Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

An inhibitor of Janus kinase 3: 4-(4-hydroxyphenylamino)-6,7-dimethoxyquinazolin-1-ium chloride methanol solvate

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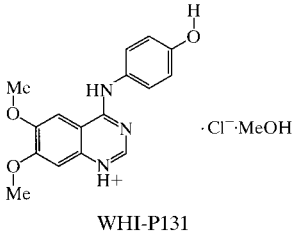
Received 1 February 2000
Accepted 22 May 2000

The crystal structure of the title compound, $C_{16}H_{16}N_3O_3^+\cdot Cl^-\cdot CH_4O$ (WHI-P131, an inhibitor of Janus kinase 3), contains four hydrogen bonds. There are two hydrogen bonds within the asymmetric unit, *i.e.* interactions between WHI-P131 OH and Cl^-, and between methanol and Cl^-. There is a third interaction between WHI-P131 NH and Cl^- (related by a 2_1 screw) and a fourth between WHI-P131 NH and methanol (related by an *n*-glide). The hydrogen-bond pattern for these interactions can be described by the first-level hydrogen-bond graph-set notation $D_1^1(2)D_1^1(2)D_1^1(2)D_1^1(2)$. The second-level graph-set notation (for combinations of two hydrogen bonds) was determined to be $D_2^1(3)D_2^1(3)D_2^2(4)D_2^2(9)D_2^2(14)C_2^1(9)$.

Comment

The title compound, WHI-P131 (Fig. 1), inhibited the kinase activity of Janus kinase 3 (JAK3), with an IC_{50} of 9.1 μ*M* (Sudbeck *et al.*, 1999). Although WHI-P131 inhibited JAK3, it did not inhibit the Janus kinases JAK1 and JAK2, the ZAP/SYK family tyrosine kinase SYK, the TEC family tyrosine kinase BTK, the SRC family tyrosine kinase LYN or the receptor family tyrosine kinase IRK, even at concentrations as high as 350 μ*M*. The relatively high potency and selectivity of WHI-P131 for JAK3 makes it a promising candidate for new treatment strategies against acute lymphoblastic leukemia, the most common form of childhood cancer. In addition to its antileukemic properties, WHI-P131 also shows clinical potential for the treatment of mast-cell-mediated immediate hypersensitivity reactions and allergic disorders (Malaviya *et al.*, 1999).



WHI-P131

The crystal structure of WHI-P131 contains four different hydrogen bonds: N1—H1···O4, N4—H4···Cl1, O3—H3···Cl1 and O4—H26···Cl1 (Fig. 2 and Table 2). Each of these can be described in graph-set notation (Bernstein *et al.*, 1990, 1995; Etter, 1990, 1991; Etter *et al.*, 1990) as $D_1^1(2)$ (Fig. 2). The second-level motif combining the N1—H1···O4 and N4—H4···Cl1 hydrogen bonds is $D_2^2(9)$, that combining

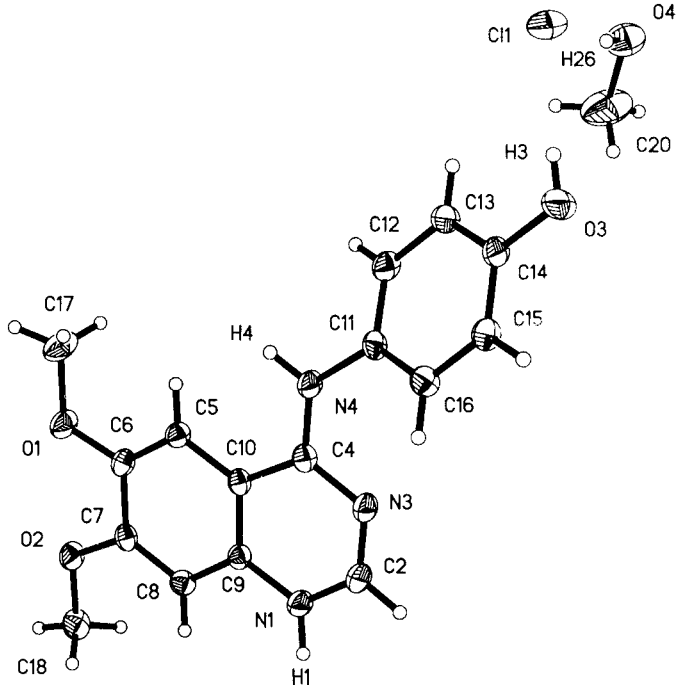


Figure 1
The X-ray crystal structure of WHI-P131 (30% probability displacement ellipsoids, T = 297 K).

