Quetiapine hemifumarate

Krishnan Ravikumar* and Balasubramanian Sridhar

Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Correspondence e-mail:
ravikumar_iict@yahoo.co.in

Key indicators

Single-crystal X-ray study
$T = 273$ K
Mean σ(C–C) = 0.003 Å
R factor = 0.055
wR factor = 0.136
Data-to-parameter ratio = 18.2

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

Quetiapine hemifumarate (systematic name: 1-[2-(2-hydroxy-ethoxy)ethyl]-4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-ium hemifumarate), $C_{21}H_{26}O_2N_3S^+ \cdot 0.5C_4H_2O_4^{2-}$, a new dibenzothiazepine antipsychotic, has international approvals for the treatment of schizophrenia. In the tricyclic framework, the central thiazepine ring has a boat conformation and the dihedral angle between the planar benzene rings is 108.6 (1)°. The protonated piperazine ring exhibits a chair conformation with its ethoxyethanol side chain oriented equatorially. The fumarate anion possesses a centre of symmetry. The quetiapinium and fumarate ions are connected by O—H⋯O and N—H⋯O hydrogen bonds.

Comment

Quetiapine, marketed by AstraZeneca under the brand name Seroquel, is a new atypical antipsychotic licensed for the treatment of schizophrenia (Lieberman, 1996). The Seroquel formulation is a fumarate salt. Quetiapine is a dibenzo-thiazepine derivative with a chemical structure reminiscent of that of other antipsychotics, *e.g.* clozapine and olanzapine. It is a dopamine, specifically D1 and D2 dopamine, inhibitor. Compared with conventional antipsychotics, such as chlor-promazine and haloperidol, quetiapine and other atypical antipsychotics provide superior efficacy or fewer side effects, particularly extrapyramidal symptoms (EPS) (Peuskens & Link, 1997; Arvanitis & Miller, 1997). Quetiapine has a well tolerated side-effect profile and in long-term open-label extension studies is found to be popular with patients, with high levels of patient acceptability and satisfaction (Casey, 1996).

(I)
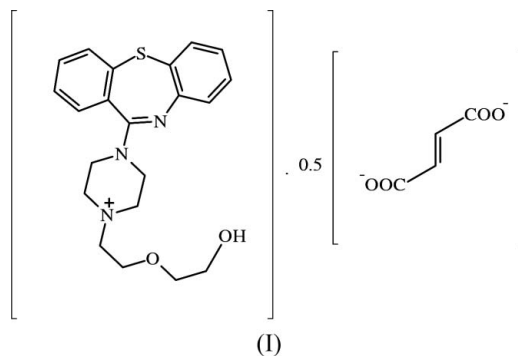
Our interest in the crystal structure of (I) is in continuation of our ongoing programmes on the structural elucidation of drug molecules and in gaining further insight into structure–activity relationships.

The asymmetric unit of (I) consists of one singly charged quetiapine cation and one-half of a doubly charged fumarate

anion; the latter is completed by inversion symmetry (Fig. 1). Bond lengths and angles in quetiapine do not differ significantly from the expected values (Table 1). The C—S bond lengths are essentially equal. The protonation site of the cation is established as N3. The N—C bonds at N3 are lengthened [mean value 1.494 (2) Å compared to 1.430 (2) Å for N2], as would be expected for a protonated system. Consequently, N3 shows quaternary character and bears a positive charge in a tetrahedral configuration, with bond angles ranging from 110.7 (1) to 114.5 (1)°. The positive charge of two cations is balanced by the negative charge of the fumarate anion, which is connected to each cation via N—H···O and O—H···O hydrogen bonding (Table 2).

The conformation of the central thiazepine ring in the (6,7,6)-tricyclic ring system can be described as a boat, with the atoms common to the benzene rings (C1, C2, C9 and C4) as the basal plane, the S atom as the bow and the N1=C3 bridge as the stern [puckering parameters (Cremer & Pople, 1975) are $q_2 = 1.009$ (2), $q_3 = 0.291$ (2) Å, $Q_T = 1.051$ (1), $\varphi_1 = 50.6$ (1)°, $\varphi_2 = -107.4$ (3)° and $\theta = 73.9$ (1)°]. The bow angle is 130.5 (1)° and the stern angle is 138.5 (1)°. This enables the dibenzothiazepine ring skeleton to form a flattened V-shaped conformation. A similar conformation is observed in the crystal structures of the related antipsychotic agents amoxapine, clozapine, loxapine, loxapine succinate monohydrate, clothiapine-modified, clothiapine, olanzapine, olanzipinium nicotinate, oxyprothepine, and metitepine maleate. Least-squares plane calculations through the aromatic rings flanking the thiazepine ring show that benzene ring B is more nearly planar [$\Sigma(\Delta/\sigma)^2 = 23.7$] than benzene ring A [$\Sigma(\Delta/\sigma)^2 = 438.9$]. The dihedral angle ($\chi$) between these benzene rings is 108.6 (1)° and falls in the range 104–127.2° observed for related antipsychotic agents (Table 3). Incidentally, molecular modelling of quetiapine using HYPERCHEM (Hypercube, 1995) predicts this angle to be 145° (Lien et al., 1996). A superimposed fit of related antipsychotic drugs with the central thiazepine ring atoms of (I) shows significant structural similarity (Fig. 2).

