

## 2-Chloro-4-hydroxyanilinium chloride

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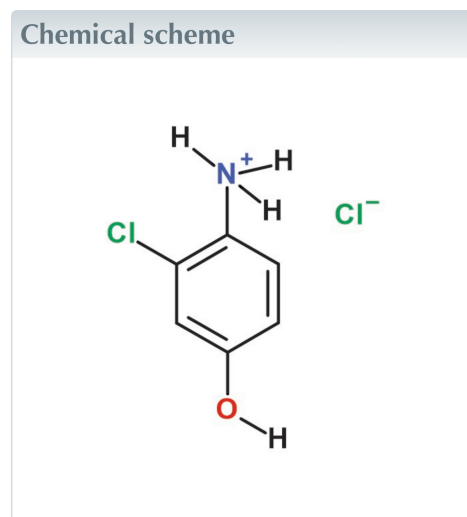
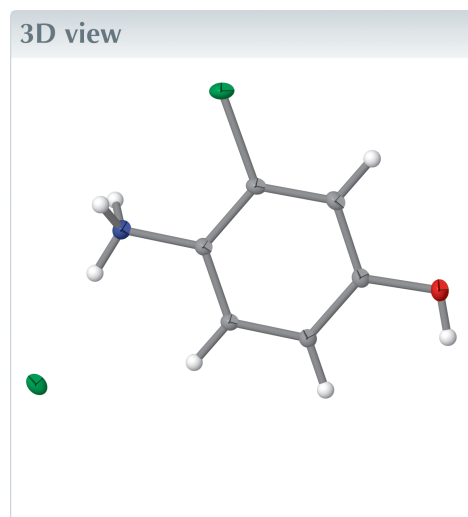
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**Keywords:** crystal structure; 4-amino-3-chloroaniline; lenvatinib and tivozanib; tyrosine kinase inhibitors; anticancer drugs and intermediates.

**CCDC reference:** 2495195

**Structural data:** full structural data are available from [iucrdata.iucr.org](http://iucrdata.iucr.org)

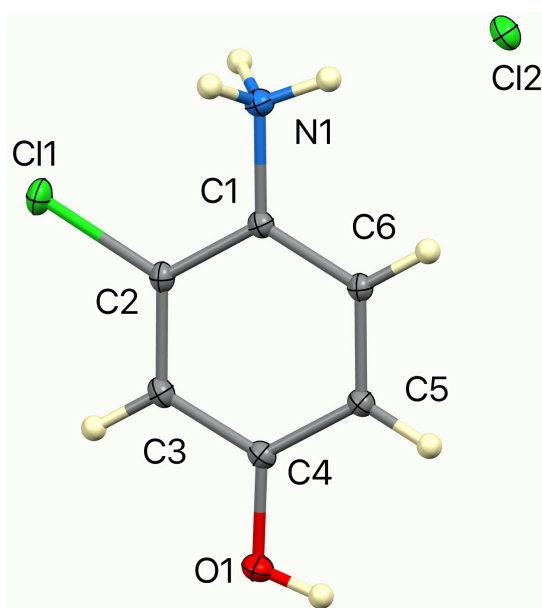
The title compound,  $C_6H_7ClNO^+ \cdot Cl^-$ , crystallizes in orthorhombic space group *Pnma* with both cations and anions lying on a mirror plane in the crystal. The C—Cl distance is 1.7289 (6) Å, the C—N distance is 1.4590 (8) Å, and the C—O distance is 1.3617 (8) Å. Parallel molecules form stacks with interplanar spacing 3.1473 (2) Å, but slipped by 1.97 Å. The  $NH_3^+$  substituent donates three intermolecular hydrogen bonds to chloride ions having  $N \cdots Cl$  distances in the range 3.1514 (6)–3.3019 (2) Å, and the OH group donates an intermolecular hydrogen bond to chloride with  $O \cdots Cl$  distance 3.0671 (6) Å. The chloro substituent and OH group do not accept hydrogen bonds from NH or OH.



