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Mometasone furoate revisited, or how did the hydrate get in the bottle?

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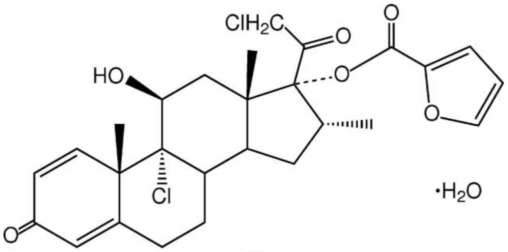
The redetermined structure of 9α,21-dichloro-11β,17α-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate monohydrate, $C_{27}H_{32}Cl_2O_7\cdot H_2O$, at 100 K has triclinic ($P1$) symmetry. The structure displays O—H$\cdots$O hydrogen bonding, which gives rise to infinite sheets extending parallel to the [110] plane. The previously published structure [Chen *et al.* (2005). *J. Pharm. Sci.* **94**, 2496–2509] was determined at room temperature and no significant anomalous signal was present. Data for the structure presented in this study were collected at low temperature and the absolute configuration could be established based solely on anomalous diffraction. Another point of interest is that the structure determined in this study is that of the monohydrate, even though the crystal was harvested from a bottle of nasal spray that was supposed to contain exclusively crystals of the anhydrous form.

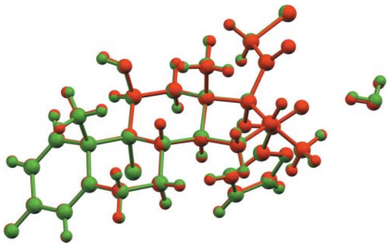
1. Introduction

Nearly 400 years ago, Galileo Galiliei coined the phrase ‘measure what can be measured, make measurable what cannot be measured’, and to this day most scientists feel driven by this credo to some extent. In Galileo’s spirit of general scientific curiosity, most crystallographers have, at one point in their career, subjected to a diffraction experiment crystals they found in a bottle of wine, only to determine once again the structure of potassium bitartrate. Similarly, in one case known to the author of this article, a crystallographer determined the crystal structure of his own kidney stone and then gleefully presented his urologist with an atomic displacement ellipsoid representation (at the 50% probability level, of course) of the structure of calcium oxalate. Yet another case in this context is the structure of struvite (magnesium ammonium phosphate). Several attempts to obtain diffraction quality crystals of struvite had failed, however, Dr M. Rosemeyer of University College, London, found a large conglomerate of high-quality struvite crystals in a can of salmon, which led to a successful structure determination by Whitaker & Jeffrey (1970).



(I)

When the author of this report came across a bottle of nasal spray (manufactured by Apotex Inc., lot number KT2277,



expiry date 2015 DE and marketed as a nasal spray in Canada) in which the active ingredient, the title compound mometasone furoate, was contained in the solid state, he tried to find a crystal large enough for single-crystal structure determination. These attempts were successful and the present report is a result of this endeavor.

2. Experimental

Following the instructions for using the nasal spray outlined in the package insert that Apotex distributes with the spray, the bottle was shaken well, then the spray nozzle was primed by pumping five times. The spray mist of an additional pump stroke was collected on a glass microscope slide. Examination under a polarizing microscope showed the presence of several crystals of sufficient size and quality for X-ray structure determination and the specimen chosen was a plate-like crystal with dimensions of 0.050 × 0.030 × 0.008 mm. The crystal was mounted with mineral oil (STP Oil Treatment) on a MiTeGen mount.

2.1. Synthesis and crystallization

The sample was manufactured by Apotex Inc. (lot number KT2277, expiry date 2015 DE) and marketed as a nasal spray in Canada. The crystals were harvested directly from the bottle.

2.2. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. The structure was solved with intrinsic phasing methods using the program *SHELXT* (Sheldrick, 2015*a*) and refined against F^2 on all data using *SHELXL* (Sheldrick, 2015*b*) using established refinement techniques (Müller, 2009). All C-bound H atoms were placed in geometrically calculated positions and refined using a riding model, with $U_{iso}(H) = 1.2U_{eq}(C)$, or $1.5U_{eq}(C)$ for methyl groups. The coordinates for the O-bound H atoms (on atoms O2 and O7) were taken from the difference Fourier synthesis and these H atoms were subsequently refined with the help of O—H distance restraints [target value = 0.84 (2) Å], with $U_{iso}(H) = 1.5U_{eq}(O)$. No other restraints were used (besides the three automatically applied floating-origin restraints that are necessary in the space group *P*1).

Table 1
Experimental details.

