 2). The molecules stack in layers lying parallel to $(10\bar{3})$, as illustrated in Fig. 3.

4. Hirshfeld surface and fingerprint plot analysis

To explore the weak intermolecular interactions in (I), Hirshfeld surfaces and 2D fingerprint plots were generated using *Crystal Explorer 3.1* to quantify the intermolecular interactions (McKinnon *et al.*, 2007; Spackman & Jayatilaka, 2009). Hirshfeld surfaces are produced through the partitioning of space within a crystal where the ratio of promolecule to procrystal electron density is equal to 0.5, generating

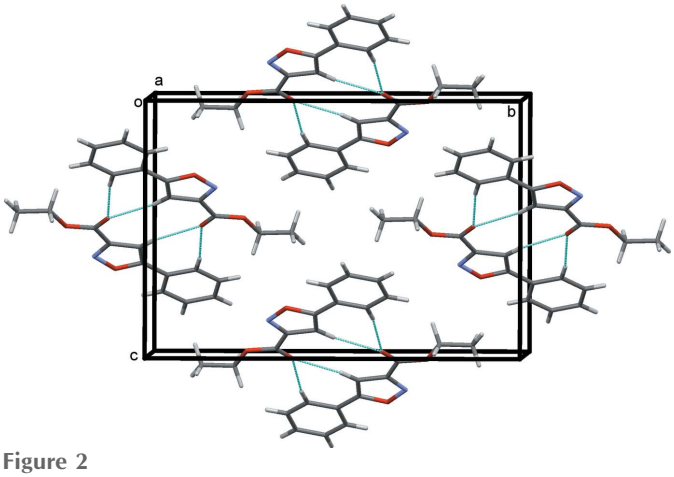


Figure 2
Crystal packing of compound (I), viewed along the *a* axis. Hydrogen bonds are shown as dashed lines (see Table 1).

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H1···O2^{i}	0.93	2.52	3.447 (2)	171
C8—H8···O2^{i}	0.93	2.36	3.260 (2)	163

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

continuous, non-overlapping surfaces which are widely used to visualize and study the significance of weak interactions in the molecular packing (McKinnon *et al.*, 2007). The Hirshfeld surface of title compound was mapped over d_{norm}, shape index and curvedness. The d_{norm} surface is the normalized function of d_i and d_e (Fig. 4*a*), with white-, red- and blue-coloured surfaces. The white surface indicates those contacts with distances equal to the sum of the van der Waals (vdW) radii, red indicates shorter contacts (< vdW radii) and blue the longer contact (> vdW radii). The Hirshfeld surface was also mapped over electrostatic potential (Fig. 4*b*) using a STO-3G basis set at the Hartee–Fock level of theory (Spackman & McKinnon, 2002; McKinnon *et al.*, 2004). In the Hirshfeld surface, a pair of interactions between the aromatic C—H···O═C atoms can be seen as the bright-red area (1) in Fig. 5*a*. The 2D fingerprint plot analysis of the O···H interactions revealed significant hydrogen-bonding spikes (d_i = 1.3, d_e = 0.9 Å and d_e = 1.9, d_i = 2.6 Å); Fig. 6*c*.

The analysis indicates that there is a weak N···H intermolecular interaction between the nitrogen atom of the

