Multiple hydrogen bonds in cytosinium zoledronate trihydrate

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The asymmetric unit of the title compound [systematic name: 4-amino-2-oxo-2,3-dihydropyrimidin-1-ium 1-hydroxy-2-(1H,3H-imidazol-3-ium-1-yl)ethylidenediphosphonate trihydrate], $C_4H_6N_3O^+ \cdot C_5H_9N_2O_7P_2^- \cdot 3H_2O$, contains one cytosinium cation, one zoledronate anion and three water molecules. The zoledronate anion has a zwitterionic character, in which each phosphonate group is singly deprotonated and an imidazole N atom is protonated. Furthermore, proton transfer takes place from one of the phosphonic acid groups of the zoledronate anion to one of the N atoms of the cytosinium cation. The cytosinium cation forms a $C(6)$ chain, while the zoledronate anion forms a rectangular-shaped centrosymmetric dimer through N—H···O hydrogen bonds. The cations and anions are held together by N—H···O and O—H···O hydrogen bonds to form a one-dimensional polymeric tape. The three water molecules play a crucial role in hydrogen bonding, resulting in a three-dimensional hydrogen-bonded network.

Comment

The interaction of drugs with DNA is one of the most important aspects of biological studies in drug discovery and pharmaceutical development processes. A number of clinically important small molecules appear to act by binding directly to DNA and subsequently inhibiting gene expression or replication by interfering with the enzymes that catalyse these functions (Krugh, 1994). Hydrogen bonding plays a pivotal role in biomolecular structure and functions. In the case of nucleosides, the building blocks of DNA and RNA, hydrogen bonding is one of the most important structural features governing their biological role. Cytosine is well known for its hydrogen-bonding capabilities in DNA and RNA, and several cytosine derivatives have been reported for use in biological applications (Blackburn & Gait, 1996; Kumar & Leonard, 1988).

Zoledronic acid or zoledronate (marketed by Novartis under the trade names Zometa, Zomera, Aclasta and Reclast), a potent bone antiresorptive bisphosphonate drug, is used to prevent skeletal fractures in patients with cancers such as multiple myeloma and prostate cancer. It can also be used to treat osteoporosis, hypercalcaemia of malignancy and pain from bone metastases (Reid, 2002; Black *et al.*, 2007), and to prevent recurring fractures in patients with a previous hip fracture (Lyles *et al.*, 2007). Compared with other bisphosphonate drugs, zoledronic acid has superior potency and pharmacological properties. To the best of our knowledge, we report here for the first time a nucleobase–drug interaction, namely cytosinium zoledronate trihydrate, (I), in continuation of our ongoing studies of hydrogen-bond interactions and molecular recognition of nucleobases in the solid state (Sridhar & Ravikumar, 2007, 2008, 2010a,b; Sridhar *et al.*, 2009).

(I)
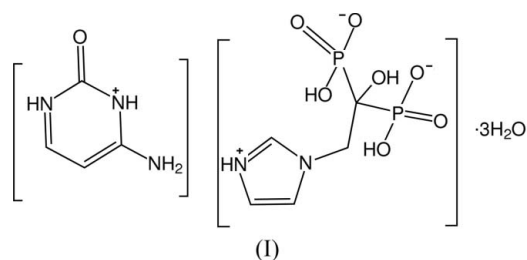
The asymmetric unit of (I) contains one cytosinium cation, one zoledronate anion and three water molecules (Fig. 1). Cytosine is quite a strong base (pK_{a1} = 1.6 and pK_{a2} = 12.2; Stecher, 1968) and, in the presence of acids, it is readily protonated at the N3 ring position. The cytosinium cation in (I) is protonated at N3, leading to an increase in the internal angle [C2—N3—C4 = 124.1 (3)°] compared with the neutral cytosine molecule [C—N—C = 119.4 (2)°; McClure & Craven, 1973]. The proton transfer takes place from one of the phosphonic acid groups of the zoledronate molecule.

