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N-(2,5-Dimethoxyphenyl)-*N*′-(4-hydroxyphenethyl)urea

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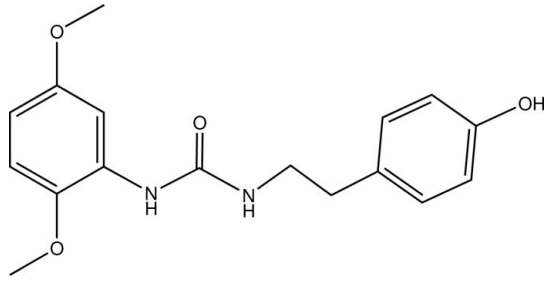
Key indicators: single-crystal X-ray study; T = 296 K; mean σ(C–C) = 0.004 Å; R factor = 0.059; wR factor = 0.186; data-to-parameter ratio = 14.6.

In the title compound, $C_{17}H_{20}N_2O_4$, the 2,5-dimethoxyphenyl unit is almost planar, with an r.m.s. deviation of 0.015 Å. The dihedral angle between the 2,5-dimethoxyphenyl ring and the urea plane is 20.95 (8)°. The H atoms of the urea NH groups are positioned *syn* to each other. The molecular structure is stabilized by a short intramolecular N—H···O hydrogen bond. In the crystal, intermolecular N—H···O and O—H···O hydrogen bonds link the molecules into a three-dimensional network.

Related literature

For general background to tyrosinase, see: Kubo *et al.* (2000); Perez-Gilbert & Garcia-Carmona (2001). For the development of tyrosinase inhibitors, see: Shiino *et al.* (2001); Khan *et al.* (2006); Garcia & Fulrton (1996); Kojima *et al.* (1995); Cabanes *et al.* (1994); Lemic-Stojcevic *et al.* 1995); Casanola-Martin *et al.* (2006); Thanigaimalai *et al.* (2010); Passi & Nazzaro-Porro (1981).



Experimental

Crystal data

$C_{17}H_{20}N_2O_4$
M_r = 316.35
Monoclinic, $P2_1/n$
a = 10.7275 (6) Å
b = 9.6016 (5) Å
c = 16.9388 (10) Å
β = 107.838 (2)°
V = 1660.84 (16) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 296 K
0.31 × 0.27 × 0.13 mm

Data collection

Bruker SMART CCD area-detector diffractometer
13358 measured reflections
3184 independent reflections
2296 reflections with $I > 2\sigma(I)$
R_{int} = 0.044

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.186
S = 1.06
3184 reflections
218 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.46 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N7—H7···O20	0.82 (3)	2.23 (2)	2.617 (3)	109 (2)
N7—H7···O19^{i}	0.82 (3)	2.48 (3)	3.182 (3)	144 (2)
N10—H10···O19^{i}	0.86 (3)	2.23 (3)	3.005 (3)	150 (2)
O19—H19···O9^{ii}	0.86 (4)	1.80 (4)	2.654 (3)	172 (4)

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

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: *DIAMOND* (Brandenburg, 2010); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: JH2214).

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N-(2,5-Dimethoxyphenyl)-*N*′-(4-hydroxyphenethyl)urea