Crystal data	
Chemical formula	$C_{27}H_{30}Cl_2O_6 \cdot H_2O$
M_r	539.42
Crystal system, space group	Triclinic, *P*1
Temperature (K)	100
a, *b*, *c* (Å)	7.2367 (6), 8.4193 (6), 11.7507 (8)
α, β, γ (°)	73.617 (5), 85.522 (6), 69.492 (5)
V (Å^3)	643.18 (9)
Z	1
Radiation type	Cu *Kα*
μ (mm^{-1})	2.65
Crystal size (mm)	0.050 × 0.030 × 0.008
Data collection	
Diffractometer	Bruker SMART APEXII CCD area-detector diffractometer
Absorption correction	Multi-scan (*SADABS*; Krause *et al.*, 2015)
T_{min}, T_{max}	0.595, 0.753
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	9890, 3691, 3309
R_{int}	0.054
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.605
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.041, 0.100, 1.03
No. of reflections	3691
No. of parameters	337
No. of restraints	6
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.25, −0.27
Absolute structure	Flack *x* parameter determined using 1106 quotients $[(I^+) - (I^-)]/[(I^+) + (I^-)]$ (Parsons *et al.*, 2013)
Absolute structure parameter	0.033 (13)

Computer programs: *APEX2* (Bruker, 2014), *SAINT* (Bruker, 2014), *SHELXT* (Sheldrick, 2015*a*) and *SHELXL2014* (Sheldrick, 2015*b*).

3. Results and discussion

The sample came from a bottle of nasal spray manufactured by Apotex Inc. that is commercially available in Canada. According to the Canadian product monograph (DPD, 2015), the active ingredient contained in the spray is delivered in the solid state, namely in the form of crystals of the orthorhombic anhydride of mometasone furoate (Chen *et al.*, 2005) suspended in aqueous solution. This polymorph is described as 'practically insoluble in water'. It seemed interesting to find out whether the spray bottle contained any crystals suitable for single-crystal structure determination and, as described above, a crystal was harvested directly from the nasal spray bottle. Determination of the unit cell revealed that the crystal found in the bottle was, in fact, not the polymorph described in

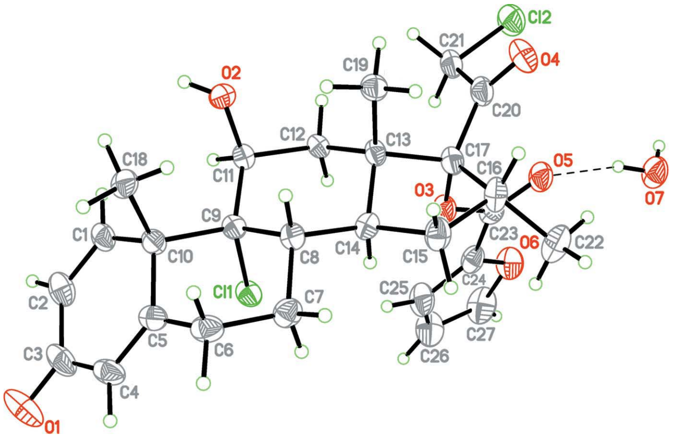


Figure 1
The structure of mometasone furoate monohydrate, (I), with the atomic labeling scheme corresponding to that of the previously published room-temperature structure (Chen *et al.*, 2005). Displacement ellipsoids are drawn at the 50% probability level. The O7—H7*A*···O5 hydrogen bond is drawn as a thin dashed line.

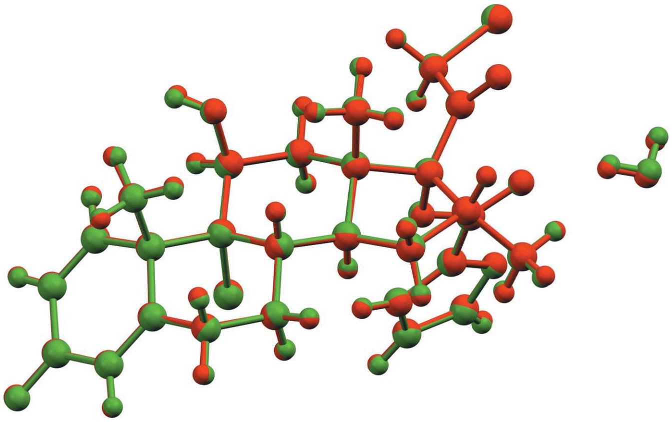


Figure 2
A least-squares fit of the room-temperature structure of (I) (green; Chen *et al.*, 2005) and the low-temperature structure (red; this study), based on all non-H atoms except for the water O atom (r.m.s. deviation = 0.02 Å). The differences between the two structures are minimal and can be explained by the different data-collection temperatures.

the product monograph, but rather the triclinic monohydrate, (I).

The structures of both the anhydrous orthorhombic polymorph and the triclinic monohydrate had been determined previously (Chen *et al.*, 2005). In the previous analysis, however, diffraction data had been collected at room temperature and Bijvoet pairs had been merged for refinement. Therefore, in order to attempt establishing the absolute structure, a full data collection at 100 K and subsequent structure determination were undertaken (molecular model shown in Fig. 1). Indeed, a significant anomalous signal is present in the low-temperature data set and the absolute structure can now be determined solely based on anomalous scattering; the Flack x parameter, as calculated by the Parsons method (Parsons *et al.*, 2013), refined to 0.033 (13). Analysis of the anomalous signal by the Hooft method (Hooft *et al.*, 2008) calculates a probability of 1 that the absolute structure is correct, a probability of 0 that the structure is a racemic twin and a probability of 0 that the absolute structure is incorrect. The Hooft method also gives an absolute structure parameter directly comparable with the Flack x. The Hooft y parameter is determined to be 0.030 (14), which is in excellent agreement with the Flack x parameter. It can therefore be determined with high confidence that the configurations of the molecule's eight chiral centers are C8 *S*, C9 *R*, C10 *S*, C11 *S*, C13 *S*, C14 *S*, C16 *R* and C17 *R*.

