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Voriconazole, an antifungal drug

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Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.006 Å
R factor = 0.059
wR factor = 0.161
Data-to-parameter ratio = 6.6

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

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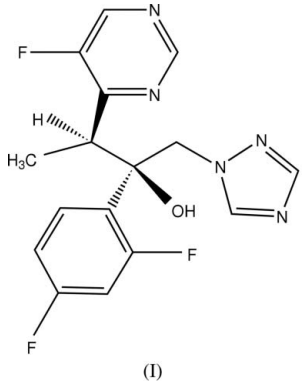
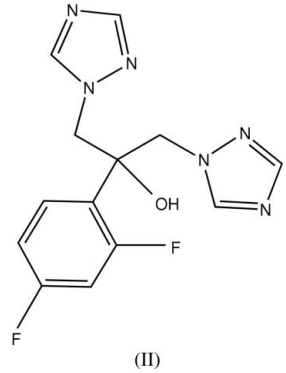
Voriconazole [systematic name 2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol], $C_{16}H_{14}F_3N_5O$, (I), is a triazole antifungal medication used to treat serious fungal infections. The dihedral angle between the planes of the fluoropyrimidine and triazole rings is 32.0 (2)° and that between the difluorophenyl and triazole rings is 47.7 (2)°. In addition to the O—H···N intramolecular hydrogen bond, C—H···O and C—H···N interactions contribute to the molecular arrangement in the crystal packing.

Comment

Azole antifungal agents, which act by inhibition of the cytochrome P450 enzyme lanosterol 14α-demethylase, thereby preventing conversion of lanosterol to ergosterol, are playing a leading role in the treatment of a variety of fungal infections (Como & Dismukes, 1994). Voriconazole, (I), is a novel broad-spectrum triazole antifungal agent with potent *in vitro* activity against the primary opportunistic pathogens: Aspergillus spp., Candida spp. and Cryptococcus spp. (Dickinson *et al.*, 1996; Martin *et al.*, 1997). Its chemical structure is similar to that of fluconazole, (II) (Caira *et al.*, 2004), except for the replacement of one triazole group with a fluoropyrimidine and the introduction of a methyl group. Pfizer Inc. markets voriconazole in the form of injection, tablets and oral suspension under the brand name Vfend. In a continuation of our crystallographic studies on drug molecules, we report the crystal structure of (I).



(I)



(II)

The absolute configuration of voriconazole, resolved through its (−)-10-camphorsulfonate methanol solvate crystal structure, (III) (Dickinson *et al.*, 1996), showed the asymmetric centres C2 and C3 to be *R* and *S*, as also in the free base (I). The twist around the central C1—C2 bond defines the primary conformation of the molecule. The torsion angle N1—C1—

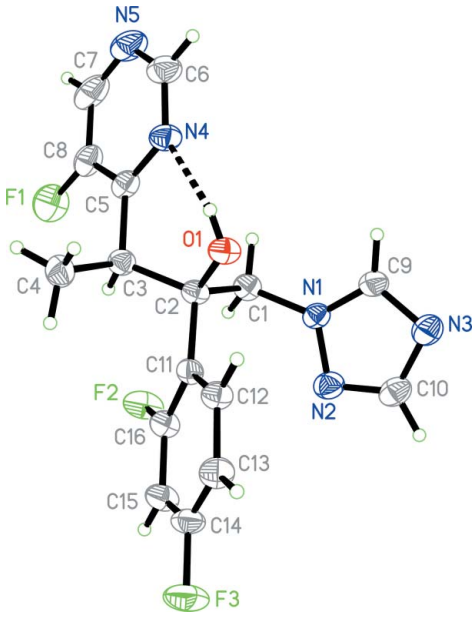


Figure 1
A view of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius. The hydrogen bond is shown as a dashed line.

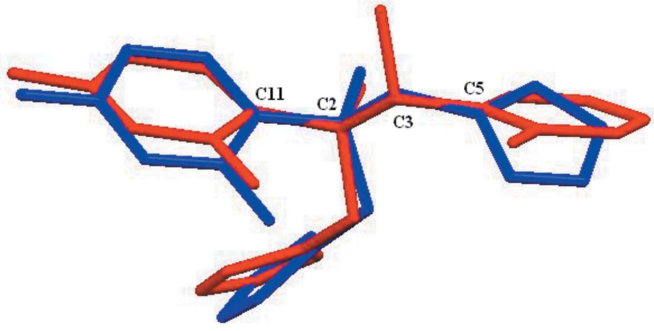


Figure 2
Least-squares fit of (I) (red) and (II) (blue), calculated using the labelled atoms (r.m.s. deviation = 0.006 Å) displaying the conformational features.

