Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Polymorphic form IV of olanzapine

Ranjit Thakuria and Ashwini Nangia*

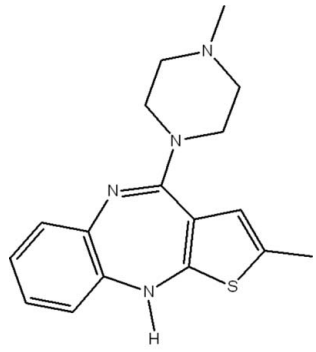
School of Chemistry, University of Hyderabad, Professor C. R. Rao Road, Gachibowli, Central University PO, Hyderabad 500 046, India
Correspondence e-mail: ashwini.nangia@gmail.com

Received 4 October 2011
Accepted 23 October 2011
Online 31 October 2011

2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-*b*][1,5]-benzodiazepine, $C_{17}H_{20}N_4S$, commonly known as olanzapine, is a psychotropic agent that belongs to the thienobenzodiazepine class of drugs. A new polymorph form IV was obtained upon attempted cocrystallization with nicotinamide in a 1:1 ratio from an ethyl acetate solution. Two butterfly-like molecules form centrosymmetric dimers stabilized by weak C—H$\cdots\pi$ interactions between the 4-methylpiperazin-1-yl fragment and the benzene/thiophene aromatic system. Form IV consists of a herringbone arrangement of dimers, whereas the previously reported form II has parallel dimers. Both crystal structures are sustained by an N—H$\cdots$N hydrogen bond.

Comment

Olanzapine [systematic name: 2-methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine], (I), is a frontline psychotropic drug marketed by Eli Lilly under the brand name Zyprexa. It is one of the top 20 prescription drugs based on a recent survey (Craig & Stitzel, 1997; Lindsley, 2010), and is a yellow crystalline solid that is practically insoluble in water (43 mg l^{-1}), sparingly soluble in acetonitrile and ethyl acetate, and freely soluble in chloroform. According to the Biopharmaceutics Classification System (BCS), olanzapine belongs to the Class II category, namely a drug with low solubility and high permeability. Six solid-state forms of olanzapine have been characterized (Bunnell *et al.*, 1996, 1998; Hamied *et al.*, 2002; Sundaram *et al.*, 2006; Reguri & Chakka, 2005; Wawrzycka-Gorczyca *et al.*, 2004), together with a few solvates and hydrates (Reutzel-Edens *et al.*, 2003; Almarsson *et al.*, 2007; Hickey & Remenar, 2006; Wawrzycka-Gorczyca *et al.*, 2004, 2007; Capuano *et al.*, 2003; Larsen, 1997; Bunnell *et al.*, 1997; Kotar-Zordan *et al.*, 2005; Dalmases Barjoan *et al.*, 2006, 2007) and salts with carboxylic acids (Keltjens, 2005; Simonic *et al.*, 2006; Kozluk, 2007; Bush, 2008; Mesar *et al.*, 2008; Ravikumar *et al.*, 2005; Sridhar & Ravikumar, 2007; Thakuria & Nangia, 2011). Only one X-ray crystal structure of olanzapine has been reported to date (Reutzel-Edens *et al.*, 2003; Wawrzycka-Gorczyca *et al.*, 2004), the powder X-ray diffraction pattern (PXRD) of which matched that of a polymorph designated form II in US patents (Bunnell *et al.*, 1996, 1998). We now report the X-ray crystal structure of a polymorph of olanzapine, designated form IV (Hamied *et al.*, 2002) by PXRD overlay.



(I)

The molecule of (I) has a central seven-membered diazepine ring which is fused with a benzene and a thiophene ring, and substituted with a 4-methylpiperazin-1-yl ring (Fig. 1). The boat conformation of the central 1,5-diazepine ring defines the overall butterfly shape of the molecule, but the 4-methylpiperazin-1-yl ring can have conformational variation (Reutzel-Edens *et al.*, 2003).

