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Key indicators

Single-crystal X-ray study
 $T = 293$ K
Mean $\sigma(\text{C}-\text{C}) = 0.009$ Å
 R factor = 0.061
 wR factor = 0.186
Data-to-parameter ratio = 12.9For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.**(+)-1-[(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionyl]-4-(4-[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy}phenyl)piperazine methanol solvate**

The crystal structure and absolute configuration of the title compound, $\text{C}_{34}\text{H}_{33}\text{Cl}_2\text{F}_3\text{N}_4\text{O}_5 \cdot \text{CH}_4\text{O}$, were determined to examine the validity of van 't Hoff's principle of additivity of optical rotations. The conformation of the dioxolane ring is halfway between an envelope, with the flap at the unsubstituted C atom, and a form twisted about $\text{C}_{\text{methylene}}-\text{O}$. The methanol molecule is hydrogen bonded *via* the OH group to the unsubstituted N atom of the imidazole group.

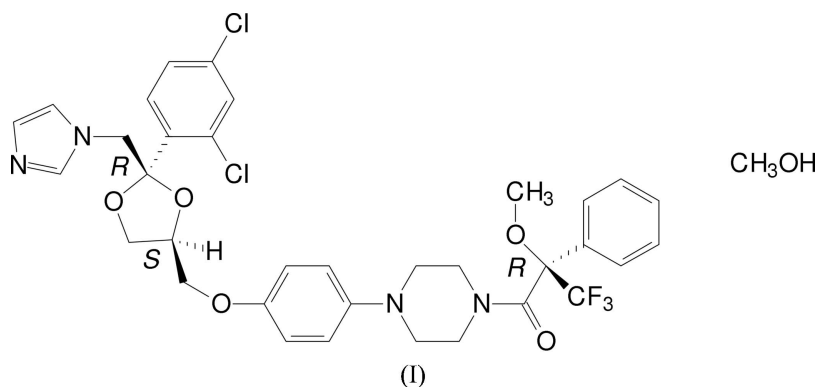
Received 16 November 2005

Accepted 7 December 2005

Online 14 December 2005

Comment

Recently we have initiated studies to examine the validity of van 't Hoff's principle of the additivity of optical rotations (van 't Hoff, 1875, 1908). For this purpose we have synthesized the title compound, (I), its epimer and their component moieties, namely (2*R*,4*S*)-(+)-ketoconazole, (II), (*R*)-3,3,3-trifluoro-2-methoxy-2-phenyl-1-piperidin-1-yl-propan-1-one and its enantiomer to determine whether the optical rotations of (I) and its epimer can be accounted for as the sum of the individual rotations. In this report we provide the determination of the absolute configuration of (I) needed for the above studies on van 't Hoff's principle.



A perspective view of (I) is given in Fig. 1. The bond lengths and angles do not show outstanding features. The molecule contains six rings of which the imidazole and the benzene rings are essentially planar, with a maximum deviation of 0.014 (8) Å for atom C41. The conformation of the dioxolane ring is halfway between an envelope with the flap at the unsubstituted C atom and a form twisted about $\text{C}10-\text{O}11$. The piperazine ring has a chair conformation, somewhat flattened at N31 due to the sp^2 hybridization of that atom. The conformation of (I) (Table 1) is similar to the conformation of (II) in the crystal structure (Peeters *et al.*, 2004). The methanol molecule is hydrogen bonded *via* the OH group to the unsubstituted N atom of the imidazole group (Table 2). There

are no other intermolecular contacts that are significantly shorter than the sum of the corresponding van der Waals radii.

Experimental

The synthesis of (I) was accomplished by first resolving racemic ketoconazole according to a literature method (Redenti *et al.*, 1999) to obtain (+)-ketoconazole, followed by removal of the *N*-acetyl group of the latter using alkaline hydrolysis according to a published procedure (Chapman *et al.*, 1990). The deacetylated compound was then acetylated with (*S*)-(+)- α -methoxy- α -trifluoromethylphenyl-acetyl chloride as described (Hoye & Renner, 1996) to obtain (I). Single crystals were grown by slow evaporation of a methanol solution.