Hyeong Choi, Byung Hee Han, Yong Suk Shim, Sung Kwon Kang and Chang Keun Sung

S1. Comment

Tyrosinase known as a polyphenol oxidase, is a multifunctional copper-containing enzyme widely distributed in nature. It is the key enzyme in the undesirable browning of fruits and vegetables, and coloring of skin, hair, and eyes in animals (Kubo *et al.*, 2000; Perez-Gilbert & Garcia-Carmona, 2001). Nowadays, tyrosinase inhibitors are thought to be clinically useful for the treatment of some dermatological disorders associated with melanin hyperpigmentation (Shiino *et al.*, 2001) and useful in cosmetic products and food industry (Khan *et al.*, 2006). Recently, various tyrosinase inhibitors have been reported such as hydroquinone (Garcia & Fulrton, 1996), ascorbic acid derivatives (Kojima *et al.*, 1995), kojic acid (Cabanes *et al.*, 1994), azelaic acid (Lemic-Stojcevic *et al.*, 1995), arbutin (Casanola-Martin *et al.*, 2006) and *N*-phenylthiourea (PTU) (Thanigaimalai *et al.*, 2010). Most of the tyrosinase inhibitors are phenol/catechol derivatives, structurally similar to tyrosine or *L*-DOPA, which act as suicide substrates of tyrosinase (Passi & Nazzaro-Porro, 1981). However, most of them are not potent enough to put into practical use due to their weak individual activities or safety concerns. Undoubtedly, it is required to search and develop novel tyrosinase inhibitors with better activities together with lower side effects. In continuing our research on the development of tyrosinase inhibitors for new whitening agents, we have synthesized the title compound, (I), from the reaction of 2-(4-hydroxyphenyl)ethyl amine and 2,5-dimethoxyphenyl isocyanate under ambient condition. Here, we report the crystal structure of the title compound, (I).

The 2,5-dimethoxyphenyl moiety is almost planar with r.m.s. deviation of 0.015 Å from the corresponding least-squares plane defined by the nine constituent atoms. The dihedral angle between the phenyl ring and the plane of urea moiety is 20.95 (8) °. The molecular structure is stabilized by a short intramolecular N7—H7···O20 hydrogen bond (Fig. 1). In the crystal, intermolecular N—H···O and O—H···O hydrogen bonds link the molecules into a three-dimensional network (Fig. 2, Table 1). The H atoms of the NH groups of urea are positioned *syn* to each other.

S2. Experimental

The tyramine and 2,5-dimethoxyphenyl isocyanate were purchased from Sigma Chemical Co. Solvents used for organic synthesis were redistilled before use. All other chemicals and solvents were of analytical grade and used without further purification. The title compound (I) was prepared from the reaction of 2-(4-hydroxyphenyl)ethyl amine (0.20 g, 1 mmol) with 2,5-dimethoxyphenyl isocyanate (0.18 g, 1.2 mmol) in acetonitrile (8 ml) and added 4-(dimethylamino)pyridine (0.06 g, 0.5 mmol) as a catalyst, with stirring. The reaction was completed within 5 h at room temperature. The solvents were removed under reduced pressure. The solids collected and washed with dichloromethane. Removal of the solvent gave a light yellow solid (69%, m.p. 436 K). Single crystals were obtained by slow evaporation of the ethanol at room temperature.

S3. Refinement

The H atoms of the NH and OH groups were located in a difference Fourier map and refined freely. The remaining H atoms were positioned geometrically and refined using a riding model with C—H = 0.93–0.97 Å, and with U_{iso}(H) = 1.2U_{eq} (C) for aromatic and metylene, and 1.5U_{eq}(C) for methyl H atoms.