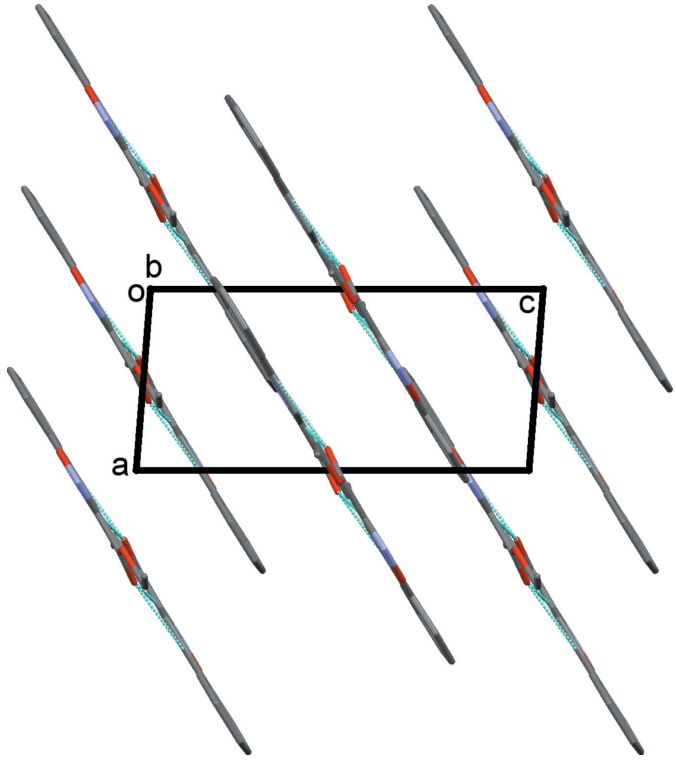


Figure 3
Crystal packing of compound (I) viewed along the *b* axis. Hydrogen bonds are shown as dashed lines and, for clarity, H atoms have been omitted.

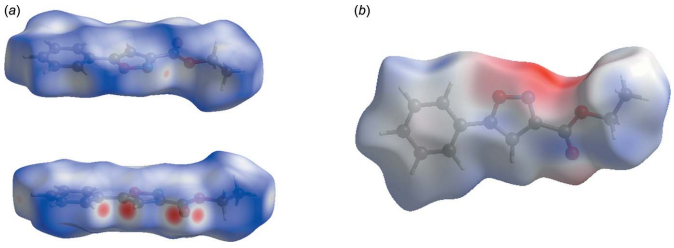


Figure 4
Hirshfeld surface mapped over (*a*) d_{norm} and (*b*) electrostatic potential.

isoxazole ring and the methylene hydrogen atom of the phenyl ring of a neighbouring molecule (Fig. 5*b*). The fingerprint plot analysis of N···H contacts reveals a significant wing-like structure (d_i = 1.2, d_e = 1.5 Å and d_e = 2.2, d_i = 2.4 Å) Fig. 6*d*.

The relative contributions to the Hirshfeld surface area for each type of intermolecular contact are illustrated in Figs. 6 and 7. The H···H interactions appear as scattered points over nearly the entire plot and have a significant composition of 41% of the Hirshfeld surface. The H···O contacts comprise of 18.7% and the C···C interactions comprise 1.6% of the total Hirshfeld surface. The C···H and N···H interactions cover 23.2% and 9.2% of the surface, respectively. Thus, these weak interactions contribute significantly to the packing of (I).

5. Database survey

A search of the Cambridge Structural Database (CSD, V5.38; last update November 2016; Groom *et al.*, 2016) for similar isoxazole derivatives, revealed only one hit, *viz*. ethyl 5-(4-aminophenyl) isoxazole-3-carboxylate (CSD refcode YAVRIY; Zhao *et al.*, 2012). This compound crystallizes with two independent molecules in the asymmetric unit. One molecule is slightly more planar than the other, with the phenyl ring being inclined to the isoxazole ring by 1.77 (10) and 5.85 (10)°. In the title compound, (I), this dihedral angle is 0.5 (1)°.

6. Synthesis and crystallization

There are several methods available in the literature for the preparation of isoxazole derivatives. We have followed a

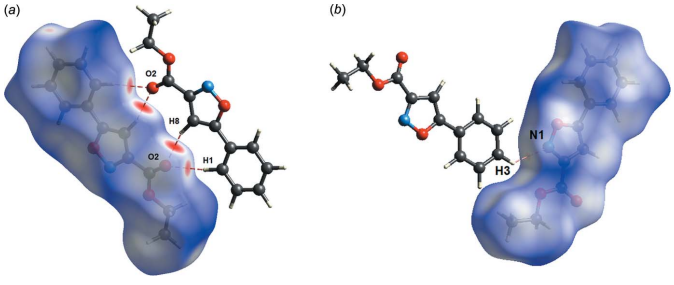


Figure 5
Hirshfeld surface mapped over (*a*) d_{norm} highlighting the regions of C—H···O hydrogen bonding and (*b*) d_{norm} highlighting the region of C—H···N hydrogen bonding.