### Structure description

4-Hydroxy-2-chloroanilinium chloride is the hydrochloride salt form of the well-established intermediate 4-amino-3-chlorophenol. This compound occupies a central role in pharmaceutical chemistry as a key starting material in the large-scale synthesis of the multikinase inhibitors lenvatinib and tivozanib, which act primarily through potent inhibition of vascular endothelial growth factor receptor (VEGFR) signaling pathways (CN 104326924 A, 2015; EP 3620452A1, 2020; Nair *et al.*, 2015). The simultaneous presence of an aniline amino and a phenolic hydroxyl group renders this scaffold a privileged synthon, particularly suited for the preparation of phenoxy-anilide derivatives. Such derivatives have been widely adopted in kinase inhibitor design and continue to attract attention as versatile structural motifs for next generation anticancer therapeutics (Kumar *et al.*, 2015).

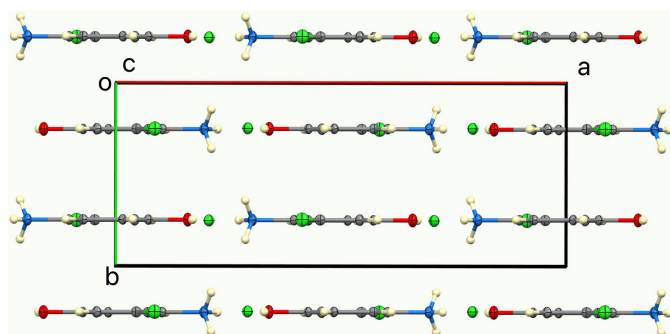
Structural biology investigations have demonstrated that the phenoxy-anilide fragment derived from this intermediate is a critical determinant of VEGFR binding. In lenvatinib, this fragment stabilizes occupancy within the ATP-binding site and an adja-



**Figure 1**  
The asymmetric unit of the title compound with 50% displacement ellipsoids.

cent hydrophobic pocket of VEGFR2 (Pan *et al.*, 2021; Okamoto *et al.*, 2014; Yamamoto *et al.*, 2014), thereby enabling potent inhibition across VEGFR1–3 as well as FGFR1–4. Tivozanib employs the same pharmacophore unit to achieve selective kinase blockade (CN 104326924A, 2015). Beyond these clinical examples, the scaffold continues to be featured in discovery libraries and in the design of dual-target inhibitors. Recent advances have further enhanced its industrial relevance, with continuous-flow synthetic routes improving both safety and efficiency (CN 107739313A, 2020).

Against this background, it was considered that the crystal structure of 4-amino-3-chlorophenol hydrochloride would provide valuable insights into its molecular conformation, hydrogen-bonding patterns, and supramolecular packing. These structural parameters are expected not only to clarify the stability of the salt form, but also to rationalize its synthetic utility in downstream coupling reactions. In view of its broad applications to mechanistic understanding and its potential for new drug development, we therefore undertook an X-ray diffraction study of the title compound at 100 K.



**Figure 2**  
A view of the unit-cell contents, in projection down the *c* axis.

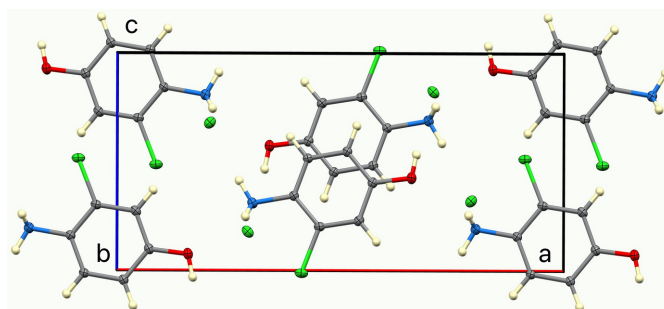
**Table 1**  
Hydrogen-bond geometry (Å, °).

