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(+)-*cis*-1-Acetyl-4-(4-{[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazine [(2*R*,4*S*)-(+)-ketoconazole]

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.038
wR factor = 0.108
Data-to-parameter ratio = 13.0

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

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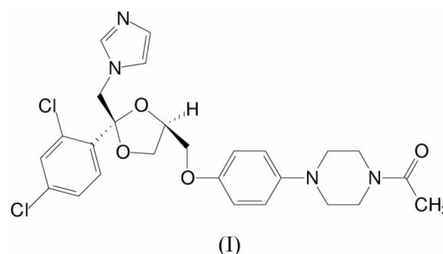
The title compound, $C_{26}H_{28}Cl_2N_4O_4$, the (+)-enantiomer of the orally active broad-spectrum antifungal agent ketoconazole, crystallizes in space group $P1$ with two molecules in the unit cell. Both molecules have the 2*R*,4*S* configuration, but the achiral parts of the molecules are packed in a pseudo-centrosymmetric fashion.

Comment

The title compound, (I), is the (+)-enantiomer of ketoconazole, an orally active broad-spectrum antimycotic. The antifungal activity of ketoconazole is thought to be due to inhibition of a fungal cytochrome P-450 mixed-function oxidase, which catalyses 14-α-demethylation of sterols in the conversion of lanosterol to ergosterol (Van den Bossche *et al.*, 1980).



(I)

As is typical for azole compounds, ketoconazole binds to many mammalian P-450 enzymes, and a number of side effects are associated with ketoconazole as a result of inhibition of these mammalian enzymes (Mason, 1993). Clinically, ketoconazole is administered as the racemic mixture of the (+)- and (−)-enantiomers. There are numerous known examples of different pharmacological properties between stereoisomers (Ariens *et al.*, 1988). The enantioselective synthesis of (+) and (−)-ketoconazole and its (+)- and (−)-*trans*-isomer are described by Rotstein *et al.* (1992). They also evaluated their selectivity in inhibiting a number of cytochrome P-450 enzymes. To check the assignment of the absolute configuration by the stereospecific synthesis, we determined the crystal structure and absolute configuration of (+)-ketoconazole by X-ray diffraction.

(+)-Ketoconazole crystallizes in space group $P1$ with two molecules in the unit cell. Both have the 2*R*,4*S* configuration, which confirms the assignment of the stereospecific synthesis. The two molecules are related to each other in a centrosymmetric fashion, to an extent of 91%, with a pseudo-inversion center at $x = \frac{1}{2}$, $y = \frac{1}{2}$, $z = \frac{1}{2}$. The largest differences in corresponding bond lengths and angles of the two molecules are in the external angles of the 1,3-dioxolane rings and the angles of the methoxy bridges, probably to accommodate the molecules

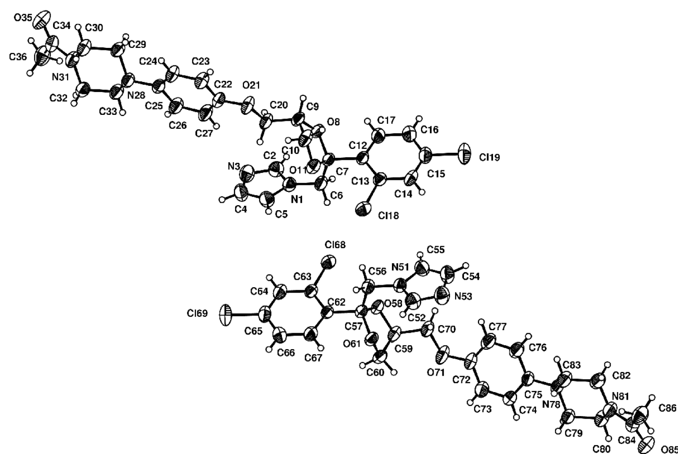


Figure 1
Perspective view of the two molecules in the asymmetric unit, with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

in the pseudo-centrosymmetric packing arrangement. The conformations of the 1,3-dioxolane rings are halfway between an envelope with flap at the unsubstituted C atom and a form twisted about C10—O11 and C60—O71, respectively. The piperazine rings have chair conformations, somewhat flattened at N31 and N81 due to sp^2 hybridization of those atoms.

