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Risperidone chloride 2.5-hydrate: a new crystalline form

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.002 Å
Disorder in solvent or counterion
R factor = 0.041
wR factor = 0.101
Data-to-parameter ratio = 18.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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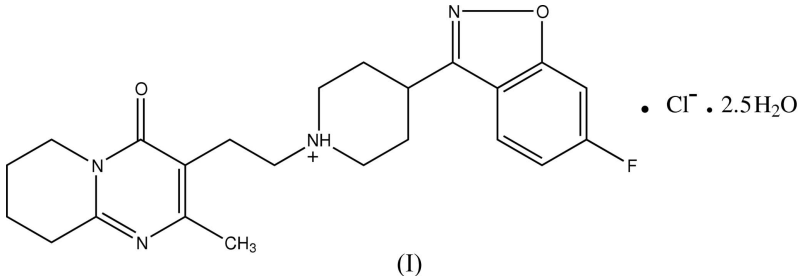
The asymmetric unit of the title compound, $C_{23}H_{28}FN_4O_2^+\cdot Cl^-\cdot 2.5H_2O$, contain one risperidone cation {systematic name: 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-[2-(2-methyl-4-oxo-3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]piperidinium}, one Cl^- anion, and two and a half water molecules. The piperidine ring adopts a chair conformation, while the tetrahydropyridine ring has a sofa conformation. Each Cl^- anion and the water molecules are linked to the risperidone molecules *via* O—H···O, O—H···N, O—H···Cl and N—H···Cl hydrogen bonds which stabilize the crystal packing.

Comment

Risperidone is an antipsychotic agent belonging to a new chemical class of benzisoxazole derivatives, available worldwide since the early 1990s (Callaghan *et al.*, 1999; Kennedy *et al.*, 2000; Tandon, 2002). It has useful central nervous system activity and shows a wide range of therapeutic effects. Pharmaceutical formulations contain solid crystalline risperidone. For this reason, well documented characteristics of its crystalline form are required. To date, four solid forms of risperidone have been reported (Krochmal *et al.*, 2004; Reddy *et al.*, 2004) and characterized by X-ray powder diffraction patterns, but only one of their crystal structures has been determined (Peeters *et al.*, 1993). In the course of our studies, we report here the crystal structure of a new 2.5-hydrate, (I).



(I)

In the structure of (I), there is one risperidone cation, one Cl^- anion and two and half water molecules in the asymmetric unit. The expected proton transfer from hydrochloric acid to risperidone occurs at atom N1 of the piperidine ring. Consequently, atom N1 shows quaternary character and bears a positive charge (Fig. 1). Compound (I) contains a piperidine ring, one end of which is connected to a pyridopyrimidine group *via* an ethyl bridge, while the other end is connected to an almost-planar fluorobenzisoxazole ring system. All bond lengths and angles (Table 1) are in good agreement with those

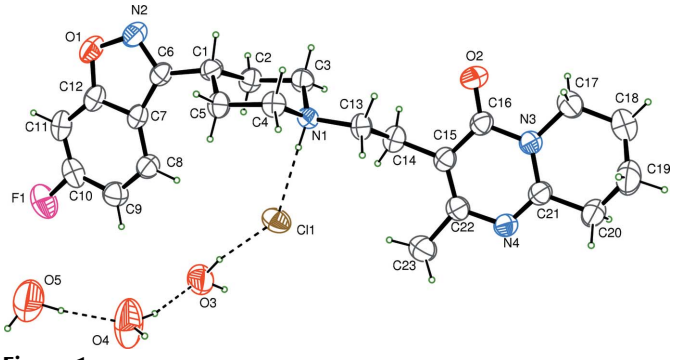


Figure 1
The structure and atom-numbering scheme for the asymmetric unit of (I). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

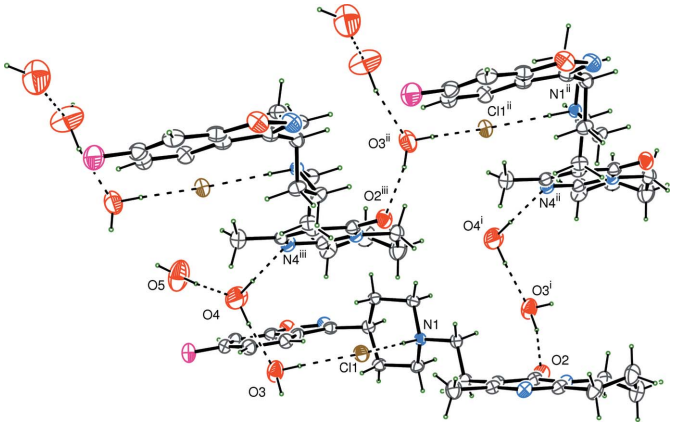


Figure 2
A partial packing diagram for (I), showing the linking of the water molecules, risperidone cations and Cl^- anions. Hydrogen bonds are shown as dashed lines. [Symmetry codes: (i) $1+x, y, z$; (ii) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; (iii) $-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$.]