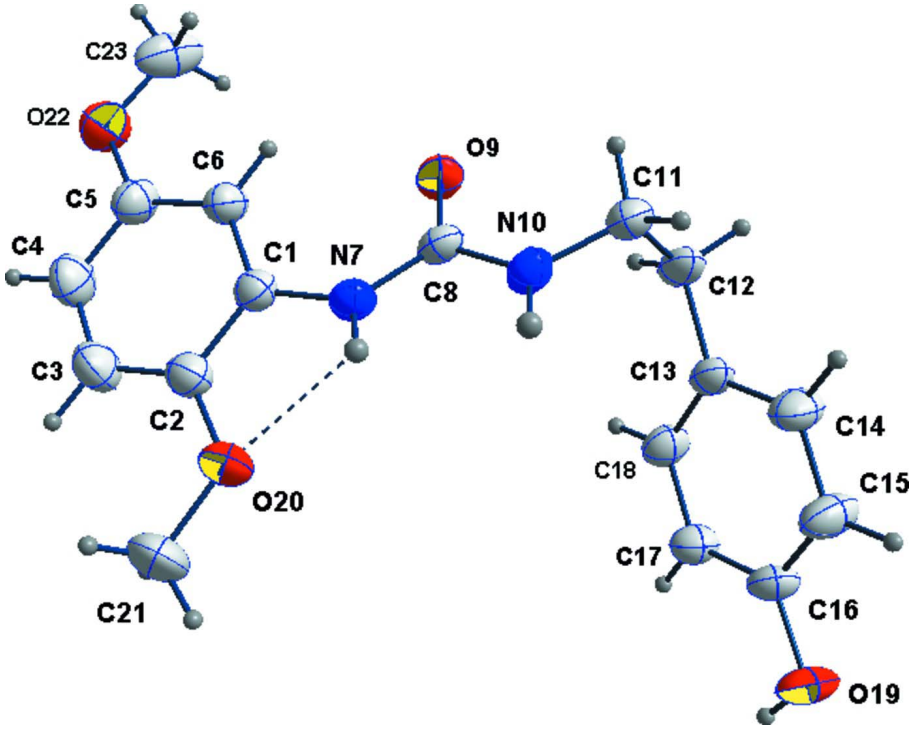

Figure 1

Molecular structure of (*I*), showing the atom-numbering scheme and 50% probability ellipsoids. Intramolecular N—H···O bond is shown as dashed lines.

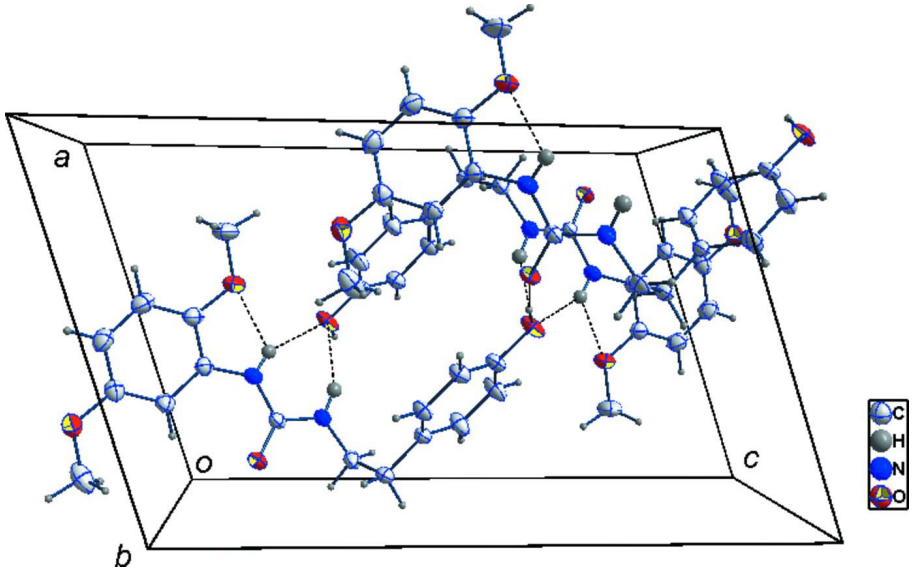

Figure 2

Part of the crystal structure of (I), showing 3-D network of molecules linked by intermolecular N—H···O and O—H···O hydrogen bonds (dashed lines).