<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>
O1–H1···Cl2 <sup>i</sup>	0.82 (1)	2.25 (1)	3.0671 (6)	177 (2)
N1–H1N···Cl2 <sup>ii</sup>	0.856 (12)	2.531 (13)	3.3019 (2)	150.4 (10)
N1–H2N···Cl2	0.90 (2)	2.25 (2)	3.1514 (6)	176 (1)
C5–H5···Cl2 <sup>i</sup>	0.95	2.90	3.6290 (6)	134
C6–H6···Cl1 <sup>iii</sup>	0.95	2.84	3.5519 (6)	132
C6–H6···Cl2	0.95	2.84	3.6195 (6)	140
C6–H6···Cl1 <sup>iii</sup>	0.95	2.84	3.5519 (6)	132

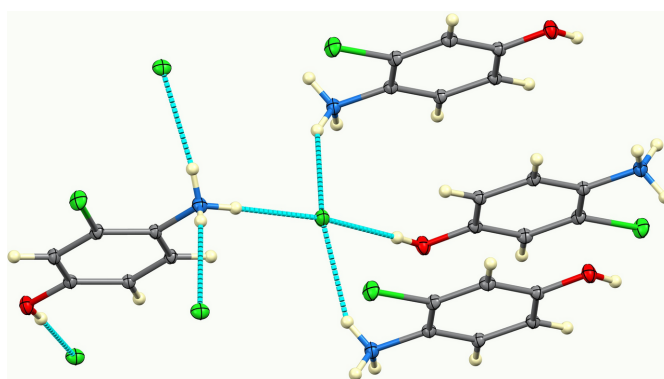
Symmetry codes: (i)  $x + \frac{1}{2}, y, -z + \frac{3}{2}$ ; (ii)  $-x + \frac{1}{2}, -y + 2, z - \frac{1}{2}$ ; (iii)  $x, y, z + 1$ .

The ellipsoids and atom numbering are shown in Fig. 1. Both cations and anions lie on a mirror plane, thus, except for two ammonium H atoms related by the mirror, the cation is rigorously planar, and all cations are parallel. This is shown in Fig. 2, a view of the unit cell down the *c* axis. The interplanar spacing is half the *b* axial length, 3.1473 (2) Å, but cations related by an inversion center are horizontally slipped by 1.97 Å, as shown in the view down the *b* axis, Fig. 3.

Hydrogen bonding from both the NH<sub>3</sub><sup>+</sup> and OH donors involve chloride only as the acceptor, not the chloro substituent nor the OH group. As shown in Fig. 4, the ammonium group donates to three different chloride ions, and the OH group donates to a fourth. Thus, chloride accepts four hydrogen bonds from NH and OH. There are longer C–H···Cl interactions to both chloride and the chloro substituent, as detailed in Table 1.



**Figure 3**  
A view of the unit-cell contents, in projection down the *b* axis.



**Figure 4**  
Hydrogen bonding shown as dashed bonds.

## Synthesis and crystallization

4-Hydroxy-2-chloroanilinium chloride (CAS 52671-64-4; purity: 98%) was obtained from AmBeed, Buffalo Grove, IL and was used without further purification. Crystallization was performed in ethanol by slow cooling of a hot, nearly saturated solution. The sample was clarified by filtration using Whatman #1 filter paper. Single crystals of the title compound were colorless needles.

## Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. Three reflections were omitted because of beamstop problems.

## Funding information

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**Table 2**

Experimental details.

Crystal data	
Chemical formula	C <sub>6</sub> H <sub>7</sub> ClNO <sup>+</sup> ·Cl <sup>-</sup>
<i>M<sub>r</sub></i>	180.03
Crystal system, space group	Orthorhombic, <i>Pnma</i>
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	15.5044 (4), 6.2945 (2), 7.5260 (2)
<i>V</i> (Å <sup>3</sup> )	734.48 (4)
<i>Z</i>	4
Radiation type	Ag <i>Kα</i> , λ = 0.56086 Å
μ (mm <sup>-1</sup> )	0.41
Crystal size (mm)	0.28 × 0.20 × 0.15
Data collection	
Diffractometer	Bruker D8 Venture DUO with Photon III C14
Absorption correction	Multi-scan ( <i>SADABS</i> ; Krause <i>et al.</i> , 2015)
<i>T<sub>min</sub></i> , <i>T<sub>max</sub></i>	0.881, 0.940
No. of measured, independent and observed [ <i>I</i> > 2σ( <i>I</i> )] reflections	41806, 3668, 3193
<i>R<sub>int</sub></i>	0.053
(sin θ/λ) <sub>max</sub> (Å <sup>-1</sup> )	1.042
Refinement	
<i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )], <i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>S</i>	0.031, 0.089, 1.05
No. of reflections	3668
No. of parameters	68
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Δρ <sub>max</sub> , Δρ <sub>min</sub> (e Å <sup>-3</sup> )	0.98, -0.50

Computer programs: *APEX5* and *SAINT* (Bruker, 2016), *SHELXT2018/2* (Sheldrick, 2015a), *SHELXL2019/1* (Sheldrick, 2015b), *Mercury* (Macrae *et al.*, 2020) and *publCIF* (Westrip, 2010).