of risperidone (Peeters *et al.*, 1993) and risperidone *N*-oxide (Ravikumar *et al.*, 2005).

The conformation of compound (I) is also similar to those of the above two compounds. The piperidine ring has the expected chair conformation, atoms C1 and N1 having deviations of 0.631 (2) and −0.710 (2) Å, respectively, from the least-squares plane through the other four atoms. The tetrahydropyridine ring adopts a sofa conformation, similar to that of risperidone *N*-oxide, with atom C19 displaced by 0.578 (3) Å from the mean plane defined by atoms C20/C21/N3/C17/C18. Interestingly, in the structure of risperidone, a half-chair conformation is reported for this ring. Similarly, the ethyl bridge between the piperidine and pyridopyrimine groups has an antiperiplanar conformation, with an N1—C13—C14—C15 torsion angle of 167.1 (1)°. The benzisoxazole ring system is almost planar.

In the crystal structure of the title compound, an elaborate hydrogen-bond network is formed. Each Cl^- anion, each water molecule, two amino groups and one carbonyl group in the risperidone molecule are involved in the hydrogen-bond network (Table 2). O—H···Cl, N—H···Cl, O—H···O and O—H···N hydrogen bonds link three molecules into a ring (Fig. 2), with atoms Cl1, O3 and O4 as a bridge. Meanwhile, a linear hydrogen-bonded chain is formed along the *a* axis (Fig. 3). Atom O5 from a solvent water molecule forms a hydrogen bond with another solvent water molecule, O4. Therefore, atom O5 has a larger displacement parameter. The crystal packing is stabilized by these hydrogen bonds.

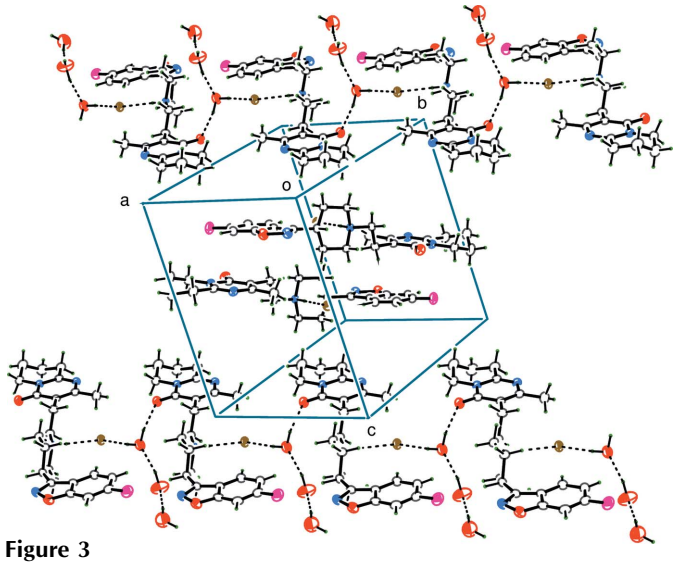


Figure 3
The crystal packing of (I), viewed along the *a* axis. Dashed lines indicate hydrogen bonds.

Experimental

The crude risperidone was supplied by Zhejiang Huahai Pharmaceutical Co. Ltd. The compound was recrystallized from a solution in a mixture of acetone and water (4:1 *v*/*v*), with the pH adjusted to 6–7 using 1.0 mol l^{-1} HCl, giving brown crystals of (I) suitable for X-ray diffraction.

