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4-[(3-Bromo-4-hydroxyphenyl)amino]-6,7-dimethoxyquinazolin-1-ium chloride methanol solvate and 4-[(3-hydroxyphenyl)amino]-6,7-dimethoxy-1-quinazolinium chloride

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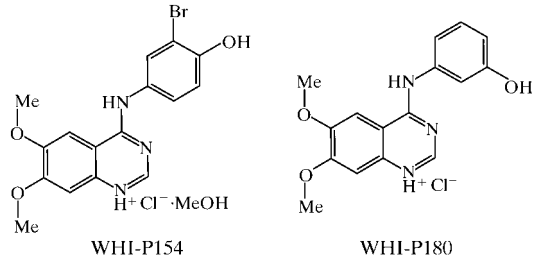
The title compounds, $C_{16}H_{15}BrN_3O_3^+\cdot Cl^-\cdot CH_4O$ (WHI–P154) and $C_{16}H_{16}N_3O_3^+\cdot Cl^-$ (WHI–P180), are potent inhibitors [WHI–P154 with IC_{50} = 5.6 μ*M* and WHI–P180 with IC_{50} = 4.0 μ*M* for epidermal growth factor receptor (EGFR) kinase inhibition] of the EGFR tyrosine kinase as well as Janus Kinase 3. The molecular structures of these compounds are very similar except for the dihedral angle between the anilino and quinazoline moieties which is 1.10 (5)° for WHI–P154, and 45.66 (6) and 25.29 (7)° for the two molecules of WHI–P180 in the asymmetric unit. The nitrogen at the N3 position is protonated in both structures and participates in hydrogen bonding with the chlorine anions.

Comment

The development of inhibitors of the epidermal growth factor receptor and Janus Kinase 3 (JAK3) signalling pathways is an active area of translational cancer research. As part of our ongoing program in structure-based design of anticancer agents, we have designed and synthesized a series of potent 4-anilinoquinazoline derivatives targeting the ATP-binding site of EGFR. Our modeling studies included the construction of a homology model of the EGFR kinase domain (Ghosh *et al.*, 1998) and the use of an advanced docking procedure to predict the energetically favorable positions of the quinazoline derivatives in the EGFR catalytic site (Ghosh *et al.*, 1999). Based on the modeling studies, several 4-anilinoquinazoline derivatives were synthesized and tested for their kinase inhibitory activity on EGFR. The compounds WHI–P154 and WHI–P180 were subsequently found to inhibit EGFR with IC_{50} values of 5.6 and 4.0 μ*M*, respectively, in kinase inhibition assays. The modeling studies (Ghosh *et al.*, 1999) of these compounds with the EGFR kinase domain revealed that the energetically favorable docked position of the quinazoline derivatives at the catalytic site of EGFR is such that the inhibitors maintain a close contact with the hinge region. The anilino group was oriented into the interior of the protein and clamped between the residues Thr^{766} and Asp^{831} from the sides, Thr^{830} from below, and Val^{702} on top, with the 6,7-OCH_3 groups of the inhibitors facing the solvent-accessible region. The torsion angles C12—C7—N1—C6 and C7—N1—C6—C1 in WHI–P154 defining the relative orientation of the quinazoline and anilino moieties were found to be 162.0 and 16.2°, respectively, in the docking studies compared with −176.0 (2) and 175.2 (2)°, respectively, in the crystal structure of WHI–P154. The corresponding torsion angles (C10—C7—N1—C5 and C7—N1—C5—C4) for WHI–P180 were found to be 163.4



WHI-P154 WHI-P180

and 14.0° in docking studies, whereas they are 178.5 (2) and −47.6 (4)° in molecule *A*, and 177.9 (2) and −30.6 (4)° in molecule *B* in the crystal structure of WHI–P180. In docking studies of the title compounds, the N3 atom of the quinazoline group was involved in hydrogen bonding with the backbone carbonyl O atom of Met^{769}, and the OH group on the anilino moiety formed an additional hydrogen bond with Asp^{831} at the EGFR catalytic site. The bridging amino group (N1) was not involved in any hydrogen-bonding interactions with the EGFR catalytic site residues. Some of these compounds also