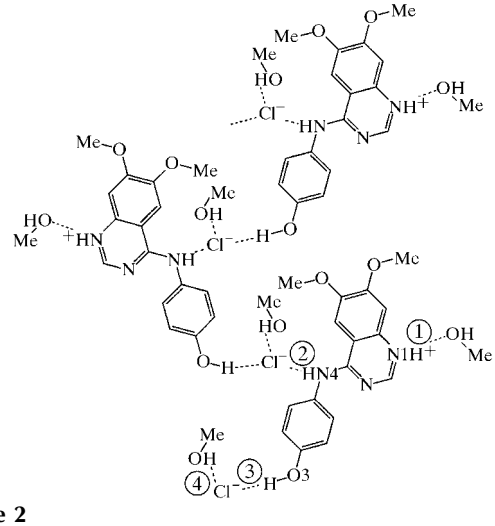


Figure 2
Hydrogen-bond patterns observed in WHI-P131. Four hydrogen bonds (labeled 1–4) are observed in the crystal structure. The complete first-level hydrogen-bond graph-set pattern is $D_1^1(2)D_1^1(2)D_1^1(2)D_1^1(2)$ and the second-level pattern is $D_2^1(3)D_2^1(3)D_2^2(4)D_2^2(9)D_2^2(14)C_2^1(9)$.

N4—H4···Cl1 and O3—H3···Cl1 is $C_2^1(9)$, and that combining N1—H1···O4 and O3—H3···Cl1 is $D_2^2(14)$. The combination of N1—H1···O4 and O4—H26···Cl1 can be described as a $D_2^2(4)$ pattern, N4—H4···Cl1 plus O4—H26···Cl1 forms a $D_2^1(3)$ pattern, and O3—H3···Cl1 plus O4—H26···Cl1 is $D_2^1(3)$. The complete first-level hydrogen-bond graph-set notation for WHI-P131 is $D_1^1(2)D_1^1(2)D_1^1(2)$-$D_1^1(2)$ and the second-level graph-set notation (for combinations of two hydrogen bonds) is $D_2^1(3)D_2^1(3)D_2^2(4)D_2^2(9)$-$D_2^2(14)C_2^1(9)$.

An alternative way to describe the two-dimensional hydrogen-bonded network in the crystal of WHI-P131 is $C_2^1(9)C_3^2(15)$, which combines the second-level motif for N4—H4···Cl1 and O3—H3···Cl1, $C_2^1(9)$, and the third-level motif for O4—H16···Cl1, O3—H3···Cl1 and N1—H1···O4, $C_3^2(15)$.

Experimental

Yellow needles of WHI-P131 were grown from methanol/dichloromethane by vapor diffusion at room temperature. The hydrochloride salt crystallized as a methanol solvate.

Crystal data

$C_{16}H_{16}N_3O_3^+\cdot Cl^-\cdot CH_4O$
M_r = 365.81
Monoclinic, $P2_1/n$
a = 7.4128 (7) Å
b = 10.7752 (10) Å
c = 22.337 (2) Å
β = 97.538 (2)°
V = 1768.8 (3) Å^3
Z = 4
D_x = 1.374 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2622 reflections
θ = 2.64–25.01°
μ = 0.243 mm^{-1}
T = 297 (2) K
Needle, yellow
0.45 × 0.15 × 0.12 mm

Data collection

CCD area-detector diffractometer
φ and ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.90, T_{max} = 0.97
8982 measured reflections
3117 independent reflections
2087 reflections with $I > 2\sigma(I)$
R_{int} = 0.050
θ_{max} = 25°
$h = -8 \rightarrow 8$
$k = -12 \rightarrow 12$
$l = -26 \rightarrow 22$
101 standard reflections
intensity decay: −0.06%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.12
S = 0.99
3117 reflections
239 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0672P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.33 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N3—C2	1.303 (3)	O4—C20	1.404 (4)
N3—C4	1.356 (3)	N4—C4	1.330 (3)
O3—C14	1.375 (3)	N4—C11	1.433 (3)
C17—O1—C6—C5	7.6 (4)	C4—N4—C11—C16	−38.2 (4)
C18—O2—C7—C8	−5.4 (3)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H26···Cl1			3.024 (2)	
O3—H3···Cl1			3.064 (2)	
N1—H1···O4^{i}	0.93 (3)	1.81 (3)	2.742 (3)	179 (2)
N4—H4···Cl1^{ii}	0.88 (3)	2.39 (3)	3.206 (2)	155 (2)

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

Table 3
First- and second-level graph-set motifs for hydrogen bonds in WHI-P131.

	O4—H26···Cl1	O3—H3···Cl1	N1—H1···O4	N4—H4···Cl1
O4—H26···Cl1	$D_1^1(2)$	$D_2^1(3)$	$D_2^2(4)$	$D_2^1(3)$
O3—H3···Cl1		$D_1^1(2)$	$D_2^2(14)$	$C_1^2(9)$
N1—H1···O4			$D_1^1(2)$	$D_2^2(9)$
N4—H4···Cl1				$D_1^1(2)$

H atoms were placed at calculated positions, except for H1 and H4, which were located in the electron-density difference map and were refined isotropically. The hydroxyl H3 and H26 atoms were not observed in the electron-density map but were included at calculated positions based on an assessment of the best hydrogen-bond interactions to nearby N, O or Cl atoms.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SHELXTL* (Bruker, 1998); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1527). Services for accessing these data are described at the back of the journal.

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