Zoledronic acid is a bisphosphonic acid, a heterocyclic nitrogen-containing bisphosphonate that has an imidazole-ring side chain. The imidazole ring contains two critically positioned N atoms. The zoledronate group presents its usual
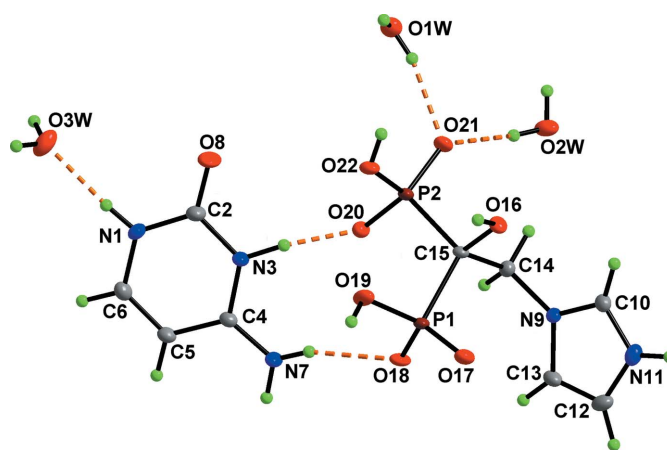

Figure 1
The molecular components of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen bonds are shown as dashed lines.
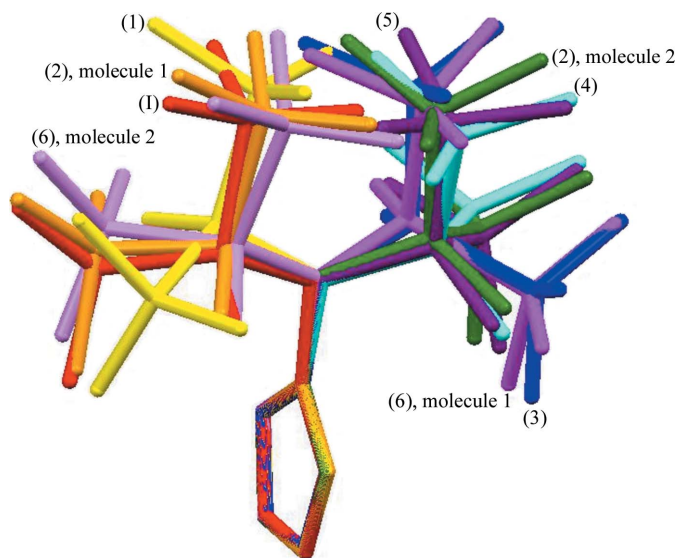
Figure 2
A superposition of the molecular conformations of zoledronate anions in various published compounds, showing the orientational differences of the phosphonate groups. The overlay was made by making a least-squares fit of the planar imidazole ring atoms with those of (I). See Table 1 for labelling and references.

zwitterionic character (Vega *et al.*, 1996, 1998), with negative charges in the singly protonated phosphonate groups and a positive charge at protonated imidazole atom N11. The resulting single negative charge is counterbalanced by the protonation of atom N3 of the cytosine molecule. The bond distances and angles are within normal ranges (Allen *et al.*, 1987) and are comparable with the corresponding values observed in zoledronic acid monohydrate [denoted (2) in Fig. 2 and Table 1; Sanders *et al.*, 2003], zoledronic acid trihydrate [(1); Ruscica *et al.*, 2010], hexa- and pentacoordinated zinc(II)–zoledronate complexes [(3) and (4); Freire & Vega, 2009a,b], and potassium and sodium complexes of zoledronate [(5) and (6); Freire *et al.*, 2010a,b].

It has already been reported that P—O bonds in which the O atom is unprotonated are between 1.47 and 1.53 Å long, while in the case of a protonated O atom they increase to 1.54–1.60 Å (Gossman *et al.*, 2003). The P—O distances of (I), as seen in Table 1, are in good agreement with this trend. The electronic state of the PO$_3$ group can be seen from the O—P—O bond angles. The O—P—O(H) angles are in the range 108.90 (15)–110.79 (15)°, while the O—P—O angles are in the range 115.68 (15)–116.77 (15)° (Table 1). Similar behaviour was observed in previously reported zoledronate structures (Sanders *et al.*, 2003; Ruscica *et al.*, 2010; Freire *et al.*, 2010a,b).

An overlay of the zoledronate molecules (Fig. 2), superimposing the planar imidazole ring, reveals significant orientational differences between the phosphonate groups. The relative orientations of the imidazole rings can be seen from the C15—C14—N9—C10 torsion angles (Table 1). In (I), this ring adopts a synclinal orientation, while the previously reported zoledronate structures have either synclinal (±30–90°, five structures) or anticlinal (±90–150°, three structures) orientations (Table 1). The orientation of the phosphonate (P1

and P2) groups of the zoledronate anion can be seen from the N9—C14—C15—P1 and N9—C14—C15—P2 torsion angles, which shows that these groups prefer to adopt either a synclinal (±30–90°) or an antiperiplanar (±150–180°) orientation. In (I), atom P1 is in a synclinal orientation and P2 is in an antiperiplanar orientation. In the case of the hydroxy group (torsion angle N9—C14—C15—O16), all the structures adopt a synclinal (±30–90°) orientation (Table 1). The above change observed in the conformation of the solid-state structures of zoledronate may be attributed to the different environments of the zoledronic acid, *viz.* hydrates or metal-coordinated.