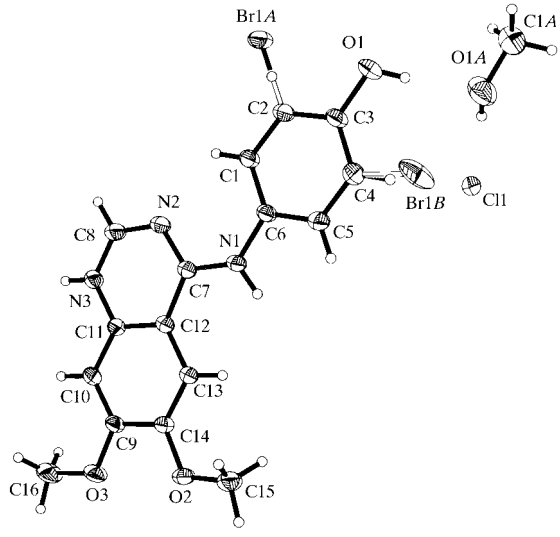


Figure 1
The molecular structure of WHI–P154 illustrating the disorder of the brominated ring and the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level for non-H atoms. H atoms are displayed as small circles of arbitrary radii.

inhibited JAK3 (Sudbeck *et al.*, 1999). This study is the first report of the structural characterization of two such 4-anilinoquinazoline derivatives (WHI–P154 and WHI–P180) which target the catalytic site of the EGFR tyrosine kinase.

The atom-numbering scheme and molecular conformation adopted by the molecules of WHI–P154 and WHI–P180 are shown in Figs. 1 and 2, respectively. There is one molecule of WHI–P154 and two molecules of WHI–P180 in the asymmetric unit and their molecular structures are similar except for the dihedral angle between the anilino and quinazoline

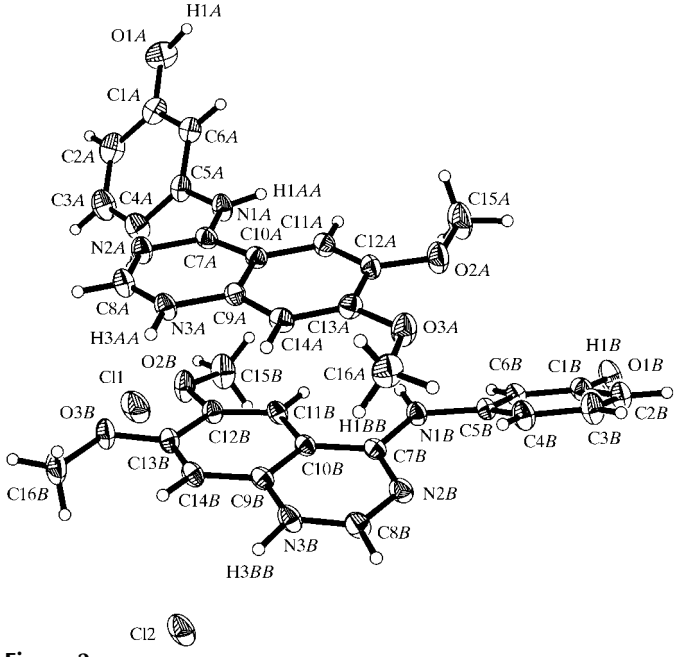


Figure 2
The molecular structures of the two independent molecules of WHI–P180 in the asymmetric unit. Displacement ellipsoids are drawn at the 30% probability level for non-H atoms. H atoms are displayed as small circles of arbitrary radii.

moieties. The dihedral angle between the anilino and quinazoline moieties is 1.10 (5)° for WHI–P154, and 45.66 (6) and 25.29 (7)° for the two molecules of WHI–P180 in the asymmetric unit. The structure of WHI–P154 was found as a chloride salt, with a molecule of methanol solvent in the asymmetric unit. The crystal structure is stabilized by an extensive network of hydrogen bonding as detailed in Table 1. The N3 atom is protonated and all the N and O atoms of the organic group are involved in hydrogen bonding with the chloride anion or the solvent molecule. The Br atom is disordered with major occupancy of 0.974 (1) at position 1*A* and 0.0264 (10) at position 1*B*. The structure of WHI–P180 was also found as an HCl salt. The N3 positions are protonated for both unique organic groups in WHI–P180. In WHI–P154, the NH groups and methanol solvate are involved in hydrogen bonding with the chloride anion and there is an additional hydrogen-bond interaction between the OH group of the phenyl ring and the methanol solvate (Table 1). In WHI–P180, the OH and NH groups are involved in hydrogen bonding with the chloride anion (Table 2).

Experimental

The synthesis and characterization of WHI–P154 and WHI–P180 have been reported earlier (Narla *et al.*, 1998). Single crystals of WHI–P154 were obtained by liquid–liquid diffusion from solutions of methanol and dichloromethane at room temperature and those of WHI–P180 by slow evaporation from a methanol solution at 289 K.

