



Synthesis, crystal structure, and *in silico* molecular docking studies of 4-hydroxy-3,5-dimethoxybenzaldehyde (6-chloropyridazin-3-yl)hydrazone monohydrate

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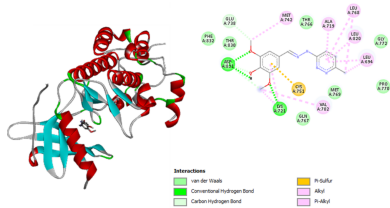
Supporting information: this article has supporting information at journals.iucr.org/e

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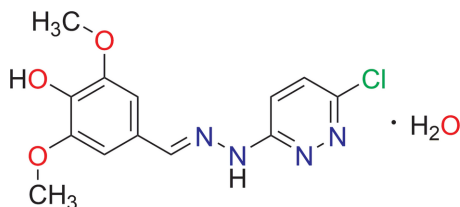
In the title compound, C₁₃H₁₃ClN₄O₃·H₂O, the organic molecule has an *E* configuration with regard to the C=N bond of the hydrazone bridge. The phenyl and pyridazine rings subtend a dihedral angle of 2.1 (1)° between their mean planes, while the hydrazone moiety makes dihedral angles of 1.6 (2) and 3.0 (2)°, respectively, with these aromatic rings. This renders the entire molecule comparably flat. A C—H···N hydrogen bond generates an inversion dimer with a large *R*₂²(14) ring motif. Within this ring, a further C—H···N hydrogen bond establishes a smaller *R*₂²(8) ring. The molecules of a dimer are thereby firmly linked by four hydrogen bonds. A bifurcated O—H···(O,O) hydrogen bond is formed between a water hydrogen atom and the hydroxyl and methoxy oxygen atoms of an adjacent molecule, leading to the formation of an *R*₂¹(5) membered ring. C—H···π and face-to-face π–π stacking interactions are also present in the two-dimensional framework, which may be of relevance for the packing. In a complementary analysis, the compound was docked *in silico* to EGFR and HER2 receptors and the results imply that the compound targets EGFR preferentially over HER2.

1. Chemical context

Hydrazone compounds are known to be associated with a wide spectrum of biological and medicinal applications, such as antimicrobial, anticonvulsant, analgesic and anti-inflammatory activities (NizamMohideen *et al.*, 2019). Compounds that target the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2) are known as tyrosine kinase inhibitors (TKIs) include gefitinib, erlotinib, neratinib, and afatinib, which act as anticancer agents (Uribe *et al.*, 2021; Weinberg *et al.*, 2020). However, these inhibitors show side effects and have adverse negative impacts on the patient's health (Riecke & Witzel, 2020). As a result, new EGFR inhibitors need to be developed that would be more effective with less toxicity. Pyridazine derivatives have been the subject of extensive study in recent years, and the results have demonstrated a broad spectrum of pharmacological actions, including antidepressant (Komkov *et al.*, 2015), COX-2 inhibitor (Harris *et al.*, 2004) and anticancer properties (Rafi *et al.*, 2019; Ahmad *et al.*, 2010). Commercially available physiologically active compounds with pyridazine as a structural component are hydralazine (vasodilator), minaprine (antidepressant), and azelastine (bronchodilator) (Contreras *et al.*, 1999; del Olmo *et al.*, 2006). Our current research is focused on the synthesis of a new compound



containing a pyridazine unit and a syringaldehyde derived moiety linked by a hydrazone motif, which may potentially act as a better TKI.



2. Structural commentary

The molecular structure of the title compound is illustrated in Fig. 1. The organic molecule features a central, essentially planar region flanked on either side by a chlorine-substituted pyridazine, and a trisubstituted phenyl ring and it crystallized together with a water molecule. The phenyl and pyridazine rings (C6–C11 and N1/N2/C1–C4, respectively) are each planar with a dihedral angle of 2.1 (1)° between their mean planes. The mean plane through the hydrazone unit (N3/N4/C5) forms angles of 1.6 (2) and 3.0 (2)° with the phenyl and pyridazine rings, respectively. In the title compound, the hydrazone molecule adopts an *E* configuration with regard to the hydrazone bridge N4=C5, with torsion angles N3–N4–C5–C6 of –178.3 (2)° and C4–N3–N4–C5 of 178.5 (2)°, which are consistent with the *trans* relationship in the central moiety (Table 1). The bond lengths and angles in the hydrazone functional group of the title compound are comparable with the values reported for related structures (NizamMohideen *et al.*, 2019; Prabhu *et al.*, 2011). The chlorine and hydroxy oxygen atoms deviate by –0.05 and 0.15 Å, respectively, from their pyridazine and phenyl ring mean planes. The C4–N3 and C5=N4 bond lengths differ by 0.075 Å, whereby these two bonds may be assigned as localized single and double bonds, respectively, while some resonance effects cannot be firmly excluded. One of the two methoxy groups is more coplanar with the C5–C11 phenyl ring