The structure determined in this study, including the absolute structure, is essentially identical to the structure of mometasone furoate monohydrate published by Chen *et al.* (2005). A least-squares fit of the two structures based on all non-H atoms (except for water oxygen O7) results in an r.m.s. deviation of 0.02 Å (Fig. 2), indicating that the two structures are perfectly identical.

It may be interesting to note that the unit-cell volume of (I) at 100 K is 2.1% smaller than that at room temperature [634.18 (9) *versus* 656.79 (11) Å^3]. Approximately half of the temperature-dependent shrinkage is accounted for by a change in the a axis, which shrinks by 1.5% of its room-temperature length [7.2367 (6) *versus* 7.3208 (7) Å], while the b and c axes only change by 0.68 and 0.53% of their room-temperature lengths, respectively [8.4193 (6) *versus* 8.4767 (8) Å for b, and 11.7507 (8) *versus* 11.8136 (11) Å for c]. This means the shortest axis shrinks by far the most and the longest axis shrinks the least.

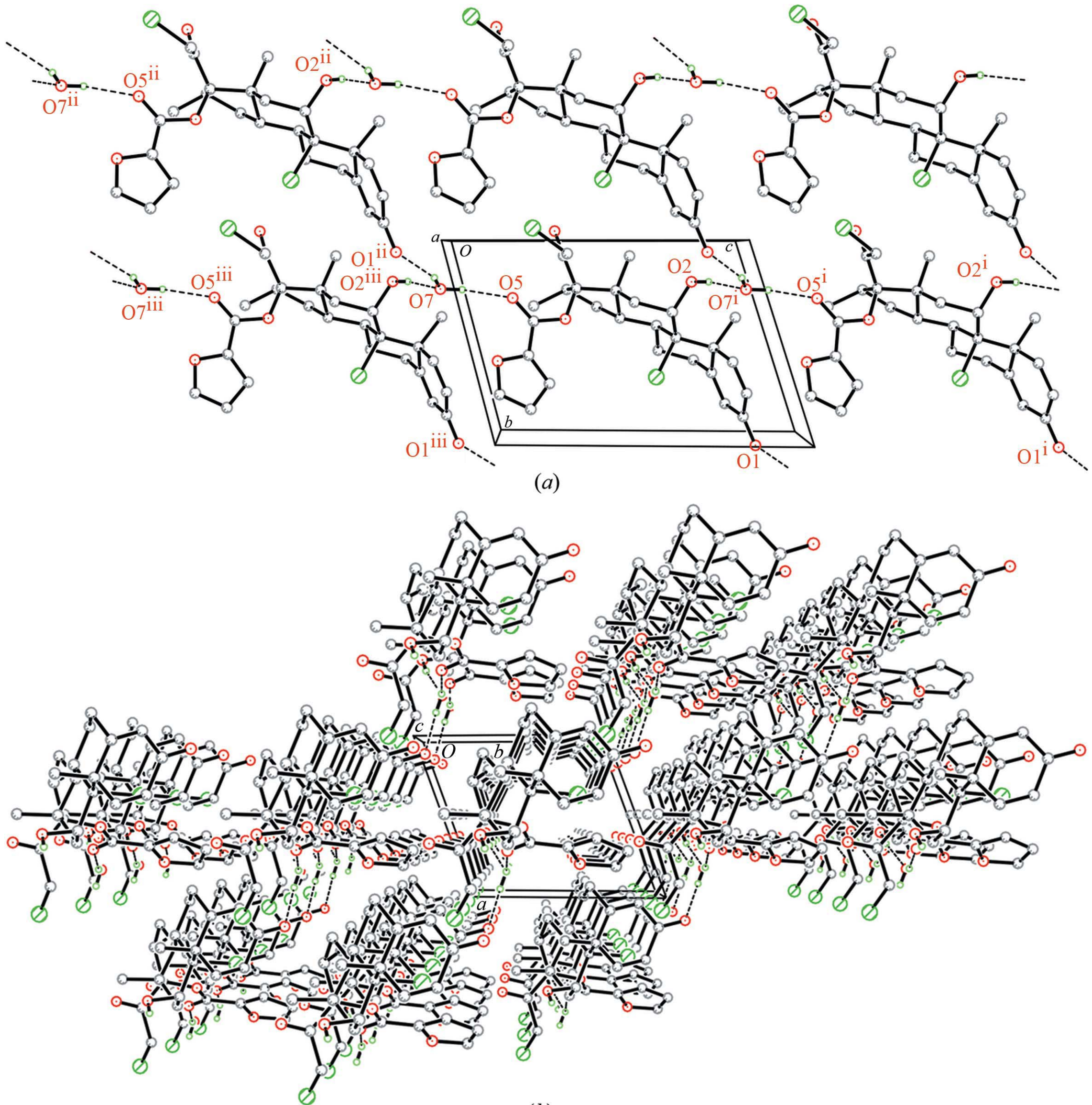
Table 2
Hydrogen-bond geometry (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O2—H2$\cdots$O7$^{\rm i}$	0.83 (3)	1.88 (3)	2.706 (4)	171 (6)
O7—H7$A\cdots$O5	0.84 (3)	2.06 (4)	2.850 (4)	158 (7)
O7—H7$B\cdots$O1$^{\rm ii}$	0.82 (3)	1.99 (4)	2.740 (5)	152 (7)

