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2-(4-Methyl-2-phenylpiperazin-4-ium-1-yl)pyridine-3-carboxylate dihydrate

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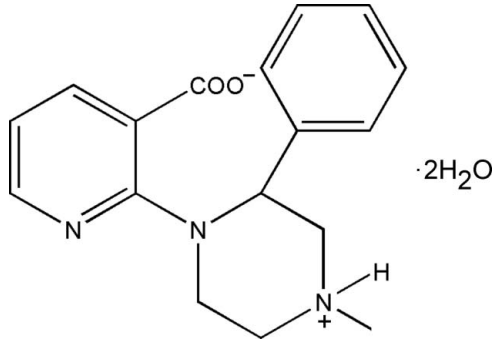
Key indicators: single-crystal X-ray study; T = 294 K; mean σ(C–C) = 0.003 Å; R factor = 0.044; wR factor = 0.117; data-to-parameter ratio = 16.3.

The title compound, $C_{17}H_{19}N_3O_2\cdot 2H_2O$, is particularly useful in the preparation of mirtazapine, which is the active agent in a new class of antidepressants. It crystallized as a zwitterion with two molecules of water in the asymmetric unit. The crystal structure is dominated by a system of hydrogen bonds involving the positively charged N atom and both water molecules.

Related literature

For details of the synthesis see: Eiichi *et al.* (2002*a*,*b*); Metzger *et al.* (2004). For related literature, see: Singer *et al.* (2004).



Experimental

Crystal data

$C_{17}H_{19}N_3O_2\cdot 2H_2O$
M_r = 333.38
Monoclinic, $P2_1/n$
a = 12.730 (7) Å
b = 8.157 (4) Å
c = 16.814 (9) Å
β = 94.031 (10)°
V = 1741.6 (16) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 294 (2) K
0.24 × 0.20 × 0.18 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2002)
T_{min} = 0.978, T_{max} = 0.984
9611 measured reflections
3550 independent reflections
2039 reflections with $I > 2\sigma(I)$
R_{int} = 0.051

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.117
S = 1.00
3550 reflections
218 parameters
7 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3A···O1^{i}	0.91	1.77	2.681 (2)	178
O3—H3C···O4^{ii}	0.87	1.92	2.781 (3)	179
O4—H4A···O2^{iii}	0.85	1.94	2.761 (2)	162
O3—H3B···O1	0.87	2.21	3.038 (3)	161
O4—H4B···N1	0.85	2.23	3.037 (3)	159

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

Data collection: *SMART* (Bruker, 2002); cell refinement: *SAINT* (Bruker, 2002); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL*.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: FL2184).

References

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Eiichi, I. & Kanami, Y. (2002*b*). US patent 6 437 120.
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Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
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supporting information

Acta Cryst. (2008). E**64**, o1234 [doi:10.1107/S1600536808011288]

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S1. Comment

The title compound, $C_{17}H_{19}N_3O_2.2H_2O$, is particularly useful in the preparation of mirtazapine which is the active agent in a new class of antidepressants. It crystallized as a zwitterion with two molecues of water in the asymmetric unit (Fig 1). The central piperazine ring has a normal chair conformation. In the molecule, the dihedral angle is 81.20 between plane 1(C7 C8 C9 C10) and plane 2(C11 C12 C13 C14 C15 C16), the dihedral angle is 68.40 between plane 2(C11 C12 C13 C14 C15 C16) and plane 3(N1 C2 C3 C4 C5 C6)and the the dihedral angle is 36.90 between plane 1 and plane 3. Packing is dominated by a system of hydrogen bonds involving the positively charged nitrogen and both water molecules (Table 1, Fig. 2)

S2. Experimental

To 162 g of 1-butanol were added 2-(4-methyl-2-phenylpiperazine-1-yl)pyridine-3-carbonitrile(54 g, 0.2 mol) and 60.93 g of potassium hydroxide. The mixture was heated to 125 - 135 centigrade degree. (Eiichi, *et al.*, 2002*a*; Eiichi, *et al.*, 2002*b*; Metzger, *et al.*, 2004) After 7 h, the reaction mixture was cooled and the butanol removed from the mixture by vacuum distilation after which fresh water and toluene were added and the two phases were separated. The water solution was neutralized with hydrochloric acid to pH=6.5–7. The water was evaporated and toluene was added. The inorganic salt were filtered and toluene solution was evaporated to dryness. Yield:52 g(90%). (Singer *et al.*, 2004) Colourless crystals suitable for X-ray analysis were obtained by slow evaporation of an methanol-toluene solution at room temperature over 30 days.