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## full crystallographic data

*IUCrData* (2025). **10**, x250893 [https://doi.org/10.1107/S2414314625008934]

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## 2-Chloro-4-hydroxyanilinium chloride

*Crystal data*

$C_6H_7ClNO^+Cl^-$

$M_r = 180.03$

Orthorhombic, *Pnma*

$a = 15.5044$  (4) Å

$b = 6.2945$  (2) Å

$c = 7.5260$  (2) Å

$V = 734.48$  (4) Å<sup>3</sup>

$Z = 4$

$F(000) = 368$

$D_x = 1.628$  Mg m<sup>-3</sup>

Ag *Kα* radiation,  $\lambda = 0.56086$  Å

Cell parameters from 9968 reflections

$\theta = 3.0$ – $35.2^\circ$

$\mu = 0.41$  mm<sup>-1</sup>

$T = 100$  K

Needle fragment, colourless

$0.28 \times 0.20 \times 0.15$  mm

*Data collection*

Bruker D8 Venture DUO with Photon III C14 diffractometer

Radiation source: *I* $\mu$ S 3.0 microfocus

$\varphi$  and  $\omega$  scans

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

$T_{\min} = 0.881$ ,  $T_{\max} = 0.940$

41806 measured reflections

3668 independent reflections

3193 reflections with  $I > 2\sigma(I)$

$R_{\text{int}} = 0.053$

$\theta_{\max} = 35.8^\circ$ ,  $\theta_{\min} = 3.0^\circ$

$h = -32 \rightarrow 32$

$k = -13 \rightarrow 11$

$l = -14 \rightarrow 15$

*Refinement*

Refinement on  $F^2$

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.031$

$wR(F^2) = 0.089$

$S = 1.05$

3668 reflections

68 parameters

1 restraint

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0489P)^2 + 0.0955P]$

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

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

$\Delta\rho_{\max} = 0.98$  e Å<sup>-3</sup>

$\Delta\rho_{\min} = -0.50$  e Å<sup>-3</sup>

*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.

**Refinement.** All H atoms were located in difference maps and those on C were thereafter treated as riding in geometrically idealized positions with C—H distances of 0.95 Å. The coordinates of the N—H and O—H hydrogen atoms were refined, with the O—H distance restrained to 0.85 Å.  $U_{\text{iso}}(\text{H})$  values were assigned as  $1.2U_{\text{eq}}$  for the attached atom (1.5 for  $\text{NH}_3$  and OH).

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ( $\text{\AA}^2$ )*

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
Cl1	0.41328 (2)	0.750000	−0.01348 (2)	0.01726 (4)
O1	0.65937 (3)	0.750000	0.42625 (8)	0.01557 (9)
H1	0.6701 (10)	0.750000	0.5329 (19)	0.023*
N1	0.30340 (4)	0.750000	0.30926 (8)	0.01320 (8)
H1N	0.2875 (7)	0.857 (2)	0.2467 (14)	0.020*
H2N	0.2735 (10)	0.750000	0.412 (2)	0.020*
C1	0.39608 (4)	0.750000	0.34282 (8)	0.01067 (8)
C2	0.45356 (4)	0.750000	0.20074 (8)	0.01172 (8)
C3	0.54184 (4)	0.750000	0.22936 (8)	0.01262 (9)
H3	0.580887	0.750000	0.132087	0.015*
C4	0.57223 (4)	0.750000	0.40361 (8)	0.01128 (8)
C5	0.51515 (4)	0.750000	0.54682 (8)	0.01106 (8)
H5	0.536501	0.750000	0.665132	0.013*
C6	0.42714 (4)	0.750000	0.51543 (8)	0.01064 (8)
H6	0.387967	0.750000	0.612496	0.013*
Cl2	0.20751 (2)	0.750000	0.67846 (2)	0.01519 (4)