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

The supramolecular structure of (I) is also worth describing. The structure contains three O—H$\cdots$O hydrogen bonds (see Table 2). Interactions O7—H7$A\cdots$O5 and O2—H2$\cdots$O7$^{\rm i}$ [symmetry code: (i) $x, y, z + 1$] link the molecules into infinite chains extending along the crystallographic c direction. These chains are crosslinked by the remaining O7—H7$B\cdots$O1$^{\rm ii}$ hydrogen bond [symmetry code: (ii) $x + 1, y - 1, z - 1$], giving rise to infinite two-dimensional sheets extending parallel to the [110] plane (Figs. 3*a* and 3*b*).

At least as interesting as establishing, and effectively confirming, the absolute configuration of the title compound is the circumstance that the bottle of nasal spray examined contained crystals of a polymorph that was not mentioned in the product monograph. To make sure there was more than just this one crystal of the monohydrate, the unit cells of several more crystals were determined, which were also of the triclinic monohydrate. No suitable crystal of the anhydrous form could be found in the nasal spray bottle. These findings raise the interesting question from the title of this report: how did the hydrate get in the bottle? Realistically, there are but two possibilities: either the monohydrate was put into the bottle by the manufacturer, or it formed during storage inside the bottle. The former possibility would suggest that Apotex's manufacturing or formulating process gives rise to a mixture of the two polymorphs or, possibly, even only the monohydrate. The latter scenario is more interesting from a crystallographic point of view: could the anhydrous form transform into the monohydrate over time? The expiry date printed on the bottle was December 2015, suggesting the bottle had been stored for a considerable amount of time, perhaps long enough to allow for polymorph conversion, or, perhaps, recrystallization. Incidentally, the triclinic monohydrate of the title compound also has an entry in the Canadian DPD and, according to the product monograph (DPD, 2015), the monohydrate, just like the anhydrous form in its monograph, is described as 'practically insoluble in water 0.02 mg ml^{-1}.' 'Practically insoluble' is not completely insoluble and a concentration of 0.02 mg ml^{-1} corresponds to 0.04 mmol l^{-1}, which is, indeed, a very low concentration. However, if the monohydrate should be the more stable



(*a*)

(*b*)

Figure 3
The supramolecular arrangement in the structure of mometasone furoate monohydrate, (I). C-bound H atoms have been omitted for clarity and hydrogen bonds are drawn as thin dashed lines. (*a*) A projection, along the crystallographic *a* axis, showing the two-dimensional hydrogen-bonding network generated by three O—H$\cdots$O interactions, *viz.* O7—H7*A*$\cdots$O5, O2—H2$\cdots$O7^{i} and O7—H7*B*$\cdots$O1^{ii}. [Symmetry codes for the acceptor O-atom labels: (i) $x, y, z + 1$; (ii) $x + 1, y - 1, z - 1$; (iii) $x, y, z - 1$.] (*b*) A packing plot, shown in a projection along the crystallographic *c* axis, illustrating the stacking of the two-dimensional sheets parallel to the [110] plane.

polymorph or slightly less soluble than the anhydrous form, the analyzed crystals could conceivably have formed during storage of the bottle. Cases of recrystallization and solid-state polymorph transformation of 'insoluble' compounds have been reported in the past (for example, Brits *et al.*, 2010). It is beyond the scope of this study to determine exactly how the monohydrate crystals may have formed and the question posed in the title remains unanswered for the time being. Rather, the author wishes to report the circumstance that such a conversion or recrystallization may be possible, hoping to trigger further research into this matter from other interested parties.

Acknowledgements

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supporting information

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Computing details

Data collection: *APEX2* (Bruker, 2014); cell refinement: *SAINT* (Bruker, 2014); data reduction: *SAINT* (Bruker, 2014); program(s) used to solve structure: SHELXT (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2014*/6 (Sheldrick, 2015b); molecular graphics: *APEX2* (Bruker, 2014); software used to prepare material for publication: *APEX2* (Bruker, 2014).