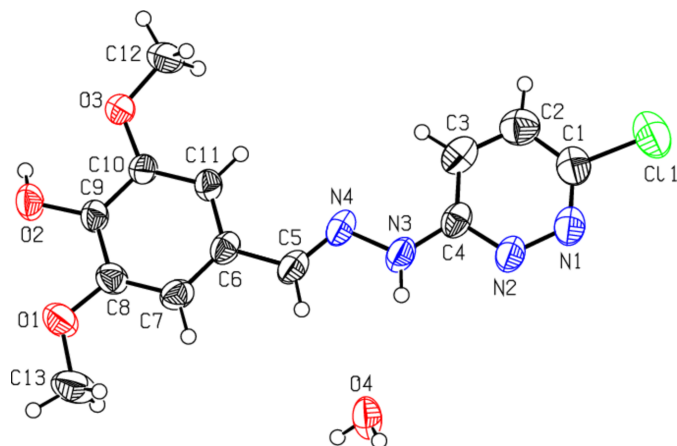


Figure 1

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

Table 1

Selected geometric parameters (Å, °).

C4–N3	1.353 (2)	N1–N2	1.350 (2)
C5–N4	1.278 (2)	N3–N4	1.3769 (17)
C4–N3–N4	121.38 (15)	C5–N4–N3	113.84 (14)
N4–C5–C6–C11	1.3 (2)	C4–N3–N4–C5	–178.52 (15)
C3–C4–N3–N4	–2.2 (3)	C7–C8–O1–C13	8.3 (3)
C6–C5–N4–N3	–178.31 (14)	C11–C10–O3–C12	5.9 (3)

Table 2

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>
C5–H5···N1 ⁱ	0.93	2.60	3.519 (2)	172
C12–H12A···N4 ⁱⁱ	0.96	2.66	3.369 (2)	132
O2–H2O···O4	0.85 (2)	1.84 (2)	2.668 (2)	164 (2)
N3–H3N···N2 ⁱ	0.87 (2)	2.12 (2)	2.993 (2)	178.3 (18)
O4–H4W···O1 ⁱⁱⁱ	0.79 (3)	2.23 (3)	2.9254 (19)	146 (3)
O4–H4W···O2 ⁱⁱⁱ	0.79 (3)	2.55 (3)	3.239 (2)	147 (3)
O4–H5W···O2 ^{iv}	0.85 (3)	2.08 (3)	2.914 (2)	169 (3)
C12–H12B···Cg(C6–C11) ^v	0.96	2.87	3.671 (1)	142
C13–H13B···Cg(C6–C11) ^{iv}	0.96	2.90	3.666 (1)	138

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

than the other one, which deviates somewhat from the benzene ring plane, with torsion angles C12–O3–C10–C11 of 5.9 (3) Å and C13–O1–C8–C7 of 8.3 (3) Å.

3. Supramolecular features

Extensive hydrogen bonding plus some van der Waals contacts are the dominant interactions in the crystal packing (Table 2). The C5–H5···N1 hydrogen bond generates an inversion dimer with an $R_2^2(14)$ ring motif (Bernstein *et al.*, 1995); within this larger ring the C3–H3N···N2 hydrogen bond links the molecules into an $R_2^2(8)$ ring motif. The two molecules of one dimer are therefore firmly connected by four hydrogen bonds. In addition, a bifurcated O4–H4W···(O2, O1)($-x + 1, -y + 1, -z + 2$) hydrogen bond is formed between the water hydrogen atom and the hydroxyl and methoxy oxygen atoms of an adjacent organic molecule, leading to the formation of an $R_2^1(5)$ ring. The same water molecule forms another hydrogen bond to the hydroxyl oxygen atom [O4–H5W···O2($x, y + 1, z$)] of a different adjacent molecule. As acceptor, the water forms a hydrogen bond within the asymmetric unit: O2–H2O···O4. All in all, the water molecules link the hydrogen-bonded dimers throughout the crystal structure into a 3D network, one dimension of which is shown in Fig. 2. Potentially C–H··· π interactions (Table 2) and/or off-centre face-to-face π – π stacking interaction [Cg1···Cg1($\frac{1}{2} - x, -\frac{1}{2} - y, 1 - z$) = 4.374 (2) with slippage of 2.929 Å, where Cg1 is the centroid of the N1/N2/C1–C4 ring] may contribute to a two-dimensional substructure. As a result of the presence of a twofold screw axis ($\frac{1}{2} - x, -\frac{1}{2} + y, \frac{3}{2} - z$), which does not lie in the plane of the organic molecule, the latter appears in two orientations relative to the cell dimensions, resulting in a folded sheet arrangement with an inter-planar angle of 88.45°,

