

Ethyl 4-chloro-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate

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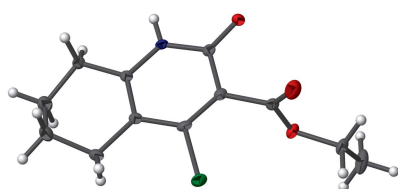
Keywords: crystal structure; quinoline derivative; human immunodeficiency virus (HIV).

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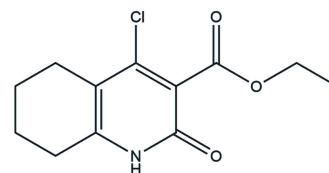
Structural data: full structural data are available from iucrdata.iucr.org

In the title compound, $C_{12}H_{14}ClNO_3$, the aliphatic ring of the hexahydroquinoline system adopts a half-chair conformation while the ethyl carboxylate substituent is inclined to the hexahydroquinoline ring system by $85.1(2)^\circ$. In the crystal, a pair of $N-H \cdots O$ hydrogen bonds form an inversion dimer. The structure is further stabilized by $C-H \cdots O$ and $C-H \cdots Cl$ hydrogen bonds, forming a three-dimensional network.

3D view



Chemical scheme



Structure description

HIV or the human immunodeficiency virus is the virus that causes AIDS. HIV attacks the immune system by destroying $CD4^+$ T lymphocytes, a cell type that is vital in fighting infections. The actual treatment consists of a group of several drugs known as anti-retroviral agents that inhibit proteins that are important for virus replication, including reverse transcriptase (Le Van *et al.*, 2009). During work on the synthesis of promising compounds to be used as anti-retroviral agents, Medina-Franco and co-workers found that compounds maintaining a pyridinone core in the base structure showed activity in the inhibition of reverse transcriptase (Medina-Franco *et al.*, 2007). As part of our ongoing research, we have synthesized another pyridin-2 (1*H*)-one analogue (Cabrera *et al.*, 2015). In this work, we report the structure of the closely related title compound, again containing a hexahydroquinoline ring system.

The molecular structure of the title molecule is shown in Fig. 1. The hexahydroquinoline ring system is almost planar, r.m.s. deviation 0.1603 \AA , with an angle of $4.86(9)^\circ$ between the best fit planes of the aromatic and half-chair aliphatic rings. The O1 and Cl1 substituents are very close to the mean plane of the aromatic ring. In contrast, the almost planar ester substituent, r.m.s. deviation 0.1108 \AA , is almost orthogonal to the hexahydroquinoline ring system, at a dihedral angle of $89.45(4)^\circ$.

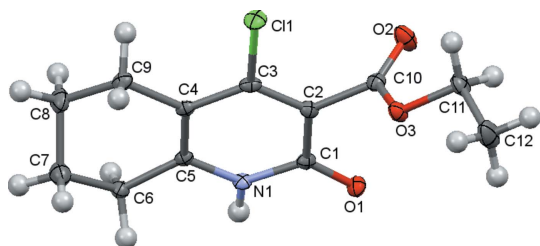


Figure 1
The molecular structure of the title compound, showing the atom labelling. Displacement ellipsoids are drawn at the 50% probability level.

The 2-pyridinone unit participates in intermolecular N1–H1···O1ⁱ hydrogen bonding, forming an inversion dimer with a classical $R_2^2(8)$ ring motif, see Fig. 2 and Table 1. These hydrogen-bonding interactions form dimers that are reminiscent of those frequently observed in carboxylic acids. The structure is further consolidated by C–H···O hydrogen bonds and inversion-related C7–H7B···Cl1 contacts that generate $R_2^2(14)$ rings. These additional contacts form a three-dimensional network with molecules stacked along *b*, see Fig. 3.

Synthesis and crystallization

The synthesis of ethyl 4-chloro-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate used reagents and reagent-grade solvents, which were used without further purification. In a 100 mL round-bottom flask equipped with a magnetic stirrer was placed 1 g of ethyl 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate (4.22 mmol) and 3.84 g of benzyltriethylammonium chloride (4 eq) in 20 mL of acetonitrile. Under continuous stirring, 0.59 mL of the phosphoryl