9*α*,21-Dichloro-11*β*,17*α*-dihydroxy-16*α*-methyl-3,20-dioxodipregna-1,4-dien-17-yl furan-2-carboxylate monohydrate

Crystal data

$C_{27}H_{30}Cl_2O_6{\cdot}H_2O$
$M_r = 539.42$
Triclinic, $P1$
$a = 7.2367\ (6)$ Å
$b = 8.4193\ (6)$ Å
$c = 11.7507\ (8)$ Å
$\alpha = 73.617\ (5)°$
$\beta = 85.522\ (6)°$
$\gamma = 69.492\ (5)°$
$V = 643.18\ (9)$ Å^3

$Z = 1$
$F(000) = 284$
$D_x = 1.393$ Mg m^{-3}
Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
Cell parameters from 2338 reflections
$\theta = 3.9$–$69.5°$
$\mu = 2.65$ mm^{-1}
$T = 100$ K
Plate, colourless
0.05 × 0.03 × 0.01 mm

Data collection

Bruker SMART APEXII CCD area-detector diffractometer
Radiation source: IμS micro-focus sealed tube
Detector resolution: 8.3 pixels mm^{-1}
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Krause *et al.*, 2015)
$T_{min} = 0.595$, $T_{max} = 0.753$

9890 measured reflections
3691 independent reflections
3309 reflections with $I > 2\sigma(I)$
$R_{int} = 0.054$
$\theta_{max} = 68.9°$, $\theta_{min} = 3.9°$
$h = -8 \rightarrow 8$
$k = -9 \rightarrow 10$
$l = -14 \rightarrow 14$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.100$
$S = 1.03$
3691 reflections
337 parameters
6 restraints
Primary atom site location: real-space vector search

Secondary atom site location: difference Fourier map
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.058P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.25$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}

Absolute structure: Flack x parameter determined using 1106 quotients $[(I^+) - (I^-)]/[(I^+) + (I^-)]$ (Parsons *et al.*, 2013)
Absolute structure parameter: 0.033 (13)

Special details

Experimental. Diffraction data (φ and ω scans) were collected at 100 K on a Bruker X8 Kappa diffractometer **[CIF states a Bruker SMART diffractometer was used - please clarify]** coupled to a Bruker APEXII CCD area detector using Cu $K\alpha$ radiation (λ = 1.54178 Å) from an IμS micro-focus sealed tube. The unit cell was determined using the *APEX2* software (Bruker, 2014). Data reduction was carried out with the program *SAINT* as implemented in *APEX2* (Bruker, 2014), and scaling and semi-empirical absorption correction based on equivalents were performed with the program *SADABS* (Krause *et al.*, 2015).

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. All H-atom positions were clearly visible in the difference Fourier synthesis.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	$U_{\rm iso}$*/$U_{\rm eq}$
Cl1	0.38869 (12)	0.70309 (11)	0.57893 (8)	0.0258 (2)
Cl2	1.05906 (15)	−0.06043 (14)	0.30986 (10)	0.0398 (3)
O1	0.1436 (6)	1.0601 (5)	0.8475 (4)	0.0497 (10)
O2	0.5986 (4)	0.2125 (4)	0.7852 (2)	0.0279 (6)
H2	0.667 (7)	0.212 (8)	0.839 (4)	0.042*
O3	0.5622 (4)	0.4035 (4)	0.3308 (2)	0.0254 (6)
O4	0.6498 (5)	−0.0488 (4)	0.3775 (3)	0.0372 (8)
O5	0.6916 (5)	0.2943 (4)	0.1761 (2)	0.0319 (7)
O6	0.7656 (5)	0.6081 (5)	0.0719 (3)	0.0370 (7)
O7	0.8155 (5)	0.2476 (5)	−0.0521 (3)	0.0429 (9)
H7A	0.812 (11)	0.249 (10)	0.019 (3)	0.064*
H7B	0.927 (5)	0.179 (8)	−0.058 (6)	0.064*
C1	0.4342 (6)	0.6235 (6)	0.8461 (3)	0.0259 (9)
H1	0.5666	0.5459	0.8635	0.031*
C2	0.3863 (7)	0.7835 (6)	0.8623 (4)	0.0322 (10)
H2A	0.4830	0.8144	0.8926	0.039*
C3	0.1874 (7)	0.9121 (6)	0.8339 (4)	0.0343 (10)
C4	0.0436 (7)	0.8558 (6)	0.7903 (4)	0.0309 (10)
H4	−0.0871	0.9367	0.7718	0.037*
C5	0.0887 (6)	0.6948 (5)	0.7753 (3)	0.0246 (9)
C6	−0.0597 (6)	0.6355 (6)	0.7320 (4)	0.0292 (9)
H6A	−0.1889	0.7322	0.7175	0.035*
H6B	−0.0764	0.5336	0.7933	0.035*
C7	0.0099 (6)	0.5832 (6)	0.6175 (4)	0.0276 (9)
H7C	0.0088	0.6891	0.5535	0.033*
H7D	−0.0825	0.5343	0.5938	0.033*
C8	0.2184 (6)	0.4459 (5)	0.6330 (3)	0.0223 (8)
H8	0.2117	0.3346	0.6899	0.027*