Cocrystallization of olanzapine with nicotinamide in a 1:1 ratio from ethyl acetate afforded block-shaped pale-yellow crystals of olanzapine form IV in the space group $P2_1/c$. The expected cocrystal with nicotinamide was not obtained. Such observations are not unusual (Day *et al.*, 2006; Li *et al.*, 2011; Sanphui *et al.*, 2011; Vishweshwar *et al.*, 2005). The asymmetric unit of olanzapine form IV contains one molecule of olanzapine, having a single hydrogen-bond donor, N2—H2, and two exposed acceptors, imine atom N1 and piperazine atom N4, which are hydrogen bonded in the crystal structure.

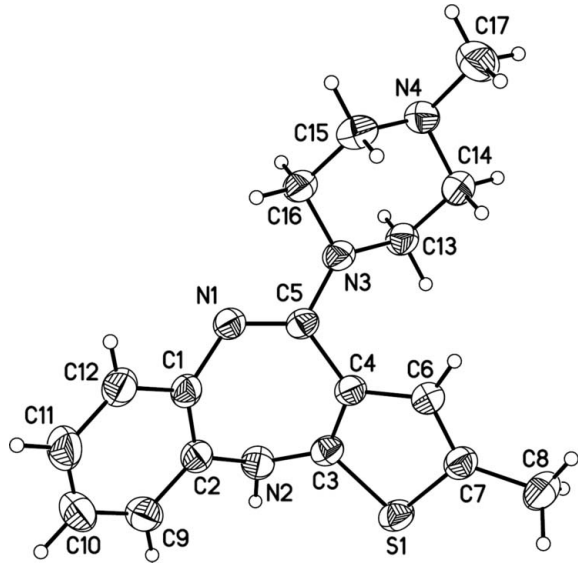


Figure 1
The molecular structure of olanzapine form IV, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

 doi:10.1107/S0108270111043952

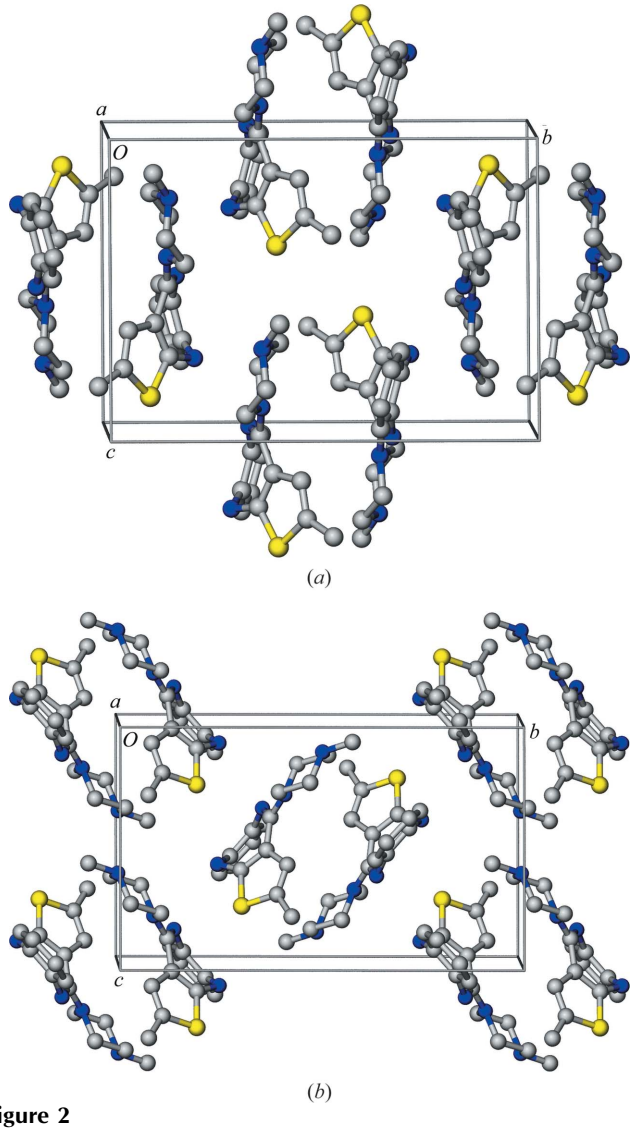


Figure 2
(*a*) The parallel stacking of olanzapine dimers in olanzapine form II. (*b*) The herringbone arrangement of dimers in form IV.