In the crystal packing of (I), the component ions are linked into complex three-dimensional networks by a combination of X—H···O (X = N and O) hydrogen bonds (Table 2). A detailed analysis of the hydrogen-bonding scheme reveals that there are 16 potentially active H atoms (four from each cation and anion, and eight from water). Five different modes of hydrogen-bonding interaction are observed, *viz.* cation–cation, anion–anion, cation–anion, cation–water and anion–water.

The cytosinium cations are linked through an N—H···O hydrogen bond, forming a $C(6)$ chain (Etter, 1990; Etter *et al.*, 1990; Bernstein *et al.*, 1995) parallel to the *b* axis. The zoledronate anions form a centrosymmetric dimer [$R_2^2(16)$] through an N—H···O hydrogen bond. The O—H···O hydrogen bonds between symmetry-related dimers of the phosphonate groups of the zoledronate anion form ribbons of anions parallel to the *b* axis. These hydrogen bonds form a rather rectangular-shaped centrosymmetric tetramer and produce a characteristic $R_4^4(26)$ motif (Fig. 3).

The cytosinium cation and zoledronate anion are held together by two N—H···O hydrogen bonds (entries 2 and 3 in Table 2), thereby generating an $R_2^2(10)$ motif. Interionic N—H···O and O—H···O interactions link adjacent $R_2^2(10)$ motifs to produce another $R_4^3(12)$ motif. Thus, the combination of N—H···O and O—H···O bonds leads to the formation of a
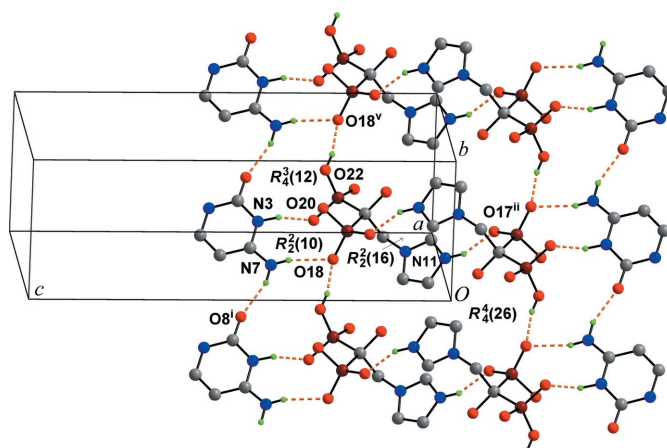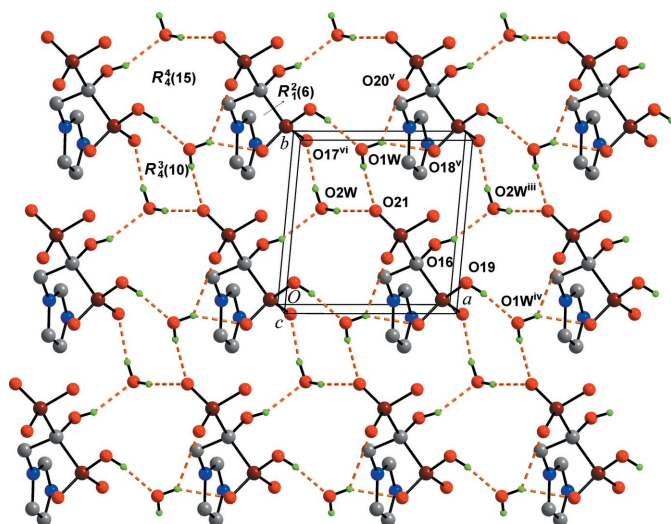