N-(2,5-Dimethoxyphenyl)-*N*′-(4-hydroxyphenethyl)urea

Crystal data

$C_{17}H_{20}N_2O_4$
$M_r = 316.35$
Monoclinic, $P2_1/n$
Hall symbol: -P 2yn
$a = 10.7275\ (6)$ Å
$b = 9.6016\ (5)$ Å
$c = 16.9388\ (10)$ Å
$\beta = 107.838\ (2)°$
$V = 1660.84\ (16)$ Å^3
$Z = 4$
$F(000) = 672$
$D_x = 1.265$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 5519 reflections
$\theta = 2.5–27.8°$
$\mu = 0.09$ mm^{-1}
$T = 296$ K
Needle, colourless
0.31 × 0.27 × 0.13 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
13358 measured reflections
3184 independent reflections
2296 reflections with $I > 2\sigma(I)$
$R_{int} = 0.044$
$\theta_{max} = 26.0°$, $\theta_{min} = 2.0°$
$h = -13\rightarrow6$
$k = -11\rightarrow9$
$l = -20\rightarrow16$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.059$
$wR(F^2) = 0.186$
$S = 1.06$
3184 reflections
218 parameters
0 restraints
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0966P)^2 + 0.4089P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.32$ e Å^{-3}
$\Delta\rho_{min} = -0.46$ 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.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.3898 (2)	0.5854 (2)	0.12845 (14)	0.0581 (5)
C2	0.5212 (2)	0.6136 (3)	0.13837 (16)	0.0698 (7)
C3	0.5565 (3)	0.6644 (3)	0.0720 (2)	0.0856 (8)
H3	0.644	0.6835	0.0783	0.103*
C4	0.4643 (3)	0.6869 (3)	−0.00277 (19)	0.0845 (8)
H4	0.4896	0.7201	−0.0471	0.101*
C5	0.3347 (3)	0.6610 (3)	−0.01298 (15)	0.0724 (7)
C6	0.2967 (2)	0.6085 (2)	0.05238 (14)	0.0636 (6)
H6	0.209	0.589	0.0452	0.076*
N7	0.35963 (18)	0.5297 (2)	0.19699 (12)	0.0639 (5)
H7	0.423 (3)	0.498 (3)	0.2325 (16)	0.068 (7)*
C8	0.24229 (19)	0.5317 (2)	0.21258 (12)	0.0540 (5)
O9	0.14248 (14)	0.58188 (19)	0.16417 (9)	0.0701 (5)
N10	0.24242 (19)	0.4718 (2)	0.28412 (11)	0.0638 (5)
H10	0.315 (3)	0.441 (3)	0.3168 (16)	0.075 (8)*
C11	0.1271 (2)	0.4629 (3)	0.31035 (13)	0.0683 (7)
H11A	0.1342	0.3814	0.3453	0.082*
H11B	0.0514	0.4501	0.2618	0.082*
C12	0.1046 (2)	0.5896 (3)	0.35756 (13)	0.0684 (7)
H12A	0.0949	0.6706	0.322	0.082*
H12B	0.0231	0.5774	0.3703	0.082*
C13	0.21277 (19)	0.6172 (2)	0.43716 (13)	0.0558 (5)
C14	0.2326 (3)	0.5296 (3)	0.50382 (15)	0.0820 (8)
H14	0.1792	0.4519	0.4992	0.098*
C15	0.3299 (3)	0.5540 (3)	0.57772 (16)	0.0874 (9)
H15	0.3413	0.4926	0.6219	0.105*
C16	0.40944 (19)	0.6679 (2)	0.58626 (13)	0.0597 (6)
C17	0.3892 (2)	0.7585 (2)	0.52187 (14)	0.0638 (6)
H17	0.4404	0.8383	0.5274	0.077*
C18	0.2917 (2)	0.7315 (2)	0.44770 (14)	0.0654 (6)
H18	0.2798	0.7935	0.4038	0.078*
O19	0.50449 (17)	0.6876 (2)	0.66089 (11)	0.0816 (6)
H19	0.552 (3)	0.759 (4)	0.658 (2)	0.122*
O20	0.60539 (16)	0.5880 (3)	0.21599 (12)	0.0954 (7)
C21	0.7414 (3)	0.6140 (7)	0.2294 (2)	0.1518 (19)
H21A	0.7898	0.5914	0.2857	0.228*
H21B	0.7541	0.7105	0.2192	0.228*
H21C	0.7719	0.5574	0.1923	0.228*
O22	0.2495 (2)	0.6902 (3)	−0.08960 (12)	0.0991 (7)