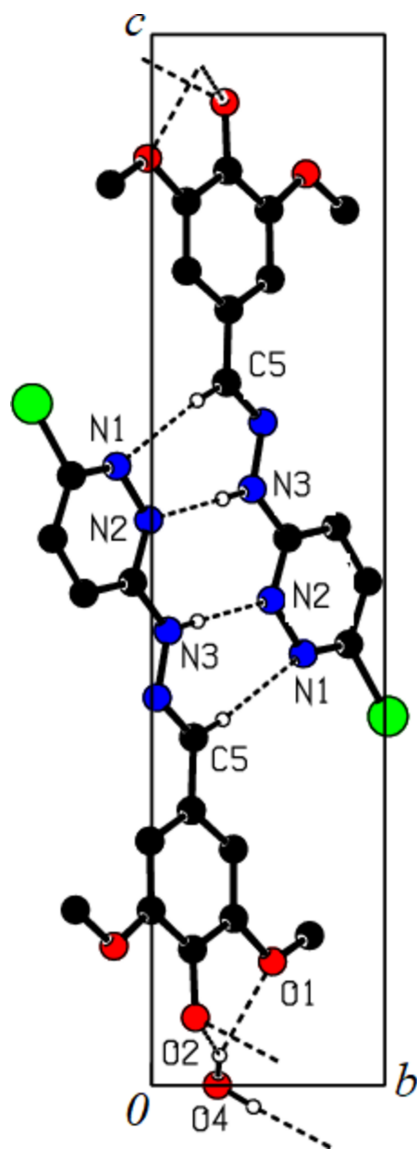


Figure 2
A view along the *a* axis of the crystal packing of title compound. Hydrogen bonds (Table 2) are shown as dashed lines, and H atoms not involved in hydrogen bonding were omitted for clarity.

when all atoms of the two aromatic rings and the hydrazone moiety are used to calculate the planes.

4. Database survey

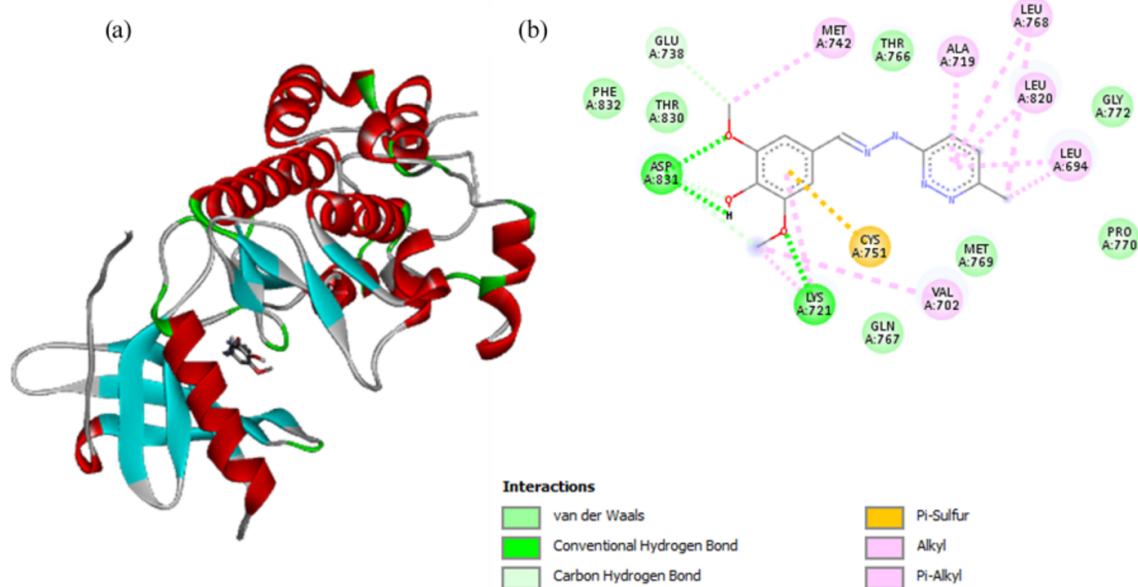
A survey of the Cambridge Structural Database (CSD, Version 5.38; Groom *et al.*, 2016) for the presence of 3-(2-benzylidenehydrazinyl)pyridazine as the main skeleton revealed three structures as closely related to the title compound. The molecule of DUTQUF (Ather *et al.*, 2010) is much less planar than the title compound. However, the bidirectional N—H···N hydrogen bonding is present here as well, albeit twisted because of the non-planarity. Chlorine acts as a hydrogen-bonding acceptor. In GUTYEB01 (Bakale *et al.*, 2018), the molecule is also less planar due to the torsion of the nitro group, and the aromatic systems are not as coplanar