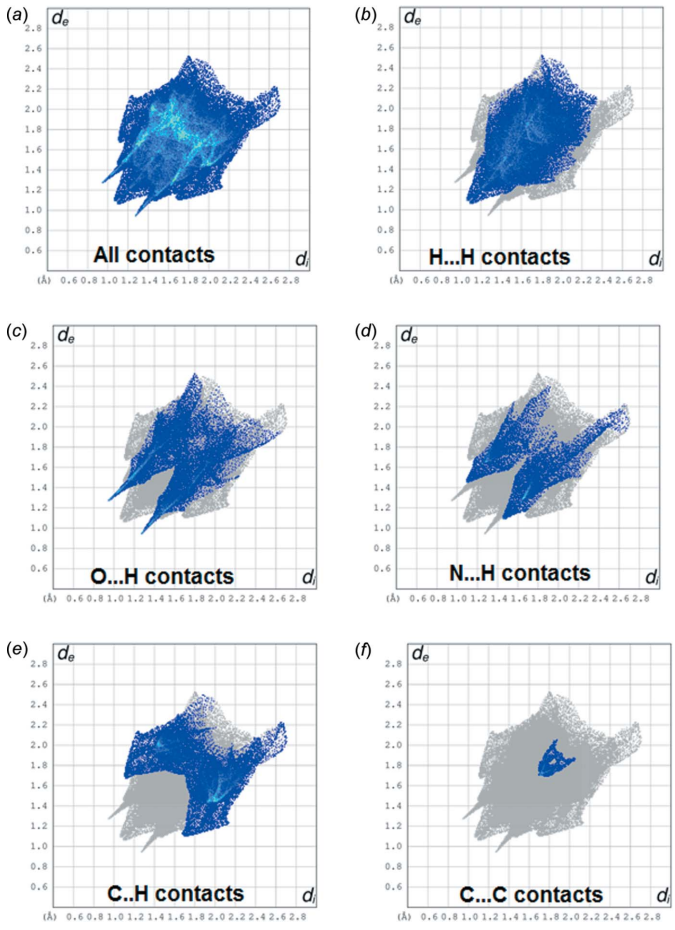


Figure 6
Two-dimensional fingerprint plot analysis (*a*) all interactions, (*b*) H···H contacts, (*c*) O···H contacts, (*d*) N···H contacts, (*e*) C···H contacts and (*f*) C···C contacts.

simple preparation from a diketoester (Tourteau *et al.*, 2013; Bastos *et al.*, 2015). After the reaction of acetophenone with diethyoxalate in a basic solution (sodium ethoxide) of ethanol for 8 h, 1*N* HCl was added to neutralize the sodium ethoxide to obtain the diketoester (ethyl 2,4-dioxo-4-phenylbutanoate; see Fig. 8) as a yellow liquid. 1 g (4.5 mmol) of the diketoester in ethanol was added to hydroxyl amine hydrochloride (0.315 g, 4.5 mmol) at room temperature and the resulting mixture was stirred at 353 K for 12 h. The progress of the reaction was monitored by TLC. After the completion of starting materials, the reaction mixture was cooled to room temperature and the excess of ethanol removed. The resulting residue was dissolved in water and extracted with ethyl

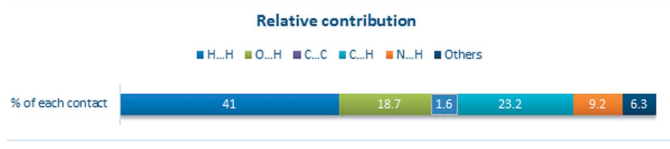


Figure 7
Relative contribution of each interaction in the two-dimensional fingerprint analysis.