Two butterfly-like molecules form centrosymmetric dimers (Reutzel-Edens *et al.*, 2003; Wawrzycka-Gorczyca *et al.*, 2004) in the crystal structures of both forms IV and II, which are stabilized by weak C—H···π interactions between the 4-methylpiperazin-1-yl fragment (C14—H14*A* in form IV) and the benzene/thiophene aromatic system. Theoretical calculations estimated that this C—H···π binding energy is about 8 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}) (Wawrzycka-Gorczyca *et al.*, 2007). The packing of such dimer motifs in the two structures is completely different: form IV consists of a herringbone arrangement of dimers, whereas the dimers are parallel in form II (Fig. 2).

The intermolecular interaction N2—H2···N1^{i} [symmetry code: (i) x, $-y+\frac{1}{2}$, $z+\frac{1}{2}$] (Table 1) links the molecules in form IV into extended chains which can be described by the graph-set notation $C(5)$ (Bernstein *et al.*, 1995), and thereby connects the inversion-related dimers to form columns along the *c* axis. A similar, slightly shorter, interaction [H···N = 2.27 (2) Å] leading to similar chains occurs in the form II structure. The chains in form IV are further enhanced by a very weak intermolecular C—H···N interaction between piperazine atom N4 and a methyl H atom, H8*B*, on the thiophene ring of the molecule two links further on in the chain. This C—H···N interaction can be described with a graph-set notation of $C(10)$.

Experimental

A solution of olanzapine (60 mg, 0.2 mmol) and nicotinamide (24 mg, 0.2 mmol) in a 1:1 ratio in ethyl acetate (approximately 10 ml) was allowed to evaporate slowly at room temperature for 5–10 d. Complete evaporation of the solvent resulted in a mixture of crytalline nicotinamide and olanzapine. Colourless transparent crystals of nicotinamide were manually separated. Olanzapine form IV, as yellow block-shaped crystals, was selected for X-ray diffraction. Because the polymorph was obtained from a cocrystallization experiment, the phase purity of the bulk sample could not be confirmed by powder diffraction.

Crystal data

$C_{17}H_{20}N_4S$
M_r = 312.44
Monoclinic, $P2_1/c$
a = 9.9130 (8) Å
b = 16.5329 (13) Å
c = 9.9992 (8) Å
β = 98.023 (1)°
V = 1622.7 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.20 mm^{-1}
T = 298 K
0.30 × 0.30 × 0.20 mm

Data collection

Bruker SMART APEX CCD area detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.942, T_{max} = 0.961
16674 measured reflections
3202 independent reflections
2963 reflections with $I > 2\sigma(I)$
R_{int} = 0.026

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.119
S = 1.12
3202 reflections
205 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···N1^{i}	0.86 (2)	2.39 (2)	3.224 (2)	165 (2)
C8—H8*B*···N4^{ii}	0.96	2.69 (1)	3.466 (2)	138

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

The N-bonded atom H2 was located from a difference-electron density map, and its positional and isotropic displacement parameters were refined freely. H atoms attached to C atoms were positioned geometrically and treated as riding on their parent C atoms, with C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl, C—H = 0.97 Å and U_{iso}(H) = 1.2U_{eq}(C) for methylene, and C—H = 0.93 Å and U_{iso}(H) = 1.2U_{eq}(C) for aromatic H atoms.

Data collection: *SMART* (Bruker, 2002); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2002); program(s) used to solve

structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *PLATON* (Spek, 2009).

The authors thank the DST for research funding (grant No. SR/S1/OC-67/2006). RT thanks the UGC for a fellowship. The Bruker SMART APEX CCD X-ray diffractometer was funded by the DST (IRPHA) and UGC is thanked for the UPE programme.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: EG3078). Services for accessing these data are described at the back of the journal.