as in the title compound. It is the only one of the three related compounds that has co-crystallized water. Hydrogen bonding involving water forms dimers of molecules. The three-dimensional hydrogen-bonding network is facilitated by including chloride as hydrogen-bonding acceptor from water O—H, phenyl C—H and hydrazine N—H. Lastly, the KUZSOP (Rafi *et al.*, 2016) molecule is less planar than the title compound in its general scaffold but more planar than the other two. It is the only one of the three related derivatives that has the exact same hydrogen-bonding pattern for the N—H···N contacts as found in the title compound. Additional C—H···O interactions lead to band structures, which protrude indefinitely through the crystal structure and are not connected to any adjacent bands. This means that the hydrogen-bonding network is two-dimensional considering the molecular dimensions and one-dimensional considering the band dimension, which is a unique feature among the four structures. All compounds have N—H···N bonds except GUTYEB01, while KUZSOP has overall similar types of hydrogen bonds (C—H···N and O—H···N) as the title compound. The N—C—N—N torsion angle between the pyridazine ring and hydrazine moiety of the title compound are comparable with those in DUTQUF and GUTYEB01 but differs slightly more from that in KUZSOP. The C—C—N—N torsion angles between the phenyl ring and hydrazine moiety of the title compound are comparable with all three compounds. Most of the bond angles of the title compound have close similarities with all three compounds, except for N—N—H and N—C—N, which may be attributed to the formation of hydrogen bonding involving these atoms.

5. Molecular docking studies

The main factors in determining the binding affinity and the efficacy of a new drug molecule are hydrogen bonding and hydrophobic interactions. Hydrogen bonds play an important role in drug-receptor interactions, which improve many biological functions (Chen *et al.*, 2016), while the hydrophobic interactions affect a wide range of biological processes. Hence, molecular docking studies were utilized to predict the *in silico* molecular interactions between the compound and the targets, namely, EGFR and HER2 protein receptors. The binding energies of the title compound with these receptors are summarized in Table S2 in the Supporting Information.

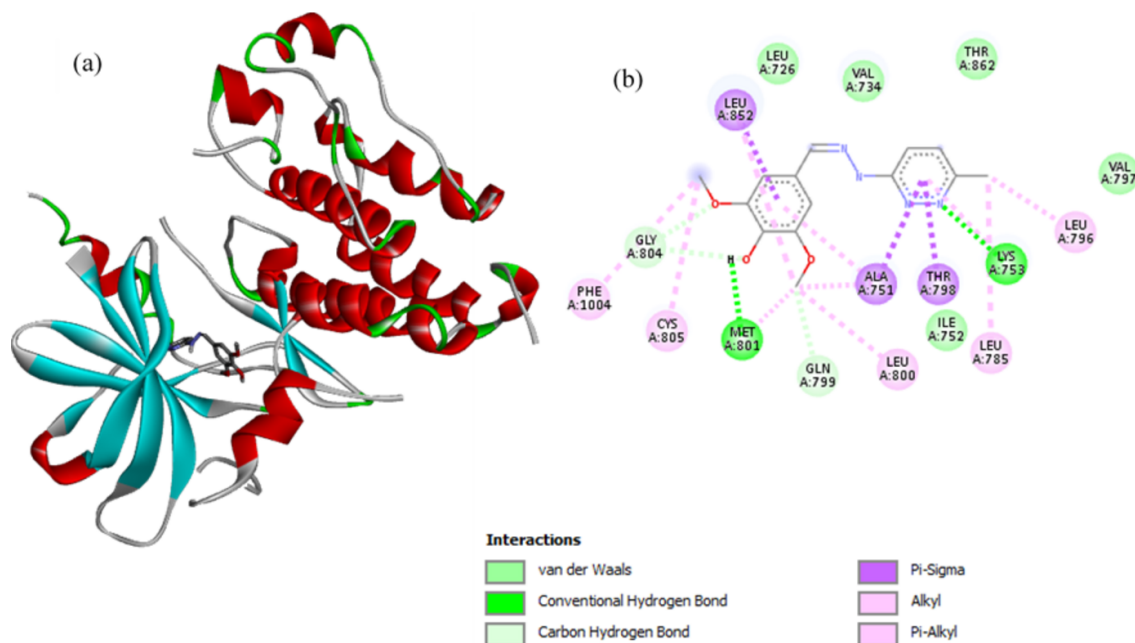
4-Hydroxy-3,5-dimethoxybenzaldehyde (6-chloropyridazin-3-yl)hydrazine exhibits hydrophobic interactions and hydrogen bonding with both the EGFR and HER2 kinases (Figs. 3 and 4). The compound interacts with the EGFR receptor through two hydrogen-bonding interactions, one between the oxygen atoms of the methoxy group with Lys721, and the second between the oxygen atoms of the hydroxyl and methoxy groups with Asp831. The compound shows π -sulfur interactions with residue Cys751, alkyl interactions with residues Leu694, Val702, Lys721 and Met742, as well as van der Waals interactions with residues Glu738, Gln767, Met769, Pro770, Gyl772, The830 and Phe832. The compound interacts with the HER2 receptor through two hydrogen-bonding