C23	0.1155 (4)	0.6852 (3)	−0.10046 (19)	0.1056 (11)
H23A	0.0681	0.7078	−0.1569	0.158*
H23B	0.094	0.7512	−0.064	0.158*
H23C	0.0919	0.5933	−0.0879	0.158*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0566 (11)	0.0614 (13)	0.0551 (12)	0.0002 (9)	0.0154 (10)	−0.0068 (10)
C2	0.0567 (13)	0.0777 (16)	0.0735 (15)	−0.0004 (11)	0.0175 (12)	−0.0106 (12)
C3	0.0665 (15)	0.097 (2)	0.100 (2)	−0.0084 (14)	0.0355 (15)	−0.0010 (17)
C4	0.0879 (18)	0.0901 (19)	0.0855 (19)	−0.0109 (15)	0.0411 (16)	0.0065 (15)
C5	0.0828 (16)	0.0724 (16)	0.0603 (14)	−0.0089 (12)	0.0195 (12)	0.0028 (11)
C6	0.0610 (12)	0.0702 (15)	0.0565 (13)	−0.0088 (10)	0.0135 (10)	−0.0019 (11)
N7	0.0488 (10)	0.0852 (14)	0.0512 (11)	0.0095 (9)	0.0059 (8)	0.0050 (9)
C8	0.0531 (11)	0.0588 (12)	0.0426 (10)	0.0045 (9)	0.0037 (9)	−0.0033 (9)
O9	0.0538 (8)	0.0941 (12)	0.0551 (9)	0.0151 (8)	0.0057 (7)	0.0144 (8)
N10	0.0603 (11)	0.0815 (13)	0.0453 (10)	0.0137 (9)	0.0100 (8)	0.0071 (9)
C11	0.0644 (13)	0.0858 (17)	0.0483 (12)	−0.0152 (11)	0.0079 (10)	−0.0045 (11)
C12	0.0465 (11)	0.1008 (18)	0.0511 (12)	0.0057 (11)	0.0050 (9)	−0.0050 (12)
C13	0.0456 (10)	0.0698 (14)	0.0466 (11)	0.0055 (9)	0.0061 (8)	−0.0026 (10)
C14	0.0843 (17)	0.0838 (17)	0.0614 (14)	−0.0297 (14)	−0.0020 (12)	0.0050 (13)
C15	0.1003 (19)	0.0795 (17)	0.0587 (14)	−0.0219 (15)	−0.0109 (13)	0.0176 (13)
C16	0.0501 (11)	0.0611 (13)	0.0541 (12)	0.0033 (9)	−0.0044 (9)	0.0008 (10)
C17	0.0597 (12)	0.0574 (12)	0.0646 (13)	−0.0045 (10)	0.0047 (10)	0.0023 (10)
C18	0.0679 (14)	0.0651 (14)	0.0544 (12)	0.0060 (11)	0.0056 (10)	0.0120 (10)
O19	0.0738 (11)	0.0760 (12)	0.0659 (10)	−0.0059 (8)	−0.0214 (8)	0.0041 (8)
O20	0.0496 (9)	0.1491 (19)	0.0801 (12)	0.0044 (10)	0.0088 (8)	−0.0044 (12)
C21	0.0506 (16)	0.283 (6)	0.114 (3)	−0.004 (2)	0.0139 (17)	−0.020 (3)
O22	0.0948 (14)	0.1328 (18)	0.0650 (11)	−0.0083 (12)	0.0173 (10)	0.0177 (11)
C23	0.136 (3)	0.073	0.0813 (19)	−0.0271 (17)	−0.0063 (19)	0.0146 (15)

Geometric parameters (Å, º)

C1—C6	1.385 (3)	C12—H12A	0.97
C1—C2	1.394 (3)	C12—H12B	0.97
C1—N7	1.403 (3)	C13—C18	1.364 (3)
C2—O20	1.370 (3)	C13—C14	1.371 (3)
C2—C3	1.381 (4)	C14—C15	1.382 (3)
C3—C4	1.364 (4)	C14—H14	0.93
C3—H3	0.93	C15—C16	1.367 (3)
C4—C5	1.370 (4)	C15—H15	0.93
C4—H4	0.93	C16—C17	1.360 (3)
C5—O22	1.368 (3)	C16—O19	1.373 (2)
C5—C6	1.387 (3)	C17—C18	1.391 (3)
C6—H6	0.93	C17—H17	0.93
N7—C8	1.363 (3)	C18—H18	0.93
N7—H7	0.82 (3)	O19—H19	0.86 (4)