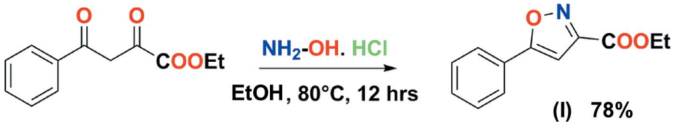


Figure 8
Synthesis of the title compound, (I).

acetate. The organic layer was dried with Na_2SO_4, filtered and the concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (3% ethyl acetate: Pet-ether) to afford the title compound, (I) (yield 76.9%, 0.75 g; m.p. 325–327 K).

Colourless crystals were obtained by slow evaporation of a solution in ethyl acetate. Spectroscopic data: ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.80 (*m*, 2H), 7.50 (*m*, 3H), 6.92 (*s*, 1H), 4.47 (*q*, 2H), 1.44 (*t*, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 171.66, 159.98, 156.96, 130.76, 129.11, 126.61, 125.89, 99.92, 62.18, 14.15.

7. Refinement

Crystal data, data collection and structure refinement parameters are given in Table 2. All H atoms were positioned geometrically and refined as riding: C—H = 0.95–0.99 Å with U_{iso}(H) = 1.2U_{eq}(C).

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{12}H_{11}NO_3$
M_r	217.22
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	100
a, b, c (Å)	5.4447 (7), 17.180 (2), 11.7603 (19)
β (°)	94.508 (5)
V (Å^3)	1096.6 (3)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.10
Crystal size (mm)	0.4 × 0.2 × 0.2
Data collection	
Diffractometer	Bruker APEXII CCD
Absorption correction	–
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	14119, 2813, 1889
R_{int}	0.075
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.676
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.064, 0.177, 1.09
No. of reflections	2813
No. of parameters	146
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.27, −0.30

Computer programs: *APEX2* and *SAINT* (Bruker, 2006), *SHELXS97* and *SHELXTL* (Sheldrick 2008), *SHELXL2014* (Sheldrick, 2015), and *Mercury* (Macrae *et al.*, 2008).

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Computing details

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick 2008); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *SHELXTL* (Sheldrick 2008) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXTL* (Sheldrick 2008).

Ethyl 5-phenylisoxazole-3-carboxylate

Crystal data

$C_{12}H_{11}NO_3$
$M_r = 217.22$
Monoclinic, $P2_1/n$
$a = 5.4447$ (7) Å
$b = 17.180$ (2) Å
$c = 11.7603$ (19) Å
$\beta = 94.508$ (5)°
$V = 1096.6$ (3) Å^3
$Z = 4$
$F(000) = 456$
$D_x = 1.316$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 5392 reflections
$\theta = 2.4$–30.5°
$\mu = 0.10$ mm^{-1}
$T = 100$ K
Blocks, colourless
0.4 × 0.2 × 0.2 mm