Figure 3

(a) Three-dimensional visualization of the binding pose of the compound within the EGFR kinase receptor. (b) Two-dimensional ligand–protein interaction plot of the title compound with the EGFR kinase receptor. Figure prepared using *Discovery Studio Visualizer* (v2021; BIOVIA, 2021).

interactions, the first being the one between the nitrogen atom of the pyridazine ring with Lys753, and the second between the oxygen atom in the hydroxyl group and Met801. Additionally, the compound has π -sigma interactions with residues Ala751, Thr798 and Leu852, alkyl interactions with residues Leu785, Leu796, Leu800, Cys805 and Phe1004, and van der Waals interactions with residues Leu726, Val734, Val797 and Thr862.

Though the title compound interacts through hydrogen bonds and hydrophobic interactions with both the receptors, it has different binding energy values. The compound has a higher binding energy for the EGFR receptor ($-8.43 \text{ kJ mol}^{-1}$) than the HER2 receptor ($-6.88 \text{ kJ mol}^{-1}$). Hence, the compound is tightly bound in the EGFR binding pocket, indicating that it can in principle act as a potent EGFR inhibitor.


Figure 4

(a) Three-dimensional visualization of the binding pose of the compound within the HER2 kinase receptor. (b) Two-dimensional ligand–protein interaction plot of the title compound with the HER2 kinase receptor. Figure prepared using *Discovery Studio Visualizer* (v2021; BIOVIA, 2021).

6. Synthesis and crystallization

An ethanolic solution (25 mL) of syringaldehyde (0.3642 g, 1 mmol) was slowly added to an ethanolic solution (25 mL) of 3-chloro-6-hydrazinopyridazine (0.289 g, 1 mmol) with constant stirring for 1 h and refluxed for 2 h. The obtained clear solution was allowed to stand and the compound crystallized under slow evaporation. Single crystals of the compound suitable for X-ray analysis were recrystallized by slow evaporation from ethanol/water at room temperature. Yellow solid. Yield: 0.4631 g (70.89%), m.p. 528 K. Selected IR data (KBr, cm^{-1}): 3452 ν (OH), 3381 ν (NH), 1695 ν (C=N), 1502 ν (N=N), 1314 ν (Ar—O).

7. Refinement

Crystal data, data collection and structure refinement details, are summarized in Table 3. The water, hydroxyl and NH hydrogen atoms were located in difference-Fourier maps and freely refined. The C-bound H atoms were positioned geometrically and constrained to ride on their parent atoms, with C—H = 0.95–0.98 Å, and with $U_{\text{iso}} = 1.5U_{\text{eq}}(\text{C})$ for methyl H atoms and $1.2U_{\text{eq}}(\text{C})$ for other H atoms.

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Table 3

Experimental details.

Crystal data	
Chemical formula	$\text{C}_{13}\text{H}_{13}\text{ClN}_4\text{O}_3 \cdot \text{H}_2\text{O}$
M_r	326.74
Crystal system, space group	Monoclinic, $C2/c$
Temperature (K)	298
a, b, c (Å)	32.1977 (19), 4.6431 (3), 26.400 (2)
β (°)	127.495 (2)
V (Å ³)	3131.4 (4)
Z	8
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.27
Crystal size (mm)	0.45 × 0.25 × 0.10
Data collection	
Diffractometer	Bruker D8 VENTURE with PHOTON II detector
Absorption correction	Multi-scan (<i>SADABS</i> ; Krause <i>et al.</i> , 2015)
$T_{\text{min}}, T_{\text{max}}$	0.580, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	32222, 3867, 3259
R_{int}	0.052
$(\sin \theta/\lambda)_{\text{max}}$ (Å ⁻¹)	0.666
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.049, 0.132, 1.07
No. of reflections	3867
No. of parameters	215
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å ⁻³)	0.32, -0.27

Computer programs: *APEX3*, *SAINT* and *XPREP* (Bruker, 2016), *SHELXT2018/2* (Sheldrick, 2015a), *SHELXL2019/3* (Sheldrick, 2015b), *ORTEP-3 for Windows* and *WinGX* (Farrugia, 2012), *PLATON* (Spek, 2009) and *publCIF* (Westrip, 2010).