C9	0.3675 (6)	0.5024 (5)	0.6844 (3)	0.0209 (8)
C10	0.2931 (6)	0.5577 (5)	0.8024 (3)	0.0232 (8)
C11	0.5815 (6)	0.3663 (5)	0.6922 (3)	0.0222 (8)
H11	0.6740	0.4208	0.7106	0.027*
C12	0.6458 (6)	0.3151 (5)	0.5755 (3)	0.0219 (8)
H12A	0.6648	0.4169	0.5153	0.026*
H12B	0.7741	0.2171	0.5892	0.026*
C13	0.4954 (6)	0.2585 (5)	0.5273 (3)	0.0216 (8)
C14	0.2919 (6)	0.4055 (5)	0.5156 (3)	0.0221 (8)
H14	0.3080	0.5151	0.4617	0.027*
C15	0.1646 (6)	0.3489 (6)	0.4480 (4)	0.0292 (9)
H15A	0.0559	0.4523	0.4033	0.035*
H15B	0.1078	0.2660	0.5031	0.035*
C16	0.3102 (7)	0.2569 (7)	0.3618 (4)	0.0316 (10)
H16	0.3105	0.1333	0.3805	0.038*
C17	0.5185 (6)	0.2469 (5)	0.3958 (3)	0.0250 (8)
C18	0.2725 (6)	0.4016 (6)	0.9070 (3)	0.0259 (9)
H18A	0.4002	0.3350	0.9487	0.039*
H18B	0.2302	0.3236	0.8753	0.039*
H18C	0.1744	0.4486	0.9623	0.039*
C19	0.4888 (6)	0.0800 (5)	0.6065 (4)	0.0259 (8)
H19A	0.6203	−0.0098	0.6118	0.039*
H19B	0.3950	0.0452	0.5718	0.039*
H19C	0.4467	0.0911	0.6860	0.039*
C20	0.6843 (7)	0.0783 (6)	0.3841 (3)	0.0292 (9)
C21	0.8967 (7)	0.0674 (6)	0.3984 (4)	0.0303 (9)
H21A	0.9392	0.0136	0.4828	0.036*
H21B	0.9035	0.1878	0.3747	0.036*
C22	0.2484 (7)	0.3444 (8)	0.2323 (4)	0.0407 (12)
H22A	0.2391	0.4681	0.2123	0.061*
H22B	0.1196	0.3380	0.2187	0.061*
H22C	0.3465	0.2835	0.1824	0.061*
C23	0.6442 (6)	0.4129 (6)	0.2236 (4)	0.0270 (9)
C24	0.6687 (6)	0.5826 (6)	0.1769 (3)	0.0283 (9)
C25	0.6224 (8)	0.7257 (7)	0.2194 (4)	0.0365 (11)
H25	0.5562	0.7402	0.2908	0.044*
C26	0.6917 (9)	0.8484 (8)	0.1368 (5)	0.0454 (12)
H26	0.6805	0.9624	0.1410	0.054*
C27	0.7770 (9)	0.7719 (8)	0.0508 (4)	0.0458 (13)
H27	0.8377	0.8254	−0.0164	0.055*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.0335 (5)	0.0205 (4)	0.0240 (4)	−0.0117 (4)	0.0070 (4)	−0.0055 (3)
Cl2	0.0385 (6)	0.0442 (7)	0.0362 (5)	−0.0074 (5)	0.0061 (4)	−0.0202 (5)
O1	0.051 (2)	0.034 (2)	0.072 (3)	−0.0163 (17)	0.0299 (19)	−0.0300 (17)
O2	0.0299 (16)	0.0251 (15)	0.0227 (14)	−0.0030 (12)	−0.0009 (11)	−0.0054 (11)