S3. Refinement

All H atoms were positioned geometrically and refined as riding, with C—H = 0.93–0.98 Å and N—H=0.949 Å U_{iso}(H) = 1.2 U_{eq}(C).

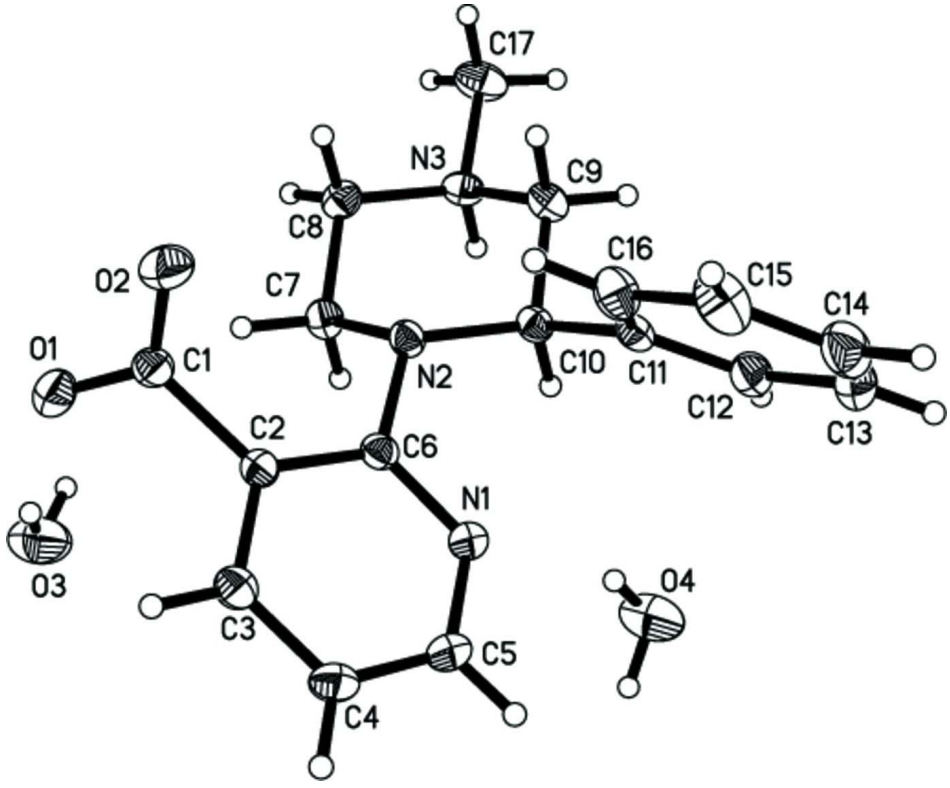

Figure 1

The molecular structure of the title compound, drawn with 30% probability ellipsoids.

