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Key indicators

Single-crystal X-ray study
T = 273 K
Mean $\sigma(\text{C}-\text{C}) = 0.003 \text{ \AA}$
R factor = 0.054
wR factor = 0.156
Data-to-parameter ratio = 13.1For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.Risperidone *N*-oxide hydrogen peroxide methanol solvate

In the crystal structure of the title compound {systematic name: 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-hydroxy-1-[2-(2-methyl-4-oxo-3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]piperidine *N*-oxide hydrogen peroxide methanol solvate}, $\text{C}_{23}\text{H}_{27}\text{FN}_4\text{O}_3 \cdot \text{H}_2\text{O}_2 \cdot \text{CH}_3\text{OH}$, the asymmetric unit contains one molecule of risperidone *N*-oxide, one methanol solvent molecule and one hydrogen peroxide molecule. The piperidine ring adopts a chair conformation, while the tetrahydropyridine ring has a sofa conformation. The hydrogen peroxide molecule links the risperidone molecules to form a chain. $\text{O}-\text{H} \cdots \text{O}$ and $\text{C}-\text{H} \cdots \text{O}$ interactions stabilize the crystal packing.

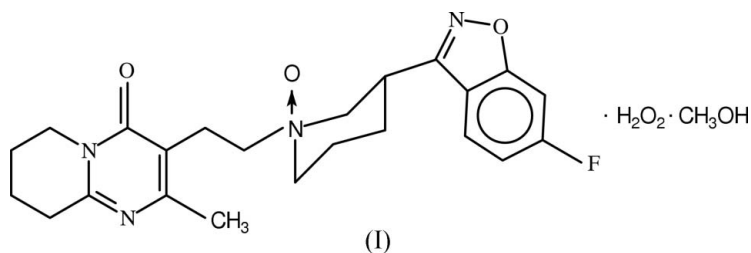
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Comment

Risperidone is a relatively new antipsychotic agent, belonging to the chemical class of benzisoxazole derivatives, available worldwide since the early 1990s. The main pharmacological activities of risperidone include serotonin 5-HT₂ receptor blockade and dopamine D₂ antagonism (Megens, 1994). Recently, Ekins *et al.* (2002) generated a pharmacophore model, based on a three-dimensional quantitative structure activity relationship (three-dimensional QSAR) for the human Ether-a-go gene (hERG), with *in vitro* inhibition data for antipsychotic agents. Their model possessed four hydrophobes and one positive ionizable feature and showed a fit of the model to 9-hydroxyrisperidone, which illustrates an identical observed and predicted IC₅₀. The presence of the positive ionizable domain in the model prompted us to study the structure of risperidone *N*-oxide. The crystal structure determination was undertaken to compare the structural features with that of risperidone itself and with other known serotonin and dopamine antagonists in the hope of obtaining a better insight into its structural features and activity.



The conformation of risperidone *N*-oxide hydrogen peroxide methanol solvate, (I), and the atomic numbering scheme are given in Fig. 1. The asymmetric unit contains one

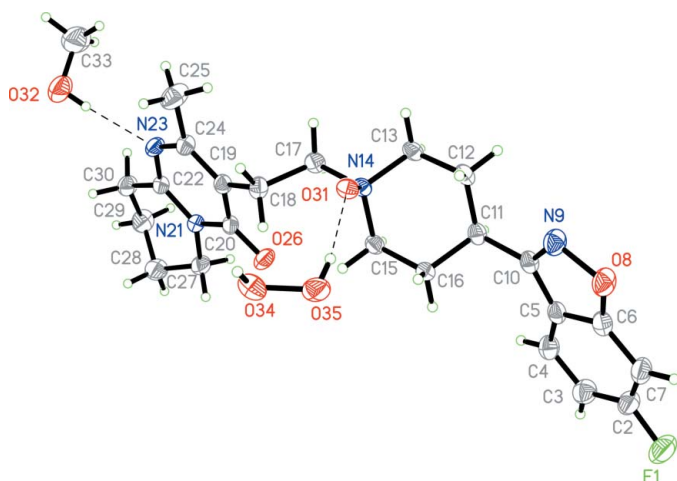


Figure 1

A view of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

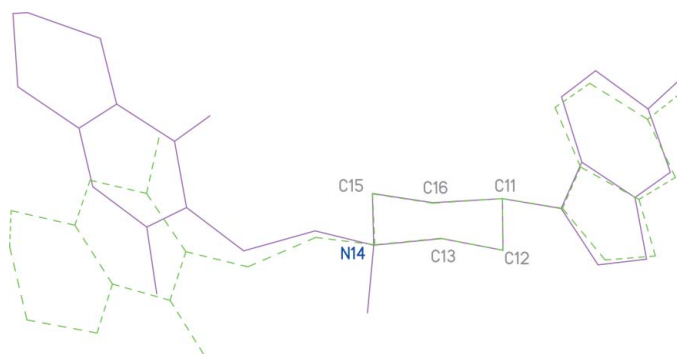


Figure 2

An r.m.s. overlay of risperidone *N*-oxide (solid lines) and risperidone (dashed lines).