Crystal data

$C_{23}H_{28}FN_4O_2^+\cdot Cl^-\cdot 2.5H_2O$
M_r = 491.99
Monoclinic, $P2_1/n$
a = 10.027 (3) Å
b = 18.431 (4) Å
c = 13.394 (4) Å
β = 100.613 (11)°
V = 2433.0 (11) Å^3
Z = 4
D_x = 1.343 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 19056 reflections
θ = 3.0–27.5°
μ = 0.20 mm^{-1}
T = 298 (1) K
Block, brown
0.30 × 0.26 × 0.20 mm

Data collection

Rigaku R-AXIS RAPID diffractometer
ω scans
Absorption correction: multi-scan (*ABSCOR*; Higashi, 1995)
T_{min} = 0.913, T_{max} = 0.960
23832 measured reflections
5562 independent reflections
3581 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.031
θ_{max} = 27.5°
$h = -13 \rightarrow 12$
$k = -23 \rightarrow 23$
$l = -17 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.102
S = 1.04
5562 reflections
308 parameters
H-atom parameters constrained
$w = 1/[0.0005F_o^2 + \sigma(F_o^2)]/(4F_o^2)$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.51 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 1.0 (2) × 10^2

Table 1
Selected geometric parameters (Å, °).

O1—N2	1.4275 (19)	N2—C6	1.3023 (18)
O1—C12	1.355 (2)	N3—C16	1.4079 (19)
O2—C16	1.2320 (19)	N3—C17	1.483 (2)
N1—C3	1.4929 (19)	N3—C21	1.363 (2)
N1—C4	1.4948 (19)	N4—C21	1.297 (2)
N1—C13	1.5004 (19)	N4—C22	1.3772 (19)
C3—N1—C4	109.77 (10)	C4—N1—C13	111.61 (10)
C3—N1—C13	114.52 (12)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H111···Cl1	0.86	2.17	3.0351 (12)	179
O3—H311···Cl1	0.90	2.21	3.1047 (14)	170
O3—H312···O2^{i}	0.93	1.93	2.8421 (18)	167
O4—H411···O3	0.98	1.95	2.909 (2)	167
O4—H412···N4^{ii}	0.96	2.04	2.997 (2)	178
O5—H511···O4	0.91	1.87	2.775 (4)	173
O5—H512···O4^{iii}	0.92	1.90	2.754 (5)	153
O5—H512···O5^{iii}	0.92	1.85	2.320 (5)	109

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

The H atoms of the amino group and the water molecules were located in difference Fourier maps and included in the refinement based on the as-found N—H and O—H bond lengths, but their isotropic displacement parameters were refined and then fixed in the final stage. All other H atoms were placed in calculated positions, with C—H = 0.93–0.98 Å, and included in the refinement in the riding model, with U_{iso}(H) = 1.2U_{eq}(carrier atom).

Data collection: *PROCESS-AUTO* (Rigaku, 1998); cell refinement: *PROCESS-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC, 2004); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *CrystalStructure*.

References

Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, C. K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Callaghan, J. T., Bergstrom, R. F., Ptak, L. R. & Beasley, C. M. (1999). *Clin. Pharm.* **37**, 177–193.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Higashi, T. (1995). *ABSCOR*. Rigaku Corporation, Tokyo, Japan.

Kennedy, J. S., Bymaster, F. P., Schuh, L., Calligaro, D. O., Nomikos, G., Felder, C. C., Bernauer, M., Kinon, B. J., Baker, R. W., Hay, D., Roth, H. J., Dossenbach, M., Kaiser, C., Beasley, C. M., Holcombe, J. H., Effron, M. B. & Breier, A. (2000). *Int. J. Geriatr. Psych. Suppl. 1*, **16**, S33–S61.

Krochmal, B., Diller, D., Dolitzky, B.-Z. & Aronhime, J. (2004). US Patent No. 2004/0229905.

Larson, A. C. (1970). *Crystallographic Computing*, edited by F. R. Ahmed, S. R. Hall & C. P. Huber, pp. 291–294. Copenhagen: Munksgaard.

Peeters, O. M., Blaton, N. M. & Ranter, C. J. (1993). *Acta Cryst.* C**49**, 1698–1700.

Ravikumar, K., Sridhar, B., Manjunatha, S. G. & Thomas, S. (2005). *Acta Cryst.* E**61**, o2515–o2517.

Reddy, R. B., Ramesh, C., Reddy, T. R. & Kumar, K. V. R. (2004). US Patent No. 2004/0209898.

Rigaku (1998). *PROCESS-AUTO*. Rigaku Corporation, 3-9-12 Akishima, Tokyo 196-8666, Japan.

Rigaku/MSC (2004). *CrystalStructure*. Version 3.6.0. Rigaku/MSC, 9009 New Trails Drive, The Woodlands, TX 77381-5209, USA.

Tandon, R. (2002). *Psychiatr. Q.* **73**, 297–311.