Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: OA1021). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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The Antifungal Agent 1-[2-(4-Chlorobenzylamino)benzyl]-1*H*-imidazole

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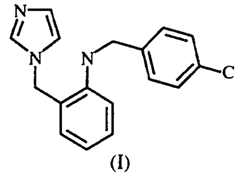
Abstract

The crystal structure of the title compound, $C_{17}H_{16}ClN_3$, and its global minimum-energy structure are not compatible with the model proposed in a recent CoMFA 3D-QSAR (comparative molecular-field analysis 3D-quantitative structure–activity relationship) analysis in which the fixed conformation of the model is used to align all the structures of the inhibitors studied. This result suggests the hypothesis that this molecule belongs to another class of antifungal agents.

Comment

Cytochrome P-450 (Ortiz de Mantellano, 1986) dependent lanosterol 14α-demethylase (P-450$_{DM}$) catalyzes the first step of the biochemically important conversion of lanosterol to cholesterol (mammals) or ergosterol (fungi), which are important constituents of the cell membrane, by causing the removal of the 14α-methyl group of lanosterol to give the Δ^{14-15} desaturated sterol.

N-Substituted imidazole and triazole antifungal compounds are used in therapy and cure mycoses inhibiting the fungal P-450$_{DM}$ at concentrations which are not expected to affect the host corresponding enzyme. We have previously reported on the synthesis and activity of several new derivatives containing different heterocyclic rings (Porretta *et al.*, 1993, 1995; Fioravanti *et al.*, 1995; Biava *et al.*, 1995) in the course of work on new potential antimicrobial compounds related to natural or synthetic agents of therapeutical value. We particularly pointed out that the title compound, (I), showed very good *in vitro* and *in vivo* activity, comparable with that of miconazole and ketoconazole (Panico, Villa, Simonetti, Porretta & Scalzo, 1990).



(I)

The conformation of the structure is described by the torsion angles given in Table 1. The dihedral angle between the imidazole ring (r.m.s. deviation 0.002 Å) and the adjacent plane formed by the atoms from C14 to N1 (r.m.s. deviation 0.027 Å) is 85.7 (1)°. The second plane makes a dihedral angle of 70.8 (1)° with a third more distorted plane (r.m.s. deviation 0.034 Å) given by the atoms from C7 to Cl. The crystal structure and the global minimum-energy structure emerging from a conformational analysis (program *BKM*; Tafi *et al.*, 1996) showed that the title compound is not compatible with the model of the more recent available CoMFA 3D-QSAR analysis (Tafi *et al.*, 1996) because it occupies a different conformational space and is not superimposable on the model following the same alignment rules. CoMFA-3D-QSAR (Cramer, Patterson & Bunce, 1988; Marshall & Cramer, 1988) is a technique which should be able to explain and predict the activity of a data set of inhibitors on the basis of structural and physiochemical

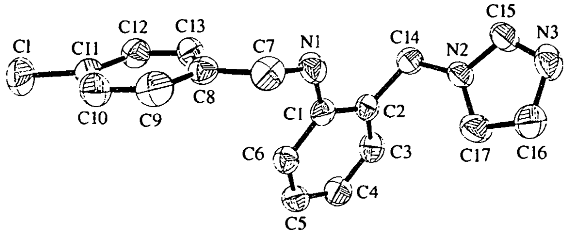


Fig. 1. The molecular structure of (I) showing 50% probability displacement ellipsoids. H atoms have been omitted for clarity.

properties of both active and inactive compounds. The result of the analysis may indicate that the title compound belongs to a different class of antifungal agents than the proposed model; further studies extended to other molecules similar to the title compound will be necessary.

Experimental

The title compound was synthesized previously by Scalzo *et al.* (1986). Single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from a hot diethyl ether solution.

Crystal data

$C_{17}H_{16}ClN_3$
$M_r = 297.78$
Monoclinic
$P2_1/n$
$a = 11.065\,(1)$ Å
$b = 5.614\,(2)$ Å
$c = 24.225\,(2)$ Å
$\beta = 90.728\,(6)°$
$V = 1504.7\,(6)$ Å^3
$Z = 4$
$D_x = 1.314$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 78.48–79.82°$
$\mu = 2.206$ mm^{-1}
$T = 293\,(2)$ K
Prism
0.4 × 0.3 × 0.2 mm
Orange

Data collection

MSC/AFC diffractometer
ω–2θ scans
Absorption correction: empirical *via* ψ scans (*TEXSAN*; Molecular Structure Corporation, 1985)
$T_{\min} = 0.431$, $T_{\max} = 0.643$
2805 measured reflections
2377 independent reflections

2157 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.013$
$\theta_{\max} = 62.1°$
$h = 0 \rightarrow 12$
$k = 0 \rightarrow 6$
$l = -27 \rightarrow 27$
3 standard reflections every 200 reflections intensity decay: none

Refinement

Refinement on F^2
$R(F) = 0.0441$
$wR(F^2) = 0.1531$
$S = 0.657$
2376 reflections
190 parameters
H atoms not refined
$w = 1/[\sigma^2(F_o^2) + (0.1754P)^2 + 1.4443P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.026$
$\Delta\rho_{\max} = 0.472$ e Å^{-3}
$\Delta\rho_{\min} = -0.580$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Cl—C11	1.739 (3)	N3—C15	1.311 (3)
N1—C1	1.382 (3)	N3—C16	1.354 (3)
N1—C7	1.445 (3)	C2—C14	1.507 (3)
N2—C15	1.345 (3)	C7—C8	1.514 (3)
N2—C17	1.357 (3)	C16—C17	1.353 (3)
N2—C14	1.473 (3)		
C1—N1—C7	122.9 (2)	N1—C7—C8	115.9 (2)
C15—N2—C17	105.7 (2)	C13—C8—C7	122.9 (2)
C15—N2—C14	126.1 (2)	C9—C8—C7	119.3 (2)
C17—N2—C14	128.1 (2)	C12—C11—Cl	119.3 (2)
C15—N3—C16	104.4 (2)	C10—C11—Cl	119.7 (2)
N1—C1—C6	121.3 (2)	N2—C14—C2	112.1 (2)
N1—C1—C2	120.7 (2)	N3—C15—N2	112.8 (2)
C3—C2—C14	118.4 (2)	C17—C16—N3	110.5 (2)
C1—C2—C14	122.4 (2)	C16—C17—N2	106.5 (2)
C7—N1—C1—C6	11.7 (3)	N1—C7—C8—C9	165.9 (2)
C7—N1—C1—C2	−170.2 (2)	C9—C10—C11—Cl	176.9 (2)
N1—C1—C2—C14	5.7 (3)	C17—N2—C14—C2	12.6 (3)
C1—N1—C7—C8	−72.6 (3)	C1—C2—C14—N2	86.7 (2)

The comparatively low value of $\theta_{\max}$ is caused by an evacuated beam collimator mounted on the diffractometer. The weak reflections, $I < 10\sigma(I)$, were rescanned and the counts accumulated to assure good counting statistics. The structure solution by direct methods, the data reduction and the empirical absorption correction were performed with *TEXSAN* (Molecular Structure Corporation, 1985), and the data were refined by full-matrix least-squares methods with *SHELXL*93 (Sheldrick, 1993). The H atoms were introduced at calculated positions and not refined. Other programs used included *SHELXTL-Plus* (Sheldrick, 1990).

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Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: AB1428). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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