Crystal data

$C_{34}H_{33}Cl_2F_3N_4O_5 \cdot CH_4O$
 $M_r = 737.59$
 Monoclinic, $P2_1$
 $a = 8.389$ (1) Å
 $b = 14.755$ (1) Å
 $c = 14.473$ (2) Å
 $\beta = 100.47$ (1)°
 $V = 1761.6$ (3) Å³
 $Z = 2$

$D_x = 1.391$ Mg m⁻³
 Cu $K\alpha$ radiation
 Cell parameters from 28 reflections
 $\theta = 6.0$ – 27.6 °
 $\mu = 2.23$ mm⁻¹
 $T = 293$ K
 Needle, colourless
 $0.44 \times 0.08 \times 0.06$ mm

Data collection

Siemens P4 four-circle diffractometer
 $\omega/2\theta$ scans
 Absorption correction: ψ scan
 XEMP (Siemens, 1989)
 $T_{min} = 0.560$, $T_{max} = 0.875$
 6518 measured reflections
 5861 independent reflections
 3978 reflections with $F^2 > 2\sigma(F^2)$

$R_{int} = 0.038$
 $\theta_{max} = 68.9$ °
 $h = -9 \rightarrow 10$
 $k = -17 \rightarrow 17$
 $l = -17 \rightarrow 17$
 3 standard reflections every 100 reflections
 intensity decay: none

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.061$
 $wR(F^2) = 0.186$
 $S = 1.07$
 5861 reflections
 455 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.09P)^2 + 0.9675P]$
 where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.001$
 $\Delta\rho_{max} = 0.28$ e Å⁻³
 $\Delta\rho_{min} = -0.31$ e Å⁻³
 Extinction correction: SHELXL97
 Extinction coefficient: 0.0119 (9)
 Absolute structure: Flack (1983), 2616 Friedel pairs
 Flack parameter: -0.01 (2)

Table 1

Selected torsion angles (°).

C2–N1–C6–C7	87.0 (8)	C9–C20–O21–C22	167.0 (5)
N1–C6–C7–O8	–51.1 (6)	C20–O21–C22–C23	19.8 (8)
N1–C6–C7–O11	64.5 (6)	C23–C24–C25–N28	172.9 (6)
N1–C6–C7–C12	–174.3 (5)	C24–C25–N28–C29	21.7 (8)
C6–C7–O8–C9	125.7 (5)	C25–N28–C29–C30	–167.7 (5)
O11–C7–O8–C9	8.4 (5)	C29–C30–N31–C34	–115.8 (6)
O8–C7–O11–C10	–29.0 (5)	C30–N31–C34–C36	176.0 (5)
C6–C7–C12–C13	76.7 (6)	N31–C34–C36–O37	48.0 (7)
C7–O8–C9–C10	14.2 (6)	N31–C34–C36–C39	–72.1 (6)
C7–O8–C9–C20	–106.7 (5)	N31–C34–C36–C45	169.4 (5)
O8–C9–C10–O11	–31.0 (6)	O35–C34–C36–O37	–134.9 (5)
O8–C9–C20–O21	–164.9 (4)	C34–C36–C39–C40	–41.6 (7)
C9–C10–O11–C7	37.2 (6)		

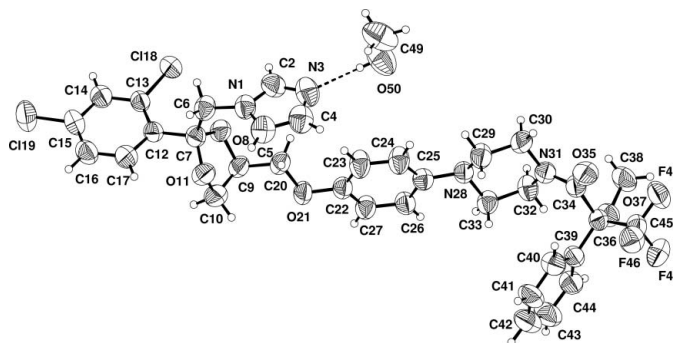


Figure 1

View of (I), with the atomic numbering scheme and displacement ellipsoids at the 50% probability level. The dashed line indicates the hydrogen bond.

Table 2

Hydrogen-bond geometry (Å, °).

D–H...A	D–H	H...A	D...A	D–H...A
O50–H50...N3	0.82	2.05	2.832 (9)	158

After checking their presence in a difference map, H atoms were inserted at their geometrically calculated positions, except for those of the methyl groups and OH group. The latter were found in a circular difference Fourier synthesis. All H atoms were allowed to ride on their parent atoms, with C–H = 0.93–0.98 Å, O–H = 0.82 Å and $U_{iso}(H) = 1.25$ – $1.50 U_{eq}$ of the parent atom.

Data collection: XSCANS (Siemens, 1996); cell refinement: XSCANS; data reduction: XSCANS; program(s) used to solve structure: SIR92 (Altomare *et al.*, 1994); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: DIAMOND (Bergerhoff, 1996); software used to prepare material for publication: PARST (Nardelli, 1983).

This work was supported in part by US Public Health Service grant 5 R01 AI 48000 from the National Institutes of Health (JG) and in part by Vanderbilt University (PP and PZ).

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