Figure 3
The one-dimensional polymeric tapes formed by N—H···O and O—H···O interactions involving the cations and anions. For the sake of clarity, the three water molecules and H atoms not involved in hydrogen bonding have been omitted. Only atoms involved in hydrogen bonding are labelled. [Symmetry codes: (i) x, $y - 1$, z; (ii) $-x + 2$, $-y$, $-z$; (v) x, $y + 1$, z.]
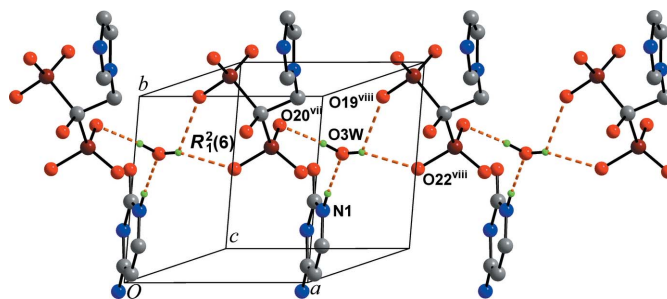
Figure 4
Part of the crystal structure of (I), showing the two-dimensional hydrogen-bonded networks built from zoledronate anions and two water molecules (O1W and O2W). For the sake of clarity, the cytosinium cation, water molecule O3W and H atoms not involved in hydrogen bonding have been omitted. Only atoms involved in hydrogen bonding are labelled. [Symmetry codes: (iii) $x + 1, y, z$; (iv) $x + 1, y - 1, z$; (v) $x, y + 1, z$; (vi) $x - 1, y + 1, z$.]

Figure 5
Part of the crystal structure of (I), showing the one-dimensional chain formed by water molecule O3W with cytosinium cations and zoledronate anions. For the sake of clarity, the other two water molecules, O1W and O2W, and H atoms not involved in hydrogen bonding have been omitted. Only atoms involved in hydrogen bonding are labelled. [Symmetry codes: (vii) $-x + 1, -y + 1, -z + 1$; (viii) $-x + 2, -y + 1, -z + 1$.]

Figure 6
Part of the crystal structure of (I), showing the hydrogen-bonding interactions. Hydrogen bonds are shown as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity.

one-dimensional polymeric ribbon along the b axis, in which the zoledronate anions are flanked by the cytosinium cations (Fig. 3).
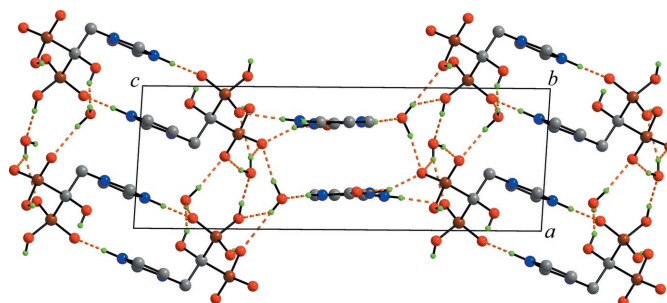
The water molecules (O1W, O2W and O3W) play a dual role as both donors and acceptors in the hydrogen-bonding interactions (Table 2). The two water molecules O1W and O2W, as donors and acceptors, link three zoledronate anions through O—H···O hydrogen bonds, while the third water molecule (O3W) links two zoledronate anions as donor, and acts as acceptor in linking the cytosinium cation via an N—H···O hydrogen bond.

Water molecule O1W, acting as donor, links the two symmetry-related atoms O18($x, y + 1, z$) and O20($x, y + 1, z$) of the zoledronate anion through three-centred hydrogen bonds (Jeffrey & Saenger, 1991) to form an $R_1^2(6)$ motif. As acceptor, it links atom O19($x - 1, y + 1, z$) of the anion and forms an infinite anion–water chain along the a axis. The second water molecule, O2W, as donor and acceptor, links the anion–water chain via atoms O21 and O16($x - 1, y, z$) to form a tetrameric hydrogen-bonded network of $R_4^4(15)$ motif. Furthermore, the two water molecules O1W and O2W link the $R_4^4(15)$ tetramers through O—H···O hydrogen bonds involving atoms O21 and O17($x - 1, y + 1, z$) of the anions and form another set of tetrameric hydrogen-bonded networks of $R_4^3(10)$ motif. The $R_4^4(15)$ and $R_4^3(10)$ motifs are arranged alternately and aggregate as infinite two-dimensional hydrogen-bonded layers parallel to the (001) plane (Fig. 4).

As donor, the third water molecule, O3W, forms hydrogen bonds to phosphonate atoms O19($-x + 2, -y + 1, -z + 1$) and O22($-x + 2, -y + 1, -z + 1$) and to O20($-x + 1, -y + 1, -z + 1$) of neighbouring zoledronate anions, forming an $R_1^2(6)$ motif (three-centred hydrogen bonds), resulting in an infinite

anion–water chain along the a axis. In addition, atom O3W acts as acceptor in a hydrogen bond from atom N1 of the cytosinium cation. Thus, the water molecule bridges the cation and anion through N—H···O and O—H···O hydrogen bonds and leads to the formation of a one-dimensional chain with alternating cations and anions (Fig. 5).