Compound WHI–P154

Crystal data

$C_{16}H_{15}BrN_3O_3^+\cdot Cl^-\cdot CH_4O$
M_r = 444.71
Triclinic, $P\overline{1}$
a = 7.113 (5) Å
b = 9.339 (7) Å
c = 14.526 (10) Å
α = 79.14 (1)°
β = 85.37 (1)°
γ = 86.49 (1)°
V = 943.5 (12) Å^3
Z = 2
D_x = 1.565 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4929 reflections
θ = 2.86–27.1°
μ = 2.35 mm^{-1}
T = 298 (2) K
Needle, yellow
0.42 × 0.29 × 0.06 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.44, T_{max} = 0.87
10811 measured reflections
4245 independent reflections
3230 reflections with $I > 2\sigma(I)$
R_{int} = 0.047
θ_{max} = 27.76°
$h = -9 \rightarrow 9$
$k = -12 \rightarrow 12$
$l = -18 \rightarrow 18$
70 standard reflections
intensity decay: 0.33%

Refinement

Refinement on F^2
$R(F)$ = 0.037
$wR(F^2)$ = 0.100
S = 0.99
4245 reflections
264 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0574P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.008
$\Delta\rho_{max}$ = 0.62 e Å^{-3}
$\Delta\rho_{min}$ = −0.47 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °) for WHI–P154.

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1*B*···O1*A*	0.82	1.83	2.643 (4)	176
O1*A*—H1*AA*···Cl1	0.82	2.32	3.132 (3)	174
N1—H1*A*···Cl1^{i}	0.89 (3)	2.49 (3)	3.333 (3)	158 (2)
N3—H3*A*···Cl1^{ii}	0.86 (3)	2.27 (3)	3.117 (3)	169 (2)

Symmetry codes: (i) $1-x, 2-y, 1-z$; (ii) $1-x, 1-y, 1-z$.

Compound WHI–P180

Crystal data

$C_{16}H_{16}N_3O_3^+\cdot Cl^-$
M_r = 333.77
Triclinic, $P\overline{1}$
a = 9.4851 (7) Å
b = 10.3688 (8) Å
c = 15.9106 (12) Å
α = 90.9540 (10)°
β = 99.1080 (10)°
γ = 95.4380 (10)°
V = 1537.3 (2) Å^3
Z = 4
D_x = 1.442 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3519 reflections
θ = 2.33–24.05°
μ = 0.268 mm^{-1}
T = 297 (2) K
Needle, pale yellow
0.30 × 0.25 × 0.01 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.92, T_{max} = 1.00
16771 measured reflections
6248 independent reflections
3389 reflections with $I > 2\sigma(I)$
R_{int} = 0.049
θ_{max} = 26.39°
$h = -11 \rightarrow 11$
$k = -12 \rightarrow 12$
$l = -19 \rightarrow 19$
59 standard reflections
intensity decay: 0.13%

Refinement

Refinement on F^2
$R(F)$ = 0.043
$wR(F^2)$ = 0.091
S = 0.90
6248 reflections
443 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0357P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.006
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

Table 2
Hydrogen-bonding geometry (Å, °) for WHI–P180.

D—H···A	D—H	H···A	D···A	D—H···A
O1*B*—H1*B*···Cl2^{i}	0.85 (2)	2.28 (2)	3.117 (2)	170 (2)
O1*A*—H1*A*···Cl1^{ii}	0.98 (3)	2.12 (3)	3.095 (2)	176 (3)
N1*B*—H1*BB*···Cl2^{iii}	0.88 (2)	2.47 (2)	3.324 (2)	165.5 (19)
N1*A*—H1*AA*···Cl1^{iii}	0.88 (2)	2.41 (2)	3.261 (2)	163 (2)
N3*B*—H3*BB*···Cl2	0.98 (2)	2.14 (2)	3.088 (2)	162.5 (19)
N3*A*—H3*AA*···Cl1	0.89 (2)	2.26 (2)	3.142 (2)	168 (2)

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

The H atoms attached to the N and O atoms of both compounds appeared well resolved in the difference Fourier maps, and were refined isotropically, with the exception of the H atoms bonded to O1 and O1*A* in WHI–P154, which proved difficult to refine freely. These two H atoms were refined by restrained methods using the *DFIX* command, where the OH distance was restrained to 0.82 Å and their U_{eq} values were allowed to refine freely. All H atoms attached to C atoms were placed in ideal positions and refined using a riding model with aromatic C—H = 0.96 Å and methyl C—H = 0.98 Å, and with fixed isotropic displacement parameters equal to 1.2 (1.5 for methyl H atoms) times the equivalent isotropic displacement parameter of the atom to which they were attached. The methyl groups were allowed to rotate about their local threefold axis during refinement.

For both compounds, data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1998); software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1562). Services for accessing these data are described at the back of the journal.

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