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supporting information

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Computing details

4-Hydroxy-3,5-dimethoxybenzaldehyde (6-chloropyridazin-3-yl)hydrazone monohydrate

Crystal data

$C_{13}H_{13}ClN_4O_3 \cdot H_2O$

$M_r = 326.74$

Monoclinic, $C2/c$

$a = 32.1977$ (19) Å

$b = 4.6431$ (3) Å

$c = 26.400$ (2) Å

$\beta = 127.495$ (2)°

$V = 3131.4$ (4) Å³

$Z = 8$

$F(000) = 1360$

$D_x = 1.386$ Mg m⁻³

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

Cell parameters from 9970 reflections

$\theta = 2.5$ – 28.2 °

$\mu = 0.27$ mm⁻¹

$T = 298$ K

Block, brown

$0.45 \times 0.25 \times 0.10$ mm

Data collection

Bruker D8 VENTURE
diffractometer equipped with PHOTON II
detector

Radiation source: fine-focus sealed tube

ω and φ scan

Absorption correction: multi-scan
(SADABS; Krause *et al.*, 2015)

$T_{\min} = 0.580$, $T_{\max} = 0.746$

32222 measured reflections

3867 independent reflections

3259 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.052$

$\theta_{\max} = 28.3$ °, $\theta_{\min} = 3.2$ °

$h = -42 \rightarrow 42$

$k = -6 \rightarrow 4$

$l = -35 \rightarrow 35$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.049$

$wR(F^2) = 0.132$

$S = 1.07$

3867 reflections

215 parameters

0 restraints

Primary atom site location: dual

Hydrogen site location: mixed

H atoms treated by a mixture of independent
and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0564P)^2 + 2.0701P]$

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

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

$\Delta\rho_{\max} = 0.32$ e Å⁻³

$\Delta\rho_{\min} = -0.27$ 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>	$U_{\text{iso}}^*/U_{\text{eq}}$
C1	0.12978 (7)	0.8456 (4)	0.41979 (9)	0.0544 (4)
C2	0.14422 (8)	0.9256 (4)	0.47956 (10)	0.0612 (5)
H2	0.125598	1.064179	0.483681	0.073*
C3	0.18687 (8)	0.7917 (4)	0.53169 (9)	0.0570 (4)
H3	0.198656	0.837253	0.572787	0.068*
C4	0.21223 (6)	0.5831 (4)	0.52099 (7)	0.0452 (4)
C5	0.31793 (6)	0.3204 (4)	0.66896 (7)	0.0473 (4)
H5	0.328952	0.194971	0.651841	0.057*
C6	0.34738 (6)	0.3305 (4)	0.73833 (7)	0.0424 (3)
C7	0.39076 (6)	0.1498 (4)	0.77521 (7)	0.0469 (4)
H7	0.400366	0.030334	0.755628	0.056*
C8	0.41951 (6)	0.1486 (4)	0.84109 (7)	0.0448 (3)
C9	0.40516 (5)	0.3252 (3)	0.87054 (6)	0.0411 (3)
C10	0.36127 (6)	0.5033 (3)	0.83331 (7)	0.0397 (3)
C11	0.33270 (6)	0.5085 (3)	0.76741 (7)	0.0411 (3)
H11	0.303949	0.630052	0.742856	0.049*
C12	0.30407 (7)	0.8281 (5)	0.83303 (9)	0.0615 (5)
H12A	0.301109	0.929493	0.862401	0.092*
H12B	0.305110	0.964118	0.806431	0.092*
H12C	0.274442	0.703171	0.806886	0.092*
C13	0.48434 (8)	−0.1772 (5)	0.85738 (12)	0.0732 (6)
H13A	0.514242	−0.283563	0.891218	0.110*
H13B	0.458548	−0.308440	0.825325	0.110*
H13C	0.494847	−0.047217	0.838793	0.110*
N1	0.15369 (6)	0.6503 (4)	0.41076 (7)	0.0542 (4)
N2	0.19538 (6)	0.5134 (3)	0.46188 (6)	0.0509 (3)
N3	0.25458 (6)	0.4304 (4)	0.56743 (6)	0.0515 (4)
N4	0.27767 (5)	0.4770 (3)	0.63098 (6)	0.0470 (3)
O1	0.46277 (5)	−0.0183 (3)	0.88222 (6)	0.0642 (4)
O2	0.43409 (5)	0.3129 (3)	0.93550 (5)	0.0548 (3)
O3	0.35056 (4)	0.6626 (3)	0.86749 (5)	0.0550 (3)
O4	0.44334 (6)	0.7811 (3)	1.00029 (6)	0.0619 (4)
Cl1	0.07736 (2)	1.01427 (14)	0.35124 (3)	0.0811 (2)
H2O	0.4312 (9)	0.472 (5)	0.9495 (11)	0.072 (7)*
H3N	0.2689 (8)	0.304 (4)	0.5582 (9)	0.054 (5)*
H4W	0.4738 (12)	0.791 (6)	1.0283 (15)	0.100 (10)*
H5W	0.4362 (10)	0.937 (6)	0.9796 (13)	0.084 (8)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0465 (8)	0.0610 (10)	0.0545 (9)	-0.0077 (8)	0.0300 (8)	0.0089 (8)
C2	0.0656 (11)	0.0575 (10)	0.0721 (12)	-0.0019 (9)	0.0478 (10)	0.0019 (9)
C3	0.0697 (11)	0.0578 (10)	0.0532 (9)	-0.0107 (9)	0.0425 (9)	-0.0058 (8)
C4	0.0478 (8)	0.0523 (9)	0.0386 (7)	-0.0127 (7)	0.0279 (7)	-0.0030 (6)
C5	0.0485 (8)	0.0610 (10)	0.0361 (7)	-0.0106 (7)	0.0277 (7)	-0.0088 (7)
C6	0.0409 (7)	0.0515 (9)	0.0347 (7)	-0.0104 (6)	0.0230 (6)	-0.0068 (6)
C7	0.0444 (8)	0.0545 (9)	0.0436 (8)	-0.0056 (7)	0.0278 (7)	-0.0133 (7)
C8	0.0360 (7)	0.0463 (8)	0.0431 (8)	0.0007 (6)	0.0194 (6)	-0.0060 (6)
C9	0.0371 (7)	0.0455 (8)	0.0311 (7)	-0.0007 (6)	0.0158 (6)	-0.0040 (6)
C10	0.0356 (7)	0.0461 (8)	0.0331 (7)	-0.0010 (6)	0.0187 (6)	-0.0054 (6)
C11	0.0350 (7)	0.0492 (8)	0.0320 (7)	-0.0006 (6)	0.0168 (6)	-0.0008 (6)
C12	0.0467 (9)	0.0736 (13)	0.0581 (10)	0.0132 (9)	0.0288 (8)	-0.0081 (9)
C13	0.0618 (11)	0.0681 (13)	0.0876 (15)	0.0153 (10)	0.0444 (11)	-0.0102 (11)
N1	0.0475 (7)	0.0687 (10)	0.0404 (7)	-0.0070 (7)	0.0237 (6)	0.0036 (7)
N2	0.0504 (7)	0.0645 (9)	0.0357 (6)	-0.0045 (6)	0.0251 (6)	-0.0007 (6)
N3	0.0536 (8)	0.0668 (9)	0.0330 (6)	-0.0029 (7)	0.0257 (6)	-0.0052 (6)
N4	0.0499 (7)	0.0603 (8)	0.0323 (6)	-0.0128 (6)	0.0258 (6)	-0.0063 (6)
O1	0.0499 (7)	0.0685 (8)	0.0518 (7)	0.0191 (6)	0.0193 (6)	-0.0089 (6)
O2	0.0540 (7)	0.0569 (7)	0.0317 (5)	0.0128 (6)	0.0148 (5)	-0.0027 (5)
O3	0.0473 (6)	0.0731 (8)	0.0345 (5)	0.0169 (6)	0.0197 (5)	-0.0053 (5)
O4	0.0582 (8)	0.0642 (9)	0.0379 (6)	-0.0048 (7)	0.0161 (6)	-0.0042 (6)
Cl1	0.0572 (3)	0.0952 (4)	0.0770 (4)	0.0074 (3)	0.0337 (3)	0.0300 (3)