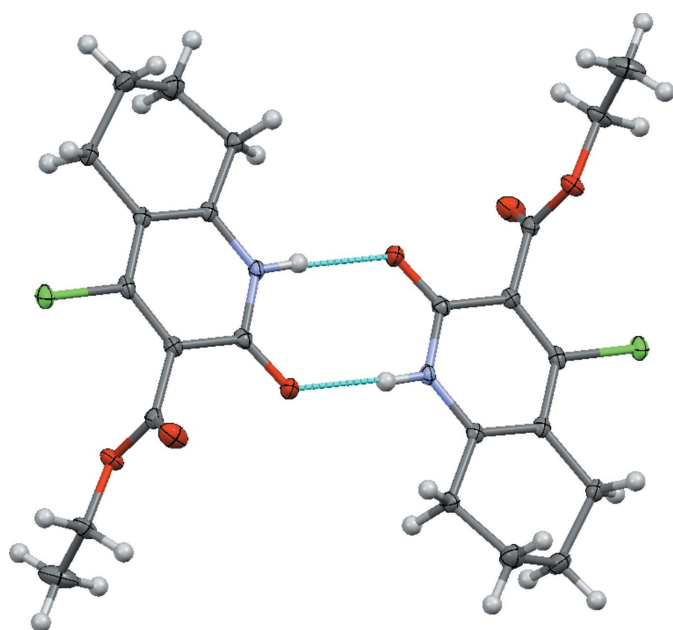


Figure 2
Dimers formed by classical N–H···O hydrogen-bonding interactions, dashed lines.

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>
N1–H1···O1 ⁱ	0.86	1.97	2.8280 (17)	176
C6–H6B···O2 ⁱⁱ	0.97	2.47	3.379 (2)	155
C8–H8B···O1 ⁱⁱ	0.97	2.60	3.492 (2)	153
C11–H11A···O2 ⁱⁱⁱ	0.97	2.70	3.502 (2)	141
C7–H7B···Cl1 ^{iv}	0.97	2.85	3.7731 (19)	160

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

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{12}H_{14}ClNO_3$
M_r	255.69
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	5.7323 (3), 9.2537 (5), 21.6899 (12)
β (°)	91.168 (5)
<i>V</i> (Å ³)	1150.30 (11)
<i>Z</i>	4
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.33
Crystal size (mm)	0.32 × 0.23 × 0.09
Data collection	
Diffractometer	Rigaku Oxford Diffraction SuperNova, Dual, Cu at zero, AtlasS2
Absorption correction	Multi-scan (<i>CrysAlis PRO</i> ; Rigaku OD, 2015)
T_{min} , T_{max}	0.773, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	13970, 3017, 2676
R_{int}	0.032
($\sin \theta/\lambda$) _{max} (Å ⁻¹)	0.690
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, <i>S</i>	0.044, 0.101, 1.09
No. of reflections	3017
No. of parameters	155
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å ⁻³)	0.86, -0.30

Computer programs: *CrysAlis PRO* (Rigaku OD, 2015), *SIR2004* (Burla *et al.*, 2007), *OLEX2* (Dolomanov *et al.*, 2009), *Mercury* (Macrae *et al.*, 2008) and *publCIF* (Westrip, 2010).

chloride (6.33 mmol, 1.5 eq) were added dropwise. The mixture was stirred at 40°C for 30 min and later at reflux for 8 h. Next the solvent was evaporated, 15 mL of cold water

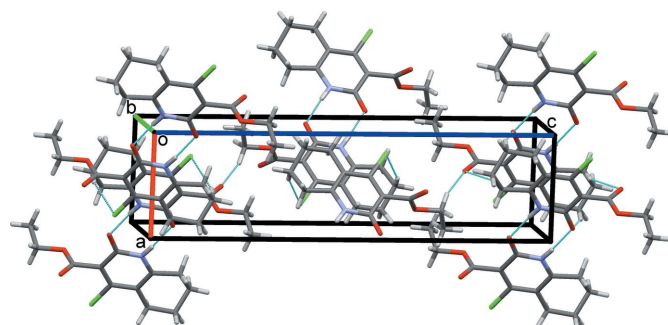


Figure 3
The crystal packing of the title compound viewed along the *b*-axis direction.

were added and the mixture stirred for 1 h. A precipitate was obtained, comprising a mixture of ethyl 4-chloro-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate (60%) and ethyl 2,4-dichloro-5,6,7,8-tetrahydroquinoline-3-carboxylate (40%). The product of interest was purified by column chromatography (dichloromethane/hexane, 2:1). NMR ^1H (CDCl_3), 400 MHz): δ 4.41 (*q*, $J = 7.2$ Hz, $\text{COOCH}_2\text{CH}_3$), 2.66 (*br s*, 2H, H-8), 2.53 (*br s*, 2H, H-5), 1.78 (*m*, 4H, H-6 and H-7), 1.38 (*t*, $J = 7.2$ Hz, $\text{COOCH}_2\text{CH}_3$). NMR ^{13}C (CDCl_3 , 100 MHz): δ 164.4, 160.6, 147.4, 146.1, 122.0, 113.8, 61.8, 27.1, 24.3, 22.2, 21.1, 14.1. EIMS m/z (Rel. Ab): $[M]^+$ 255 (42), $[M]^+ + 2$ 257 (14), 212 (19), 210 (60), 185 (27), 183 (100), 181 (51) amu.