A piperazine ring attached to the tricyclic system and its orientation with respect to the tricyclic system is essential for activity (Chakrabarti et al., 1982). The piperazine ring is in a normal chair conformation. The thiazepine nucleus can be viewed as being in an equatorial orientation to the piperazine ring. Interestingly, in related antipsychotics, the corresponding torsion angles are observed as similar. The ethoxyethanol side chain at the cationic N-atom site of the piperazine ring occupies an equatorial orientation and is in a folded conformation. The torsion angles about C19, O1, C20 and C21 indicate that these atoms do not have fully extended bonds, suggesting possible accommodation of the receptor site of dopamine. However, the solid-state conformation need not reflect the conformational preference at the receptor (or in solution).

It has been shown that these drugs are capable of competing with dopamine in synaptosinal preparations (Seeman et al., 1975; Burt et al., 1975). The relationship of the protonated piperazine ring system to the aromatic ring system may be
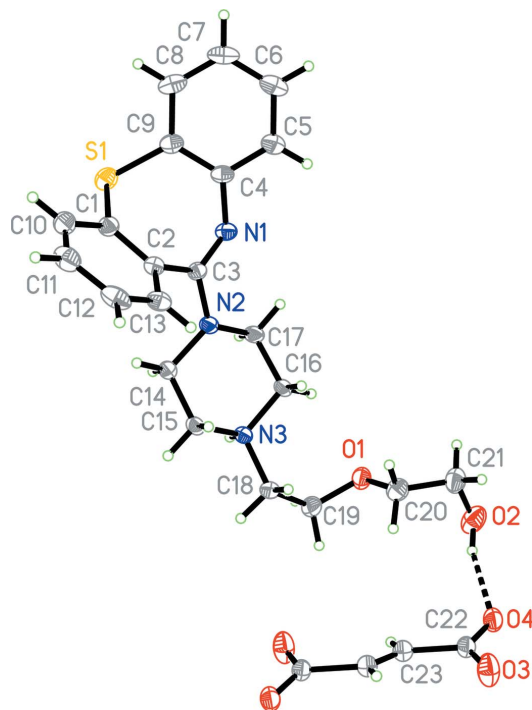

Figure 1
A view of the title compound in the crystal structure, including the symmetry-generated half of the fumarate anion. Displacement ellipsoids are drawn at the 50% probability level. H atoms are shown as small spheres of arbitrary radii and the hydrogen bond as a dashed line. Unlabelled atoms are generated by the symmetry code ($-x, 1 - y, 1 - z$).
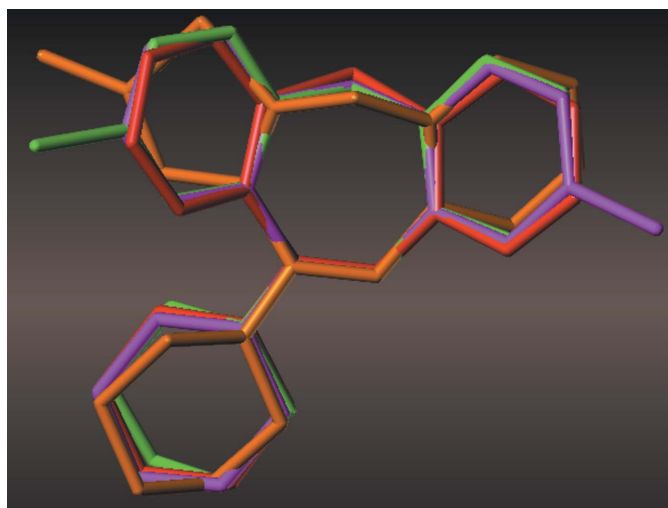

Figure 2
The superposition of the title compound (I) (red) with clozapine (magenta), amoxapine (green) and olanzapine (orange), revealing the structural similarities. Substituents at the piperazine ring and H atoms have been omitted for clarity.

important for neuroleptic activity (Horn & Snyder, 1971). Further parameters have been compiled in Table 3. These data show a remarkable similarity in the disposition of the molecular fragments for the analysed compounds and may be useful for postulating receptor interactions towards structure–activity relationship.