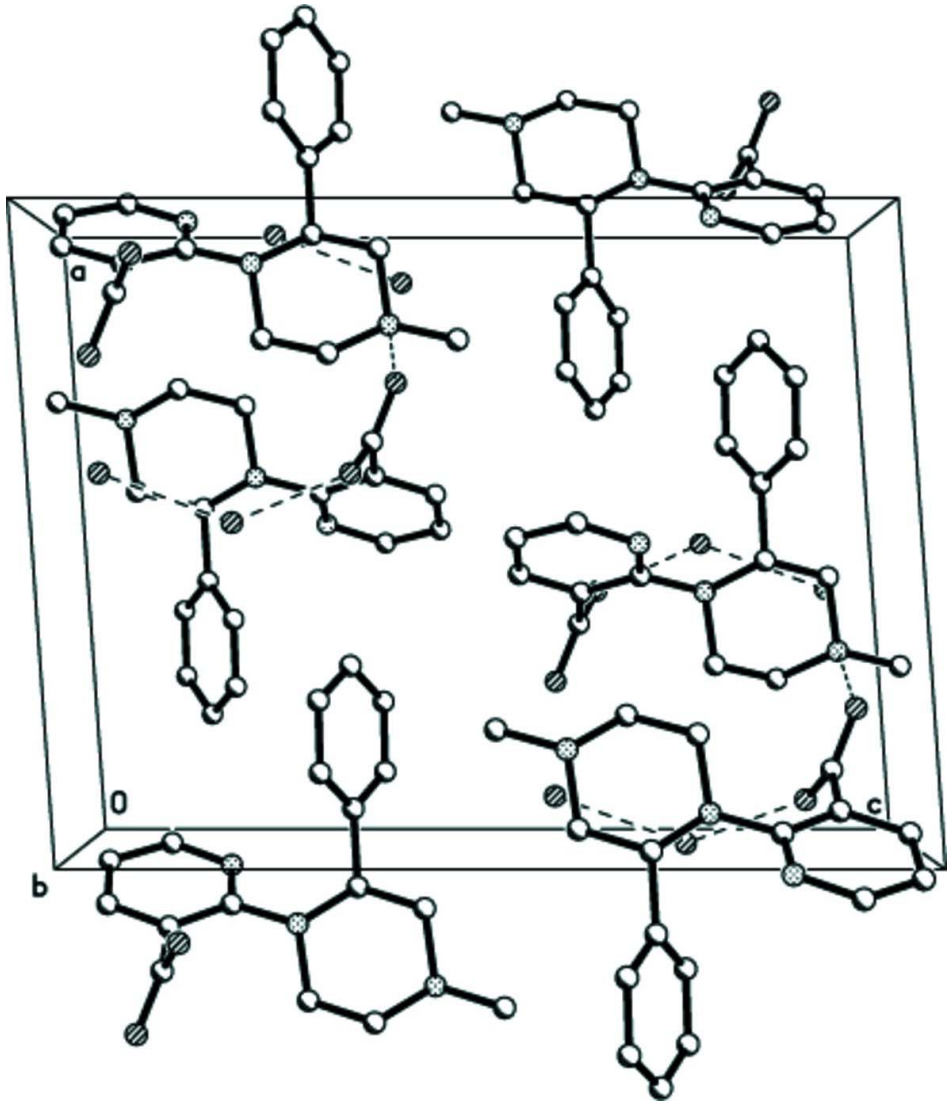

Figure 2

The crystal structure of (I), viewed along *a* axis

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$\beta = 94.031\ (10)°$
$V = 1741.6\ (16)$ Å^3
$Z = 4$
$F(000) = 712$
$D_x = 1.271$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 1949 reflections
$\theta = 3.0–22.9°$
$\mu = 0.09$ mm^{-1}
$T = 294$ K
Block, colorless
0.24 × 0.20 × 0.18 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2002)
T_{min} = 0.978, T_{max} = 0.984
9611 measured reflections
3550 independent reflections
2039 reflections with $I > 2\sigma(I)$
R_{int} = 0.051
θ_{max} = 26.5°, θ_{min} = 1.9°
h = −14→15
k = −10→9
l = −21→18

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.117
S = 1.00
3550 reflections
218 parameters
7 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
$w = 1/[\sigma^2(F_o^2) + (0.0459P)^2 + 0.2854P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 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}
O1	0.23746 (11)	−0.07865 (17)	0.91677 (8)	0.0468 (4)
O2	0.09369 (12)	−0.19110 (17)	0.85735 (9)	0.0523 (4)
N1	0.01524 (12)	0.33067 (19)	0.81432 (9)	0.0336 (4)
N2	0.09094 (11)	0.12896 (18)	0.73567 (8)	0.0276 (4)
N3	0.18394 (12)	0.11644 (19)	0.58307 (8)	0.0317 (4)
H3A	0.2110	0.2203	0.5847	0.038*
C1	0.14487 (17)	−0.0721 (2)	0.88370 (10)	0.0326 (5)
C2	0.09270 (14)	0.0949 (2)	0.88117 (10)	0.0284 (4)
C3	0.06312 (16)	0.1573 (2)	0.95305 (11)	0.0377 (5)
H3	0.0816	0.1015	1.0002	0.045*
C4	0.00669 (17)	0.3009 (3)	0.95524 (12)	0.0433 (5)
H4	−0.0156	0.3411	1.0030	0.052*
C5	−0.01572 (17)	0.3828 (3)	0.88490 (12)	0.0412 (5)
H5	−0.0543	0.4795	0.8860	0.049*
C6	0.06542 (14)	0.1873 (2)	0.81196 (10)	0.0276 (4)
C7	0.20574 (14)	0.1119 (2)	0.72897 (10)	0.0322 (5)