*Atomic displacement parameters ( $\text{\AA}^2$ )*

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
Cl1	0.01969 (8)	0.02336 (9)	0.00874 (6)	0.000	−0.00069 (4)	0.000
O1	0.00992 (15)	0.0218 (2)	0.01502 (19)	0.000	0.00072 (13)	0.000
N1	0.01106 (17)	0.0165 (2)	0.01204 (18)	0.000	−0.00098 (14)	0.000
C1	0.01023 (17)	0.0120 (2)	0.00982 (18)	0.000	0.00045 (14)	0.000
C2	0.0131 (2)	0.0133 (2)	0.00879 (17)	0.000	0.00073 (15)	0.000
C3	0.0121 (2)	0.0145 (2)	0.01128 (19)	0.000	0.00239 (15)	0.000
C4	0.01043 (17)	0.01161 (19)	0.0118 (2)	0.000	0.00095 (14)	0.000
C5	0.01029 (17)	0.0120 (2)	0.01085 (18)	0.000	0.00049 (14)	0.000
C6	0.01086 (18)	0.0119 (2)	0.00919 (18)	0.000	0.00044 (13)	0.000
Cl2	0.01500 (7)	0.01586 (7)	0.01472 (7)	0.000	0.00405 (4)	0.000

*Geometric parameters ( $\text{\AA}$ ,  $^\circ$ )*

Cl1—C2	1.7289 (6)	C1—C2	1.3919 (8)
O1—C4	1.3617 (8)	C2—C3	1.3856 (9)
O1—H1	0.820 (14)	C3—C4	1.3935 (9)
N1—C1	1.4590 (8)	C3—H3	0.9500
N1—H1N	0.856 (12)	C4—C5	1.3946 (8)
N1—H2N	0.899 (15)	C5—C6	1.3848 (8)
N1—H1N <sup>i</sup>	0.856 (12)	C5—H5	0.9500

C1—C6	1.3854 (8)	C6—H6	0.9500
C4—O1—H1	108.8 (12)	C2—C3—C4	118.71 (6)
C1—N1—H1N	112.3 (7)	C2—C3—H3	120.6
C1—N1—H2N	111.1 (10)	C4—C3—H3	120.6
H1N—N1—H2N	108.8 (9)	O1—C4—C3	116.96 (6)
C1—N1—H1N <sup>i</sup>	112.3 (7)	O1—C4—C5	122.20 (6)
H1N—N1—H1N <sup>i</sup>	103.2 (15)	C3—C4—C5	120.84 (6)
H2N—N1—H1N <sup>i</sup>	108.8 (9)	C6—C5—C4	119.57 (6)
C6—C1—C2	119.86 (6)	C6—C5—H5	120.2
C6—C1—N1	120.31 (5)	C4—C5—H5	120.2
C2—C1—N1	119.84 (5)	C5—C6—C1	120.16 (5)
C3—C2—C1	120.86 (6)	C5—C6—H6	119.9
C3—C2—C11	120.12 (5)	C1—C6—H6	119.9
C1—C2—C11	119.02 (5)		

Symmetry code: (i)  $x, -y+3/2, z$ .

#### Hydrogen-bond geometry ( $\text{\AA}, ^\circ$ )

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O1—H1 $\cdots$ C12 <sup>ii</sup>	0.82 (1)	2.25 (1)	3.0671 (6)	177 (2)
N1—H1N $\cdots$ C12 <sup>iii</sup>	0.856 (12)	2.531 (13)	3.3019 (2)	150.4 (10)
N1—H2N $\cdots$ C12	0.90 (2)	2.25 (2)	3.1514 (6)	176 (1)
C5—H5 $\cdots$ C12 <sup>ii</sup>	0.95	2.90	3.6290 (6)	134
C6—H6 $\cdots$ C11 <sup>iv</sup>	0.95	2.84	3.5519 (6)	132
C6—H6 $\cdots$ C12	0.95	2.84	3.6195 (6)	140
C6—H6 $\cdots$ C11 <sup>iv</sup>	0.95	2.84	3.5519 (6)	132

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