Crystals of the title compound suitable for X-ray diffraction were obtained by dissolving 15 mg of ethyl 4-chloro-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate in 0.5 mL of chloroform and placing the solution in a glass vial. The solution was allowed to stand at room temperature for two days and the crystals formed were filtered.

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2.

Funding information

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full crystallographic data

IUCrData (2019). 4, x190016 [https://doi.org/10.1107/S2414314619000166]

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Crystal data

$C_{12}H_{14}ClNO_3$

$M_r = 255.69$

Monoclinic, $P2_1/c$

$a = 5.7323$ (3) Å

$b = 9.2537$ (5) Å

$c = 21.6899$ (12) Å

$\beta = 91.168$ (5)°

$V = 1150.30$ (11) Å³

$Z = 4$

$F(000) = 536$

$D_x = 1.476$ Mg m⁻³

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

Cell parameters from 5245 reflections

$\theta = 2.4$ – 28.8 °

$\mu = 0.33$ mm⁻¹

$T = 100$ K

Block, translucent intense colourless

$0.32 \times 0.23 \times 0.09$ mm

Data collection

Rigaku Oxford Diffraction SuperNova, Dual,
Cu at zero, AtlasS2
diffractometer

Radiation source: micro-focus sealed X-ray
tube, SuperNova (Mo) X-ray Source

Mirror monochromator

Detector resolution: 5.1980 pixels mm⁻¹

ω scans

Absorption correction: multi-scan
(CrysAlisPro; Rigaku OD, 2015)

$T_{\min} = 0.773$, $T_{\max} = 1.000$

13970 measured reflections

3017 independent reflections

2676 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.032$

$\theta_{\max} = 29.4$ °, $\theta_{\min} = 1.9$ °

$h = -7 \rightarrow 7$

$k = -12 \rightarrow 11$

$l = -29 \rightarrow 29$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.044$