H7A	0.2362	0.0515	0.7746	0.039*
H7B	0.2377	0.2198	0.7296	0.039*
C8	0.23032 (16)	0.0240 (2)	0.65354 (10)	0.0345 (5)
H8A	0.3060	0.0155	0.6509	0.041*
H8B	0.2013	−0.0860	0.6535	0.041*
C9	0.06793 (15)	0.1316 (2)	0.58939 (10)	0.0333 (5)
H9A	0.0367	0.0231	0.5880	0.040*
H9B	0.0375	0.1924	0.5439	0.040*
C10	0.04152 (14)	0.2186 (2)	0.66603 (10)	0.0278 (4)
H10	0.0702	0.3300	0.6658	0.033*
C11	−0.07784 (15)	0.2284 (2)	0.66480 (10)	0.0302 (5)
C12	−0.12829 (16)	0.3603 (3)	0.62727 (11)	0.0396 (5)
H12	−0.0887	0.4409	0.6042	0.048*
C13	−0.23716 (18)	0.3743 (3)	0.62352 (13)	0.0502 (6)
H13	−0.2699	0.4638	0.5981	0.060*
C14	−0.29645 (18)	0.2561 (3)	0.65735 (13)	0.0530 (6)
H14	−0.3693	0.2660	0.6556	0.064*
C15	−0.24739 (17)	0.1225 (3)	0.69391 (13)	0.0530 (6)
H15	−0.2875	0.0418	0.7164	0.064*
C16	−0.13856 (16)	0.1075 (3)	0.69733 (11)	0.0419 (5)
H16	−0.1062	0.0162	0.7215	0.050*
C17	0.20966 (18)	0.0401 (3)	0.50601 (11)	0.0486 (6)
H17A	0.1818	−0.0693	0.5028	0.073*
H17B	0.2847	0.0364	0.5033	0.073*
H17C	0.1790	0.1040	0.4624	0.073*
O3	0.40776 (15)	0.1829 (2)	0.92970 (9)	0.0746 (5)
H3B	0.3615	0.1080	0.9385	0.112*
H3C	0.4310	0.1736	0.8827	0.112*
O4	0.01683 (14)	0.6489 (2)	0.72071 (9)	0.0695 (5)
H4A	0.0391	0.7172	0.7563	0.104*
H4B	0.0095	0.5500	0.7353	0.104*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0447 (10)	0.0401 (9)	0.0542 (9)	0.0108 (7)	−0.0058 (7)	−0.0023 (7)
O2	0.0587 (11)	0.0337 (9)	0.0632 (10)	−0.0008 (8)	−0.0061 (8)	−0.0103 (8)
N1	0.0378 (10)	0.0320 (10)	0.0306 (9)	0.0057 (8)	0.0001 (7)	−0.0031 (7)
N2	0.0271 (9)	0.0327 (9)	0.0230 (8)	0.0018 (7)	0.0017 (6)	−0.0002 (7)
N3	0.0354 (10)	0.0322 (9)	0.0282 (8)	−0.0069 (7)	0.0073 (7)	−0.0036 (7)
C1	0.0419 (13)	0.0324 (12)	0.0242 (10)	0.0035 (10)	0.0065 (9)	0.0006 (9)
C2	0.0286 (11)	0.0301 (11)	0.0264 (10)	0.0013 (8)	0.0006 (8)	−0.0015 (8)
C3	0.0480 (13)	0.0394 (12)	0.0258 (10)	0.0048 (10)	0.0033 (9)	0.0010 (9)
C4	0.0550 (15)	0.0448 (13)	0.0307 (11)	0.0100 (11)	0.0075 (10)	−0.0093 (10)
C5	0.0489 (14)	0.0374 (12)	0.0373 (12)	0.0131 (10)	0.0026 (10)	−0.0088 (10)
C6	0.0261 (10)	0.0290 (11)	0.0275 (10)	−0.0016 (9)	0.0000 (8)	−0.0032 (8)
C7	0.0297 (11)	0.0376 (12)	0.0294 (10)	0.0010 (9)	0.0037 (8)	0.0016 (9)
C8	0.0356 (12)	0.0325 (11)	0.0359 (11)	0.0026 (9)	0.0066 (9)	0.0000 (9)