The combination of the N—H···O and O—H···O hydrogen bonds involving cations, anions and water molecules leads to the formation of three-dimensional hydrogen-bonded networks (Fig. 6). This structure displays segregation of its molecular components.

C—H···O interactions are also observed in the crystal structure of (I). Incidentally, the C—H···O interaction between the imidazole and bisphosphonate group [C13—H13···O21($x, -1 + y, z$)] is one of the most favourable interactions observed in zoledronate complexes (Freire et al., 2010a,b). It is very interesting to note that there is no water–water interaction in the structure of (I).

Experimental

To obtain crystals of (I) suitable for X-ray study, cytosine (0.111 g, 1 mmol) and zoledronic acid (USV Ltd, Mumbai; 0.272 g, 1 mmol) were dissolved in water (25 ml) and the solution was allowed to evaporate slowly.

Table 1
Selected bond distances (Å), bond angles (°) and torsion angles (°) for zoledronate species.

Parameter	(I)	(1)	(2), molecule 1	(2), molecule 2	(3)	(4)	(5)	(6), molecule 1	(6), molecule 2
P1—O17	1.489 (3)	1.512 (2)	1.517 (2)	1.516 (2)	1.501 (4)	1.508 (2)	1.503 (1)	1.498 (4)	1.497 (3)
P1—O18	1.500 (3)	1.503 (2)	1.519 (2)	1.504 (2)	1.509 (4)	1.508 (2)	1.508 (1)	1.522 (4)	1.530 (3)
P1—O19	1.566 (3)	1.59 (2)	1.567 (2)	1.564 (2)	1.567 (4)	1.580 (2)	1.557 (1)	1.579 (3)	1.574 (4)
P2—O20	1.505 (3)	1.501 (2)	1.499 (2)	1.505 (2)	1.498 (4)	1.506 (2)	1.503 (1)	1.482 (4)	1.498 (4)
P2—O21	1.492 (3)	1.522 (2)†	1.538 (2)†	1.537 (2)†	1.502 (4)	1.497 (2)	1.512 (1)	1.521 (4)	1.510 (4)
P2—O22	1.569 (2)	1.563 (2)	1.553 (2)	1.561 (2)	1.578 (4)	1.569 (2)	1.566 (1)	1.594 (4)	1.581 (4)
O17—P1—O18	115.68 (15)	116.0 (1)	113.6 (1)	116.1 (1)	108.9 (2)	115.4 (1)	113.96 (9)	115.5 (2)	113.4 (2)
O17—P1—O19	110.34 (16)	112.25 (9)	112.2 (1)	105.0 (1)	115.5 (2)	108.1 (1)	110.93 (9)	110.2 (2)	110.5 (2)
O18—P1—O19	110.12 (16)	107.7 (1)	110.0 (1)	114.8 (1)	109.9 (2)	110.5 (1)	111.03 (8)	108.1 (2)	107.7 (2)
O21—P2—O20	116.77 (16)	109.1 (1)‡	114.3 (1)‡	110.9 (1)‡	108.0 (3)	110.0 (1)	115.33 (8)	119.0 (2)	117.1 (2)
O21—P2—O22	110.79 (15)	114.0 (1)	102.8 (1)	106.4 (1)	110.9 (22)	117.3 (1)	108.42 (8)	105.3 (2)	111.1 (2)
O20—P2—O22	108.90 (15)	112.3 (1)	116.1 (1)	113.9 (1)	115.7 (2)	109.0 (1)	112.28 (8)	111.2 (2)	105.7 (2)
C2—N3—C4	124.1 (3)								
C15—C14—N9—C10	−77.6 (4)	−104.6 (3)	−79.0 (3)	78.2 (3)	104.1 (8)	−78.6 (4)	75.9 (2)	−104.8 (5)	77.4 (5)
N9—C14—C15—P1	−56.7 (3)	58.3 (2)	−59.5 (3)	62.8 (3)	−59.4 (7)	−162.3 (2)	63.8	167.9 (3)	−167.7 (3)
N9—C14—C15—P2	−179.3 (2)	−177.7 (2)	175.3 (2)	−171.5 (2)	177.1 (5)	76.6 (3)	−170.5 (1)	46.4 (4)	69.0 (4)
N9—C14—C15—O16	62.9 (3)	−61.6 (2)	58.7 (3)	−51.7 (3)	62.2 (7)	−39.8 (3)	−55.3 (2)	−75.5 (5)	−51.5 (4)