$wR(F^2) = 0.101$

$S = 1.09$

3017 reflections

155 parameters

0 restraints

Primary atom site location: structure-invariant
direct methods

Hydrogen site location: inferred from
neighbouring sites

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0349P)^2 + 1.0951P]$

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

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

$\Delta\rho_{\max} = 0.86$ 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 (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
Cl1	0.75996 (7)	0.62470 (5)	0.40163 (2)	0.01866 (12)
O1	0.0556 (2)	0.94748 (14)	0.42371 (5)	0.0162 (3)
O2	0.4402 (2)	0.87426 (15)	0.31021 (6)	0.0240 (3)
O3	0.2426 (2)	0.66734 (14)	0.32599 (5)	0.0162 (3)
N1	0.2608 (2)	0.87959 (15)	0.51040 (6)	0.0124 (3)
H1	0.169504	0.931850	0.532114	0.015*
C1	0.2208 (3)	0.87798 (18)	0.44748 (7)	0.0129 (3)
C2	0.3831 (3)	0.79147 (18)	0.41342 (7)	0.0130 (3)
C3	0.5600 (3)	0.72128 (18)	0.44430 (7)	0.0133 (3)
C4	0.5911 (3)	0.72343 (18)	0.50944 (7)	0.0123 (3)
C5	0.4335 (3)	0.80509 (18)	0.54128 (7)	0.0117 (3)
C6	0.4387 (3)	0.81981 (19)	0.61038 (7)	0.0145 (3)
H6A	0.281068	0.811392	0.625398	0.017*
H6B	0.496584	0.915069	0.621399	0.017*
C7	0.5925 (3)	0.7056 (2)	0.64185 (8)	0.0235 (4)
H7A	0.623150	0.732936	0.684420	0.028*
H7B	0.512014	0.613363	0.641614	0.028*
C8	0.8206 (3)	0.6912 (2)	0.60853 (8)	0.0226 (4)
H8A	0.920094	0.622654	0.630360	0.027*
H8B	0.899644	0.783933	0.608639	0.027*
C9	0.7836 (3)	0.64067 (19)	0.54209 (7)	0.0152 (3)
H9A	0.927464	0.652904	0.519912	0.018*
H9B	0.745109	0.538585	0.541940	0.018*
C10	0.3596 (3)	0.78524 (19)	0.34424 (7)	0.0141 (3)
C11	0.2272 (3)	0.6444 (2)	0.25915 (7)	0.0189 (4)
H11A	0.374809	0.608271	0.244386	0.023*
H11B	0.192908	0.734998	0.238396	0.023*
C12	0.0378 (4)	0.5373 (3)	0.24549 (9)	0.0325 (5)
H12A	0.024954	0.522164	0.201769	0.049*
H12B	-0.107534	0.573636	0.260352	0.049*
H12C	0.074284	0.447459	0.265581	0.049*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.01586 (19)	0.0218 (2)	0.0184 (2)	0.00599 (16)	0.00289 (14)	-0.00607 (16)
O1	0.0162 (5)	0.0169 (6)	0.0154 (5)	0.0053 (5)	-0.0006 (4)	-0.0014 (5)
O2	0.0338 (7)	0.0209 (7)	0.0173 (6)	-0.0080 (6)	0.0019 (5)	0.0014 (5)
O3	0.0198 (6)	0.0169 (6)	0.0118 (5)	-0.0038 (5)	0.0012 (4)	-0.0031 (5)
N1	0.0122 (6)	0.0118 (7)	0.0132 (6)	0.0027 (5)	0.0022 (5)	-0.0027 (5)
C1	0.0121 (7)	0.0123 (8)	0.0143 (7)	-0.0018 (6)	0.0009 (5)	-0.0020 (6)
C2	0.0138 (7)	0.0123 (8)	0.0131 (7)	-0.0008 (6)	0.0018 (5)	-0.0019 (6)
C3	0.0117 (7)	0.0105 (8)	0.0178 (7)	-0.0011 (6)	0.0041 (6)	-0.0038 (6)
C4	0.0106 (7)	0.0101 (8)	0.0161 (7)	-0.0012 (6)	0.0007 (5)	-0.0004 (6)
C5	0.0109 (7)	0.0095 (8)	0.0147 (7)	-0.0017 (6)	0.0005 (5)	0.0000 (6)

C6	0.0138 (7)	0.0168 (9)	0.0131 (7)	0.0011 (6)	0.0012 (5)	-0.0013 (6)
C7	0.0257 (9)	0.0263 (10)	0.0185 (8)	0.0054 (8)	0.0005 (7)	0.0019 (7)
C8	0.0214 (8)	0.0276 (11)	0.0188 (8)	0.0083 (8)	-0.0026 (6)	0.0018 (7)
C9	0.0135 (7)	0.0130 (8)	0.0190 (8)	0.0020 (6)	0.0007 (6)	0.0001 (6)
C10	0.0129 (7)	0.0148 (8)	0.0148 (7)	0.0024 (6)	0.0007 (5)	-0.0024 (6)
C11	0.0247 (8)	0.0211 (10)	0.0108 (7)	-0.0028 (7)	0.0009 (6)	-0.0031 (6)
C12	0.0376 (11)	0.0428 (14)	0.0168 (8)	-0.0178 (10)	-0.0057 (8)	-0.0007 (9)

Geometric parameters (Å, °)