C9	0.0321 (11)	0.0389 (12)	0.0288 (10)	−0.0060 (9)	0.0027 (8)	−0.0013 (9)
C10	0.0297 (11)	0.0288 (10)	0.0248 (10)	−0.0026 (8)	0.0009 (8)	0.0010 (8)
C11	0.0313 (12)	0.0376 (12)	0.0215 (9)	−0.0016 (9)	−0.0004 (8)	−0.0035 (9)
C12	0.0370 (13)	0.0410 (12)	0.0401 (12)	−0.0013 (10)	−0.0026 (9)	−0.0009 (10)
C13	0.0420 (14)	0.0486 (14)	0.0579 (14)	0.0055 (11)	−0.0114 (11)	−0.0019 (12)
C14	0.0327 (13)	0.0750 (18)	0.0506 (14)	0.0020 (13)	−0.0014 (11)	−0.0101 (13)
C15	0.0366 (14)	0.0773 (18)	0.0455 (13)	−0.0175 (13)	0.0051 (10)	0.0070 (13)
C16	0.0383 (13)	0.0498 (14)	0.0373 (12)	−0.0060 (11)	−0.0002 (9)	0.0063 (10)
C17	0.0517 (14)	0.0610 (15)	0.0350 (12)	−0.0073 (12)	0.0166 (10)	−0.0150 (11)
O3	0.1035 (15)	0.0632 (12)	0.0586 (10)	−0.0064 (11)	0.0167 (9)	−0.0125 (9)
O4	0.0919 (14)	0.0659 (11)	0.0516 (10)	−0.0169 (10)	0.0098 (9)	−0.0118 (9)

Geometric parameters (Å, º)

O1—C1	1.269 (2)	C9—C10	1.529 (2)
O2—C1	1.234 (2)	C9—H9A	0.9700
N1—C6	1.335 (2)	C9—H9B	0.9700
N1—C5	1.346 (2)	C10—C11	1.520 (3)
N2—C6	1.427 (2)	C10—H10	0.9800
N2—C7	1.480 (2)	C11—C12	1.382 (3)
N2—C10	1.482 (2)	C11—C16	1.389 (3)
N3—C8	1.491 (2)	C12—C13	1.388 (3)
N3—C9	1.493 (2)	C12—H12	0.9300
N3—C17	1.495 (2)	C13—C14	1.373 (3)
N3—H3A	0.9140	C13—H13	0.9300
C1—C2	1.514 (3)	C14—C15	1.379 (3)
C2—C3	1.388 (2)	C14—H14	0.9300
C2—C6	1.409 (2)	C15—C16	1.388 (3)
C3—C4	1.376 (3)	C15—H15	0.9300
C3—H3	0.9300	C16—H16	0.9300
C4—C5	1.371 (3)	C17—H17A	0.9600
C4—H4	0.9300	C17—H17B	0.9600
C5—H5	0.9300	C17—H17C	0.9600
C7—C8	1.509 (2)	O3—H3B	0.8682
C7—H7A	0.9700	O3—H3C	0.8664
C7—H7B	0.9700	O4—H4A	0.8512
C8—H8A	0.9700	O4—H4B	0.8504
C8—H8B	0.9700		
C6—N1—C5	118.28 (16)	H8A—C8—H8B	108.2
C6—N2—C7	112.85 (13)	N3—C9—C10	112.07 (14)
C6—N2—C10	115.78 (14)	N3—C9—H9A	109.2
C7—N2—C10	110.66 (13)	C10—C9—H9A	109.2
C8—N3—C9	108.89 (14)	N3—C9—H9B	109.2
C8—N3—C17	112.30 (16)	C10—C9—H9B	109.2
C9—N3—C17	111.98 (14)	H9A—C9—H9B	107.9
C8—N3—H3A	108.5	N2—C10—C11	113.90 (14)
C9—N3—H3A	107.1	N2—C10—C9	109.32 (15)