molecule of risperidone *N*-oxide, one methanol solvent molecule and, interestingly, one molecule of hydrogen peroxide. Generally, co-crystallization of H_2O_2 with organic molecules is a rare occurrence. Compound (I) contains a hydroxy-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. In all essential details, the molecular geometry (Table 1) is in good agreement with risperidone (Peeters *et al.*, 1993), ocaperidone (Jottier *et al.*, 1992) and pirenperone (Blaton *et al.*, 1995). The O—O bond distance in hydrogen peroxide is in the normal range and similar to the value observed in a comparable structure (Neda *et al.*, 1994)

As expected, the piperidine ring adopts a chair conformation with asymmetry parameter (Nardelli, 1983) $\Delta C_2(\text{C11} - \text{C16}) = 0.004(1) \text{ \AA}$. A chair conformation is also observed in ocaperidone and pirenperone. Atom O31 attached to N14 is in an axial position. The N—O distance is $1.396(2) \text{ \AA}$, which is in the normal range.

The tetrahydropyridine ring adopts a sofa conformation [asymmetry parameter $\Delta C_2(\text{N21} - \text{C22}) = 0.0170(1) \text{ \AA}$], with

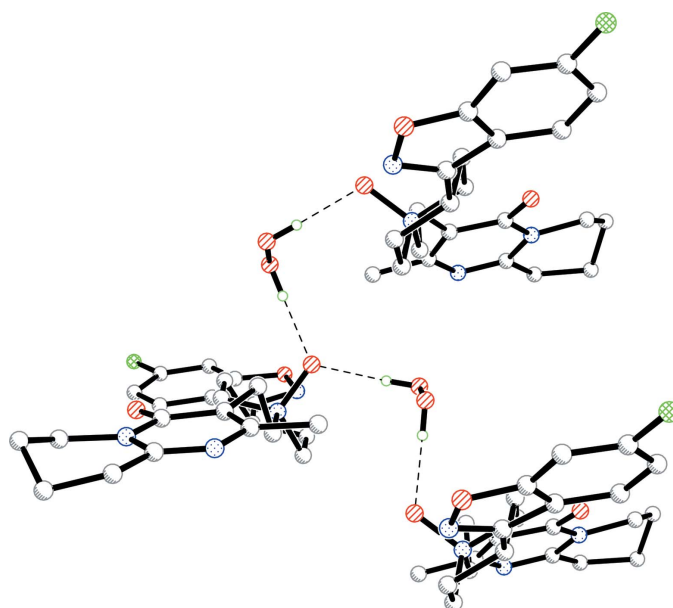


Figure 3

Part of the crystal structure of (I), showing the linking of hydrogen peroxide to the risperidone *N*-oxide molecules (glide-related) by O—H...O hydrogen bonds (dashed lines). H atoms attached to C atoms have been omitted for clarity.

atom C29 displaced by $0.571(3) \text{ \AA}$ from the mean plane defined by the atoms C22/N21/C27/C28/C30. Interestingly, in the risperidone structure, a half-chair conformation is reported for this ring, while it is planar in ocaperidone.

The ethyl bridge between the piperidine ring and pyridopyrimidine group has an antiperiplanar conformation with a torsion angle N14—C17—C18—C19 of $-152.8(2)^\circ$. A similar antiperiplanar conformation is observed in risperidone [$173.8(4)^\circ$], ocaperidone [$163.2(6)$ and $179.4(6)^\circ$] and pirenperone [$-169.9(5)^\circ$]. An r.m.s. overlay using the central piperidine ring atoms (r.m.s. deviation = 0.0213 \AA) of risperidone *N*-oxide and risperidone shows the tilt in the orientation of the pyridopyrimidine ring (Fig. 2).

The benzisoxazole ring system is almost planar, with a maximum out-of-plane deviation from the least-squares plane for atom C2 [$0.012(3) \text{ \AA}$]. The benzisoxazole ring is in an equatorial position [N9—C10—C11—C16 = $-109.2(2)^\circ$] with respect to the piperidine ring.

The hydrogen peroxide molecule links the risperidone molecules through O—H...O bonding (Table 2). The *N*-oxide atom O31 is an acceptor for two hydrogen peroxide molecules (Fig. 3). The methanol molecule is hydrogen bonded to an N atom of the pyridopyrimidine ring (Fig. 4). In addition, C—H...O interactions are observed between the O atoms of methanol and hydrogen peroxide and risperidone molecules (Table 2).

Experimental

The title compound, (I), was prepared by oxidation of risperidone with 30% aqueous hydrogen peroxide. Crystals suitable for an X-ray study were obtained by recrystallization from methanol.