O3	0.0302 (15)	0.0276 (15)	0.0202 (13)	−0.0115 (12)	0.0056 (11)	−0.0088 (11)
O4	0.0461 (19)	0.0337 (18)	0.0404 (17)	−0.0174 (15)	0.0083 (14)	−0.0203 (14)
O5	0.0363 (17)	0.0384 (18)	0.0213 (13)	−0.0111 (14)	0.0039 (12)	−0.0116 (12)
O6	0.0410 (18)	0.048 (2)	0.0239 (14)	−0.0202 (15)	0.0136 (13)	−0.0105 (13)
O7	0.0344 (17)	0.059 (2)	0.0310 (16)	−0.0013 (16)	0.0009 (14)	−0.0240 (16)
C1	0.027 (2)	0.028 (2)	0.0226 (18)	−0.0087 (18)	0.0086 (16)	−0.0112 (16)
C2	0.036 (2)	0.037 (3)	0.033 (2)	−0.020 (2)	0.0123 (18)	−0.0173 (19)
C3	0.041 (3)	0.028 (2)	0.035 (2)	−0.013 (2)	0.0197 (19)	−0.0144 (18)
C4	0.030 (2)	0.024 (2)	0.030 (2)	−0.0021 (18)	0.0117 (17)	−0.0047 (16)
C5	0.024 (2)	0.023 (2)	0.0210 (17)	−0.0045 (16)	0.0077 (15)	−0.0030 (15)
C6	0.022 (2)	0.029 (2)	0.029 (2)	−0.0030 (17)	0.0049 (16)	−0.0048 (16)
C7	0.023 (2)	0.032 (2)	0.0266 (19)	−0.0084 (17)	0.0000 (15)	−0.0078 (16)
C8	0.0214 (19)	0.025 (2)	0.0228 (18)	−0.0095 (16)	0.0034 (15)	−0.0079 (15)
C9	0.025 (2)	0.0184 (19)	0.0196 (17)	−0.0098 (16)	0.0037 (15)	−0.0042 (14)
C10	0.025 (2)	0.021 (2)	0.0236 (19)	−0.0069 (16)	0.0023 (15)	−0.0081 (15)
C11	0.023 (2)	0.024 (2)	0.0218 (19)	−0.0087 (17)	0.0021 (15)	−0.0092 (15)
C12	0.023 (2)	0.021 (2)	0.0230 (18)	−0.0062 (16)	0.0028 (15)	−0.0095 (15)
C13	0.028 (2)	0.022 (2)	0.0198 (17)	−0.0125 (16)	0.0030 (15)	−0.0081 (14)
C14	0.023 (2)	0.026 (2)	0.0192 (18)	−0.0124 (17)	0.0008 (15)	−0.0042 (15)
C15	0.025 (2)	0.040 (2)	0.0276 (19)	−0.014 (2)	0.0021 (17)	−0.0136 (17)
C16	0.033 (2)	0.043 (3)	0.026 (2)	−0.017 (2)	0.0012 (18)	−0.0159 (18)
C17	0.032 (2)	0.026 (2)	0.0219 (18)	−0.0145 (18)	0.0032 (15)	−0.0084 (15)
C18	0.026 (2)	0.030 (2)	0.0191 (18)	−0.0083 (17)	0.0047 (15)	−0.0048 (15)
C19	0.031 (2)	0.023 (2)	0.0251 (19)	−0.0114 (17)	0.0015 (16)	−0.0057 (15)
C20	0.040 (2)	0.031 (2)	0.0204 (18)	−0.0141 (19)	0.0040 (17)	−0.0105 (16)
C21	0.035 (2)	0.032 (2)	0.0273 (19)	−0.010 (2)	0.0011 (18)	−0.0155 (17)
C22	0.034 (2)	0.061 (3)	0.027 (2)	−0.016 (2)	−0.0029 (19)	−0.012 (2)
C23	0.0220 (19)	0.034 (2)	0.0214 (18)	−0.0051 (17)	0.0023 (15)	−0.0084 (17)
C24	0.028 (2)	0.040 (2)	0.0172 (18)	−0.0122 (19)	0.0034 (15)	−0.0072 (16)
C25	0.049 (3)	0.045 (3)	0.023 (2)	−0.025 (2)	0.0108 (19)	−0.0115 (18)
C26	0.063 (4)	0.047 (3)	0.037 (2)	−0.034 (3)	0.006 (2)	−0.010 (2)
C27	0.058 (3)	0.061 (3)	0.026 (2)	−0.037 (3)	0.013 (2)	−0.006 (2)

Geometric parameters (Å, º)

Cl1—C9	1.840 (4)	C11—H11	1.0000
Cl2—C21	1.782 (4)	C12—C13	1.531 (5)
O1—C3	1.227 (6)	C12—H12A	0.9900
O2—C11	1.413 (5)	C12—H12B	0.9900
O2—H2	0.83 (3)	C13—C14	1.542 (6)
O3—C23	1.344 (5)	C13—C19	1.543 (5)
O3—C17	1.452 (5)	C13—C17	1.568 (5)
O4—C20	1.204 (6)	C14—C15	1.531 (6)
O5—C23	1.213 (5)	C14—H14	1.0000
O6—C27	1.361 (7)	C15—C16	1.562 (6)
O6—C24	1.372 (5)	C15—H15A	0.9900
O7—H7A	0.84 (3)	C15—H15B	0.9900
O7—H7B	0.82 (3)	C16—C22	1.516 (6)

C1—C2	1.334 (6)	C16—C17	1.557 (6)
C1—C10	1.501 (6)	C16—H16	1.0000
C1—H1	0.9500	C17—C20	1.538 (6)
C2—C3	1.461 (7)	C18—H18A	0.9800
C2—H2A	0.9500	C18—H18B	0.9800
C3—C4	1.462 (7)	C18—H18C	0.9800
C4—C5	1.338 (7)	C19—H19A	0.9800
C4—H4	0.9500	C19—H19B	0.9800
C5—C6	1.505 (7)	C19—H19C	0.9800
C5—C10	1.514 (6)	C20—C21	1.527 (6)
C6—C7	1.526 (6)	C21—H21A	0.9900
C6—H6A	0.9900	C21—H21B	0.9900
C6—H6B	0.9900	C22—H22A	0.9800
C7—C8	1.532 (6)	C22—H22B	0.9800
C7—H7C	0.9900	C22—H22C	0.9800
C7—H7D	0.9900	C23—C24	1.447 (6)
C8—C14	1.524 (5)	C24—C25	1.357 (7)
C8—C9	1.543 (6)	C25—C26	1.408 (7)
C8—H8	1.0000	C25—H25	0.9500
C9—C11	1.562 (5)	C26—C27	1.345 (8)
C9—C10	1.581 (5)	C26—H26	0.9500
C10—C18	1.567 (6)	C27—H27	0.9500
C11—C12	1.541 (5)		