Data collection

Bruker APEXII CCD diffractometer
φ and ω scans
14119 measured reflections
2813 independent reflections
1889 reflections with $I > 2\sigma(I)$
$R_{int} = 0.075$
$\theta_{max} = 28.7°$, $\theta_{min} = 2.4°$
$h = -5\rightarrow7$
$k = -23\rightarrow23$
$l = -15\rightarrow14$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.064$
$wR(F^2) = 0.177$
$S = 1.09$
2813 reflections
146 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
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.30$ 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}
O1	0.1048 (2)	0.62026 (7)	0.20002 (11)	0.0221 (4)
O3	−0.4360 (3)	0.73867 (7)	0.01862 (12)	0.0230 (4)
O2	−0.6161 (2)	0.62208 (7)	−0.01700 (11)	0.0243 (4)
C10	−0.4499 (3)	0.66119 (10)	0.02530 (16)	0.0184 (4)
C6	0.1914 (3)	0.48387 (10)	0.22525 (16)	0.0181 (4)
N1	−0.0666 (3)	0.67215 (8)	0.14685 (14)	0.0225 (4)
C4	0.5520 (4)	0.44302 (11)	0.34137 (19)	0.0256 (5)
H4	0.692513	0.455560	0.387897	0.031*
C7	0.0322 (4)	0.54579 (9)	0.17410 (16)	0.0174 (4)
C9	−0.2320 (3)	0.62718 (10)	0.09196 (15)	0.0180 (4)
C5	0.4000 (4)	0.50161 (10)	0.29503 (17)	0.0234 (5)
H5	0.438869	0.553372	0.311094	0.028*
C3	0.4941 (4)	0.36559 (11)	0.31817 (17)	0.0249 (5)
H3	0.596502	0.326217	0.348598	0.030*
C1	0.1308 (4)	0.40540 (10)	0.20262 (16)	0.0203 (4)
H1	−0.010182	0.392615	0.156628	0.024*
C12	−0.5855 (4)	0.86283 (11)	−0.04174 (18)	0.0273 (5)
H12A	−0.579681	0.880375	0.035929	0.041*
H12B	−0.711938	0.890614	−0.086440	0.041*
H12C	−0.429204	0.872225	−0.071751	0.041*
C8	−0.1780 (3)	0.54715 (9)	0.10639 (16)	0.0185 (4)
H8	−0.267753	0.504983	0.075862	0.022*
C11	−0.6410 (4)	0.77721 (11)	−0.04635 (18)	0.0243 (5)
H11A	−0.794720	0.766468	−0.012878	0.029*
H11B	−0.654755	0.759053	−0.124690	0.029*
C2	0.2846 (4)	0.34724 (10)	0.24996 (17)	0.0237 (5)
H2	0.245566	0.295307	0.235394	0.028*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0236 (8)	0.0114 (6)	0.0300 (8)	0.0009 (5)	−0.0065 (6)	0.0016 (5)
O3	0.0239 (8)	0.0128 (6)	0.0314 (8)	0.0024 (5)	−0.0047 (6)	0.0009 (5)
O2	0.0233 (8)	0.0170 (6)	0.0319 (8)	−0.0022 (5)	−0.0028 (6)	−0.0018 (6)
C10	0.0199 (10)	0.0140 (8)	0.0215 (10)	−0.0001 (7)	0.0026 (8)	−0.0025 (7)
C6	0.0190 (10)	0.0150 (8)	0.0207 (10)	0.0016 (7)	0.0047 (8)	0.0019 (7)
N1	0.0246 (10)	0.0139 (7)	0.0280 (9)	0.0031 (6)	−0.0052 (7)	0.0029 (7)
C4	0.0195 (11)	0.0220 (10)	0.0345 (12)	−0.0005 (8)	−0.0036 (8)	0.0034 (8)
C7	0.0234 (11)	0.0102 (8)	0.0190 (10)	−0.0019 (7)	0.0041 (8)	−0.0019 (7)

C9	0.0209 (10)	0.0131 (8)	0.0204 (10)	−0.0019 (7)	0.0035 (8)	0.0001 (7)
C5	0.0211 (11)	0.0146 (9)	0.0345 (12)	−0.0003 (7)	0.0017 (9)	0.0006 (8)
C3	0.0224 (11)	0.0195 (9)	0.0331 (11)	0.0057 (8)	0.0038 (9)	0.0064 (8)
C1	0.0218 (11)	0.0161 (8)	0.0228 (10)	−0.0003 (7)	0.0005 (8)	−0.0010 (7)
C12	0.0294 (12)	0.0197 (9)	0.0320 (12)	0.0047 (8)	−0.0019 (9)	0.0042 (8)
C8	0.0208 (10)	0.0108 (8)	0.0243 (10)	−0.0014 (7)	0.0032 (8)	−0.0020 (7)
C11	0.0219 (11)	0.0197 (9)	0.0300 (11)	0.0041 (8)	−0.0055 (8)	0.0009 (8)
C2	0.0276 (11)	0.0150 (8)	0.0289 (11)	0.0020 (8)	0.0042 (8)	−0.0001 (8)

Geometric parameters (Å, º)