The molecular topography of this class of drugs studied by X-ray crystallography features some important structural and conformational determinants: (*a*) two benzene rings (*A* and *B*) linked by a seven-membered ring are drawn towards each other to form a semi-rigid V-shaped conformation; (*b*) the central seven-membered ring consisting of one or two heteroatoms, similar or dissimilar, exists in a boat conformation; (*c*) the conformation of the piperazine ring is in a chair form.

The packing (Fig. 3) shows the hydrogen bond which binds the quetiapine cationic species to the anionic fumarate. The protonated distal atom N3 of the piperazine ring and O2 of the ethoxyethanol side chain hydrogen bonds to the fumarate dianion through atom O4.

Experimental

To obtain crystals suitable for X-ray studies, quetiapine fumarate (procured from Ind-Swift Laboratories Ltd, Punjab, India) was dissolved in a methanol–water solution (95:5) and the solution was allowed to evaporate slowly.

Crystal data

$C_{21}H_{26}O_2N_3S^+ \cdot 0.5C_4H_2O_4{}^{2-}$	$D_x = 1.332$ Mg m^{-3}
$M_r = 441.54$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 5025
$a = 11.9479$ (8) Å	reflections
$b = 13.2197$ (9) Å	$\theta = 2.3$–27.6°
$c = 13.9479$ (9) Å	$\mu = 0.18$ mm^{-1}
$\beta = 92.327$ (1)°	$T = 273$ (2) K
$V = 2201.2$ (3) Å^3	Block, colourless
$Z = 4$	$0.22 \times 0.13 \times 0.08$ mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer	$R_{int} = 0.024$
	$\theta_{max} = 28.0°$
ω scans	$h = -15 \rightarrow 15$
24936 measured reflections	$k = -17 \rightarrow 17$
5179 independent reflections	$l = -18 \rightarrow 18$
4655 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0578P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.055$	$+ 0.9667P]$
$wR(F^2) = 0.136$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.12$	$(\Delta/\sigma)_{max} < 0.001$
5179 reflections	$\Delta\rho_{max} = 0.33$ e Å^{-3}
285 parameters	$\Delta\rho_{min} = -0.25$ e Å^{-3}
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected geometric parameters (Å, °).

S1—C1	1.7710 (18)	N2—C14	1.460 (2)
S1—C9	1.773 (2)	N3—C15	1.493 (2)
N2—C3	1.374 (2)	N3—C16	1.493 (2)
N2—C17	1.457 (2)	N3—C18	1.496 (2)
C15—N3—C16	110.65 (12)	N3—C15—C14	110.80 (13)
C15—N3—C18	109.41 (12)	N3—C18—C19	114.46 (15)
C16—N3—C18	113.33 (13)		
C9—S1—C1—C10	118.05 (16)	N3—C18—C19—O1	72.8 (2)
C20—O1—C19—C18	69.2 (2)	C19—O1—C20—C21	152.51 (17)

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O2—H2$\cdots$O4	0.82	1.96	2.747 (2)	162
N3—H1$N\cdots$O4^{i}	0.90 (2)	1.71 (2)	2.606 (2)	176 (2)

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

Table 3
Selected conformational parameters (Å and °) derived from crystal structures of antipsychotic compounds.
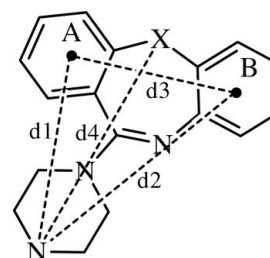
Reference	d1	d2	d3	d4	χ
1	6.005	7.727	4.763	6.980	108.6
2	6.148	7.694	4.603	6.699	119.5
3	5.965	7.718	4.603	6.903	115.0
4	6.196	7.737	4.615	6.729	113.7
5	6.130	7.773	4.624	6.865	121.5
6	5.977	7.749	4.698	6.886	105.3
7	6.098	7.730	4.697	6.699	105.0
8	5.881	7.783	4.639	6.967	127.2
9	5.926	7.759	4.550	6.974	119.9
10	6.025	7.765	4.786	6.512	104.0
11	6.618	7.683	5.107	7.219	123.1

References: (1) quetiapine fumarate (this work); (2) amoxapine (Cosulich & Lovell, 1977); (3) clozapine (Fillers & Hawkinson, 1982*a*); (4) loxapine (Cosulich & Lovell, 1977); (5) loxapine succinate monohydrate (Fillers & Hawkinson, 1982*b*); (6) clothiapine-modified (Dupont *et al.*, 1992); (7) clothiapine (Sbit *et al.*, 1987); (8) olanzapine (Wawrzycka-Gorczyca *et al.*, 2004); (9) olanzipinium niconitate (Ravikumar *et al.*, 2005); (10) oxyprothepine (Koch & Evrard, 1974); (11) metitepine maleate (Blaton *et al.*, 1995).