Geometric parameters (Å, °)

C1—N1	1.302 (2)	C9—C10	1.399 (2)
C1—C2	1.397 (3)	C10—O3	1.3636 (18)
C1—C11	1.7374 (19)	C10—C11	1.3874 (19)
C2—C3	1.366 (3)	C11—H11	0.9300
C2—H2	0.9300	C12—O3	1.415 (2)
C3—C4	1.402 (3)	C12—H12A	0.9600
C3—H3	0.9300	C12—H12B	0.9600
C4—N2	1.343 (2)	C12—H12C	0.9600
C4—N3	1.353 (2)	C13—O1	1.418 (2)
C5—N4	1.278 (2)	C13—H13A	0.9600
C5—C6	1.463 (2)	C13—H13B	0.9600
C5—H5	0.9300	C13—H13C	0.9600
C6—C11	1.392 (2)	N1—N2	1.350 (2)
C6—C7	1.396 (2)	N3—N4	1.3769 (17)
C7—C8	1.386 (2)	N3—H3N	0.87 (2)
C7—H7	0.9300	O2—H2O	0.85 (2)
C8—O1	1.3706 (19)	O4—H4W	0.79 (3)
C8—C9	1.388 (2)	O4—H5W	0.85 (3)
C9—O2	1.3664 (17)		