O1—C7	1.366 (2)	C9—C8	1.413 (2)
O1—N1	1.4018 (19)	C5—H5	0.9300
O3—C10	1.336 (2)	C3—C2	1.379 (3)
O3—C11	1.461 (2)	C3—H3	0.9300
O2—C10	1.203 (2)	C1—C2	1.391 (3)
C10—C9	1.489 (3)	C1—H1	0.9300
C6—C5	1.382 (3)	C12—C11	1.502 (2)
C6—C1	1.408 (2)	C12—H12A	0.9600
C6—C7	1.471 (2)	C12—H12B	0.9600
N1—C9	1.317 (2)	C12—H12C	0.9600
C4—C3	1.389 (3)	C8—H8	0.9300
C4—C5	1.387 (3)	C11—H11A	0.9700
C4—H4	0.9300	C11—H11B	0.9700
C7—C8	1.342 (3)	C2—H2	0.9300
C7—O1—N1	108.98 (13)	C4—C3—H3	120.1
C10—O3—C11	115.97 (14)	C2—C1—C6	119.14 (18)
O2—C10—O3	125.19 (16)	C2—C1—H1	120.4
O2—C10—C9	122.75 (16)	C6—C1—H1	120.4
O3—C10—C9	112.06 (15)	C11—C12—H12A	109.5
C5—C6—C1	119.53 (17)	C11—C12—H12B	109.5
C5—C6—C7	120.93 (16)	H12A—C12—H12B	109.5
C1—C6—C7	119.54 (17)	C11—C12—H12C	109.5
C9—N1—O1	104.55 (14)	H12A—C12—H12C	109.5
C3—C4—C5	119.89 (19)	H12B—C12—H12C	109.5
C3—C4—H4	120.1	C9—C8—C7	104.35 (15)
C5—C4—H4	120.1	C9—C8—H8	127.8
O1—C7—C8	109.53 (15)	C7—C8—H8	127.8
O1—C7—C6	115.78 (16)	O3—C11—C12	106.35 (15)
C8—C7—C6	134.68 (16)	O3—C11—H11A	110.5
C8—C9—N1	112.59 (16)	C12—C11—H11A	110.5
C8—C9—C10	126.49 (16)	O3—C11—H11B	110.5
N1—C9—C10	120.92 (15)	C12—C11—H11B	110.5
C6—C5—C4	120.69 (17)	H11A—C11—H11B	108.7
C6—C5—H5	119.7	C3—C2—C1	120.87 (17)
C4—C5—H5	119.7	C3—C2—H2	119.6
C2—C3—C4	119.87 (18)	C1—C2—H2	119.6

C2—C3—H3	120.1		
C11—O3—C10—O2	−0.4 (3)	O3—C10—C9—N1	7.3 (2)
C11—O3—C10—C9	179.40 (15)	C1—C6—C5—C4	1.1 (3)
C7—O1—N1—C9	−0.10 (19)	C7—C6—C5—C4	−178.82 (18)
N1—O1—C7—C8	0.15 (19)	C3—C4—C5—C6	−0.4 (3)
N1—O1—C7—C6	−179.04 (15)	C5—C4—C3—C2	−0.6 (3)
C5—C6—C7—O1	0.1 (3)	C5—C6—C1—C2	−0.9 (3)
C1—C6—C7—O1	−179.73 (15)	C7—C6—C1—C2	179.02 (17)
C5—C6—C7—C8	−178.8 (2)	N1—C9—C8—C7	0.1 (2)
C1—C6—C7—C8	1.3 (3)	C10—C9—C8—C7	−178.89 (17)
O1—N1—C9—C8	0.0 (2)	O1—C7—C8—C9	−0.13 (19)
O1—N1—C9—C10	179.04 (15)	C6—C7—C8—C9	178.9 (2)
O2—C10—C9—C8	6.0 (3)	C10—O3—C11—C12	179.89 (15)
O3—C10—C9—C8	−173.78 (16)	C4—C3—C2—C1	0.8 (3)
O2—C10—C9—N1	−172.86 (18)	C6—C1—C2—C3	0.0 (3)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H1···O2^{i}	0.93	2.52	3.447 (2)	171
C8—H8···O2^{i}	0.93	2.36	3.260 (2)	163

Symmetry code: (i) −*x*−1, −*y*+1, −*z*.