The conformation of molecule N1—C36 is similar to that of conformer *A* of the crystal structure of racemic ketoconazole (Peeters *et al.*, 1979). An r.m.s. fit (Hypercube, 1993) of all the non-H atoms gave an r.m.s. deviation of 0.09 Å.

Packing of the molecules is achieved by C—H···*A* (*A* = O, N, Cl) interactions.

Experimental

The title compound, (I), was obtained from the racemic mixture *via* semi-preparative HPLC resolution, as described by Dilmaghanian *et al.* (2004). Single crystals were grown by slow evaporation of a methanol/4-methyl-2-pentanone solution.

Crystal data

$C_{26}H_{28}Cl_2N_4O_4$
$M_r = 531.42$
Triclinic, *P*1
$a = 10.3740$ (5) Å
$b = 10.8633$ (7) Å
$c = 13.2251$ (4) Å
$\alpha = 67.725$ (3)°
$\beta = 79.262$ (4)°
$\gamma = 65.743$ (4)°
$V = 1256.60$ (12) Å^3
$Z = 2$
$D_x = 1.405$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 38 reflections
$\theta = 11.2$–28.0°
$\mu = 2.66$ mm^{-1}
$T = 293$ K
Prism, colorless
0.60 × 0.36 × 0.22 mm

Data collection

Siemens *P*4 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan *XEMP* (Siemens, 1989)
$T_{min} = 0.344$, $T_{max} = 0.557$
8445 measured reflections
8445 independent reflections
8257 reflections with $F^2 > 2\sigma(F^2)$
$\theta_{max} = 69.2°$
$h = -12 \rightarrow 12$
$k = -12 \rightarrow 12$
$l = -16 \rightarrow 16$
3 standard reflections every 100 reflections intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.039$
$wR(F^2) = 0.108$
$S = 1.05$
8445 reflections
652 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0737P)^2 + 0.1938P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0274 (9)
Absolute structure: Flack (1983); 3977 Friedel pairs
Flack parameter = 0.017 (8)

Table 1
Selected geometric parameters (°).

