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2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine methanol solvate monohydrate

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Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.003 Å
R factor = 0.044
wR factor = 0.092
Data-to-parameter ratio = 19.2

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

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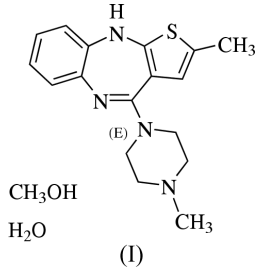
The thienobenzodiazepine nucleus of the title compound, olanzapine methanol solvate monohydrate, $C_{17}H_{20}N_4S\cdot CH_4O\cdot H_2O$, is buckled, with the central seven-membered heterocycle in a boat conformation and the dihedral angle between the planes of the aromatic rings being 118°. The piperazine ring displays an almost perfect chair conformation with the methyl group assuming an equatorial orientation. The relative position of the thienobenzodiazepine and piperazine ring system is controlled by the planarity of the piperazine N in the amidine moiety.

Comment

Schizophrenia is a debilitating mental disorder, characterized by the chaotic jumbling and breakdown of internal thought processes. This devastating disease afflicts approximately 1% of the world population. The symptoms of this disease can be divided into two distinct categories, positive (delusions and hallucinations) and negative (social and emotional withdrawal) (Andreasen *et al.*, 1994). Therapeutics used to treat this disorder are divided into two clinical classes; typical and atypical (Gerlach, 1991). Typical antipsychotics exhibit efficacy against the positive symptoms of schizophrenia and have a propensity to induce extrapyramidal symptoms (EPS): movement disorders such as parkinsonism, dystonia and motor restlessness. Long-term administration of typical agents can lead to an irreversible condition known as tardive dyskinesia (TD) which is characterized by involuntary facial contortions. Atypical antipsychotics are efficacious against both positive and negative symptoms of schizophrenia, as well as associated cognitive deficits, and are virtually devoid of EPS and TD.



(I)

The title compound, olanzapine (ZYPREXA™), (I) (Fig. 1), is an atypical antipsychotic produced by Eli Lilly and Company that obtained approval by the FDA in 1996 for the treatment of schizophrenia and related psychoses. Olanzapine is effective in ameliorating the positive and negative symptoms of schizophrenia and is practically free of movement

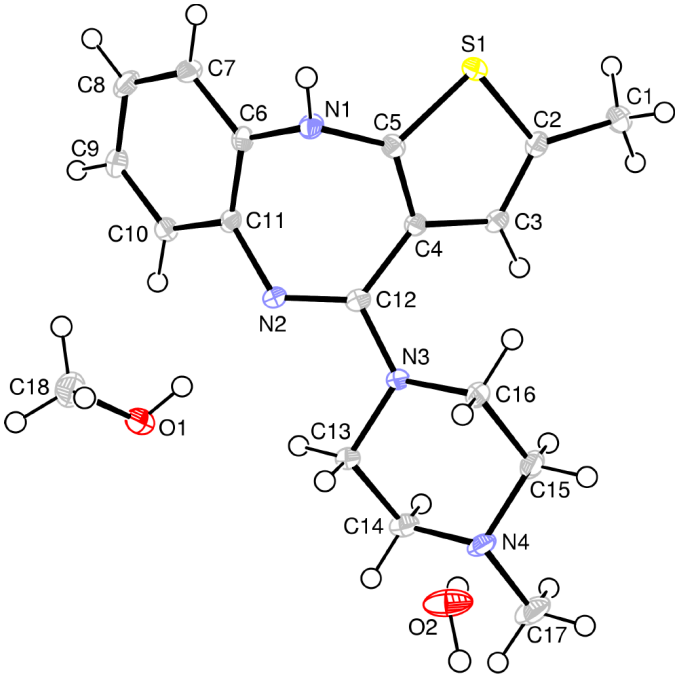


Figure 1
View of (I) (50% probability displacement ellipsoids).

disorders (Fulton & Goa, 1997). The theraputic action of olanzapine against the symptoms of schizophrenia is thought to be due to its high affinity for dopaminergic D_2 and serotonergic 5-HT_{2A} receptors (Bever & Perry, 1998), receptor systems implicated in the pathogenesis of this disease state. As a consequence, olanzapine is commonly referred to as a 'serotonin-dopamine antagonist' (SDA). Electrophysiologic studies (Stockton & Rasmussen, 1996) have demonstrated olanzipine's preferential affinity for dopaminergic receptors in the mesolimbic area (A10 neurons) of the brain compared to the striatum (A9 neurons). This finding may account for its improved therapeutic profile compared to typical antipsychotics, and low incidence of EPS.