N1—C1—C2	124.38 (17)	O3—C10—C9	114.20 (12)
N1—C1—C11	115.54 (14)	C11—C10—C9	120.45 (13)
C2—C1—C11	120.07 (16)	C10—C11—C6	119.51 (14)
C3—C2—C1	117.16 (18)	C10—C11—H11	120.2
C3—C2—H2	121.4	C6—C11—H11	120.2
C1—C2—H2	121.4	O3—C12—H12A	109.5
C2—C3—C4	117.59 (17)	O3—C12—H12B	109.5
C2—C3—H3	121.2	H12A—C12—H12B	109.5
C4—C3—H3	121.2	O3—C12—H12C	109.5
N2—C4—N3	113.48 (16)	H12A—C12—H12C	109.5
N2—C4—C3	121.83 (16)	H12B—C12—H12C	109.5
N3—C4—C3	124.68 (15)	O1—C13—H13A	109.5
N4—C5—C6	122.62 (15)	O1—C13—H13B	109.5
N4—C5—H5	118.7	H13A—C13—H13B	109.5
C6—C5—H5	118.7	O1—C13—H13C	109.5
C11—C6—C7	120.26 (13)	H13A—C13—H13C	109.5
C11—C6—C5	122.03 (15)	H13B—C13—H13C	109.5
C7—C6—C5	117.69 (14)	C1—N1—N2	118.93 (15)
C8—C7—C6	119.86 (14)	C4—N2—N1	120.08 (15)
C8—C7—H7	120.1	C4—N3—N4	121.38 (15)
C6—C7—H7	120.1	C4—N3—H3N	121.0 (13)
O1—C8—C7	125.21 (14)	N4—N3—H3N	117.6 (13)
O1—C8—C9	114.48 (13)	C5—N4—N3	113.84 (14)
C7—C8—C9	120.32 (14)	C8—O1—C13	118.39 (15)
O2—C9—C8	118.24 (13)	C9—O2—H2O	109.7 (16)
O2—C9—C10	122.15 (13)	C10—O3—C12	117.64 (12)
C8—C9—C10	119.59 (13)	H4W—O4—H5W	104 (3)
O3—C10—C11	125.35 (13)		
N1—C1—C2—C3	1.1 (3)	C8—C9—C10—C11	-1.3 (2)
C11—C1—C2—C3	-177.81 (14)	O3—C10—C11—C6	-178.86 (15)
C1—C2—C3—C4	-0.7 (3)	C9—C10—C11—C6	1.3 (2)
C2—C3—C4—N2	-0.6 (3)	C7—C6—C11—C10	-0.5 (2)
C2—C3—C4—N3	-179.46 (17)	C5—C6—C11—C10	178.22 (14)
N4—C5—C6—C11	1.3 (2)	C2—C1—N1—N2	-0.1 (3)
N4—C5—C6—C7	-179.98 (15)	C11—C1—N1—N2	178.86 (12)
C11—C6—C7—C8	-0.3 (2)	N3—C4—N2—N1	-179.38 (14)
C5—C6—C7—C8	-179.12 (15)	C3—C4—N2—N1	1.6 (2)
C6—C7—C8—O1	-179.85 (15)	C1—N1—N2—C4	-1.3 (2)
C6—C7—C8—C9	0.4 (2)	N2—C4—N3—N4	178.88 (14)
O1—C8—C9—O2	-1.0 (2)	C3—C4—N3—N4	-2.2 (3)
C7—C8—C9—O2	178.82 (15)	C6—C5—N4—N3	-178.31 (14)
O1—C8—C9—C10	-179.37 (15)	C4—N3—N4—C5	-178.52 (15)
C7—C8—C9—C10	0.4 (2)	C7—C8—O1—C13	8.3 (3)
O2—C9—C10—O3	0.5 (2)	C9—C8—O1—C13	-171.94 (17)
C8—C9—C10—O3	178.88 (15)	C11—C10—O3—C12	5.9 (3)
O2—C9—C10—C11	-179.61 (14)	C9—C10—O3—C12	-174.30 (16)

Hydrogen-bond geometry (\AA , $^\circ$)

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C5—H5 \cdots N1 ⁱ	0.93	2.60	3.519 (2)	172
C12—H12A \cdots N4 ⁱⁱ	0.96	2.66	3.369 (2)	132
O2—H2O \cdots O4	0.85 (2)	1.84 (2)	2.668 (2)	164 (2)
N3—H3N \cdots N2 ⁱ	0.87 (2)	2.12 (2)	2.993 (2)	178.3 (18)
O4—H4W \cdots O1 ⁱⁱⁱ	0.79 (3)	2.23 (3)	2.9254 (19)	146 (3)
O4—H4W \cdots O2 ⁱⁱⁱ	0.79 (3)	2.55 (3)	3.239 (2)	147 (3)
O4—H5W \cdots O2 ^{iv}	0.85 (3)	2.08 (3)	2.914 (2)	169 (3)
C12—H12B \cdots Cg(C6—C11) ^v	0.96	2.87	3.671 (1)	142
C13—H13B \cdots Cg(C6—C11) ^{iv}	0.96	2.90	3.666 (1)	138

Symmetry codes: (i) $-x+1/2, -y+1/2, -z+1$; (ii) $-x+1/2, y+1/2, -z+3/2$; (iii) $-x+1, -y+1, -z+2$; (iv) $x, y+1, z$; (v) $x, y-1, z$.