C8—O9	1.230 (2)	O20—C21	1.429 (3)
C8—N10	1.341 (3)	C21—H21A	0.96
N10—C11	1.440 (3)	C21—H21B	0.96
N10—H10	0.86 (3)	C21—H21C	0.96
C11—C12	1.515 (4)	O22—C23	1.394 (4)
C11—H11A	0.97	C23—H23A	0.96
C11—H11B	0.97	C23—H23B	0.96
C12—C13	1.509 (3)	C23—H23C	0.96
C6—C1—C2	119.7 (2)	C13—C12—H12B	108.7
C6—C1—N7	123.2 (2)	C11—C12—H12B	108.7
C2—C1—N7	117.1 (2)	H12A—C12—H12B	107.6
O20—C2—C3	125.5 (2)	C18—C13—C14	116.88 (19)
O20—C2—C1	115.2 (2)	C18—C13—C12	122.3 (2)
C3—C2—C1	119.3 (2)	C14—C13—C12	120.8 (2)
C4—C3—C2	120.7 (2)	C13—C14—C15	121.7 (2)
C4—C3—H3	119.7	C13—C14—H14	119.1
C2—C3—H3	119.7	C15—C14—H14	119.1
C3—C4—C5	120.5 (3)	C16—C15—C14	120.3 (2)
C3—C4—H4	119.7	C16—C15—H15	119.8
C5—C4—H4	119.7	C14—C15—H15	119.8
O22—C5—C4	116.1 (2)	C17—C16—C15	119.08 (19)
O22—C5—C6	123.9 (2)	C17—C16—O19	122.8 (2)
C4—C5—C6	120.0 (2)	C15—C16—O19	118.1 (2)
C1—C6—C5	119.8 (2)	C16—C17—C18	119.7 (2)
C1—C6—H6	120.1	C16—C17—H17	120.1
C5—C6—H6	120.1	C18—C17—H17	120.1
C8—N7—C1	127.99 (19)	C13—C18—C17	122.2 (2)
C8—N7—H7	118.4 (18)	C13—C18—H18	118.9
C1—N7—H7	113.4 (18)	C17—C18—H18	118.9
O9—C8—N10	122.0 (2)	C16—O19—H19	110 (2)
O9—C8—N7	122.9 (2)	C2—O20—C21	117.5 (3)
N10—C8—N7	115.05 (18)	O20—C21—H21A	109.5
C8—N10—C11	122.76 (19)	O20—C21—H21B	109.5
C8—N10—H10	118.8 (17)	H21A—C21—H21B	109.5
C11—N10—H10	118.4 (17)	O20—C21—H21C	109.5
N10—C11—C12	114.0 (2)	H21A—C21—H21C	109.5
N10—C11—H11A	108.8	H21B—C21—H21C	109.5
C12—C11—H11A	108.8	C5—O22—C23	118.7 (2)
N10—C11—H11B	108.8	O22—C23—H23A	109.5
C12—C11—H11B	108.8	O22—C23—H23B	109.5
H11A—C11—H11B	107.7	H23A—C23—H23B	109.5
C13—C12—C11	114.19 (19)	O22—C23—H23C	109.5
C13—C12—H12A	108.7	H23A—C23—H23C	109.5
C11—C12—H12A	108.7	H23B—C23—H23C	109.5

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N7—H7···O20	0.82 (3)	2.23 (2)	2.617 (3)	109 (2)
N7—H7···O19^{i}	0.82 (3)	2.48 (3)	3.182 (3)	144 (2)
N10—H10···O19^{i}	0.86 (3)	2.23 (3)	3.005 (3)	150 (2)
O19—H19···O9^{ii}	0.86 (4)	1.80 (4)	2.654 (3)	172 (4)

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