Our interest in the structure of (I) was to examine its solid-state conformation and use this information, in conjunction with crystallographic data of other antischizophrenic agents, to design and synthesize novel potential atypical antipsychotics without clinically limited side effects.

The conformation of olanzipine shows the buckled nature of the thienobenzodiazepine nucleus, with the central seven-membered heterocycle in a boat conformation. The dihedral angle between the planes of the aromatic rings is 117.67 (5)°, which is similar to the 115° observed for the prototypical atypical antipsychotic, clozapine (Petcher & Weber, 1976). Interestingly, molecular modelling of olanzapine with HyperChem predicts an interplanar angle of 135° between the benzene and thiophene rings (Lien *et al.*, 1996). The dihedral angles between the plane of the four C atoms in the piperazine ring and the methyl-substituted thiophene ring and unsubstituted benzene ring are 34.6 (1) and 32.9 (1)°, respectively, a consequence of the planarity of the piperizine N in the amidine moiety and the partial double bond character of N3—C12. The piperazine ring adopts an almost perfect chair conformation with the methyl group assuming an equatorial orientation.

Experimental

The title compound was patented by Chakrabarti *et al.* (1991). Eli Lilly and Company, West Rhyde, New South Wales, Australia, supplied a sample of (I) as a pale-yellow powder. (I) was recrystallized by the diffusion method, from a methanol solution of the compound layered onto water, as bright yellow prisms.

Crystal data

$C_{17}H_{20}N_4S{\cdot}CH_4O{\cdot}H_2O$
$M_r = 362.49$
Monoclinic, $C2/c$
$a = 25.3587\ (2)$ Å
$b = 11.9729\ (2)$ Å
$c = 15.6010\ (2)$ Å
$\beta = 127.582\ (1)°$
$V = 3753.77\ (8)$ Å^3
$Z = 8$
$D_x = 1.283$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 21 650 reflections
$\theta = 2.6$–$28.3°$
$\mu = 0.19$ mm^{-1}
$T = 123\ (2)$ K
Prism, yellow
0.15 × 0.14 × 0.14 mm

Data collection

Nonuis KappaCCD diffractometer
CCD rotation images in φ and ω, thick-slice scans
Absorption correction: none
20 806 measured reflections
4643 independent reflections
3683 reflections with $I > 2\sigma(I)$
$R_{int} = 0.041$
$\theta_{max} = 28.3°$
$h = -33 \rightarrow 33$
$k = -15 \rightarrow 15$
$l = -20 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.092$
$S = 1.03$
4643 reflections
242 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0341P)^2 + 3.6138P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.40$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N2	0.84	2.00	2.835 (2)	172
O2—H2A···N4	0.86 (3)	1.95 (3)	2.810 (2)	175 (2)
O2—H2B···O1^{i}	0.85 (2)	1.93 (2)	2.779 (2)	177 (2)
N1—H1N···O2^{ii}	0.85 (2)	2.00 (2)	2.834 (2)	167 (2)

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

Most H atoms were included in the riding-model approximation [C—H(methylene) = 0.99 Å, C—H(methyl) = 0.98 Å, C—H(aromatic) = 0.95 Å and O—H(methanol) = 0.84 Å], with U_{iso}(aromatic-H and methylene-H) = 1.2U_{eq}(C) and U_{iso}(methyl-H and methanol-H) = 1.5U_{eq}(C or O). The H atoms on O2 and N1 were refined.

Data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* publication routines (Farrugia, 1999).

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