C2—C3 [−178.6 (3)°] indicates an extended conformation. The orientation of the rings in (I) compared with that of fluconazole, being of conformational interest, is shown in Fig. 2.

It is interesting to observe in the crystal structure of (III) that the two fluoro-substituted ring planes are almost parallel to each other [dihedral angle 3.72 (2)°], whereas in (I), the planes are inclined at an angle of 17.3 (2)°. The triazole ring plane intersects the fluoropyrimidine ring plane at an angle of 32.0 (2)° and the fluorophenyl plane at 47.7 (2)°, whilst in (III) it subtends an angle of 53.1° with both. The methyl group is believed to show a stronger hydrophobic interaction with aromatic amino acids and more extensive filling of the substrate-binding site (Fukuoka *et al.*, 2003). The methyl and hydroxyl groups are in an anticlinal orientation with respect to each other [C4—C3—C2—O1 = −65.3 (4)°], as also in the voriconazole-camphorsulfonate (−57.8°).

The molecular conformation is stabilized by an intramolecular O—H···N hydrogen bond and the crystal packing

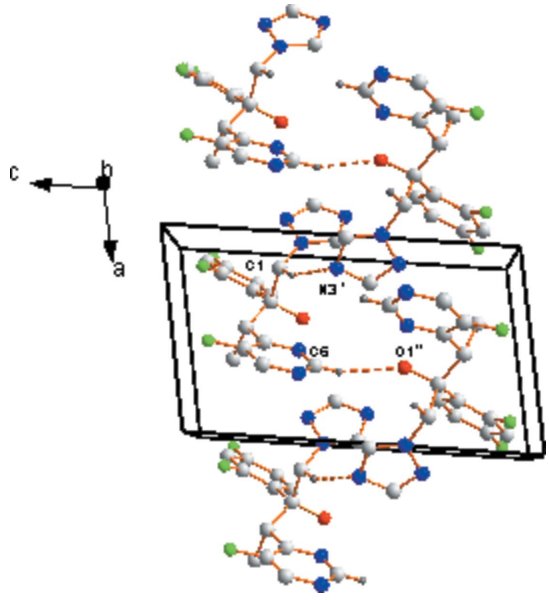


Figure 3
Packing diagram of (I), viewed down the *b* axis, showing an infinite helical chain (dashed lines indicate hydrogen bonds). H atoms not involved in hydrogen bonding have been omitted. The intramolecular O—H···N hydrogen bond is not shown for clarity. Only atoms involved in hydrogen bonding are labelled [Symmetry codes: (i) $-x, y+\frac{1}{2}, 1-z$; (ii) $1-x, y+\frac{1}{2}, 1-z$.]

is characterized by C—H···O and C—H···N (Steiner, 1997) interactions (Table 2).

Experimental

To obtain crystals suitable for X-ray studies, voriconazole (Natco Pharma Ltd, Hyderabad) was dissolved in a methanol–water solution (90:10 *v*/*v*) and the solvents were allowed to evaporate slowly.

Crystal data

$C_{16}H_{14}F_3N_5O$
M_r = 349.32
Monoclinic, $P2_1$
a = 7.5332 (19) Å
b = 8.349 (2) Å
c = 12.989 (3) Å
β = 100.062 (4)°
V = 804.4 (3) Å^3
Z = 2
D_x = 1.442 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.12 mm^{-1}
T = 294 (2) K
Block, colourless
0.15 × 0.12 × 0.10 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scan
Absorption correction: none
7364 measured reflections
1529 independent reflections
1398 reflections with $I > 2\sigma(I)$
R_{int} = 0.040
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.161
S = 1.20
1529 reflections
231 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1192P)^2 + 0.0109P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.41 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C1—C2	1.546 (5)	C6—N4	1.325 (6)
C2—C3	1.558 (5)	N1—N2	1.353 (5)
C3—C4	1.541 (6)		
O1—C2—C11	106.4 (3)	C4—C3—C2	112.2 (3)
C1—C2—C3	109.3 (3)	N2—N1—C1	120.7 (3)
C5—C3—C2	112.7 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1O···N4	0.79 (7)	1.97 (7)	2.679 (5)	150 (6)
C1—H1*B*···N3^{i}	0.97	2.47	3.382 (6)	156
C6—H6···O1^{ii}	0.93	2.54	3.357 (6)	146

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

The H atom attached to the O atom was located in a difference density map and refined isotropically. All other H atoms were positioned geometrically and were treated as riding on their parent C atoms, with C—H distances of 0.93–0.98 Å, and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl atoms and $1.2U_{eq}$(C) for the other H atoms. The methyl group was allowed to rotate but not to tip. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration of the material was known in advance.

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), *DIAMOND* (Brandenburg & Putz, 2005) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

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