C11—C3	1.7357 (16)	C6—H6B	0.9700
O1—C1	1.248 (2)	C6—C7	1.528 (2)
O2—C10	1.205 (2)	C7—H7A	0.9700
O3—C10	1.336 (2)	C7—H7B	0.9700
O3—C11	1.4660 (19)	C7—C8	1.513 (3)
N1—H1	0.8600	C8—H8A	0.9700
N1—C1	1.379 (2)	C8—H8B	0.9700
N1—C5	1.370 (2)	C8—C9	1.526 (2)
C1—C2	1.442 (2)	C9—H9A	0.9700
C2—C3	1.367 (2)	C9—H9B	0.9700
C2—C10	1.505 (2)	C11—H11A	0.9700
C3—C4	1.421 (2)	C11—H11B	0.9700
C4—C5	1.375 (2)	C11—C12	1.495 (3)
C4—C9	1.508 (2)	C12—H12A	0.9600
C5—C6	1.505 (2)	C12—H12B	0.9600
C6—H6A	0.9700	C12—H12C	0.9600
C10—O3—C11	115.52 (13)	C8—C7—H7A	109.6
C1—N1—H1	117.2	C8—C7—H7B	109.6
C5—N1—H1	117.2	C7—C8—H8A	109.2
C5—N1—C1	125.60 (13)	C7—C8—H8B	109.2
O1—C1—N1	120.85 (14)	C7—C8—C9	111.90 (15)
O1—C1—C2	124.52 (14)	H8A—C8—H8B	107.9
N1—C1—C2	114.64 (14)	C9—C8—H8A	109.2
C1—C2—C10	119.09 (14)	C9—C8—H8B	109.2
C3—C2—C1	119.48 (14)	C4—C9—C8	111.98 (14)
C3—C2—C10	121.38 (14)	C4—C9—H9A	109.2
C2—C3—C11	118.33 (12)	C4—C9—H9B	109.2
C2—C3—C4	123.88 (14)	C8—C9—H9A	109.2
C4—C3—C11	117.80 (12)	C8—C9—H9B	109.2
C3—C4—C9	122.42 (14)	H9A—C9—H9B	107.9
C5—C4—C3	115.89 (14)	O2—C10—O3	124.98 (15)
C5—C4—C9	121.69 (14)	O2—C10—C2	123.85 (16)
N1—C5—C4	120.45 (14)	O3—C10—C2	111.15 (14)
N1—C5—C6	116.16 (13)	O3—C11—H11A	109.9
C4—C5—C6	123.39 (14)	O3—C11—H11B	109.9
C5—C6—H6A	109.1	O3—C11—C12	108.71 (14)
C5—C6—H6B	109.1	H11A—C11—H11B	108.3

C5—C6—C7	112.44 (14)	C12—C11—H11A	109.9
H6A—C6—H6B	107.8	C12—C11—H11B	109.9
C7—C6—H6A	109.1	C11—C12—H12A	109.5
C7—C6—H6B	109.1	C11—C12—H12B	109.5
C6—C7—H7A	109.6	C11—C12—H12C	109.5
C6—C7—H7B	109.6	H12A—C12—H12B	109.5
H7A—C7—H7B	108.2	H12A—C12—H12C	109.5
C8—C7—C6	110.10 (15)	H12B—C12—H12C	109.5
C11—C3—C4—C5	177.91 (12)	C3—C4—C5—N1	-0.7 (2)
C11—C3—C4—C9	-2.6 (2)	C3—C4—C5—C6	179.81 (15)
O1—C1—C2—C3	179.14 (16)	C3—C4—C9—C8	164.73 (16)
O1—C1—C2—C10	1.5 (2)	C4—C5—C6—C7	-15.1 (2)
N1—C1—C2—C3	-0.8 (2)	C5—N1—C1—O1	178.55 (15)
N1—C1—C2—C10	-178.38 (14)	C5—N1—C1—C2	-1.5 (2)
N1—C5—C6—C7	165.33 (15)	C5—C4—C9—C8	-15.8 (2)
C1—N1—C5—C4	2.3 (2)	C5—C6—C7—C8	44.9 (2)
C1—N1—C5—C6	-178.14 (15)	C6—C7—C8—C9	-62.2 (2)
C1—C2—C3—C11	-177.15 (12)	C7—C8—C9—C4	46.6 (2)
C1—C2—C3—C4	2.4 (3)	C9—C4—C5—N1	179.79 (15)
C1—C2—C10—O2	83.9 (2)	C9—C4—C5—C6	0.3 (2)
C1—C2—C10—O3	-97.36 (17)	C10—O3—C11—C12	-163.49 (16)
C2—C3—C4—C5	-1.6 (2)	C10—C2—C3—C11	0.4 (2)
C2—C3—C4—C9	177.91 (16)	C10—C2—C3—C4	179.91 (15)
C3—C2—C10—O2	-93.6 (2)	C11—O3—C10—O2	3.7 (2)
C3—C2—C10—O3	85.09 (19)	C11—O3—C10—C2	-174.97 (13)

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>
N1—H1...O1 ⁱ	0.86	1.97	2.8280 (17)	176
C6—H6B...O2 ⁱⁱ	0.97	2.47	3.379 (2)	155
C8—H8B...O1 ⁱⁱ	0.97	2.60	3.492 (2)	153
C11—H11A...O2 ⁱⁱⁱ	0.97	2.70	3.502 (2)	141
C7—H7B...C11 ^{iv}	0.97	2.85	3.7731 (19)	160

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