C17—N3—H3A	107.9	C11—C10—C9	106.98 (14)
O2—C1—O1	125.09 (19)	N2—C10—H10	108.8
O2—C1—C2	118.56 (18)	C11—C10—H10	108.8
O1—C1—C2	116.26 (18)	C9—C10—H10	108.8
C3—C2—C6	117.18 (17)	C12—C11—C16	118.62 (19)
C3—C2—C1	116.78 (16)	C12—C11—C10	118.64 (17)
C6—C2—C1	125.90 (16)	C16—C11—C10	122.70 (18)
C4—C3—C2	120.64 (18)	C11—C12—C13	121.0 (2)
C4—C3—H3	119.7	C11—C12—H12	119.5
C2—C3—H3	119.7	C13—C12—H12	119.5
C5—C4—C3	118.00 (18)	C14—C13—C12	120.0 (2)
C5—C4—H4	121.0	C14—C13—H13	120.0
C3—C4—H4	121.0	C12—C13—H13	120.0
N1—C5—C4	123.40 (19)	C13—C14—C15	119.7 (2)
N1—C5—H5	118.3	C13—C14—H14	120.2
C4—C5—H5	118.3	C15—C14—H14	120.2
N1—C6—C2	122.34 (16)	C14—C15—C16	120.5 (2)
N1—C6—N2	117.30 (15)	C14—C15—H15	119.8
C2—C6—N2	120.36 (16)	C16—C15—H15	119.8
N2—C7—C8	111.90 (14)	C15—C16—C11	120.2 (2)
N2—C7—H7A	109.2	C15—C16—H16	119.9
C8—C7—H7A	109.2	C11—C16—H16	119.9
N2—C7—H7B	109.2	N3—C17—H17A	109.5
C8—C7—H7B	109.2	N3—C17—H17B	109.5
H7A—C7—H7B	107.9	H17A—C17—H17B	109.5
N3—C8—C7	109.50 (16)	N3—C17—H17C	109.5
N3—C8—H8A	109.8	H17A—C17—H17C	109.5
C7—C8—H8A	109.8	H17B—C17—H17C	109.5
N3—C8—H8B	109.8	H3B—O3—H3C	111.9
C7—C8—H8B	109.8	H4A—O4—H4B	117.0

O2—C1—C2—C3	106.1 (2)	C17—N3—C8—C7	177.34 (15)
O1—C1—C2—C3	−70.7 (2)	N2—C7—C8—N3	59.1 (2)
O2—C1—C2—C6	−69.5 (3)	C8—N3—C9—C10	58.5 (2)
O1—C1—C2—C6	113.8 (2)	C17—N3—C9—C10	−176.74 (16)
C6—C2—C3—C4	2.0 (3)	C6—N2—C10—C11	−55.0 (2)
C1—C2—C3—C4	−174.01 (19)	C7—N2—C10—C11	175.00 (15)
C2—C3—C4—C5	−2.4 (3)	C6—N2—C10—C9	−174.59 (14)
C6—N1—C5—C4	3.7 (3)	C7—N2—C10—C9	55.40 (18)
C3—C4—C5—N1	−0.5 (3)	N3—C9—C10—N2	−57.03 (19)
C5—N1—C6—C2	−4.1 (3)	N3—C9—C10—C11	179.19 (15)
C5—N1—C6—N2	175.71 (16)	N2—C10—C11—C12	151.89 (16)
C3—C2—C6—N1	1.4 (3)	C9—C10—C11—C12	−87.2 (2)
C1—C2—C6—N1	176.95 (18)	N2—C10—C11—C16	−30.5 (2)
C3—C2—C6—N2	−178.48 (16)	C9—C10—C11—C16	90.4 (2)
C1—C2—C6—N2	−2.9 (3)	C16—C11—C12—C13	1.4 (3)
C7—N2—C6—N1	117.95 (18)	C10—C11—C12—C13	179.18 (17)
C10—N2—C6—N1	−11.0 (2)	C11—C12—C13—C14	0.0 (3)

C7—N2—C6—C2	−62.2 (2)	C12—C13—C14—C15	−1.0 (3)
C10—N2—C6—C2	168.87 (15)	C13—C14—C15—C16	0.6 (3)
C6—N2—C7—C8	170.43 (15)	C14—C15—C16—C11	0.8 (3)
C10—N2—C7—C8	−58.0 (2)	C12—C11—C16—C15	−1.8 (3)
C9—N3—C8—C7	−58.05 (19)	C10—C11—C16—C15	−179.48 (18)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*A*···O1^{i}	0.91	1.77	2.681 (2)	178
O3—H3*C*···O4^{ii}	0.87	1.92	2.781 (3)	179
O4—H4*A*···O2^{iii}	0.85	1.94	2.761 (2)	162
O3—H3*B*···O1	0.87	2.21	3.038 (3)	161
O4—H4*B*···N1	0.85	2.23	3.037 (3)	159

Symmetry codes: (i) −*x*+1/2, *y*+1/2, −*z*+3/2; (ii) −*x*+1/2, *y*−1/2, −*z*+3/2; (iii) *x*, *y*+1, *z*.