C11—O2—H2	107 (4)	C8—C14—C15	118.6 (3)
C23—O3—C17	120.4 (3)	C8—C14—C13	113.1 (3)
C27—O6—C24	105.2 (4)	C15—C14—C13	103.8 (3)
H7A—O7—H7B	104 (7)	C8—C14—H14	106.9
C2—C1—C10	124.4 (4)	C15—C14—H14	106.9
C2—C1—H1	117.8	C13—C14—H14	106.9
C10—C1—H1	117.8	C14—C15—C16	104.4 (3)
C1—C2—C3	121.0 (4)	C14—C15—H15A	110.9
C1—C2—H2A	119.5	C16—C15—H15A	110.9
C3—C2—H2A	119.5	C14—C15—H15B	110.9
O1—C3—C2	121.1 (5)	C16—C15—H15B	110.9
O1—C3—C4	121.8 (4)	H15A—C15—H15B	108.9
C2—C3—C4	117.1 (4)	C22—C16—C17	115.5 (4)
C5—C4—C3	122.6 (4)	C22—C16—C15	113.0 (4)
C5—C4—H4	118.7	C17—C16—C15	105.7 (3)
C3—C4—H4	118.7	C22—C16—H16	107.4
C4—C5—C6	122.8 (4)	C17—C16—H16	107.4
C4—C5—C10	122.2 (4)	C15—C16—H16	107.4
C6—C5—C10	115.0 (3)	O3—C17—C20	111.3 (3)
C5—C6—C7	110.0 (3)	O3—C17—C16	111.6 (3)
C5—C6—H6A	109.7	C20—C17—C16	113.4 (3)
C7—C6—H6A	109.7	O3—C17—C13	104.5 (3)
C5—C6—H6B	109.7	C20—C17—C13	112.0 (3)
C7—C6—H6B	109.7	C16—C17—C13	103.4 (3)

H6A—C6—H6B	108.2	C10—C18—H18A	109.5
C6—C7—C8	111.4 (3)	C10—C18—H18B	109.5
C6—C7—H7C	109.4	H18A—C18—H18B	109.5
C8—C7—H7C	109.4	C10—C18—H18C	109.5
C6—C7—H7D	109.4	H18A—C18—H18C	109.5
C8—C7—H7D	109.4	H18B—C18—H18C	109.5
H7C—C7—H7D	108.0	C13—C19—H19A	109.5
C14—C8—C7	110.8 (3)	C13—C19—H19B	109.5
C14—C8—C9	109.7 (3)	H19A—C19—H19B	109.5
C7—C8—C9	112.8 (3)	C13—C19—H19C	109.5
C14—C8—H8	107.8	H19A—C19—H19C	109.5
C7—C8—H8	107.8	H19B—C19—H19C	109.5
C9—C8—H8	107.8	O4—C20—C21	120.3 (4)
C8—C9—C11	112.0 (3)	O4—C20—C17	121.7 (4)
C8—C9—C10	112.2 (3)	C21—C20—C17	117.5 (4)
C11—C9—C10	115.0 (3)	C20—C21—Cl2	111.1 (3)
C8—C9—Cl1	108.7 (3)	C20—C21—H21A	109.4
C11—C9—Cl1	103.3 (3)	Cl2—C21—H21A	109.4
C10—C9—Cl1	104.8 (3)	C20—C21—H21B	109.4
C1—C10—C5	112.7 (3)	Cl2—C21—H21B	109.4
C1—C10—C18	106.1 (3)	H21A—C21—H21B	108.0
C5—C10—C18	106.8 (3)	C16—C22—H22A	109.5
C1—C10—C9	111.1 (3)	C16—C22—H22B	109.5
C5—C10—C9	106.9 (3)	H22A—C22—H22B	109.5
C18—C10—C9	113.2 (3)	C16—C22—H22C	109.5
O2—C11—C12	109.2 (3)	H22A—C22—H22C	109.5
O2—C11—C9	110.4 (3)	H22B—C22—H22C	109.5
C12—C11—C9	112.9 (3)	O5—C23—O3	124.0 (4)
O2—C11—H11	108.0	O5—C23—C24	126.5 (4)
C12—C11—H11	108.0	O3—C23—C24	109.5 (4)
C9—C11—H11	108.0	C25—C24—O6	110.4 (4)
C13—C12—C11	112.7 (3)	C25—C24—C23	132.7 (4)
C13—C12—H12A	109.0	O6—C24—C23	116.8 (4)
C11—C12—H12A	109.0	C24—C25—C26	106.5 (4)
C13—C12—H12B	109.0	C24—C25—H25	126.7
C11—C12—H12B	109.0	C26—C25—H25	126.7
H12A—C12—H12B	107.8	C27—C26—C25	106.3 (5)
C12—C13—C14	108.8 (3)	C27—C26—H26	126.9
C12—C13—C19	111.4 (3)	C25—C26—H26	126.9
C14—C13—C19	111.9 (3)	C26—C27—O6	111.6 (4)
C12—C13—C17	117.2 (3)	C26—C27—H27	124.2
C14—C13—C17	99.3 (3)	O6—C27—H27	124.2
C19—C13—C17	107.7 (3)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2···O7^{i}	0.83 (3)	1.88 (3)	2.706 (4)	171 (6)

O7—H7*A*···O5	0.84 (3)	2.06 (4)	2.850 (4)	158 (7)
O7—H7*B*···O1$^{\mathrm{ii}}$	0.82 (3)	1.99 (4)	2.740 (5)	152 (7)

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