† P—OH distance. ‡ O—P—OH angle. References: (I), present structure; (1), zoledronic acid trihydrate (Ruscica *et al.*, 2010); (2), zoledronic acid monohydrate (Sanders *et al.*, 2003); (3), hexacoordinated zinc(II) zoledronate (Freire & Vega, 2009*a*); (4), pentacoordinated zinc(II) zoledronate (Freire & Vega, 2009*b*); (5), potassium complex of zoledronate (Freire *et al.*, 2010*a*); (6), sodium complex of zoledronate (Freire *et al.*, 2010*b*).

Crystal data

$C_4H_6N_3O^+ \cdot C_5H_9N_2O_7P_2^- \cdot 3H_2O$
$M_r = 437.25$
Triclinic, $P\bar{1}$
$a = 6.7292$ (16) Å
$b = 6.8032$ (16) Å
$c = 19.193$ (5) Å
$\alpha = 89.875$ (4)°
$\beta = 86.747$ (5)°

$\gamma = 84.726$ (4)°
$V = 873.5$ (4) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.32$ mm^{-1}
$T = 294$ K
$0.14 \times 0.12 \times 0.06$ mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
7859 measured reflections

3035 independent reflections
2805 reflections with $I > 2\sigma(I)$
$R_{int} = 0.033$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.060$
$wR(F^2) = 0.143$
$S = 1.21$
3035 reflections

247 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.50$ e Å^{-3}
$\Delta\rho_{min} = -0.38$ e Å^{-3}

Table 2
Hydrogen-bond geometry (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N1—H1$\cdots$O3W	0.86	1.89	2.747 (4)	177
N3—H3$\cdots$O20	0.86	1.87	2.675 (4)	155
N7—H7A$\cdots$O18	0.86	2.07	2.874 (4)	155
N7—H7B$\cdots$O8[i]	0.86	1.98	2.783 (4)	154
O16—H16$\cdots$O2W[ii]	0.82	1.97	2.703 (4)	148
O19—H19$\cdots$O1W[iii]	0.82	1.78	2.592 (4)	172
O22—H22$\cdots$O18[iv]	0.82	1.78	2.578 (3)	163
N11—H11$\cdots$O17[v]	0.86	1.83	2.620 (4)	152
O1W—H1W$\cdots$O18[iv]	0.85	2.18	2.895 (4)	141
O1W—H1W$\cdots$O20[iv]	0.85	2.41	3.050 (4)	133
O1W—H2W$\cdots$O21	0.84	1.95	2.774 (4)	165
O2W—H3W$\cdots$O21	0.85	1.92	2.770 (4)	170
O2W—H4W$\cdots$O17[vi]	0.85	1.91	2.746 (4)	168
O3W—H5W$\cdots$O20[vii]	0.85	2.01	2.849 (4)	171
O3W—H6W$\cdots$O22[viii]	0.85	2.34	3.158 (4)	161
O3W—H6W$\cdots$O19[viii]	0.85	2.48	3.027 (4)	123
C5—H5$\cdots$O8[i]	0.93	2.43	3.130 (5)	132
C6—H6$\cdots$O1W[vii]	0.93	2.37	3.203 (5)	148
C13—H13$\cdots$O21[i]	0.93	2.43	3.350 (5)	173
C14—H14A$\cdots$O1W[i]	0.97	2.59	3.534 (5)	165

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

All H atoms attached to C, N and hydroxy O atoms were located in difference Fourier maps and subsequently geometrically optimized and allowed for as riding atoms, with C—H = 0.93 (aromatic) or 0.97 Å (methylene), N—H = 0.86 Å and O—H = 0.82 Å, with $U_{iso}(H) = 1.2U_{eq}(C,N)$ or $1.5U_{eq}(O)$. Water H atoms were located in a difference Fourier map and included in the subsequent refinement using restraints O—H = 0.85 (1) Å and H$\cdots$H = 1.40 (2) Å, with $U_{iso}(H) = 1.5U_{eq}(O)$. In the final cycle of refinement, they were treated as riding on their parent O atoms.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); 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 & Putz, 2005); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3157). Services for accessing these data are described at the back of the journal.

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