Crystal data

$C_{23}H_{27}FN_4O_3 \cdot H_2O_2 \cdot CH_4O$
 $M_r = 492.54$
 Monoclinic, $C2/c$
 $a = 37.007$ (4) Å
 $b = 7.7558$ (8) Å
 $c = 17.214$ (2) Å
 $\beta = 105.503$ (2)°
 $V = 4761.0$ (9) Å³
 $Z = 8$

$D_x = 1.374$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 5217 reflections
 $\theta = 2.3$ – 27.6 °
 $\mu = 0.10$ mm⁻¹
 $T = 273$ (2) K
 Block, colorless
 $0.20 \times 0.15 \times 0.10$ mm

Data collection

Bruker CCD area-detector diffractometer
 ω scans
 Absorption correction: none
 11481 measured reflections
 4173 independent reflections

3527 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.023$
 $\theta_{max} = 25.0$ °
 $h = -43 \rightarrow 43$
 $k = -9 \rightarrow 8$
 $l = -20 \rightarrow 20$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.054$
 $wR(F^2) = 0.156$
 $S = 1.08$
 4173 reflections
 319 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0833P)^2 + 3.9805P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} < 0.001$
 $\Delta\rho_{max} = 0.55$ e Å⁻³
 $\Delta\rho_{min} = -0.30$ e Å⁻³

Table 1

Selected geometric parameters (Å, °).

N9—O8	1.436 (3)	N23—C24	1.375 (3)
N14—C13	1.503 (3)	O26—C20	1.224 (2)
N14—C15	1.503 (3)	C10—C11	1.505 (3)
N14—C17	1.507 (3)	O32—C33	1.378 (4)
N21—C27	1.477 (3)	O34—O35	1.430 (3)
N23—C22	1.295 (3)		
C10—N9—O8	106.70 (18)	C13—N14—C17	108.81 (15)
O31—N14—C13	109.02 (14)	C15—N14—C17	110.27 (15)
O31—N14—C15	110.43 (14)	C22—N23—C24	119.40 (18)
C13—N14—C15	108.86 (15)	N14—C17—C18	113.56 (17)
O31—N14—C17	109.41 (14)	C19—C18—C17	111.71 (18)
O31—N14—C15—C16	-62.4 (2)	C18—C19—C24—N23	-176.0 (2)
O31—N14—C17—C18	-48.7 (2)		

Table 2

Hydrogen-bond geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O32—H32 ⁱ ···N23	0.82	2.07	2.882 (3)	173
O34—H34 ⁱ ···O31 ⁱ	0.82	1.84	2.659 (2)	172
O35—H35 ⁱ ···O31	0.82	1.82	2.634 (2)	170
C4—H4 ⁱ ···O34 ⁱⁱ	0.93	2.39	3.267 (3)	156
C7—H7 ⁱ ···O32 ⁱⁱⁱ	0.93	2.48	3.392 (3)	166
C13—H13B ⁱ ···O35 ^{iv}	0.97	2.54	3.192 (3)	124

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

H atoms were included in calculated positions ($C-H = 0.93$ – 0.98 Å) using a riding model, with $U_{iso}(H)$ values set at 1.2 (O and CH H atoms) and 1.5 (CH₃) times the U_{eq} values of the parent atoms. The hydroxy groups were allowed to rotate but not to tip.

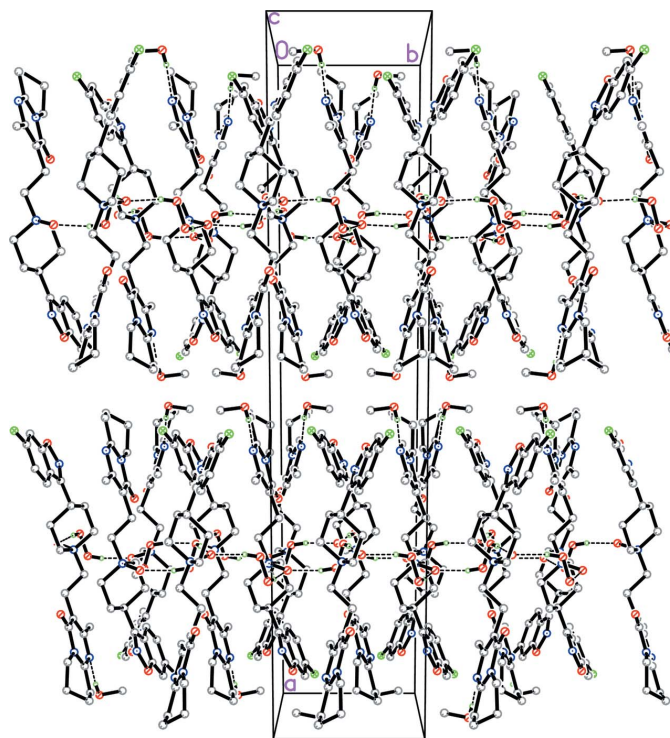


Figure 4

Crystal packing of (I), viewed down the c axis. Dashed lines indicate O—H···O and O—H···N hydrogen bonds. H atoms attached to C atoms have been omitted for clarity.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990); software used to prepare material for publication: *SHELXL97*.

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