References

Almarsson, Ö., Hickey, M. B., Peterson, M., Zaworotko, M. J., Moulton, B. & Rodríguez-Hornedo, N. (2007). US Patent No. 2007/0059356A1.
Bernstein, J., Davis, R. E., Shimon, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed.* **34**, 1555–1573.
Bruker (2002). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Bunnell, C. A., Hendriksen, B. A. & Larsen, S. D. (1996). EP Patent No. 733635.
Bunnell, C. A., Hendriksen, B. A. & Larsen, S. D. (1998). US Patent No. 5736541.
Bunnell, C. A., Hotten, T. M., Larsen, S. D. & Tupper, D. E. (1997). US Patent No. 5703232.
Bush, J. K. (2008). US Patent No. 2008/0096871A1.
Capuano, B., Crosby, I. T., Fallon, G. D., Lloyd, E. J., Yuriev, E. & Egan, S. J. (2003). *Acta Cryst.* E**59**, o1367–o1369.
Craig, C. R. & Stitzel, R. E. (1997). *Modern Pharmacology with Clinical Applications*, 5th ed., pp. 385–405. Boston, Massachusetts: Little, Brown & Company.
Dalmases Barjoan, P. & Bessa Bellmunt, J. (2006). WO Patent No. 2006/013435A1.
Dalmases Barjoan, P. & Herbera Espinal, R. (2007). WO Patent No. 2007/077134A1.
Day, G. M., Trask, A. V., Motherwell, W. D. S. & Jones, W. (2006). *Chem. Commun.* pp. 54–56.
Hamied, Y. K., Kankan, R. N. & Rao, D. R. (2002). US Patent No. 6348458B1.
Hickey, M. B. & Remenar, J. (2006). US Patent No. 2006/0223794A1.
Keltjens, R. (2005). US Patent No. 2005/0272721A1.
Kotar-Zordan, B., Lenarsic, R., Grcman, M., Smrkolj, M., Meden, A., Simonic, I., Zupet, R., Gnidovec, J. & Benkic, P. (2005). WO Patent No. 2005/085256A1.
Kozluk, T. (2007). WO Patent No. 2007/032695A1.
Larsen, S. D. (1997). US Patent No. 5637584.
Li, J., Bourne, S. A. & Caira, M. R. (2011). *Chem. Commun.* **47**, 1530–1532.
Lindsley, C. W. (2010). *Am. Chem. Soc. Chem. Neurosci.* **1**, 407–408.
Mesar, T., Copar, A., Sturm, H. & Ludescher, J. (2008). US Patent No. 2008/0161557A1.
Ravikumar, K., Swamy, G. Y. S. K., Sridhar, B. & Roopa, S. (2005). *Acta Cryst.* E**61**, o2720–o2723.
Reguri, B. R. & Chakka, R. (2005). US Patent No. 2005/0153954A1.
Reutzel-Edens, S. M., Bush, J. K., Magee, P. A., Stephenson, G. A. & Byrn, S. R. (2003). *Cryst. Growth Des.* **3**, 897–907.
Sanphui, P., Goud, N. R., Khandavilli, U. B. R., Bhanoth, S. & Nangia, A. (2011). *Chem. Commun.* **47**, 5013–5015.
Sheldrick, G. M. (2003). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Simonic, I., Lenarsic, R., Kotar-Jordan, B., Zupet, R. & Gnidovec, J. (2006). WO Patent No. 2006/010620A2.
Spek, A. L. (2009). *Acta Cryst.* D**65**, 148–155.
Sridhar, B. & Ravikumar, K. (2007). *J. Struct. Chem.* **48**, 198–202.
Sundaram, V., Pandurang, S., Dayaram, V. & Bommareddy, S. K. R. (2006). WO Patent No. 2006/102176A2.
Thakuria, R. & Nangia, A. (2011). *CrystEngComm*, **13**, 1759–1764.
Vishweshwar, P., McMahon, J. A., Oliveira, M., Peterson, M. L. & Zaworotko, M. J. (2005). *J. Am. Chem. Soc.* **127**, 16802–16803.
Wawrzycka-Gorczyca, I., Borowski, P., Osypiuk-Tomasik, J., Mazur, L. & Koziol, A. E. (2007). *J. Mol. Struct.* **830**, 188–197.
Wawrzycka-Gorczyca, I., Koziol, A. E., Glice, M. & Cybulski, J. (2004). *Acta Cryst.* E**60**, o66–o68.