The H atom on N3 was located in a difference density map and refined freely. All other H atoms were positioned geometrically and treated as riding, with C—H distances in the range 0.93–0.98 Å and with $U_{iso}(H) = 1.2U_{eq}(CH)$.

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) and *MERCURY* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

References

Arvanitis, L. A. & Miller, B. G. (1997). *Biol. Psychiatr.* **42**, 233–246.
Blaton, N. M., Peeters, O. M. & De Ranter, C. J. (1995). *Acta Cryst.* C**51**, 777–780.
Bruker (2001). *SAINT* (Version 6.28a) and *SMART* (Version 5.625). Bruker AXS Inc., Madison, Wisconsin, USA.
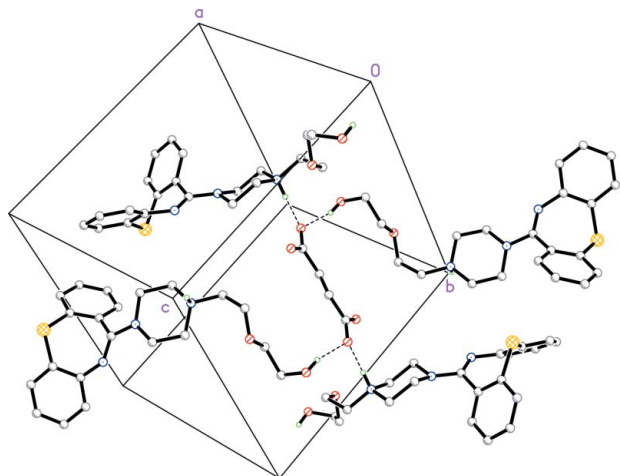
organic papers

Figure 3
Part of the crystal packing, showing the fumarate bridge between the quetiapinium cations, through O—H···O and N—H···O hydrogen bonds. For clarity, H atoms bonded to C atoms have been omitted.

Bruno, I. J., Cole, J. C., Edgington, P. R., Kessler, M., Macrae, C. F., McCabe, P., Pearson, J. & Taylor, R. (2002). *Acta Cryst.* B**58**, 389–397.

Burt, D. R., Enna, S. J., Creese, I. & Snyder. (1975). *Proc. Natl Acad. Sci. USA*, **72**, 4655–4659.

Casey, D. E. (1996). *J. Clin. Psychiatry*, **57**, 40–45.

Chakrabarti, J. K., Hotten, T. M., Morgan, S. E., Pullar, I. A., Rackham, D. M., Risius, F. C., Wedley, S., Chaney, M. O. & Jones, N. D. (1982). *J. Med. Chem.* **25**, 1133–1140.

Cosulich, D. B. & Lovell, F. M. (1977). *Acta Cryst.* B**33**, 1147–1154.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Dupont, L., Dideberg, O., Liegeois, J. F. & Delarge, J. (1992). *Acta Cryst.* C**48**, 1851–1853.

Fillers, J. P. & Hawkinson, S. W. (1982a). *Acta Cryst.* B**38**, 1750–1753.

Fillers, J. P. & Hawkinson, S. W. (1982b). *Acta Cryst.* B**38**, 3041–3045.

Horn, A. S. & Snyder, S. H. (1971). *Proc. Natl Acad. Sci. USA*, **68**, 2325–2328.

Hypercube (1995). *HYPERCHEM*. Release 4.5. Hypercube Inc., 419 Phillip Street, Waterloo, Ontario, Canada N2L 3X2.

Koch, M. H. J. & Evrard, G. (1974). *Acta Cryst.* B**30**, 2925–2928.

Lieberman, J. A. (1996). *J. Clin. Psychiatr.* **57**, 68–71.

Lien, E. J., Das, A. & Lien, L. I. (1996). *Chin. Pharm. J.* **48**, 387–396.

Peuskens, J. & Link, C. G. (1997). *Acta Psychiatr. Scand.* **96**, 265–273.

Ravikumar, K., Swamy, G. Y. S. K., Sridhar, B. & Roopa, S. (2005). *Acta Cryst.* E**61**, o2720–o2723.

Sbit, M., Dupont, L., Dideberg, O., Liégeois, J. F. & Delarge, J. (1987). *Acta Cryst.* C**43**, 720–722.

Seeman, P., Chau-Wong, M., Tedesco, J. & Wong, K. (1975). *Proc. Natl Acad. Sci. USA*, **72**, 4376–4380.

Sheldrick, G. M. (1990). *SHELXTL/PC User's Manual*. Bruker AXS Inc., Madison, Wisconsin, USA.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

Wawrzycka-Gorczyca, I., Koziol, A. E., Glice, M. & Cybulski, J. (2004). *Acta Cryst.* E**60**, o66–o68.