C6—C7—O8	109.6 (2)	C56—C57—O58	111.4 (2)
C6—C7—O11	109.2 (2)	C56—C57—O61	108.5 (2)
C6—C7—C12	108.3 (2)	C56—C57—C62	107.9 (2)
O8—C7—O11	106.6 (2)	O58—C57—O61	106.0 (2)
O8—C7—C12	109.3 (2)	O58—C57—C62	112.5 (2)
O11—C7—C12	113.8 (2)	O61—C57—C62	110.4 (2)
C7—O8—C9	108.7 (2)	C57—O58—C59	108.5 (2)
O8—C9—C10	102.8 (2)	O58—C59—C60	103.0 (2)
O8—C9—C20	107.4 (2)	O58—C59—C70	110.5 (2)
C10—C9—C20	115.7 (2)	C60—C59—C70	112.6 (2)
C9—C10—O11	102.9 (2)	C59—C60—O61	101.8 (2)
C7—O11—C10	106.2 (2)	C57—O61—C60	105.5 (2)
C9—C20—O21	106.9 (2)	C59—C70—O71	105.1 (2)
C20—O21—C22	115.4 (2)	C70—O71—C72	117.8 (2)
C2—N1—C6—C7	92.1 (3)	N51—C56—C57—O58	−60.8 (3)
N1—C6—C7—O8	−54.4 (3)	N51—C56—C57—O61	55.5 (3)
N1—C6—C7—O11	62.1 (3)	N51—C56—C57—C62	175.2 (2)
N1—C6—C7—C12	−173.6 (2)	C56—C57—O58—C59	124.8 (2)
C6—C7—O8—C9	124.7 (2)	O61—C57—O58—C59	6.9 (3)
O11—C7—O8—C9	6.6 (3)	O58—C57—O61—C60	−29.2 (2)
O8—C7—O11—C10	−27.3 (3)	C56—C57—C62—C63	73.9 (3)
C6—C7—C12—C13	−75.6 (3)	C57—O58—C59—C60	17.0 (3)
C7—O8—C9—C10	15.4 (3)	C57—O58—C59—C70	−103.5 (2)
C7—O8—C9—C20	−107.1 (2)	O58—C59—C60—O61	−33.8 (3)
O8—C9—C10—O11	−31.1 (3)	O58—C59—C70—O71	−171.2 (2)
O8—C9—C20—O21	−171.1 (2)	C59—C70—O71—C72	−161.0 (2)
C20—O21—C22—C23	−170.1 (3)	C70—O71—C72—C73	166.5 (3)
C24—C25—N28—C29	40.6 (4)	C74—C75—N78—C79	−0.5 (4)
C29—C30—N31—C34	−130.9 (3)	C79—C80—N81—C84	142.3 (3)
C30—N31—C34—C36	175.3 (3)	C80—N81—C84—C86	−179.3 (3)
C52—N51—C56—C57	−87.3 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C2—H2···O61^{i}	0.93	2.46	3.365 (3)	166
C6—H6*A*···O35^{ii}	0.97	2.38	3.296 (5)	158
C20—H20*A*···O85^{iii}	0.97	2.51	3.147 (3)	123
C52—H52···O8^{iv}	0.93	2.54	3.451 (4)	166
C56—H56*B*···O85^{v}	0.97	2.27	3.186 (4)	157
C60—H60*B*···O35^{vi}	0.97	2.40	3.321 (3)	159

Symmetry codes: (i) $x, y, 1+z$; (ii) $1+x, y-1, 1+z$; (iii) $x-1, 1+y, z$; (iv) $x, y, z-1$; (v) $x-1, 1+y, z-1$; (vi) $1+x, y-1, z$.

After checking their presence in a difference map, H atoms were inserted at their geometrically calculated positions, except for those of the methyl groups. The latter were found from a circular difference Fourier synthesis. All H atoms were allowed to ride on their parent atoms (C—H = 0.93–0.98 Å) and, for the methyl groups, to rotate around their local threefold axis. The isotropic displacement parameters of the H atoms were fixed at 1.2 U_{eq} of their parent atoms.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *DIAMOND* (Bergerhoff, 1996); software used to prepare material for publication: *PARST* (Nardelli, 1983).

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References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Ariens, E. J., Wuis, E. W. & Veringa, E. J. (1988). *Biochem. Pharmacol.* **37**, 9–18.

Bergerhoff, G. (1996). *DIAMOND*. Crystal Impact GbR, Bonn, Germany.

Dilmaghanian, S., Gerber, J. G., Filler, S. G., Sanchez, A. & Gal, J. (2004). *Chirality*, **16**, 79–85.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Hypercube (1993). *Chemplus: Extensions for Hyperchem*. Hypercube Inc., Waterloo, Ontario, Canada.

Mason, J. I. (1993). *Biochem. Soc. Trans.* **21**, 1057–1060.

Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.

Peeters, O. M., Blaton, N. M. & De Ranter, C. J. (1979). *Acta Cryst.* B**35**, 2461–2464.

Rotstein, D. M., Kertesz, D. J., Walker, K. A. M. & Swinney, D. C. (1992). *J. Med. Chem.* **35**, 2818–2825.

Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.

Siemens (1996). *XSCANS*. Version 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Siemens (1989). *XEMP*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Van den Bossche, H., Willemsens, G., Cools, W., Cornelissen, F., Lauwers, W. F. & Van Cutsem, J. (1980). *Antimicrob. Agents Chemother.* **17**, 922–928.